Complete Summary

GUIDELINE TITLE

Multiple brain metastases.

BIBLIOGRAPHIC SOURCE(S)

Videtic GM, Gaspar LE, Aref AM, Imperato JP, Marcus KJ, Rogers CL, Simpson JR, Suh JH, Wolfson AH, McDermott MW, Rogers L, Expert Panel on Radiation Oncology-Brain Metastases. Multiple brain metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 8 p. [31 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Shaw EG, Gaspar LE, Gibbs FA, Lewin AA, Wharam MD Jr, Larson D, Bloomer WD, Buckley JA, Loeffler JS, Malcolm AW, Mendenhall WM, Schneider JF, Schupak KD, Simpson JR, Gutin PH, Rogers L, Leibel S. Multiple brain metastases. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1121-8.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

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. Radiosensitizer plus whole brain radiotherapy (WBRT)
3. Stereotactic radiosurgery (SRS)
    - SRS alone
    - SRS plus WBRT
4. Surgery
    - Excise dominant lesion(s)
    - Excise all lesions
    - Surgery plus WBRT

MAJOR OUTCOMES CONSIDERED

- Morbidity or mortality
- Improved care
- Median survival time
- Local control rate
- Improvement in neurologic symptoms

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and major applicable articles were identified and collected.

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 Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed to reach agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as

developed by the topic leader(s). Questionnaires are completed by the participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Multiple Brain Metastases

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

Treatment	Appropriateness Rating	Comments

Treatment	Appropriateness Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
2000 cGy/5 fractions	7	Poor KPS and systemic disease favors shorter courses.
3000 cGy/10 fractions	8	
3750 cGy/15 fractions	5	
4000 cGy/20 fractions	2	
5000 cGy/25 fractions	2	
Radiosensitizer		
Radiosensitizer + WBRT	2	
Stereotactic Radiosurgery (SRS)		
SRS alone	2	
SRS + WBRT	2	
Surgery Alone		
Excise dominant lesion(s)	1	
Excise all lesions	1	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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

Variant 2: 50-year-old man, two newly diagnosed, surgically accessible, supratentorial brain metastases on MRI. KPS 90. One brain metastasis 3 cm in maximum diameter in right frontal area. Other one <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	Appropriateness Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
2000 cGy/5 fractions	2	

Treatment	Appropriateness Rating	Comments
3000 cGy/10 fractions	5	
3750 cGy/15 fractions	6	
4000 cGy/20 fractions	4	
5000 cGy/25 fractions	2	
Radiosensitizer		
Radiosensitizer + WBRT	2	
Stereotactic Radiosurgery (SRS)		
SRS + WBRT	8	Best for durable CNS control.
SRS alone	5	
Surgery Alone		
Excise dominant lesion(s)	2	
Excise all lesions	3	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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

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

Treatment	Appropriateness Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
2000 cGy/5 fractions	2	
3000 cGy/10 fractions	8	
3750 cGy/15 fractions	8	
4000 cGy/20 fractions	2	

Treatment	Appropriateness Rating	Comments
5000 cGy/25 fractions	2	
Radiosensitizer		
Radiosensitizer + WBRT	2	
Stereotactic Radiosurgery (SRS)		
SRS alone	2	
SRS + WBRT	2	WBRT (upfront); SRS only for progressive or new lesions.
Surgery Alone		
Excise dominant lesion(s)	2	
Excise all lesions	1	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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

Variant 4: 47-year-old woman with two 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 s/p right modified radical mastectomy and adjuvant chemotherapy for T2 N1 adenocarcinoma of breast. Newly diagnosed pulmonary nodules also present.

Treatment	Appropriateness Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
2000 cGy/5 fractions	2	
3000 cGy/10 fractions	7	
3750 cGy/15 fractions	8	
4000 cGy/20 fractions	4	
5000 cGy/25 fractions	2	

Treatment	Appropriateness Rating	Comments
Radiosensitizer		
Radiosensitizer + WBRT	2	
Stereotactic Radiosurgery (SRS)		
SRS plus WBRT	8	WBRT alone is reasonable as SRS does not impact survival.
SRS alone	6	
Surgery Alone		
Excise dominant lesion(s)	2	
Excise all lesions	3	
Surgery + WBRT	7	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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

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

Treatment	Appropriateness Rating	Comments
Whole Brain Radiotherapy (WBRT) Alone		
2000 cGy/5 fractions	2	
3000 cGy/10 fractions	5	
3750 cGy/15 fractions	5	
4000 cGy/20 fractions	2	
5000 cGy/25 fractions	2	
Radiosensitizer		
Radiosensitizer +	2	

Treatment	Appropriateness Rating	Comments
WBRT		
Stereotactic Radiosurgery (SRS)		
SRS alone	7	
SRS + WBRT	8	
Surgery Alone		
Excise dominant lesion(s)	3	
Excise all lesions	2	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

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

Summary of Literature Review

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 15% of cancer patients, particularly those with lung cancer, breast cancer, and melanoma, who account for 39%, 17%, and 11%, respectively, of patients with brain metastases. Clinical, imaging, and autopsy series have shown that about half of brain metastases will be solitary and half will be multiple. Renal cell and prostate cancer are more likely than average to manifest a solitary metastasis, whereas melanoma is more prone to develop multiple metastases. Among the 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 are no randomized trials of WBRT vs. supportive care showing a survival advantage for treatment. Attempts to improve outcome in patients with multiple brain metastases have included the use of different dose/fractionation schedules, radiation sensitizers, and, more recently, surgery and stereotactic radiosurgery (SRS).

Prognostic Factors

The median survival time of a patient with brain metastases following WBRT is reproducibly in the 4 to 6 month range. Certain clinical prognostic factors are associated with a better or worse outcome. For instance, patients younger than 65 years of age 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. Imaging prognostic factors, such as the number of metastases, presence of midline shift, and post-WBRT response, can also influence outcome.

Whole Brain Radiation Therapy with and without Radiation Sensitizers

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, 3600/6, 4000/20, 5000/20, and 5440/34 (160 cGy twice a day [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 selecting treatment regimens appropriate for individual patients, clinicians should consider the Radiation Therapy Oncology Group (RTOG®) recursive partitioning analysis (RPA) brain metastasis classification, which supports short course treatment in poor risk patients, (i.e., poor performance status, elderly, progressive systemic disease.) In a recently published trial for patients with one to three 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 series suggesting that 300 cGy fractions given after resection of a solitary brain metastasis was associated with a greater likelihood of late effects to the normal brain. Another study of patients with small-cell-lung cancer found that prophylactic cranial irradiation with 250 cGy fractions (10 fractions) was not associated with late effects.

Even 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%). Various radiation sensitizers have been added to WBRT without a demonstrated improvement in survival. Recent randomized studies with efaproxiral and motexafin gadolinium have not demonstrated survival benefits; however, subset analyses in each of these trials have been provocative and suggested possible benefits for these drugs for specific histologies (breast, non-small-cell lung), prompting ongoing phase III studies. A randomized phase II study with temozolomide suggested improved response rates and neurologic outcomes for patients randomized to receive the drug. Overall, there is no strong evidence to date to support the use of any radiation sensitizer in standard practice.

Surgery and Stereotactic Radiosurgery

Surgery has traditionally not had a role to play in the management of patients with multiple brain metastases, and its role in this setting remains controversial. Retrospective studies have suggested a survival benefit for surgery in this setting.

Selection of patients clearly influences outcomes. One study used the RTOG® recursive partitioning analysis (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 class 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).

There are now three phase III trials addressing the role of stereotactic radiosurgery (SRS) in the management of multiple brain metastases. One study reported a small randomized trial in which 27 patients with two to four brain metastases ≤25 mm in diameter received WBRT alone or with an SRS boost. Local control at 1 year was 92% with SRS vs. 0% without SRS. Median survival time was also better with SRS (11 months vs. 7.5 months). RTOG® has published the results of its phase III trial in which 333 patients were randomized to WBRT with or without SRS boost if they had one to three brain metastases. The median survival with SRS was 6.5 months vs. 5.7 months, a nonsignificant difference. Subset analysis suggested a survival advantage in the WBRT and SRS group for patients with a single brain metastasis (median survival time 6.5 months vs. 4.9 months) but no survival advantage to SRS for multiple metastases. Another study recently reported on a study of 132 patients to SRS plus WBRT versus SRS alone for the treatment of brain metastases. 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 at a minimum the importance of WBRT in patients with multiple metastases, and the role of selection in the application of SRS for this class of patients. Given the absence of survival impact with SRS, careful patient selection for this intervention needs to be practiced by clinicians, use of the RTOG® RPA brain metastasis classification may prove useful in decision-making.

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. Any perceived benefits from surgery need verification in prospective, randomized phase III clinical trials. The role of SRS for patients with multiple metastases may be primarily a function of proper patient selection but likely cannot replace the benefits of WBRT. Effective radiation sensitizers are needed, because WBRT alone, even in doses of 50 to 54.4 Gy, has not been associated with an improved survival outcome.

Abbreviations

- CNS, central nervous system
- KPS, Karnofsky Performance Status
- MRI, magnetic resonance imaging
- s/p, status post
- SRS, stereotactic radiosurgery

- TN, primary tumor, regional lymph node
- WBRT, whole brain radiotherapy

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

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

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An 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 exams 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.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Videtic GM, Gaspar LE, Aref AM, Imperato JP, Marcus KJ, Rogers CL, Simpson JR, Suh JH, Wolfson AH, McDermott MW, Rogers L, Expert Panel on Radiation Oncology-Brain Metastases. Multiple brain metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 8 p. [31 references]

ADAPTATION

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

DATE RELEASED

1999 (revised 2006)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®

GUIDELINE COMMITTEE

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

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Gregory M. Videtic, MD; Laurie E. Gaspar, MD, MBA; Amr M. Aref, MD; Joseph P. Imperato, MD; Karen J. Marcus, MD; C. Leland Rogers, MD; Joseph R. Simpson, MD; John H. Suh, MD; Aaron H. Wolfson, MD; Michael W. McDermott, MD; Lisa Rogers, DO

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

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The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the 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 is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable

Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 30, 2001. The information was verified by the guideline developer as of February 20, 2001. This NGC summary was updated by ECRI Institute on May 16, 2007.

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