

**American College of Radiology
ACR Appropriateness Criteria®**

Clinical Condition: Pre-Irradiation Evaluation and Management of Brain Metastases

Variant 1: 50-year-old patient with newly diagnosed cancer of any stage and new intracranial signs or symptoms.

Radiologic Procedure	Rating	Comments
MRI head with standard dose contrast	8	
CT head with contrast	7	
MRI head with high dose contrast	3	
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate		

Variant 2: 50-year-old man with no known diagnosis of cancer, but with CT scan evidence of solitary metastasis.

Radiologic Procedure	Rating	Comments
MRI head with standard dose contrast	8	
MRI head with high dose contrast	8	
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate		

Variant 3: 50-year-old patient with newly diagnosed non-small cell lung cancer with resectable primary and CT scan evidence of solitary brain metastasis.

Radiologic Procedure	Rating	Comments
MRI head with standard dose contrast	8	
MRI head with high dose contrast	8	
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate		

Variant 4: 50-year-old patient with no known diagnosis of cancer, MRI consistent with solitary metastasis in anterior left frontal lobe, mild headaches, and workup of chest and abdomen negative.

Treatment	Rating	Comments
Resection (craniotomy)	9	
Biopsy only of suspicious intracranial lesion	2	
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate		

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Clinical Condition:

Pre-Irradiation Evaluation and Management of Brain Metastases

Variant 5:

50-year-old patient with melanoma and supratentorial brain metastases, mild edema on imaging, no hydrocephalus, mild neurologic symptoms present, and no history of seizures.

Treatment	Rating	Comments
Corticosteroids 4 mg/day	8	
Corticosteroids 16 mg/day	5	
Anticonvulsants (prophylactic)	4	

Rating Scale: 1=Least appropriate, 9=Most appropriate

Variant 6:

50-year-old patient with non-small cell lung cancer and supratentorial brain metastases, mild edema on imaging, no hydrocephalus, mild neurologic symptoms, and no history of seizures.

Treatment	Rating	Comments
Corticosteroids 4 mg/day	8	
Corticosteroids 16 mg/day	5	
Anticonvulsants (prophylactic)	2	

Rating Scale: 1=Least appropriate, 9=Most appropriate

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PRE-IRRADIATION EVALUATION AND MANAGEMENT OF BRAIN METASTASES

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Summary of Literature Review

The pretreatment evaluation for brain metastases occurs primarily in two situations: as part of the staging investigations in a patient who has known systemic cancer, or in the patient who has cerebral or cerebellar symptoms, with or without known systemic cancer. In either case, the evaluation is critical when the presence of brain metastases would alter therapy. The evaluation is also important to identify and appropriately manage brain metastases. Although brain metastases can arise from virtually any primary cancer, lung and breast are the two most common primary sites of cancer in patients presenting with brain metastases. The literature regarding pretreatment evaluation and management is dominated by patients with these primary malignancies.

The choice of treatment for brain metastases is often based on the location and number of metastases identified on imaging studies [1,2]. Contrast-enhanced magnetic resonance imaging (MRI) is the imaging test of choice in the patient with suspected brain metastases if surgery or radiosurgery is being considered [3,4]. Otherwise, computed tomography (CT) with contrast enhancement is a reasonable study, albeit less sensitive than MRI.

During the CT era as many as 50% of patients with brain metastases were found to have a single metastasis [5]. However, it is almost certain that the current percentage is lower, given the increased sensitivity of modern MRI. Current patient data, acquired with modern CT and MRI technology, indicate that about 20% of patients thought to have a single brain metastasis based on CT actually have

multiple lesions on MRI [6]. Recommended pre-gadolinium studies include T2-weighted and T1-weighted sequences. Recommended post-gadolinium studies include T1-weighted sequences (in at least two orthogonal planes); fluid-attenuated inversion-recovery (FLAIR) sequences have also been shown to complement, but not replace, contrast-enhanced T1 sequences. Contiguous thin slices without skips are necessary to ensure that small lesions are detected.

Several studies have demonstrated that the dose of intravenous contrast selected for MRI may be important in determining the number of lesions as well as the confidence level associated with the radiologic interpretation [3,4,7,8]. Yuh et al [8] reported that high-dose contrast (0.3 mmol/kg gadolinium) is superior to standard-dose contrast (0.1 mmol/kg gadolinium) in lesion detection without any increase in serious toxicity. However, high-dose contrast is not commonly used, and its role in individual patient treatment decisions has not been determined. There is also evidence that the strength of the MRI magnet is important in the ability to detect brain metastases. Ba-Ssalamah et al [9] analyzed the subjective assessment of MRIs done with standard-dose or triple-dose contrast in both 1.5 and 3 T magnetic fields. Improved images were obtained with both higher dose of contrast and higher magnet strength. High-dose contrast MRI is potentially most valuable in patients thought to have a single brain metastasis, if the therapeutic approach might change if multiple metastases are found. Dynamic contrast enhanced MRI, (perfusion imaging) and MR Spectroscopy have also been found to be helpful for differentiating single metastases from primary cerebral neoplasms [10,11].

The bulk of the literature regarding the use of brain CT or MRI for staging purposes has dealt with lung cancer. Nevertheless, there is still no general agreement on when to use CT or MRI as part of the initial staging evaluation for a patient newly diagnosed with lung cancer. The decision may vary with the type and stage of lung cancer. One prospective study found that MRI did not change the initial stage of asymptomatic patients with small-cell lung cancer [12]. The only patients with asymptomatic brain metastases were those with extensive disease already demonstrated by other tests such as a positive bone scan or liver metastases on CT scan of the abdomen. Although brain MRI appears to be superior to a brain CT scan, CT is still widely used as a staging procedure because of its accessibility and lower cost. One retrospective study reported by Ferrigno and Buccheri [13] concluded that 10% of patients with otherwise operable non-small-cell lung cancer had brain metastases identified on CT scans. The absence of neurologic symptoms did not exclude

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brain metastases since 64% of patients with metastases detected by CT were asymptomatic. Conversely, Hooper et al [14] found that CT scans did not reveal unsuspected brain metastases in patients without strong evidence of disseminated disease, such as neurologic signs or symptoms, bone pain, or elevated serum calcium. Hooper et al [14] did not address the utility of CT scans in otherwise operable patients, and it is possible that their patient group had a more advanced stage of disease at presentation than that seen by Ferrigno [13], which would account for the different conclusions reached by the two authors.

Positron emission tomography with 2-deoxy-2-fluoro-D-glucose (FDG-PET) has been evaluated as a means of identifying brain metastases [15,16]. PET studies in small numbers of patients have been associated with low sensitivity and specificity rates in the detection of brain metastases. PET scans have also been tested as a means of differentiating various abnormalities already detected by more conventional imaging studies such as CT or MRI. Whole-body FDG-PET is more useful in locating the primary lesion and sites of extracranial metastases in a patient with documented brain metastases. The low sensitivity and specificity of cerebral FDG-PET are likely due to the large background of glucose activity within the brain. Alternative tracers to FDG such as 3-deoxy-3-fluorothymidine (FLT) or thallium-201 may in the future prove to be more useful in the imaging of brain metastases [17,18].

Several authors have sought to determine whether histologic confirmation is required following the identification of a suspected solitary metastasis or multiple brain metastases [2,19]. In one study in which stereotactic biopsy or resection was performed in patients with suspected solitary brain metastasis, 11% of these patients were found to have other tumor histology, or lesions of infectious or inflammatory origin [2]. Stereotactic biopsy is equivalent to resection in determining the correct tissue diagnosis in the majority of patients if an appropriate number of biopsies are obtained with immediately available frozen section confirmation [20]. While multifocal malignant gliomas are relatively uncommon compared with brain metastases, the two clinical conditions may be difficult to distinguish on the basis of current conventional imaging studies [19]. However, new MRI methods (perfusion and MR spectroscopy) have shown improvement in specificity (Law et al, see above). Together, these observations argue for 1) MRI with increased dose of contrast and, if no additional lesions are identified, 2) histologic verification of the solitary brain lesion in the patient with a controlled primary (noncentral nervous system) cancer after systemic evaluation fails to disclose other sites of disease. With multiple brain lesions that have imaging characteristics compatible with brain metastases, the

decision to biopsy or not is based on the clinical picture. Patients with progressive extracranial cancer are seldom subjected to histologic confirmation of multiple brain lesions or new solitary lesions.

It is common practice to obtain a neurosurgical opinion regarding surgical intervention to debulk or completely resect brain metastases in a patient presenting with hydrocephalus due to a posterior fossa metastasis, or in the patient with impending cerebral or cerebellar herniation.

While clinical experience has established the effectiveness of corticosteroids such as dexamethasone in reducing symptoms and MRI evidence of peritumoral edema, the need for corticosteroids in all patients with brain metastases, as well as the appropriate dose of such medication, is the point of some research and controversy [21]. Early studies that concluded that patients with newly diagnosed brain metastases should be placed on steroids prior to whole-brain radiation therapy used unconventional radiation dose/fractionation regimens [22,23]. For example, in one prospective clinical trial in which various whole-brain radiation dose/fraction schedules were utilized, steroids were started only when there was concern about high intracranial pressure [23]. The results of this study suggest that patients undergoing whole-brain radiation therapy with high doses per fraction should be started on steroids prior to treatment. Twenty-seven percent of patients treated with a single dose of 1000 cGy single-fraction whole-brain radiation therapy experienced acute signs or symptoms of increased intracranial pressure. This dose fractionation of whole-brain radiation therapy is not in common use at this time. Another study, conducted by the Radiation Therapy Oncology Group (RTOG) nearly two decades ago, found that patients with moderate neurologic signs or symptoms experienced more rapid improvement in their clinical state when radiation treatment was accompanied by steroids [22]. However, steroids did not result in prolongation of progression-free survival or overall survival.

Despite the acknowledged benefits of steroids in reducing edema and alleviating symptoms, the acute and chronic side effects of dexamethasone cannot be ignored. A randomized study comparing dosages of 4, 8, and 16 mg of dexamethasone per day found no advantage to higher dosages compared with 4 mg per day in the patient with no evidence of impending herniation [24]. Steroid-related toxicity was more common at the higher doses. There was, however, a trend toward improved performance 28 days after starting dexamethasone in patients on the high doses of steroids. Vecht et al [24] attributed this trend of improvement in the higher-dose group to the early steroid taper in the low-dose group, beginning on the seventh day of cranial irradiation, which led to clinical deterioration in some patients. Based on this observation, Vecht et al [24]

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recommended 4 mg per day without a dose taper for 28 days in patients without symptoms or signs of mass effect. Another small prospective study suggests that high doses of intravenous steroids given only in the 48 hours before cranial radiation results in objective responses and survival rates similar to those seen in patients continued on steroids throughout radiation therapy [25]. More recently Hempen et al [26] studied 138 patients with primary or metastatic brain tumors treated with radiotherapy. Ninety-one patients with brain metastases were treated with standard-fraction whole brain radiation therapy over 2-3 weeks. Most of these patients received dexamethasone with tapering doses, for a mean duration of 6.9 weeks. Clinical improvements, possibly attributable to dexamethasone, were observed in 33% of patients shortly after it was initiated, in 44% during radiotherapy, and in 11% after radiotherapy. However, side effects possibly attributable to dexamethasone were frequently observed, including hyperglycemia (47%), peripheral edema (11%), psychiatric disorder (10%), oropharyngeal candidiasis (7%), Cushing's syndrome (4%), muscular weakness (4%), and pulmonary embolism (2%). Among thirteen patients receiving radiotherapy without dexamethasone, treatment was well tolerated, except in one patient with brain stem symptoms. In summary, the panel concluded that there is little compelling evidence suggesting that steroids have a role in the management of brain metastases unless the patients have clinical symptoms caused by elevated intracranial pressure. Likewise, there is no compelling evidence that in the absence of clinical signs, steroids should be started simply because the patient has a brain tumor or because the patient is about to start radiation therapy. Steroids cause toxicity, and any recommendation for steroids must be rendered in light of this fact. Steroid treatment should be tapered as clinically indicated.

Another controversy revolves around the need to initiate prophylactic anticonvulsants in the patient with brain metastases. Approximately 15% of patients with brain metastasis present with seizures, and most such patients are found to have supratentorial lesions [27]. Patients who present with seizures or who develop seizures during therapy should be started on antiseizure medications. Randomized prospective studies have found no significant reduction in the incidence of first seizures in brain tumor patients placed on prophylactic anticonvulsants [28-30]. New onset of seizures was experienced by approximately 25% of patients treated with prophylactic anticonvulsants, not significantly different than the percentage of patients experiencing new onset of seizures in the control arm. To determine the benefit of prophylactic anticonvulsants Glantz et al [27] performed a meta-analysis of 12 studies (10 of which included patients with brain metastasis) that reported the frequency of seizures following diagnosis of a primary or metastatic brain tumor. There was no evidence that prophylactic anticonvulsants significantly

decreased the incidence of first seizure. In the aggregate, these studies recorded a 26% incidence of seizures at or before brain tumor diagnosis (range, 14%-51%), and a 19% incidence of seizures after brain tumor diagnosis (range, 10%-45%). Seizures were more common, both before and after brain tumor diagnosis, in patients with primary as compared to metastatic brain tumors. More than 20% of patients had side effects severe enough to warrant a change in or discontinuation of the anticonvulsants. A subsequent randomized study of prophylactic anticonvulsants versus observation by Forstythe et al [28] reached a similar conclusion regarding the lack of benefit of prophylactic anticonvulsants.

One clinical situation in which prophylactic anticonvulsants may be warranted is in the patient with malignant melanoma brain metastases. A retrospective study reported by Byrne et al [31] found that prophylactic anticonvulsants in patients with brain metastases from metastatic melanoma reduced the subsequent seizure frequency from 37% to 17%. Possible explanations for the high incidence of seizures in patients with brain metastases from melanoma, as opposed to other histologies, include the tendency for these metastases to be located in the superficial cerebral cortex rather than at the gray-white matter junction. The meta-analysis by Glantz et al [27] did not indicate a significant benefit to anticonvulsants in patients with malignant melanoma brain metastases but concluded that further prospective studies of prophylactic anticonvulsants were warranted in this subgroup.

Physicians should also be aware of the potential interaction between anticonvulsants and chemotherapy. Anticonvulsants that induce the P450 system of hepatic metabolism can result in clinically significant reduction of plasma levels of chemotherapies that are metabolized by this system. Anticonvulsants that do not induce this system are available and should be selected if this is a concern.

In summary, the pretreatment evaluation should determine the number, location, and size of the brain metastases. MRI is the recommended imaging technique, preferably with a high-strength magnet, particularly in patients being considered for surgery or radiosurgery. Double or triple-dose contrast during the MRI should be considered if it is important to know the precise number of metastases, such as at the time of radiosurgery. A noncontrast scan should accompany the contrast scan to exclude hemorrhage or fat as the cause of the high signal on postcontrast imaging. A systemic workup and medical evaluation are important given that subsequent treatment for the brain metastases will also depend on the extent of the extracranial disease and the age and performance status of the patient [32]. Patients with hydrocephalus or impending brain herniation should be started on high doses of corticosteroids and evaluated for possible

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neurosurgical intervention. Patients with moderate symptoms should receive approximately 4-6 mg per day of dexamethasone in divided doses. Routine use of corticosteroids in patients without neurological symptoms is not necessary. There is no proven benefit of anticonvulsants in the patient who has not experienced seizures, although there may be exceptional subgroups of patients, such as those with melanoma.

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