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MULTIPLE BRAIN METASTASES

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Summary of Literature Review

Introduction/Background

It is estimated that as many as 170,000 cancer patients per year will develop brain metastases [1]. Brain metastases represent the most common neurologic manifestation of cancer, occurring in about 30% of cancer patients [2], particularly those with lung cancer, breast cancer, and melanoma, who account for up to 64%, 21%, and 16%, respectively, of patients with brain metastases [3].

Clinical [4], imaging [5], and autopsy [6] 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 [7]. Among patients with multiple lesions, 70% are supratentorial, 26% are supratentorial and cerebellar**,** 3% are cerebellar, and 1% are located in the brainstem [4]. 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%–20% of patients [4].

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) [8]. 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-month 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 [9]. 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. Sperduto et al [10] proposed a newer

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prognostic index for brain metastases patients. They compared it to 3 other indices—including the RTOG RPA classification—and found it to be the least subjective and most quantitative. In a subsequent analysis, Sperduto et al [11] 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. Sperduto et al [12] 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 [13-15].

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, 2000/4, 2000/5, 3000/10, 3000/15, 3600/6, 4000/15, 4000/20, 4000/20 (200 cGy twice daily [BID]), 5000/20, and 5440/34 (160 cGy BID) [16-26]. Although 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 frequently used dose/fractionation schedules in the United States [27].

In selecting treatment regimens appropriate for individual patients, clinicians should consider the RTOG RPA brain metastasis classification [9], which supports short-course treatment in poor-risk patients (ie, poor performance status, elderly, progressive systemic disease). (See Variant 1.)

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 (ie, 250 cGy per fraction) was used as the standard treatment arm [28] 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 [29]. However, this 1989 retrospective report of dementia in 12 patients with long survival [29] 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 [22], 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 [30]. Aoyama et al [31] 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) [32]. Impairment was found in >90% of patients at baseline, and the results suggested that only tumor control correlated with NCF [33], suggesting a potential benefit if WBRT conveys more tumor control [34]. Further substantiating the neurocognitive benefits of WBRT was an analysis of the 208 patients in the control arm of this trial [29], which looked at the relationship between NCF and tumor volume regression. Li et al [15] 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.

Chang et al [35] 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%–70%) [16,18,21].

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 [36] 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) [37] 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 [38], misonidazole [39], bromodeoxyuridine [40], and the nitrosourea (ACNU), either alone or with fluorouracil [41]. The addition of biological modifiers such as efaproxiral [42] and MGd [32] has not demonstrated survival benefits. A subgroup analysis of the interval to investigator-determined neurologic progression and the interval to neurocognitive progression [32] suggested a trend toward prolongation of time to neurological progression with the early use of MGd, but this finding was not demonstrated in the overall study population [43]. Phase III studies with biological agents melatonin [44] and thalidomide [45] 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 [46].

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 [41,47,48], chemotherapy with or without concurrent WBRT [49,50], concurrent versus delayed WBRT [51], and chemotherapy followed by WBRT versus WBRT followed by chemotherapy [52].

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 [4,53,54], 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 1 to 3 brain metastases showed that WBRT reduced local relapse and neurologic death but did not improve the duration of functional independence or overall survival [55]. Health-related quality-of-life (HRQOL) results were subsequently reported for this trial [56]. 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.

Pollock et al [57] 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 [58] 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).

Kondziolka et al [59] 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 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 [28]. The overall median survival time with the addition of SRS was 6.5 months versus 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 versus 4.9 months, P=.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.)

Aoyama et al [31] 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 [9]. (See Variant 4.)

A phase III neurocognition trial by Chang et al [35] 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 versus 5.7 months, 63% versus 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 [60]. (See Variant 5.)

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 to 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.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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The 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 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.

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	
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 the 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**

Clinical Condition: **Multiple Brain Metastases**

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 1 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	The 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**		

Clinical Condition: **Multiple Brain Metastases**

Variant 3: **50-year-old man with 2 newly diagnosed, surgically accessible, supratentorial brain metastases on MRI. KPS 90. One brain metastasis is 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**

Clinical Condition: **Multiple Brain Metastases**

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 measures 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	7	Consider this treatment in the case 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.
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 2 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 is judged to be an important component in overall brain and lesion 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 lesion control require 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		

Clinical Condition: **Multiple Brain Metastases**

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 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 2 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 the 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 the patient's metastases are asymptomatic, there is no need to take surgical risks.
Excise all lesions	2	
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**