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# PRE-IRRADIATION EVALUATION AND MANAGEMENT OF BRAIN METASTASES

Expert Panel on Radiation Oncology–Brain Metastases: Simon Shek-Man Lo, MB, ChB[1]; Elizabeth M. Gore, MD[2]; Jeffrey D. Bradley, MD[3]; John M. Buatti, MD[4]; Isabelle Germano, MD[5]; A. Paiman Ghafoori, MD[6]; Mark A. Henderson, MD[7]; Gregory J. A. Murad, MD[8]; Roy A. Patchell, MD[9]; Samir H. Patel, MD[10]; Jared R. Robbins, MD[11]; H. Ian Robins, MD, PhD[12]; Andrew D. Vassil, MD[13]; Franz J. Wippold II, MD[14]; Michael J. Yunes, MD[15]; Gregory M. M. Videtic, MD.[16]

## Summary of Literature Review

### Introduction/Background

The pretreatment evaluation for brain metastases occurs either as part of the staging investigations in a patient who has known systemic cancer or in a 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 the overall oncologic management. The patient's clinical symptomatology and overall oncologic picture as well as the findings on diagnostic imaging of the brain will determine the appropriate treatment for brain metastases. Although brain metastases can arise from virtually any primary cancer, lung and breast are the 2 most common primary sites of cancer in patients presenting with brain metastases. Other common histologies include melanoma, renal cell carcinoma, and colorectal cancer. 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 patient symptomatology, histology, location, and number of metastases identified on imaging studies [1-3]. 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 [4,5]. Otherwise, computed tomography (CT) with contrast injection is a reasonable study, albeit less sensitive than MRI.

### Computed Tomography/Magnetic Resonance Imaging

During the CT era as many as 50% of patients with brain metastases were found to have a single metastasis [6]. However, it is almost certain that the current percentage is lower, given the increased sensitivity of modern MRI, especially when a volumetric sequence with contiguous thin cuts is included. 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 are found to have multiple lesions on MRI [7]. However, CT with contrast remains the best imaging option for investigation of brain metastasis in patients with automatic implantable cardioverter defibrillators or pacemakers. If treatment is to be determined according to the number of brain metastases, MRI with pregadolinium T1-weighted and T2-weighted sequences and postgadolinium T1-weighted imaging, preferably a thin-cut contiguous volumetric sequence in axial, coronal, and sagittal planes, is recommended.

Fluid-attenuated inversion-recovery (FLAIR) sequences have also been shown to complement, but not replace, contrast-enhanced T1 sequences, and can be correlated with the T1 sequences to determine whether a punctuate contrast-enhanced lesion is a metastatic lesion, which frequently shows signal intensity on FLAIR imaging.

[1]Principal Author, UH Seidman Cancer Center, Cleveland, Ohio. [2]Panel Vice-chair, Medical College of Wisconsin, Milwaukee, Wisconsin. [3]Washington University School of Medicine, St. Louis, Missouri. [4]University of Iowa Hospital, Iowa City, Iowa. [5]Mount Sinai School of Medicine, New York, New York, American Association of Neurological Surgeons/Congress of Neurological Surgeons. [6]University Medical Center Brackenridge, Austin, Texas. [7]Indiana University School of Medicine, Indianapolis, Indiana. [8]University of Florida, Gainesville, Florida, American Association of Neurological Surgeons/Congress of Neurological Surgeons. [9]Capital Health Medical Center-Hopewell, Pennington, New Jersey, American Academy of Neurology. [10]Mayo Clinic Arizona, Scottsdale Arizona. [11]Henry Ford Hospital, Detroit, Michigan. [12]University of Wisconsin, Paul P. Carbone Comprehensive Cancer Center, Madison, Wisconsin, American Society of Clinical Oncology. [13]Clevelend Clinic, Strongsville, Ohio. [14]Mallinckrodt Institute of Radiology, Saint Louis, Missouri, Chair, Expert Panel on Neurologic Imaging. [15]Baystate Medical Center, Springfield, Massachusetts. [16]Panel Chair, Cleveland Clinic Foundation, Cleveland, Ohio.



Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.

Contiguous thin slices without skips are necessary to ensure that small lesions are detected [8]. To reduce costs, a more limited MRI can be done when the intent is merely to determine whether brain metastases are present [9].

Kim et al [9] demonstrated that a limited MRI scan (T2 axial, proton density axial, and contrast-enhanced T1 sagittal images) could be considered for screening purposes. In 183 patients with newly diagnosed non–small-cell lung cancer (NSCLC), this limited MRI detected brain metastases in approximately 20% of patients. In a historical control group of similar patients with NSCLC who underwent limited MRI only if they had neurologic signs or symptoms at the time of diagnosis, 6% were found to have brain metastases. The cost of the limited MRI was approximately 40% of the estimated cost of the normal diagnostic MRI. For a patient with neurologic signs or symptoms, a CT with contrast is reasonable as a first test, but an MRI is required if the decision regarding treatment requires knowledge of the exact number of metastases (see Variant 1).

Several older studies have demonstrated that the dose of intravenous contrast used for MRI is important in determining the number of lesions detected as well as the confidence level associated with the radiologic interpretation [4,5,10,11]. Yuh et al [11] reported that high-dose contrast (0.3 mmol/kg gadolinium) is superior in lesion detection without any increase in serious toxicity compared to standard-dose contrast (0.1 mmol/kg gadolinium). However, there is also evidence that the strength of the MRI magnet is important in the ability to detect brain metastases [12,13]. Ba-Ssalamah et al [12] analyzed the subjective assessment of MRI with standard-dose or triple-dose contrast in both 1.5T and 3T magnetic fields. Improved images were obtained with both higher dose of contrast and higher magnet strength. The double-dose concept was introduced using gadolinium [11]. Since then, new contrast media have become available and seem to offer significantly greater diagnostic information and lesion enhancement even at lower doses [14]. Therefore, the concept of double-dose contrast has more or less become obsolete, even with 1.5T magnets, with the availability of the newer contrast agents (see Variant 2). Small studies have suggested that other tests such as dynamic contrast-enhanced MRI, perfusion imaging, and MR spectroscopy may help differentiate between brain metastases and high-grade gliomas [15,16].

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 [17]. The only patients found to have asymptomatic brain metastases already had extensive stage disease 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 a superior imaging technique compared with brain CT, CT is still widely used as a staging procedure because of its easy accessibility and lower cost. A retrospective study reported by Ferrigno and Buccheri [18] concluded that 10% of patients with otherwise operable NSCLC had brain metastases identified on CT scans of the brain. The absence of neurologic symptoms did not exclude brain metastases since 64% of patients with metastases detected by CT were asymptomatic. Conversely, Hooper et al [19] 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 [19] 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 and Buccheri [18], which would account for the different conclusions reached by the 2 authors. A prospective study of brain CT in 105 patients with potentially resectable NSCLC cancer found brain metastases in 4.8% of patients [20]. The authors concluded that the cost savings achieved by avoiding thoracotomy was far larger than the cost associated with the CT scans.

**Positron Emission Tomography**

Positron emission tomography (PET) with fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) has been evaluated as a means of identifying brain metastases [21,22]. 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 lack of sensitivity or specificity of cerebral FDG-PET is likely due to the large background of glucose activity within the brain. Alternative tracers to FDG such as 3-deoxy-3-fluorothymidine, thallium-201, or $^{11}$C-methionine PET may in the future prove to be more useful in the imaging of brain metastases [23,24].

**Pathologic Confirmation**

Several authors have sought to determine whether histologic confirmation is required following the identification of a suspected solitary metastasis or multiple brain metastases [3,25]. In one study in which stereotactic biopsy or resection was performed in patients with suspected solitary brain metastases, 11% of these patients were found to have other tumor histology or lesions of infectious or inflammatory origin [3]. Stereotactic biopsy is equivalent to resection in determining the correct tissue diagnosis in most patients if an appropriate number of biopsies are obtained and confirmation is immediately available by frozen section histology. Although multifocal malignant gliomas are relatively uncommon compared with brain metastases, the 2 clinical conditions may be difficult to distinguish on the basis of current conventional imaging studies [25]. However, new MRI methods (perfusion and MR spectroscopy) have shown improvement in specificity [15,16]. Identification of a solitary brain lesion in a patient with a controlled extracranial primary cancer with no other sites of disease on systemic evaluation should be followed by 1) MRI with increased dose of contrast and, if no additional lesions are identified, 2) histologic verification. In patients found to have multiple brain lesions with imaging characteristics compatible with metastases, the decision whether to pursue histological confirmation is based on the clinical picture. Patients with progressive extracranial cancer are seldom subjected to histological 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 a patient with impending cerebral or cerebellar herniation from mass effect caused by a bulky brain metastasis.

**Steroids**

Although 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 and the appropriate dose of such medication are points of some research and controversy [26,27]. Sturdza et al [27] surveyed 38 oncologists at a single large cancer center who managed patients with brain metastases to document the use of steroids and the frequency of their side effects. Ninety percent of physicians responded to the survey. Fifty-five percent determined the dose of steroid according to the presence or absence of neurological symptoms. The other 45% routinely started 4 mg dexamethasone 4 times a day. Sixty percent tapered the steroid dose in the 4 weeks following completion of whole-brain radiation therapy.

Early studies concluded that patients with newly diagnosed brain metastases should be placed on steroids prior to whole-brain radiation therapy using unconventional radiation dose/fractionation regimens [28,29]. For example, in one prospective clinical trial in which various whole-brain radiation dose/fraction schedules were used, steroids were started only when there was concern about high intracranial pressure [29]. 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 10 Gy 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® nearly 2 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 [28]. 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 patients with no evidence of impending herniation [30]. 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 high doses of steroids. This improvement in the high-dose group was attributed to the early steroid taper in the low-dose group, which began on the seventh day of cranial irradiation and led to clinical deterioration in some patients. Based on this observation, the authors recommended 4 mg per day without a dose taper for 28 days in patients without symptoms or signs of mass effect.

Hempen et al [31] studied 138 patients with primary or metastatic brain tumors treated with radiation therapy. Ninety-one patients with brain metastases were treated with standard-fraction whole-brain radiation therapy for 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 dexamethasone was initiated, in 44% of patients during radiotherapy, and in 11% of patients 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 syndrome (4%), muscular weakness (4%), and pulmonary embolism (2%). Among 13 patients treated without dexamethasone, treatment was well tolerated except in one patient with initial brain stem symptoms.

Patients with brain metastases from melanoma and renal cell carcinoma deserve separate considerations. Patients with these cancers are frequently treated with agents such as interleukin-2 (melanoma and renal cell carcinoma) [32], ipilimumab (melanoma) [33], and sunitinib (renal cell carcinoma), whose anticancer efficacy may be lessened when a corticosteroid is taken concurrently. It is crucial that the radiation oncologist communicates with the treating medical oncologist to discuss the pros and cons of using a corticosteroid, especially when the patient is only very mildly symptomatic (see Variant 3).

In summary, there is little compelling evidence to support the routine use of steroids in the newly diagnosed patient with brain metastases who has no neurological signs or symptoms. Likewise, there is no compelling evidence that, in the absence of neurological symptoms, steroids should be started simply because the patient is about to start radiation therapy. Steroids cause toxicity and may mitigate the therapeutic effects of systemic therapy for renal cell carcinoma and melanoma. Therefore, any recommendation for steroids must be rendered in light of this fact. For patients with minimal neurological symptoms the panel recommends either starting with 4–8 mg/day or starting with 16 mg/day but tapering after a few days. In all cases, steroids should be tapered as clinically indicated and tolerated (see Variant 4).

**Prophylactic Anticonvulsants**

Another controversy revolves around the need to initiate prophylactic anticonvulsants in patients with brain metastases. A meta-analysis estimated that 15% of patients with brain metastases present with seizures, and most of them are found to have supratentorial lesions [34]. 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 [35-37]. 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. The meta-analysis by Glantz et al [34] concluded that there was no evidence that prophylactic anticonvulsants significantly decreased the incidence of first seizure. In the aggregate, these 12 studies included in the meta-analysis 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 Forstyth et al [35] reached a similar conclusion regarding the lack of benefit of prophylactic anticonvulsants.

One clinical situation in which a benefit to prophylactic anticonvulsants has been suggested is in the patient with brain metastases from malignant melanoma. A retrospective study reported by Byrne et al [38] 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 junction between gray and white matter. The meta-analysis by Glantz et al [34] 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. The panel consensus is to not start anticonvulsants prophylactically in patients with brain metastases due to any primary cancer, including melanoma (see Variant 3 and Variant 4).

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 a 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.

**Summary**

- Pretreatment evaluation should determine the number, location, and size of the brain metastases.
- MRI is the recommended imaging technique, particularly in patients being considered for surgery or radiosurgery.
- Contiguous thin-cut volumetric MRI with gadolinium can improve detection of small brain metastases.
- Use of double-dose or triple-dose contrast at the time of MRI may be no longer necessary with the availability of newer gadolinium-based agents.
- 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 on the age and performance status of the patient.
- Patients with hydrocephalus or impending brain herniation should be started on high doses of corticosteroids and evaluated for possible neurosurgical intervention.
- Patients with moderate symptoms should receive approximately 4–8 mg per day of dexamethasone in divided doses.
- The 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.

**Supporting Documents**

- ACR Appropriateness Criteria® Overview
- Evidence Table

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**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 | 9 | Several members of the panel considered MRI needed only if the exact number of metastases is necessary to make decisions regarding stereotactic radiosurgery or surgery. |
| CT head with contrast | 6 | Approximately 50% of cases would still need MRI to determine exact number of metastases and determine if patient is a good candidate for stereotactic radiosurgery or surgery. If the CT is negative it is very likely that the radiologist will recommend an MRI since this patient has new intracranial signs or symptoms. CT was thought by many to be indicated only in those patients in whom MRI is contraindicated or unavailable. |
| **Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate | | |

**Variant 2:** **50-year-old patient with newly diagnosed non–small-cell lung cancer with resectable primary and CT evidence of solitary brain metastasis.**

| Radiologic Procedure | Rating | Comments |
|---|---|---|
| MRI head with standard dose contrast | 9 | |
| MRI head with high dose contrast | 6 | High-dose contrast may not be needed with the availability of new gadolinium-based contrast agents that offer significantly greater diagnostic information and lesion enhancement even at lower doses. |
| **Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate | | |

**Variant 3:** **45-year-old patient with metastatic melanoma and newly diagnosed multiple small supratentorial brain metastases. On treatment with ipilimumab. Mild edema on imaging. No hydrocephalus, neurologic symptoms, or history of seizures.**

| Treatment | Rating | Comments |
|---|---|---|
| Corticosteroids 4–8 mg/day | 2 | Corticosteroids are not absolutely indicated and may interfere with efficacy of ipilimumab. |
| Corticosteroids 16 mg/day | 2 | Corticosteroids are not absolutely indicated and may interfere with efficacy of ipilimumab. |
| Anticonvulsants (prophylactic) | 2 | In a patient with no history of seizures, the use of prophylactic anticonvulsants is deemed inappropriate. |
| **Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate | | |

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

**Variant 4:** **50-year-old patient with non–small-cell lung cancer and multiple supratentorial brain metastases. Mild edema on imaging. No hydrocephalus. Mild neurologic symptoms present. No history of seizures.**

| Treatment | Rating | Comments |
|---|---|---|
| Corticosteroids 4–8 mg/day | 8 | |
| Corticosteroids 16 mg/day | 7 | Some panel members recommended starting at 16 mg/day and then lowering to 4–8 mg after a few days. |
| Anticonvulsants (prophylactic) | 3 | In a patient with no history of seizures, the use of prophylactic anticonvulsants is deemed inappropriate. |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |