ACR Appropriateness Criteria®: Single Brain Metastasis

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Single brain metastasis represents a common neurologic complication of cancer. Given the number of treatment options that are available for patients with brain metastasis and the strong opinions that are associated with each option, appropriate treatment for these patients has become controversial. Prognostic factors such as recursive partitioning analysis and graded prognostic assessment can help guide treatment decisions. Surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery or combination of these treatments can be considered based

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on a number of factors. Despite Class I evidence suggestive of best therapy, the treatment recommendation is quite varied among physicians as demonstrated by the American College of Radiology's Appropriateness Panel on single brain metastasis. Given the potential concerns of the neurocognitive effects of WBRT, the use of SRS alone or SRS to a resection cavity has gained support. Since aggressive local therapy is beneficial for survival, local control and quality of life, the use of these various treatment modalities needs to be carefully investigated given the growing number of long-term survivors. Enrollment of patients onto clinical trials is important to advance our understanding of brain metastasis.

Summary of Literature Review

The appropriate treatment for a patient with a single brain metastasis has become controversial given the number of management strategies that are available and the strong opinions that are associated with each option. As a result, there is no clear consensus regarding optimal or ideal treatment for these patients despite Class I evidence suggestive of best therapy.

Prognostic Factors

To help categorize patients into prognostic groups, a number of clinical factors have been evaluated to help guide treatment decisions. The most commonly used prognostic scale for patients with brain metastases is from the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis of three consecutive Phase III brain metastases trials.[1] This study determined the four most important factors were Karnofsky performance score (KPS), age, control of primary and status of extracranial disease. More recently, a less subjective, more quantifiable scale (Graded Prognostic Assessment) from five Phase III RTOG® trials revealed that extracranial disease status, age and KPS were still prognostic.[2] This analysis, however, demonstrated the importance of the number of lesions (1 vs 2-3 vs >3) in determining outcomes for patients with brain metastases.

Surgery

Advances in surgery and imaging have allowed for safer resection of brain metastases. If the patient is suffering from significant mass effect or has no pathologic confirmation of the primary, then surgical resection of the lesion, if feasible, is warranted. For patients with a single lesion who are relatively asymptomatic, the decision process is somewhat more complicated. The decision to use aggressive therapy depends on the extent and activity of extracranial disease, number of brain lesions as well as the patient's general medical condition, performance status, and patient's preference. For patients with stable or absent extracranial disease, two randomized studies have clearly shown the benefit of surgical resection followed by whole brain radiotherapy (WBRT).[3,4] The benefits are expressed not only in terms of freedom from neurologic progression but also in terms of overall survival. However, a third study by Mintz et al[5] failed to show a survival advantage with the addition of surgery, or an advantage in terms of quality-of-life. Thus, two of three randomized studies have shown a benefit of surgical resection and WBRT versus WBRT alone.

Whole Brain Radiation Therapy

The dose used with WBRT in patients with single brain metastasis is based mainly on studies performed in patients with multiple brain metastases. Prospective, randomized Phase III clinical trials in patients with multiple brain metastases have included 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 BID).[6-12] Since none of these regimens has proved superior in terms of survival or efficacy (about half of patients have an improvement in their neurologic symptoms), 3000 cGy in 10 fractions or 3750 cGy in 15 fractions represent frequently utilized dose/fractionation schedules. A randomized trial in patients with 1 to 3 brain metastases by the RTOG® used 3750 cGy in 15 fractions WBRT (ie, 250 cGy per fraction) as the standard treatment arm.[13] This schedule is an extrapolation from 2 other series in the literature, one of which suggests that 300 cGy fractions given following resection of a single brain metastasis are associated with a greater likelihood of late effects to the normal brain,[14] and another in which prophylactic cranial irradiation given in case of small-cell lung cancer with 250 cGy fractions (10 fractions) was not associated with late effects.[15] WBRT alone can provide excellent palliation for many patients with brain metastases (Tables 1 and 2).

Surgery Versus Stereotactic Radiosurgery

Whether stereotactic radiosurgery (SRS) is as effective as surgical resection has not been evaluated within a Phase III randomized trial for patients with single brain metastasis. Auchter et al[16] performed a multi-institutional outcome study on patients treated with radiosurgery and WBRT who met the same entry criteria as the patients treated in the two positive

TABLE 1. Variant 1: 77-year-old man, PET scan demonstrated widely metastatic melanoma with a 2 cm right thalamic lesion. Neurosurgeon believes surgery would be high risk. KPS 60. Patient refuses further systemic therapy

Treatment	Rating*	Comments
Focal Therapy Alone		
Stereotactic radiosurgery (SRS) alone	7	Considerable debate regarding role of SRS for patient with KPS of 60. Some felt SRS alone provided quicker palliation compared with WBRT.
Surgical resection alone	1	
Whole Brain RT (WBRT) Alone		
2000 cGy/5 fractions	7	Debate regarding role of this fractionation scheme. Given low KPS and patient refusal for further systemic therapy, short fractionation deemed appropriate.
3000 cGy/10 fractions	8	
3750 cGy/15 fractions	5	Did not favor more prolonged WBRT schedule.
4000 cGy/20 fractions	1	
Combination Therapy		
SRS + WBRT	3	Aggressive therapy for patient with short life expectancy.
Surgery + WBRT	1	
Surgery + SRS to resection cavity	1	
Observation	6	

*Rating scale: 1-3, usually not appropriate; 4-6, may be appropriate; 7-9, usually appropriate.

TABLE 2. Variant 2: 54-year-old man found to have wide spread metastatic small cell carcinoma to lung, bone, and liver by PET/CT imaging with a 2 cm asymptomatic left anterior temporal lobe lesion. KPS 70. Systemic therapy is planned. No prior WBRT

Treatment	Rating*	Comments
Focal Therapy Alone		
Stereotactic radiosurgery (SRS) alone	2	
Surgical resection alone	1	
Whole Brain RT (WBRT) Alone		
2000 cGy/5 fractions	5	
3000 cGy/10 fractions	8	
3750 cGy/15 fractions	8	
4000 cGy/20 fractions	2	
Combination Therapy		
SRS + WBRT	2	Considered too aggressive for radiosensitive tumor
Surgery + WBRT	1	
Surgery + SRS to resection cavity	1	
Observation	1	

*Rating scale: 1-3, usually not appropriate; 4-6, may be appropriate; 7-9, usually appropriate.

TABLE 3. Variant 3: 68-year-old woman status-post chemotherapy/radiotherapy and surgery for esophageal carcinoma. No evidence of extracranial disease with 5 cm lesion in right anterior frontal lobe with 15 mm midline shift. KPS 90 on high dose steroids

Treatment	Rating*	Comments
Focal Therapy Alone		
Stereotactic radiosurgery (SRS) alone	1	
Surgical resection alone	2	
Whole Brain RT (WBRT) Alone		
2000 cGy/5 fractions	1	
3000 cGy/10 fractions	5	Consider if patient refuses surgery or is medically unfit for surgery
3750 cGy/15 fractions	5	Consider if patient refuses surgery or is medically unfit for surgery
4000 cGy/20 fractions	1	
Combination Therapy		
SRS + WBRT	1	
Surgery + WBRT	9	
Surgery + SRS to resection cavity	2	
Observation	1	

*Rating scale: 1-3, usually not appropriate; 4-6, may be appropriate; 7-9, usually appropriate.

randomized trials of surgery and WBRT versus WBRT alone. The results of this nonrandomized study indicate that radiosurgery plus WBRT produces the same local control, freedom from neurological deterioration, and overall survival as surgery plus WBRT. Another retrospective study from Bindal et al[17] showed improved median and 1-year survival for those undergoing surgery compared with SRS. The rates of local recurrence and neurologic death were lower in the surgery group. More recent studies have suggested that the results of SRS and WBRT are equivalent to surgery and WBRT.[18-20] For tumors greater that 4 cm in greatest diameter or causing significant mass effect, surgery rather than SRS is the preferred treatment (Table 3).

Brachytherapy

Some studies looking at stereotactic interstitial brachytherapy for patients with single lesions indicate that control rates are similar to those obtained with radiosurgery.[21,22] However, stereotactic brachytherapy is an invasive procedure and requires hospitalization. A more recent Phase II trial evaluating balloon brachytherapy demonstrated local control rates of 80% but higher rates of radiation necrosis.[23] Given the invasive nature of brachytherapy, this approach is not routinely practiced.

TABLE 4. Variant 4: 48-year-old man status-post left upper lobe resection for NSCLC 1 year earlier, now with 3 cm right frontal lobe lesion. No clinical or radiographic evidence of extracranial disease. The right frontal lesion was completely resected, confirmed by contrast MRI scan 24 hours after surgery. Two weeks after surgery, KPS is 80

Treatment	Rating*	Comments
Focal Therapy Alone		
Stereotactic radiosurgery (SRS) alone	5	No Phase III trial demonstrating superiority over WBRT
Whole Brain RT (WBRT) Alone		
2000 cGy/5 fractions	1	
3000 cGy/10 fractions	7	
3750 cGy/15 fractions	7	
4000 cGy/20 fractions	4	
Combination Therapy		
SRS + WBRT	1	
Observation	1	

*Rating scale: 1-3, usually not appropriate; 4-6, may be appropriate; 7-9, usually appropriate.

Surgery With or Without Whole Brain Radiation Therapy

The use of WBRT for patients with a single metastasis has been a subject of growing controversy.[24] The question of whether surgical resection can be performed without the addition of WBRT was tested in a Phase III randomized trial.[25] This trial demonstrated that the overall local and distant recurrence rates in the brain were 46% and 70% in the surgery arm versus 10% and 18%, in the surgery and WBRT arm. Overall survival was not improved; however, the study was not powered to detect such a difference (Tables 4 and 5).

Stereotactic Radiosurgery With or Without Whole Brain Radiation Therapy

The analogous question, of whether radiosurgery can be performed without the addition of WBRT, has been studied retrospectively in several institutional and multi-institutional studies.[26-29] Several radiosurgery studies investigating patients treated with radiosurgery alone versus radiosurgery plus WBRT for single and multiple lesions have not shown an improvement in survival with the addition of WBRT. One study suggested that patients without extracranial disease had a trend toward better median survival of 15.4 months for the WBRT plus SRS group versus 8.3 months survival for the SRS alone group.[30] A Phase III trial conducted in Japan randomizing patients with one to four brain metastases between radiosurgery and radiosurgery plus WBRT and demonstrated significantly improved local and distant brain

TABLE 5. Variant 5: 35-year-old woman with metastatic breast cancer to multiple boney sites with a 3 cm left parietal lesion. Systemic disease is no longer responding to chemo-hormonal therapy. Surgical resection was subtotal in nature, confirmed by postoperative MRI. KPS 90

Treatment	Rating*	Comments
Focal Therapy Alone		
Stereotactic radiosurgery (SRS) alone	6	Concern that patient may live long enough to develop other brain metastases without use of WBRT
Surgical resection (repeat)	2	
Whole Brain RT (WBRT) Alone		
2000 cGy/5 fractions	3	
3000 cGy/10 fractions	8	
3750 cGy/15 fractions	8	
4000 cGy/20 fractions	3	Prolonged course of WBRT is discouraged
Combination Therapy		
SRS + WBRT	8	Because patient had subtotal resection, some recommend combination approach to maximize local control.
Surgery + WBRT	1	
Surgery + SRS to resection cavity	1	
Observation	1	

*Rating scale: 1-3, usually not appropriate; 4-6, may be appropriate; 7-9, usually appropriate.

control for the WBRT plus radiosurgery arm.[31] Since the primary end point of the study was local control and not overall survival, the study was not powered properly to evaluate survival differences. More recently, a randomized Phase III trial of SRS versus SRS and WBRT demonstrated a decline in neurocognitive outcome based on Hopkins Verbal Learning Test (HVLT) at 4 months for patients undergoing WBRT and SRS.[32] The North Central Cancer Treatment Group (NCCTG) has an ongoing Phase III trial for patients with one to three brain metastases of SRS versus SRS followed by WBRT. The primary endpoint is neurocognitive function (Table 6).

Whole Brain Radiation Therapy With or Without Stereotactic Radiosurgery

Another question, whether patients receiving WBRT for a single brain metastasis benefit from the addition of radiosurgery, has been answered in an RTOG® randomized trial in patients with one to three brain metastases.[13] In patients with a single brain metastasis, the addition of radiosurgery increased median survival from 4.9 to 6.5 months ($P = 0.04$). Local control was significantly improved for all patients. Based on the results of this trial, the RTOG® started a Phase III trial (RTOG® 0320) for patients with nonsmall-cell lung cancer with one to three brain metastases, which closed secondary to poor accrual (Table 7).

TABLE 6. Variant 6: 49-year-old woman (nonsmoker) recently diagnosed with 2 cm NSCLC left upper lobe with no hilar and mediastinal lymphadenopathy, and asymptomatic 2 cm right frontal lesion. Abdominal CT and bone scan were negative. KPS 90

Treatment	Rating*	Comments
Focal Therapy Alone		
Stereotactic radiosurgery (SRS) alone	7	
Surgical resection alone	5	
Whole Brain RT (WBRT) Alone		
2000 cGy/5 fractions	1	
3000 cGy/10 fractions	5	
3750 cGy/15 fractions	5	
4000 cGy/20 fractions	1	
Combination Therapy		
SRS + WBRT	8	
Surgery + WBRT	8	
Surgery + SRS to resection cavity	5	More data are needed for SRS to resection cavity.
Observation	1	

*Rating scale: 1-3, usually not appropriate; 4-6, may be appropriate; 7-9, usually appropriate.

TABLE 7. Variant 7: 42-year-old woman status-post nephrectomy for renal cell carcinoma 6 years earlier with a 1-cm lesion in the right lateral cerebellum found incidentally after MRI for head injury. CT of chest/abdomen and bone scan was negative. KPS 90

Treatment	Rating*	Comments
Focal Therapy Alone		
Stereotactic radiosurgery (SRS) alone	7	
Surgical resection alone	4	
Whole Brain RT (WBRT) Alone		
2000 cGy/5 fractions	1	
3000 cGy/10 fractions	5	Some concern that WBRT would not sufficiently control RCC metastasis
3750 cGy/15 fractions	5	Some concern that WBRT would not sufficiently control RCC metastasis
4000 cGy/20 fractions	1	
Combination Therapy		
SRS + WBRT	8	
Surgery + WBRT	8	
Surgery + SRS to resection cavity	6	
Observation	1	

*Rating scale: 1-3, usually not appropriate; 4-6, may be appropriate; 7-9, usually appropriate.

Neurocognitive Effect of Whole Brain Radiation Therapy

Concerns about the potential neurocognitive effects of WBRT have received much attention and scrutiny. As part of a Phase III trial evaluating the use of a novel radiation sensitizer with WBRT, all patients underwent evaluation of neurocognitive function using a battery of tests.[32] Baseline neurocognitive testing demonstrated that 91% of patients had a significant decline in at least 1 domain before WBRT. Further analysis of the 208 patients in the WBRT arm of the study demonstrated WBRT-induced tumor shrinkage correlated with better survival and neurocognitive function.[33] In addition, neurocognitive deterioration preceded quality of life declines, which suggests that strategies that delay neurocognitive decline appear worthwhile.[34] When Mini-Mental Status Examination was used to evaluate neurocognitive function as part of the Phase III trial of SRS versus SRS plus WBRT for patients with 1 to 4 brain metastases, the omission of WBRT led to faster time to neurologic deterioration based on Mini-Mental State Examination.[35] In addition, the omission of WBRT significantly increased the risk for tumor recurrence and decline in neurologic function. A pilot study of neurocognitive function in patients with 1 to 3 brain metastases treated with SRS alone showed 60% of the patients had impairment at presentation.[36] A recent Phase III trial demonstrated worse neurocognitive outcomes at 4 months as measured by HVLT for patients randomized to the WBRT and SRS arm versus SRS alone.[37]

Stereotactic Radiosurgery to Resection Cavity

The use of SRS to the resection cavity has also been investigated.[38] This study showed actuarial local control rates at 6 and 12 months of 88% and 79%, respectively. Since less conformal plans led to better local control, the authors recommended inclusion of a 2 mm margin around the resection cavity. When the inclusion of a 2-mm margin was retrospectively evaluated for 93 patients with a single metastasis undergoing SRS for an unresected metastasis, higher rates of severe complications were reported.[39]

Long Term Survival After Surgery or SRS

More aggressive treatment with surgery or SRS has led to greater number of patients being long-term survivors. Retrospective review of patients undergoing SRS reported that 6.5% survived at least 4 years.[40] Another review of long-term survivors showed that 2.6% of patients in a large single institution database survived a minimum of 5 years.[41]

Conclusions

Compelling evidence suggests that aggressive local therapy for patients with a single brain metastasis is beneficial for survival. There is also evidence to suggest that aggressive local therapy for a patient with a single lesion improves quality of life. If patients have no evidence of progressive extracranial disease, surgical resection or radiosurgery is appropriate therapy. While it appears that the addition of WBRT does not add to survival or duration of functional independence, it does reduce the risk of further intracranial failure and delays neurocognitive decline, particularly for those patients whose tumors have responded to WBRT. Recently, completed and ongoing studies will help address the impact of WBRT on neurocognitive function and quality of life, which have been major reasons why WBRT is being omitted despite Class I evidence supporting the use of WBRT after surgery or SRS.

Since much controversy exists regarding optimal treatment for a patient with a single brain metastasis, patient participation in clinical trials is important to evaluate best treatment. For those patients who do not participate in clinical trials, the roles of surgery and SRS in improving outcomes for patients with a single lesion are evident.

Disclaimer:

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 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 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.

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