Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

ACR Appropriateness Criteria® multiple brain metastases.

Bibliographic Source(s)

Videtic GM, Gore EM, Bradley JD, Buatti JM, Germano I, Ghafoori AP, Henderson MA, Lo SS, Lutz ST, Murad GJ, Patchell RA, Patel SH, Robbins JR, Robins HI, Vassil AD, Wippold FJ II, Yunes MJ, Expert Panel on Radiation Oncology-Brain Metastases. ACR AppropriatenessÂ® multiple brain metastases [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 13 p. [60 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Videtic GM, Gore EM, Bradley JD, Gaspar LE, Germano I, Ghafoori P, Henderson MA, Lutz ST, McDermott MW, Patchell RA, Patel SH, Robins HI, Vassil AD, Wippold FJ II, Expert Panel on Radiation Oncology-Brain Metastases. ACR Appropriateness Criteria® multiple brain metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 9 p. [46 references]

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Multiple Brain Metastases

Variant 1: 70-year-old man with 4 newly diagnosed, asymptomatic, surgically accessible supratentorial brain metastases on MRI. All brain metastases 1 to 3 cm in maximum diameter. KPS 50. Newly diagnosed T3 N2 adenocarcinoma of lung. Bone and liver metastases also present.

Treatment	Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	8	Consider this treatment for patients with poor KPS, active extracranial disease, or no evidence of dose benefit with respect to symptom control. Longer treatment schedules are difficult to justify in such a patient.
30 Gy/10 fractions	8	

Treatment	Rating	Comments
37.5 Gy/15 fractions	6	
40 Gy/20 fractions	2	
Stereotactic Radiosurgery (SRS)		
SRS alone	2	Without evidence to support a benefit, SRS as a component of therapy is not recommended in view of patient and disease status.
SRS + WBRT	2	
Surgery Alone		
Excise dominant lesion(s)	1	Surgery alone, or in combination with radiation therapy, is not appropriate given this patient's status.
Excise all lesions	1	
Radiosensitizer		
Radiosensitizer + WBRT	1	There is no evidence for any benefit to this treatment. It can only be done in a trial setting.
Observation	6	This treatment is not unreasonable given status of patient. It requires best supportive care with optimized medical management.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 50-year-old man with 6 newly diagnosed, asymptomatic, supratentorial brain metastases on MRI (3 surgically accessible, 3 inaccessible). KPS 90. Primary completely resected (T2 N0 adenocarcinoma of lung). No other systemic metastases present.

Treatment	Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	4	
30 Gy/10 fractions	8	The number of brain metastases in this patient strongly supports use of WBRT only. Schedule choice may depend on KPS, although randomized evidence to date does not favor one schedule over others.
37.5 Gy/15 fractions	8	
40 Gy/20 fractions	2	
Stereotactic Radiosurgery (SRS)		
SRS alone	1	The number of lesions and absence of evidence for this treatment do not support SRS in this patient.
SRS + WBRT	2	
Surgery Alone		
Excise dominant lesion(s)	1	The number of lesions, absence of focal symptoms, and absence of evidence do not support surgery in this patient.
Excise all lesions	1	
Radiosensitizer		
Radiosensitizer + WBRT	1	There is no evidence for any role of this treatment. It should only be done in a trial setting.
Observation	1	Patient's lack of symptoms and high KPS would preclude this option.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 50-year-old man with 2 newly diagnosed, surgically accessible, supratentorial brain metastases on MRI. KPS 90. One brain metastasis 3 cm in maximum diameter in right frontal area. Other is <1 cm in maximum diameter in lateral cerebellum. No hydrocephalus. Primary completely resected 6 months ago (T2 N0 adenocarcinoma of lung). No other systemic metastases.

Treatment	Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	3	
30 Gy/10 fractions	7	The use of WBRT alone in this patient could be controversial for some clinicians given patient and disease status. Some trials have used extended RT fractionations for this presentation.
37.5 Gy/15 fractions	7	
40 Gy/20 fractions	3	
Stereotactic Radiosurgery (SRS)		
SRS alone	6	
SRS+WBRT	8	There is significant controversy among clinicians with respect to the application of trial-derived data to this clinical scenario. The weight of opinion, however, favors inclusion of WBRT as an adjunct to SRS, given evidence of improved local control, steroid requirements and decreased probability of brain relapse.
Surgery Alone		
Excise dominant lesion(s)	2	Surgery offers no clear benefit in this scenario, given the absence of symptoms and multiple lesions.
Excise all lesions	1	
Radiosensitizer		
Radiosensitizer + WBRT	1	There is no evidence for this treatment in any role. It can only be done in a trial setting.
Observation	1	KPS would preclude this option.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 47-year-old woman with 2 newly diagnosed, surgically accessible, supratentorial brain metastases on MRI. KPS 80. Mild symptoms related to 2-cm lesion in right parietal area. Other metastasis in left frontal region measuring 1 cm in maximum diameter. Two years status/post right modified radical mastectomy and adjuvant chemotherapy for T2 N1 adenocarcinoma of breast. Newly diagnosed pulmonary nodules also present.

Treatment	Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	3	
30 Gy/10 fractions	3	Given the presence of active extracranial disease at the time of brain metastases diagnosis. However, age and high KPS may suggest optimizing local brain control with other modalities like SRS.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
37.5 Gy/15 fractions	7	
40 Gy/20 fractions	3	
Stereotactic Radiosurgery (SRS)		
SRS alone	6	There is some controversy about indication for SRS alone in a patient with two brain metastases and progression of extracranial disease. Risk of overall brain relapse is felt by some to argue against selecting SRS alone on basis of age and KPS.
SRS + WBRT	8	WBRT judged to be an important component in overall brain and lesional control when SRS is to be used.
Surgery Alone		
Excise dominant lesion(s)	3	Mild symptoms do not strongly suggest utility of surgery alone in a patient with extracranial disease and multiple brain metastases.
Excise all lesions	2	
Surgery + WBRT	5	Symptoms may prompt consideration of surgery for a dominant symptomatic lesion in this patient but overall brain control and other lesional control requires addition of WBRT.
Radiosensitizer		
Radiosensitizer + WBRT	1	There is no evidence for this treatment in any role. It should only be done in a trial setting.
Observation	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 35-year-old woman with 2 newly diagnosed, asymptomatic, surgically accessible, supratentorial brain metastases <3 cm in size on MRI. KPS 100. Status/post wide local excision of Clark's level IV melanoma 1 month ago. No other metastases.

Treatment	Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	2	
30 Gy/10 fractions	5	Use of WBRT alone in a patient with two melanoma brain metastases is felt by many to be insufficient therapy.
37.5 Gy/15 fractions	5	
40 Gy/20 fractions	2	
Stereotactic Radiosurgery (SRS)		
SRS alone	7	
SRS + WBRT	8	The role of WBRT in addition to SRS in the management of a few melanoma brain metastases is controversial given patient's age, KPS, absence of extracranial metastases, and histology. Multiplicity of metastases is felt to weigh somewhat in favor of the addition of WBRT at presentation to minimize distant brain relapse.
Surgery Alone		
Excise dominant lesion(s)	2	Since patient's metastases are asymptomatic, there is no need to take surgical risks.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
Radiosensitizer		
Radiosensitizer + WBRT	1	There is no evidence for this treatment in any role. It can only be done in a trial setting.
Observation	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction/Background

It is estimated that as many as 170,000 cancer patients per year will develop brain metastases. Brain metastases represent the most common neurologic manifestation of cancer, occurring in about 30% of cancer patients, particularly those with lung cancer, breast cancer, and melanoma, who account for up to 64%, 21%, and 16%, respectively, of patients with brain metastases.

Clinical, imaging, and autopsy series have shown that about half of brain metastases will be single and half will be multiple. Solitary metastatic disease refers to 1 metastasis to the brain in the setting of *no other* extracranial metastatic disease. Single (or singular) metastatic disease refers to 1 metastasis in the brain in the setting of metastatic disease elsewhere in the body. The term "multiple metastases" refers to more than 1 lesion in the brain, with some clinicians distinguishing fewer than 4 metastases as being more favorable than 4 or greater. Among patients with multiple lesions, 70% are supratentorial, 26% are supratentorial and cerebellar, 3% are cerebellar, and 1% are located in the brainstem. The most common symptoms of brain metastases are headache, altered mental status, and focal weakness, occurring in about one-third to one-half of patients. The next most common symptoms include seizures and gait ataxia, which are seen in about 10% to 20% of patients.

Historically, whole brain radiation therapy (WBRT) has been a standard of care in patients with multiple brain metastases, although there have been no randomized trials showing that it offers a survival advantage over supportive care. Of interest, the QUARTZ (Quality of Life After Treatment for Brain Metastases) trial is an ongoing UK Medical Research Council phase III multicenter study assessing whether optimal supportive care alone (including dexamethasone) is as effective as optimal supportive care including dexamethasone plus WBRT for patients with inoperable brain metastases from non-small-cell lung cancer (NSCLC). Numerous prospective randomized trials have looked at ways to improve outcomes in patients with multiple brain metastases, including the use of different dose/fractionation schedules, radiation sensitizers, chemotherapy, surgery and stereotactic radiosurgery (SRS), and are the focus of the present review.

Prognostic Factors

The median survival time of a patient with brain metastases following WBRT is in the 4- to 6-month range. Certain clinical prognostic factors are associated with a better or worse outcome. The most commonly used prognostic system is the Radiation Therapy Oncology Group® (RTOG®) recursive partitioning analysis (RPA) classification. On the basis of this analysis, patients younger than age 65 whose Karnofsky performance status (KPS) is ≥70 and who have a controlled primary cancer without other systemic metastases have a median survival time of 7.1 months. Those with a KPS <70, independent of other factors, have a median survival time of 2.3 months, whereas all other patients have a 4.2 month median survival time. A group of researchers proposed a new prognostic index for brain metastases patients. They compared it to three other indices — including the RTOG RPA classification — and found it to be the least subjective and most quantitative. In a subsequent analysis, researchers retrospectively analyzed 5,067 brain metastases patients and found that prognosis factors varied by diagnosis, and this resulted in a disease-specific classification of outcomes. Out of these data, these authors generated the Graded Prognostic Assessment (GPA), a prognostic index for patients with brain metastases to create diagnosis-specific GPA indices. The authors recently updated these diagnosis-specific GPA indices into a single, unified, user-friendly schema to allow ease of access and use by treating physicians when making clinical decisions for their brain metastases patients. Thus, for any given tumor type, clinicians may make more accurate survival predictions using relevant tumor-specific prognostic criteria to aid in better treatment selection. These factors include cancer type (lung [non-small, small], gastrointestinal, breast, renal, melanoma); presence of extracranial metastases; estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status (for primary breast cancer); KPS; and number of brain metastases [1, 2-3, >3]. Imaging-based prognostic factors, such as presence of midline shift and post WBRT response, may also influence outcome.

Whole Brain Radiation Therapy

A variety of total doses and doses per fraction have been used in prospective, randomized phase III clinical trials, primarily in patients with multiple brain metastases. These regimens include 1000 cGy in 1 fraction (1000/1), 1200/2, 1800/3, 2000/5, 3000/10, 3000/15, 3600/6, 4000/15,

4000/20, 4000/20 (200 cGy twice a day [BID]), 5000/20, and 5440/34 (160 cGy BID). While none of these regimens has proven better than another in terms of survival or efficacy (about half of patients have an improvement in their neurologic symptoms), 3000 cGy in 10 fractions and 3750 cGy in 15 fractions represent the most frequently used dose/fractionation schedules in the United States.

In selecting treatment regimens appropriate for individual patients, clinicians should consider the RTOG RPA brain metastasis classification, which supports short-course treatment in poor risk patients (i.e., poor performance status, elderly, progressive systemic disease). (See Variant 1 above.)

Whole-Brain Radiation Therapy and Neurocognitive Function

Neurocognitive morbidity from WBRT remains a potential concern but is poorly understood. For example, in a contemporary trial for patients with 1 to 3 brain metastases carried out by the RTOG, 3750 cGy in 15 fractions WBRT (i.e., 250 cGy per fraction) was used as the standard treatment arm based on concerns regarding late effects from a historical retrospective series suggesting that a regimen of 300 cGy fractions given after resection of a solitary brain metastasis was associated with a greater likelihood of late effects to the normal brain. However, this 1989 retrospective report of dementia in 12 patients with long survival has been highly criticized for its reported radiation total doses and fractionation schemes. Contemporary WBRT trials have been more appropriately designed to better understand the neurologic status of patients with multiple brain metastases and in defining the safety and appropriateness of conventional WBRT in their care. (See Variant 2.)

Some studies, for example RTOG 9104, have used the mini-mental status exam (MMSE) to measure neurologic impairment, with no differences found in terms of neurologic performance between the arms at baseline or on follow-up. A group of researchers used the MMSE for neurocognitive assessment of the patients in their randomized trial of SRS versus WBRT plus SRS and found time to neurocognitive deterioration was marginally prolonged in those receiving WBRT plus SRS. However, many authors consider the MMSE a relatively insensitive test. Neurocognitive function (NCF) with a neuropsychometric battery before and after WBRT (3000 cGy in 10 fractions) was assessed prospectively in a phase III trial of WBRT with or without motexafin gadolinium (MGd). Impairment was found in >90% of patients at baseline, and the results suggested that only tumor control correlated with NCF, suggesting a potential benefit if WBRT conveys more tumor control. Further substantiating the neurocognitive benefits of WBRT was an analysis of the 208 patients in the control arm of this trial, which looked at the relationship between NCF and tumor volume regression. Another group of authors found that WBRT-induced tumor shrinkage correlated with better survival and NCF preservation. NCF was found to be stable or improved in long-term survivors, and tumor progression, more than WBRT dose, adversely affected NCF.

Researchers conducted a phase III trial of SRS compared to SRS plus WBRT for patients with 1 to 3 brain metastases; the primary endpoint was a change in neurocognitive function at 4 months as measured by the Hopkins Verbal Learning Test (HVLT). They found that patients treated with SRS plus WBRT had a significant impairment in learning and memory function by HVTL compared to patients treated with SRS alone. This study, however, has been controversial based on unexpected survival differences favoring the SRS arm and for the timing of the neurocognitive assessment to one time point.

Though it is common for patients with multiple brain metastases to have active primary and other systemic metastatic disease, progression of brain disease is the cause of death in about half of these patients (range, 26% to 70%).

In view of these concerns regarding WBRT and its potentially detrimental effect on long-term cognitive performance, various strategies aimed at preventing such decline are now being investigated. The RTOG 0614 recently published the results of a placebo-controlled, double-blind, randomized trial to evaluate the potential protective effect of memantine on neurocognitive function in patients receiving WBRT. Memantine is a neuroreceptor antagonist drug used in dementia patients that has been shown to be neuroprotective in preclinical models. The study accrued 554 patients, and its results showed that there was less of a decline in delayed recall testing in the memantine arm at 24 weeks (P=.059) compared to placebo, but the difference was not statistically significant. Overall, patients treated with memantine appeared to have better cognitive function over time; specifically, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBRT. Optimal use of this drug based on patient performance and diagnosis remains under investigation. With respect to WBRT radiation delivery, there has been interest in the use of modern technology to spare the hippocampus during the cranial irradiation, since damage to neural progenitor cells located in the subgranular zone of the hippocampus is associated with radiation-induced neurocognitive decline. Although not formally published yet, a recently completed RTOG phase II study (#0933) was designed to be hippocampal-sparing and measured changes in delayed recall compared to historical controls as its primary endpoint. This approach remains investigational.

Whole-Brain Radiation Therapy and Drug Therapies

Various radiation sensitizers have been added to WBRT without a demonstrated improvement in survival, including lonidamine, misonidazole, bromodeoxyuridine, and the nitrosourea 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl) 3-nitrosourea hydrochloride (ACNU), either alone or with fluorouracil. The addition of biological modifiers such as efaproxiral and MGd has not demonstrated survival benefits. A subgroup analysis of the interval to investigator-determined neurologic progression and the interval to neurocognitive progression suggested a trend towards prolongation of time to neurological progression with the early use of MGd, but this finding was not demonstrated in the overall study

population. Phase III studies with biological agents melatonin and thalidomide likewise showed no improvement in overall survival. Phase III studies with biological agents melatonin and thalidomide likewise showed no improvement in overall survival. RTOG 0320, a phase III trial, randomized NSCLC patients with 1 to 3 brain metastases to the addition of temozolomide or erlotinib with WBRT plus SRS and found no improvement in survival and a possible deleterious effect of the drugs.

Overall, there is no strong evidence to date to support the use of any radiation sensitizer or biologic agent in standard practice. The routine use of chemotherapy in the setting of WBRT has not been shown to increase survival in any randomized trial to date, including studies of WBRT with or without concurrent chemotherapy, chemotherapy with or without concurrent WBRT, concurrent versus delayed WBRT, and chemotherapy followed by WBRT versus WBRT followed by chemotherapy.

Surgery and Stereotactic Radiosurgery

Surgery has not had a major role in the management of patients with multiple brain metastases. Some retrospective studies have suggested that it can offer a survival benefit, but its role is controversial. The European Organisation for Research and Treatment of Cancer (EORTC) phase III trial (22952-26001) of the addition of adjuvant WBRT after surgery or radiosurgery of one to three brain metastases showed that WBRT reduced local relapse and neurologic death but did not improve the duration of functional independence or overall survival. Health-related quality-of-life (HRQOL) results were subsequently reported for this trial. Overall, patients in the observation-only arm reported better HRQOL scores than did patients who received WBRT, and the authors concluded that observation with close monitoring of patients with limited brain disease by MRI is not detrimental for HRQOL.

One study used the RTOG® RPA brain metastasis classification to analyze the results of tumor resection and radiosurgery in the management of 52 patients with multiple brain metastases and found that RPA classification correlates best with improved survival. Another study investigated the role of surgery in the treatment of 138 patients with multiple brain metastases when performed with radiation therapy. Median survival times were 8.7 months for patients with single metastases and 9.2 months for those with multiple metastases (no significant difference).

A group of researchers reported a small randomized trial in which 27 patients with 2 to 4 brain metastases ≤25 mm in diameter received WBRT alone or with an SRS boost. Local control at 1 year was 92% with SRS versus 0% without SRS. Median survival time was also better with SRS (11 months versus [vs] 7.5 months).

RTOG® 9508 was a phase III trial in which 333 patients with 1 to 3 brain metastases were randomized to WBRT with or without SRS boost. The overall median survival with the addition of SRS was 6.5 months vs 5.7 months, a nonsignificant difference. The trial included a predefined analysis of patients with a single brain metastasis, which showed a survival advantage with the addition of SRS to WBRT for these patients (median survival time 6.5 months vs 4.9 months, P=0.0393) but not for patients with multiple metastases. Post-hoc subset analysis suggested a survival benefit with the addition of SRS for RTOG RPA class 1 patients and those with squamous NSCLC histology. Additionally, an improved KPS and decreasing need for steroids were noted in patients treated with WBRT plus SRS, suggesting a role for SRS in select patients with 2 to 3 brain metastases. (See Variant 3 above.)

Another group of researchers published a study of 132 patients with 1 to 4 brain metastases randomized to SRS plus WBRT versus SRS alone. Median survival times were 7.5 months for the SRS alone arm and 8.0 months for the SRS plus WBRT arm, a nonsignificant difference. Of interest, intracranial relapse occurred more frequently in those who did not receive WBRT. These results suggest the value of WBRT in patients with multiple brain metastases and the influence of patient selection on the effectiveness of SRS. Given the finding that SRS does not increase survival of patients with 2 or more brain metastases, clinicians need to practice careful selection of patients for this intervention. The RTOG® RPA brain metastasis classification may prove useful in making this selection. (See Variant 4 above.)

A phase III neurocognition trial of SRS compared to SRS plus WBRT for patients with 1 to 3 brain metastases reported a significant decline in learning and memory function at 4 months in the WBRT arm compared with the SRS arm. The results of this trial, which was stopped after accruing 58 patients based on early stopping rules, remain controversial and found that the median survival time and the 1-year survival rate was higher for the SRS-alone group than for patients in the SRS plus WBRT group (15.2 vs 5.7 months, 63% vs 21%; P=0.003). Some authors suggest the survival advantage in the SRS group is due to an imbalance in the prognostic factors between the arms and differences in salvage therapy, favoring the SRS arm. (See Variant 5 above.)

Summary

- WBRT is an effective palliative treatment for patients with multiple brain metastases. About half of these patients experience an improvement in their neurologic symptoms. However, a majority of them do not achieve local control and frequently succumb from progressive brain disease.
- Stratification of brain metastases patients using prognostic indices aids in estimation of patient survival and appropriate decision making for treatment.

- Any perceived benefits from surgery or SRS need verification in prospective, randomized phase III clinical trials.
- The effectiveness of SRS for patients with multiple metastases may be primarily a function of proper patient selection, but it probably cannot replace the benefits of WBRT for the majority of patients with multiple brain metastases.
- Continued research with radiation sensitizers, biologics, targeted agents, or systemic agents is warranted, because WBRT alone, even in doses of 5000 to 5440 cGy, has not been associated with an improved survival outcome.
- Future trials of WBRT must include prospective measurement of neurocognitive function and quality of life before and after treatment as a standard component of the patient's assessment.

Abbreviations

- KPS, Karnofsky Performance Status
- MRI, magnetic resonance imaging
- N, regional lymph node
- T, primary tumor

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Multiple brain metastases

Guideline Category

Treatment

Clinical Specialty

Neurological Surgery

Neurology

Oncology

Radiation Oncology

Radiology

Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of treatment procedures for patients with multiple brain metastases

Target Population

Patients with multiple brain metastases

Interventions and Practices Considered

1. Whole brain radiotherapy (WBRT)
2. Stereotactic radiosurgery (SRS)
    - SRS alone
    - SRS plus WBRT
3. Surgery
    - Excise dominant lesion(s)
    - Excise all lesions
    - Surgery plus WBRT
4. Radiosensitizer plus WBRT
5. Observation

Major Outcomes Considered

- Median survival time
- Local control rate
- Improvement in neurologic symptoms and overall survival
- Time to progression
- Response rate
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Procedure

Staff search in PubMed only for peer reviewed medical literature for routine searches. Any article or guideline may be used by the author in the narrative but those materials may have been identified outside of the routine literature search process.

The Medline literature search is based on keywords provided by the topic author. The two general classes of keywords are those related to the condition (e.g., ankle pain, fever) and those that describe the diagnostic or therapeutic intervention of interest (e.g., mammography, MRI).

The search terms and parameters are manipulated to produce the most relevant, current evidence to address the American College of Radiology Appropriateness Criteria (ACR AC) topic being reviewed or developed. Combining the clinical conditions and diagnostic modalities or therapeutic procedures narrows the search to be relevant to the topic. Exploding the term "diagnostic imaging" captures relevant results for diagnostic topics.

The following criteria/limits are used in the searches:

1. Articles that have abstracts available and are concerned with humans.
2. Restrict the search to the year prior to the last topic update or in some cases the author of the topic may specify which year range to use in the search. For new topics, the year range is restricted to the last 10 years unless the topic author provides other instructions.
3. May restrict the search to Adults only or Pediatrics only.
4. Articles consisting of only summaries or case reports are often excluded from final results.

The search strategy may be revised to improve the output as needed.

Number of Source Documents

The total number of source documents identified as the result of the literature search is not known.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Study Quality Category Definitions

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - There are important study design limitations.

Category 4 - The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

a. The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description).
b. The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence.
c. The study is an expert opinion or consensus document.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author drafts or revises the narrative text summarizing the evidence found in the literature. American College of Radiology (ACR) staff draft an evidence table based on the analysis of the selected literature. These tables rate the strength of the evidence (study quality) for each article included in the narrative text.

The expert panel reviews the narrative text, evidence table, and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the table. Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The appropriateness ratings for each of the procedures included in the Appropriateness Criteria topics are determined using a modified Delphi methodology. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. American College of Radiology (ACR) staff distribute surveys to the panelists along with the evidence table and narrative. Each panelist interprets the available evidence and rates each procedure. The surveys are completed by panelists without consulting other panelists. The appropriateness rating scale is an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate"; 4, 5, or 6 are in the category "may be appropriate"; and 7, 8, or 9 are in the category "usually appropriate." Each panel member assigns one rating for each procedure for a clinical scenario. The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating.

If consensus is reached, the median rating is assigned as the panel's final recommendation/rating. Consensus is defined as eighty percent (80%) agreement within a rating category. A maximum of three rounds may be conducted to reach consensus. Consensus among the panel members must be achieved to determine the final rating for each procedure.

If consensus is not reached, the panel is convened by conference call. The strengths and weaknesses of each imaging procedure that has not reached consensus are discussed and a final rating is proposed. If the panelists on the call agree, the rating is proposed as the panel's consensus. The document is circulated to all the panelists to make the final determination. If consensus cannot be reached on the call or when the document is circulated, "No consensus" appears in the rating column and the reasons for this decision are added to the comment sections.

This modified Delphi method enables each panelist to express individual interpretations of the evidence and his or her expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. A more detailed explanation of the complete process can be found in additional methodology documents found on the ACR Web site (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Selection of appropriate treatment procedures for patients with multiple brain metastases
- Improved outcomes in patients with multiple brain metastases

Potential Harms

Neurocognitive morbidity from whole-brain radiation therapy (WBRT) remains a potential concern.

Qualifying Statements

Qualifying Statements

The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Videtic GM, Gore EM, Bradley JD, Buatti JM, Germano I, Ghafoori AP, Henderson MA, Lo SS, Lutz ST, Murad GJ, Patchell RA, Patel SH, Robbins JR, Robins HI, Vassil AD, Wippold FJ II, Yunes MJ, Expert Panel on Radiation Oncology-Brain Metastases. ACR AppropriatenessÂ® multiple brain metastases [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 13 p. [60 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

American College of Radiology - Medical Specialty Society

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Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology-Brain Metastases

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Videtic GM, Gore EM, Bradley JD, Gaspar LE, Germano I, Ghafoori P, Henderson MA, Lutz ST, McDermott MW, Patchell RA, Patel SH, Robins HI, Vassil AD, Wippold FJ II, Expert Panel on Radiation Oncology-Brain Metastases. ACR Appropriateness Criteria® multiple brain metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 9 p. [46 references]

Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site .

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available from the American College of Radiology (ACR) Web site .
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 1 p. Electronic copies: Available from the ACR Web site .
- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available from the ACR Web site .
- ACR Appropriateness Criteria®. Evidence table development – diagnostic studies. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available from the ACR Web site .
- ACR Appropriateness Criteria® multiple brain metastases. Evidence table. Reston (VA): American College of Radiology; 2014. 32 p. Electronic copies: Available the ACR Web site .

Patient Resources

None available

NGC Status

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