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CLINICAL INVESTIGATION **ACR Report**

AMERICAN COLLEGE OF RADIOLOGY APPROPRIATENESS CRITERIA ON MULTIPLE BRAIN METASTASES

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BACKGROUND

As many as 170,000 cancer patients will develop brain metastases each year (1). Brain metastases represent the most common neurologic manifestation of cancer, occurring in 15% of cancer patients, particularly those with lung and breast cancer diagnoses (2). Clinical (2), imaging (3), and autopsy (4) series have shown that approximately half of brain metastases will be solitary and half will be multiple. Among patients with multiple lesions, the majority of metastases (70%) are found supratentorially (2). The most common symptoms of brain metastases are headache, altered mental status, and focal weakness, occurring in up to half of patients. The next most common symptoms include seizures and gait ataxia, which are seen in approximately 10–20% of patients (2).

Whole-brain radiotherapy (WBRT) is the established standard of care for the vast majority of patients with multiple brain metastases, although there have been no randomized trials showing that WBRT offers a survival advantage over supportive care. Even a recent randomized pilot study that compared primary chemotherapy for newly diagnosed non–small-cell lung cancer brain metastases with up-front WBRT found no differences in survival or response rates (5). Nonetheless, attempts to improve outcomes in patients with multiple brain metastases are warranted given the modest outcomes and have included the use of different dose/fractionation schedules, radiation sensitizers, surgery, and stereotactic radiosurgery (SRS).

PROGNOSTIC FACTORS

The median survival time of a patient with brain metastases after WBRT is between 4 and 6 months. Certain clinical prognostic factors are associated with a better or worse outcome. The Radiation Therapy Oncology Group (RTOG) carried out a recursive partitioning analysis (RPA) of three Phase III brain metastases trials to produce a prognostic classification: Class I: patients <65 years of age with Karnofsky performance status (KPS) ≥70 and a controlled primary cancer without other systemic metastases have a median survival time of 7.1 months; Class III: patients with KPS <70, independent of other factors, have a median survival time of

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This article summarizes the American College of Radiology (ACR) Appropriateness Criteria on Multiple Brain Metastases, excerpts of which are reprinted here with permission. Practitioners are encouraged to refer to the complete version at www.acr.org/ac.

The ACR seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply society endorsement of the final document.

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2.3 months; Class II: all other patients have a 4.2-month median survival time (6). Sperduto *et al.* (7) have recently proposed a new prognostic index for brain metastases patients. They compared it with three other indices—including the RTOG RPA classification—and found it to be the least subjective and most quantitative. Imaging factors, such as the number of metastases, presence of midline shift, and post-WBRT response, may also influence prognosis (8, 9).

WHOLE-BRAIN RADIOTHERAPY

A variety of total doses, fractionation schedules, and doses per fraction have been tested in prospective, randomized, Phase III clinical trials, primarily in patients with multiple brain metastases (10–17). None of these regimens has proven better than another in terms of survival or efficacy (approximately half of patients have an improvement in their neurologic symptoms). In the United States, 3000 cGy in 10 fractions and 3750 cGy in 15 fractions represent the most frequently used dose/fractionation schedules.

Selecting treatment regimens appropriate for individual patients should be facilitated by considering prognostic classifications such as the RTOG RPA classes (6); thus, short-course treatment is appropriate for poor-risk patients (*i.e.*, poor performance status, elderly, progressive systemic disease) (Table 1, Variant 1). That said, some clinicians may have concerns regarding the late effects of WBRT, especially for better-prognosis patients. A 1989 retrospective report of dementia in 12 patients with long survival has been influential in that regard, suggesting that WBRT of $\geqslant$300 cGy was associated with a greater likelihood of late neurocognitive effects (18). This study has been highly criticized, including for its reported radiation total doses and fractionation schemes. Contemporary prospective data have been critical in defining the safety of conventional WBRT (Table 1, Variant 3).

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 (19). Impairment was found in >90% of patients at baseline, and results suggested only tumor control correlated with NCF (20), suggesting a potential benefit if WBRT conveys more tumor control (21). Further substantiating the neurocognitive benefits of WBRT was an analysis of the 208 patients in the control arm of this trial (20), which looked at the relationship between NCF and tumor volume regression. Li *et al.* (22) found that WBRT-induced tumor shrinkage correlated with better survival and NCF preservation. Neurocognitive function was found to be stable or improved in long-term survivors, and tumor progression adversely affected NCF more than WBRT dose.

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 approximately half of these patients (range, 26–70%) (10, 12, 15).

Various radiation sensitizers have been added to WBRT without a demonstrated improvement in survival (23). Recent randomized studies with efaproxiral (24) and motexafin gadolinium (19) have not demonstrated survival benefits. Two recent Phase III studies with the biologic agents melatonin (25) and thalidomide (26) likewise showed no improvement in overall survival. A randomized Phase II study with temozolomide suggested improved response rates and neurologic outcomes for patients randomized to receive the drug (27). Overall, there is no strong evidence to date to support the use of any radiation sensitizer in standard practice.

SURGERY AND SRS

Surgery has not had a major role to play in the management of patients with multiple brain metastases. Some retrospective studies have suggested that it can offer a survival benefit (2, 28, 29), but its role is controversial.

Pollock *et al.* (30) 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. Iwadate *et al.* (31) investigated the role of surgery in the treatment of 138 patients with multiple brain metastases when performed with radiotherapy. Median survival times were 8.7 months for patients with single metastases and 9.2 months for those with multiple metastases (no significant difference).

Three Phase III trials have addressed the role of SRS in the management of multiple brain metastases. Kondziolka *et al.* (32) reported a small randomized trial in which 27 patients with two to four brain metastases $\leq$25 mm in diameter received WBRT alone or with an SRS boost. Local control at 1 year was 92% with SRS vs. none without SRS. Median survival time was also better with SRS (11 months vs. 7.5 months).

The RTOG 9508 trial enrolled 333 patients with one to three brain metastases and randomized them to WBRT with or without SRS boost (33). 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 non–small-cell lung cancer 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 two to three brain metastases (Table 1, Variant 2).

Aoyama *et al.* (34) reported results for 132 patients with one to four brain metastases randomized to SRS plus WBRT vs. 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

Table 1. Sample clinical scenarios (variants) with consensus scores for selected treatment intervention based on ACR Expert Panel voting.

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

Treatment	Rating	Comments
WBRT alone		
2000 cGy/5 fractions	8	Poor KPS, active extracranial disease, no evidence of dose benefit with respect to symptom control. Extension of treatment schedules is not justified in this patient so shorter schedule appropriate.
3000 cGy/10 fractions	8	
3750 cGy/15 fractions	6	
4000 cGy/20 fractions	2	
SRS		
SRS alone	2	SRS as any component of therapy is not recommended in view of patient and disease status, without evidence to support benefit.
SRS + WBRT	2	
Surgery alone		
Excise dominant lesion(s)	1	Surgery in any combination is not appropriate, given patient status.
Excise all lesions	1	
Radiosensitizer		
Radiosensitizer + WBRT	1	No evidence for any role. Can only be done in trial setting.
Observation	4	Not unreasonable given status of patient. Requires best supportive care with optimized medical management.

Variant 2: 50-year-old man with 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 mo ago (T2 N0 adenocarcinoma of lung). No other systemic metastases.

Treatment	Rating	Comments
WBRT alone		
2000 cGy/5 fractions	3	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.
3000 cGy/10 fractions	7	
3750 cGy/15 fractions	7	
4000 cGy/20 fractions	3	
SRS		
SRS alone	6	There is significant controversy among clinicians with respect to the application of trial-derived data to the current clinical scenario, the weight of opinion, however, favors inclusion of WBRT as adjunct to SRS given evidence of local control and overall improvements in brain relapse rates.
SRS + WBRT	8	
Surgery alone		Surgery offers no clear benefit in this scenario, given absence of symptoms and multiple lesions.
Excise dominant lesion(s)	2	
Excise all lesions	1	
Radiosensitizer		No evidence for any role. Can only be done in trial setting.
Radiosensitizer + WBRT	1	KPS would preclude this option.
Observation	1	

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	Rating	Comments
WBRT alone		
2000 cGy/5 fractions	4	
3000 cGy/10 fractions	8	Multiple brain metastases in this patient strongly support use of WBRT only. Schedule choice may depend on KPS, although randomized evidence to date does not suggest one schedule over others.
3750 cGy/15 fractions	8	
4000 cGy/20 fractions	2	
SRS		
SRS alone	1	Number of lesions and absence of evidence do not support any strong role for SRS in this patient.
SRS + WBRT	2	

(*Continued*)

Table 1. Sample clinical scenarios (variants) with consensus scores for selected treatment intervention based on ACR Expert Panel voting. (*Continued*)

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	Rating	Comments
Surgery alone		
Excise dominant lesion(s)	1	Number of lesions, absence of focal symptoms and absence of evidence do not support any role for surgery in this patient.
Excise all lesions	1	
Radiosensitizer		
Radiosensitizer + WBRT	1	No evidence for any role. Can only be done in trial setting.
Observation	1	Patient's lack of symptoms and high KPS preclude this option.

Variant 4: 35-year-old woman with two 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 mo ago. No other metastases.

Treatment	Rating	Comments
WBRT alone		
2000 cGy/5 fractions	2	Use of WBRT alone in a patient with two melanoma brain metastases is believed by many to be insufficient therapy.
3000 cGy/10 fractions	5	
3750 cGy/15 fractions	5	
4000 cGy/20 fractions	2	
SRS		
SRS alone	7	Controversy about the role of WBRT addition to SRS in the management of a few melanoma brain metastases given age, KPS, absence of extracranial metastases, and histology. Multiplicity of metastases thought to weigh somewhat in favor of the addition of WBRT at presentation to minimize distant brain relapse.
SRS + WBRT	8	
Surgery alone		Because patient's metastases are asymptomatic, there is no need to take surgical risks.
Excise dominant lesion(s)	2	
Excise all lesions	2	
Radiosensitizer		No evidence for any role. Can only be done in trial setting.
Radiosensitizer + WBRT	1	
Observation	1	

Abbreviations: MRI = magnetic resonance imaging; KPS = Karnofsky performance status; WBRT = whole-brain radiotherapy; SRS = stereotactic radiosurgery.

Rating scale: 1 = least appropriate, 9 = most appropriate.

(Table 1, Variant 4). Given the finding that SRS does not increase survival of patients with two 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 (6).

SUMMARY

Whole-brain radiotherapy is an effective palliative treatment for patients with multiple brain metastases. Approximately half of these patients experience an improvement in their neurologic symptoms. However, a majority of them do not achieve local control and frequently die of progressive brain disease.

Any perceived benefits from surgery 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, as demonstrated in the Aoyama trial (34).

Effective radiation sensitizers are needed because WBRT alone, even in doses of 5000–5440 cGy, has not been associated with an improved survival outcome.

Future trials of WBRT must include prospective measurement of neurocognitive functioning before and after treatment as a standard component of the patient's assessment.

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