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FOLLOW-UP AND RETREATMENT OF BRAIN METASTASES

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Summary of Literature Review

Introduction/Background

Progress in the management of locally advanced and metastatic cancer has resulted in an increase in the number of patients diagnosed and living with brain metastases. Current estimates suggest that nearly 200,000 new patients develop brain metastases annually in the United States. It has also been estimated that up to 40% of patients with cancer will develop brain metastases [1]. Hence, although progress has been made in decreasing the incidence of lung cancer deaths (largely due to fewer smokers) and prolonging survival in other systemic cancers such as breast and colorectal, the incidence of brain metastases continues to increase as patients with metastatic disease live longer.

The most common source of brain metastases is lung cancer. A report on 177 patients with surgically staged IIIA non–small-cell lung cancer (NSCLC) found that 34% of them had cancer recur in the brain as the first site of failure, and that 40% developed brain metastases at some point in their course [2]. In the past, brain metastases were thought to herald the onset of a rapidly fatal course in patients with cancer due to the limited efficacy of systemic therapies and whole-brain radiation therapy (WBRT) (median survival 4–7 months; 2-year survival ≤10%) [3]. Survival rates for patients with brain metastases become significant only when extracranial disease is controlled, as pointed out by Tan and Black [4].

Reports are emerging, however, describing long-term survivorship on the order of multiple years after treatment of brain metastasis. Several single and multi-institutional retrospective reviews revealed 2.5%–6% 5-year overall survival after treatment of brain metastases with some patients living longer than 10 years. As expected, patients with initially higher Karnofsky performance status (KPS), fewer brain metastases, and limited extracranial disease experienced longer survival [3,5,6]. In addition, a recent phase III trial of 359 patients randomized to local therapy alone for 1–3 brain metastases followed by observation or WBRT reported >20% survival at 2 years [7]. Thus, as a growing percentage of treated patients may live long enough to experience relapse again in the brain, there is a greater need for appropriate follow-up and management of recurrent brain metastases.

Retreatment for brain metastases may be required following a variety of initial treatments such as WBRT, surgery, radiosurgery, chemotherapy, and combinations of these. The choice of treatment modality after recurrence will depend on the size, number, timing, and location of the recurrent metastases, the patient's performance status, extracranial disease control, and prior treatment of the intracranial disease. There appears to be an increasing number of patients who have received only surgery or radiosurgery as their initial management of brain metastases. This trend is likely driven by the increasing availability of stereotactic radiosurgery (SRS) and improvements in neuroimaging and surgical techniques. For the purpose of general review, these guidelines

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do not elaborate on the unique aspects of small-cell/neuroendocrine lung cancer due to its high propensity of brain metastasis and patients receiving prophylactic cranial irradiation as part of their upfront treatment.

Whole-Brain Radiation Therapy

Historically, WBRT has been a fundamental part of the initial treatment of brain metastases, but due to the increasing use of local therapy alone initially for selected patients with brain metastases; WBRT is often being used in the salvage setting. Two large randomized trials involving initial local therapy followed by observation reported on the use of WBRT after failure in 16% and 31% of patients in the observation arms [7,8] (see Variant 1). In patients who initially received WBRT, repeat WBRT has not been routinely administered for retreatment, primarily due to concerns about severe neurotoxicity. However, one institution reviewed 72 patients who underwent 2 courses of WBRT for brain metastases [9]. The most common initial fractionation scheme was 20 Gy in 5 fractions, whereas the most frequent reirradiation schedule was 25 Gy in 10 fractions. The median survival time after reirradiation was 4.1 months. Performance status (Eastern Cooperative Oncology Group criteria), neurological function class (Radiation Therapy Oncology Group classification), and documented response to reirradiation were predictive of survival times.

Another review of 31 patients undergoing repeat WBRT with the most common first and second course being 30 Gy in 10 fractions revealed a median survival after reirradiation of 4 months with 68% symptomatic improvement after treatment. Grade ≥2 encephalopathy or cognitive disturbance was noted in 32% of patients after reirradiation with 74% of patients having magnetic resonance imaging (MRI) findings suggestive of brain atrophy after reirradiation, which highlights the concern of neurologic deterioration in this setting [10]. These studies suggest that there may be a role for WBRT for the retreatment of progressive brain metastases after prior WBRT.

Radiosurgery

Radiosurgery for recurrent brain metastases is a viable option if size and number permits, and has been described in the setting of prior surgery, radiosurgery, and WBRT. In addition, this modality is becoming increasingly available at many centers. In patients undergoing radiosurgery for recurrence following initial WBRT, Chao et al and Maranzano et al reported 1-year and 2-year local control rates of 68%–74% and 58%, respectively [11]. Maranzano et al [12] reported a 91% response rate of treated lesions with acute grade 2 toxicity requiring steroids in 16% of patients and an eventual radionecrosis rate of 6%. Good local control, as high as 90%, has been reported in patients who underwent repeat SRS to previously treated or newly developed sites, but risk for radiation necrosis increased with repeat treatments to the same areas [13]. Favorable prognostic factors for survival after SRS for recurrent brain metastases included age <50, KPS >60, and longer interval between WBRT and SRS [14]. Recently there has been a trend to use radiosurgery in the setting of adjuvant therapy to the tumor bed after surgical resection as part of initial therapy of brain metastases, but only one report by Kim et al [15] evaluated this scheme in the recurrent setting after prior WBRT. In their retrospective cohort of 79 patients, the local control rate was 94.9% with a symptomatic radionecrosis rate of only 3.8%. Similarly, studies in the setting of the initial treatment of brain metastases suggest that the resection cavity can be treated effectively with 1–5 fractions of stereotactic radiation therapy [16,17]. Together these data suggest that SRS is one valid approach in managing those patients having brain relapses alone or in combination with other modalities even after prior therapies including WBRT and especially if limited new foci are present (see Variant 2 and Variant 3).

Surgery

Surgery may be indicated for palliation of mass effect from progressive or hemorrhagic brain metastases [18] and may also be an important diagnostic and management tool in determining the nature of a progressive lesion after radiation treatment. Factors to consider regarding the use of surgical resection after prior irradiation include clinical or radiographic evidence of a progressive lesion, KPS >60, and stable or absent extracranial disease [19]. Crude reported local control rates range from 69% to 79% [18-20], and one retrospective study comparing resection to no resection showed a modest survival benefit [19] (see Variant 4).

Chemotherapy

Chemotherapy has occasionally been a successful strategy for chemosensitive tumors [21]. Some evidence suggests that some chemotherapy and biological treatments may be effective in brain metastases. These studies are mostly based on smaller experiences using various agents. Temozolomide, capecitabine, and gefitinib have been reported to be used in treating brain metastases from melanoma, breast cancer, and lung cancer, respectively [22]. A phase II study of salvage chemotherapy using dose-dense temozolomide in 157 patients with brain metastases not amenable to surgery or radiosurgery revealed a 26% control rate defined as complete or partial

response or stable disease [23]. Response of brain metastases to antiepidermal growth factor inhibitors such as gefitinib or erlotinib provides some new alternatives for the management of brain metastases [24]. These targeted agents may be particularly attractive for patients with less symptomatic, smaller recurrent brain metastases. Dual tyrosine kinase inhibitors (eg, lapatinib) have recently been shown to benefit some Her2neu-positive breast cancer patients and also those with recurrent brain metastases [25].

Although chemotherapy has been traditionally believed to have poor central nervous system penetrance and therefore poor efficacy in brain metastases, a recent prospective phase II trial evaluating 43 patients with brain metastases from NSCLC treated initially with pemetrexed and cisplatin followed by delayed WBRT, as well as a pilot study of 48 patients with brain metastases from NSCLC randomized to up front WBRT versus WBRT after chemotherapy revealed intracerebral response rates of 41% and 28%, respectively in the chemotherapy upfront setting [26,27].

Supportive Care

Best supportive care (BSC) is always an option for select patients with recurrent brain metastases. Factors important in evaluating prognosis in these patients include, but are not limited to, performance status, status of extracranial disease, number of brain metastases, and age. Patients with a poorer prognosis may be better served with an earlier discussion of BSC considering their reduced survival rates. Some data suggest that BSC is an appropriate option in select patients. Nieder et al [28] conducted a matched pair analysis of 113 patients with brain metastases treated with BSC alone matched to a similar group of patients treated with WBRT. They observed no survival difference, but overall survival was limited in both groups (median overall survival 2 months). In addition, the interim data from an ongoing randomized phase III noninferiority trial comparing quality-adjusted life years after optimal supportive care (OSC) or OSC + WBRT in NSCLC patients with inoperable brain metastases suggests that there is no evidence of inferior quality of life or overall survival for patients managed by OSC alone [29] (see Variant 5). Given that these studies pertain to patients managed with BSC in the initial setting, this strategy may be even more appropriate in the recurrent setting, when previous treatment modalities have already been employed.

Follow-up of Brain Metastases

After the treatment of brain metastasis, determining the proper timing and modality of follow-up imaging and distinguishing treatment response from recurrence are major management considerations. This issue is complicated by the lack of reliable early indicators of response versus progression. Sheehan et al [30] reported a median time of 8.8 months to new metastasis after initial SRS. They recommended close surveillance with a 3-month interval between MRI in order to identify new metastasis early in order to facilitate the most effective treatment. Additionally, Kocher et al [7] performed 3-month interval MRI scans in their study of local therapy with or without WBRT and recommended that when WBRT is withheld, close serial imaging follow-up should be performed to identify early asymptomatic brain recurrences. Although the optimal timing and method of radiographic follow-up of treated brain metastases is the subject of some debate, MRI has become the preferred imaging modality, especially given its wide availability and the development of newer applications such as spectroscopy and diffusion and perfusion-weighted imaging. Given the costs associated with serial MR imaging, decisions regarding its use should take into account the individual patient situation and the likelihood of gaining useful information that may influence management decisions.

A common difficulty encountered during the radiographic follow-up of treated brain metastases is differentiating tumor recurrence or progression from radiation effect. This is particularly vexing in asymptomatic patients with high performance status. Although invasive pathological evaluation remains the only definitive test to make this distinction, it is not always practical or feasible, and some cases of radiation necrosis can be managed nonsurgically. For this reason, several imaging modalities including standard and advanced MRI sequences, MR spectroscopy, perfusion computed tomography (PCT), and fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) and methionine positron emission tomography (PET) have been investigated to differentiate between these entities. Wang et al [31] and Terakawa et al [32] showed that FDG-PET as well as C-11 methionine PET imaging is effective in detecting tumor recurrence compared to radiation changes in patients with suspected recurrent lesions. PCT has been evaluated in a recent prospective trial of 20 patients previously treated with radiosurgery and normalized cerebral blood volume had a sensitivity of 86% and specificity of 100% for identification of radiation necrosis compared to for suspected recurrence [33]. A study of 68 patients who underwent surgical resection after previous SRS for brain metastases due to suspected lesion progression showed that lack of correspondence between T1 contrast-enhanced volume and the T2 hypointense lesion margin (T1/T2 mismatch) on standard MR

sequencing was significantly associated with radiation effect as opposed to tumor progression with a sensitivity and specificity of 83% and 91% [34]. Advanced MRI sequences including dynamic susceptibility-weighted contrast-enhanced MRI-produced metrics such as relative cerebral blood volume have been used to assess the microvascularity and permeability of brain tissue and have shown the ability to distinguish between necrosis and recurrence with high sensitivity and specificity in patients with suspected or pathologically confirmed tumor recurrence. These findings suggest that examination of cerebral blood volume ratios can predict for tumor recurrence [35-37]. Further research in this arena will likely contribute to better determination of imaging changes after radiation treatments. When recurrence of brain metastases is confirmed, surgery, radiosurgery, or WBRT may be considered to achieve disease control (see Variant 6). In addition to serial imaging, clinical assessment and toxicity management for patients treated for brain metastases are paramount, as delayed complications have been reported for patients as many as 10 years after treatment [38].

Summary of Recommendations

The issues regarding postirradiation management and retreatment of brain metastases revolve around several concerns:

- The need to assess the effects of and manage the sequelae of treatment.
- The need for appropriate surveillance and the ability to accurately distinguish late treatment effects from recurrence, so that further treatment can be administered as appropriately as possible.
- The goal of detecting recurrences prior to the onset of symptoms, when patients may best tolerate additional treatment, and when lesion size does not result in symptomatology or preclude the use of radiosurgery.
- The need to determine the most appropriate among the various management options based on patient characteristics and preferences, previous treatments employed, and potential risks and toxicities of treatment.

Summary of Evidence

Of the 38 references cited in the *ACR Appropriateness Criteria® Follow-up and Retreatment of Brain Metastases* document, 32 are categorized as therapeutic references including 8 well-designed studies and 19 good quality studies. Additionally, 6 references are categorized as diagnostic references including 1 good quality study, and 4 quality studies that may have design limitations. There are 6 references that may not be useful as primary evidence.

The 38 references cited in the *ACR Appropriateness Criteria® Follow-up and Retreatment of Brain Metastases* document were published between 2004–2013.

Most of the references are well-designed or good quality studies and provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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Clinical Condition: **Follow-up and Retreatment of Brain Metastases**

Variant 1: **70-year-old man with non–small-cell lung cancer status post lobectomy 3 years ago with a single brain metastasis 6 months ago treated with radiosurgery. Now with new contralateral metastasis in nondominant temporal lobe measuring 2 cm. No extracranial disease present. Mild neurologic symptoms. KPS 80.**

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	3	
SRS alone	8	Given the time interval, good KPS, small metastasis, and toxicity of WBRT, SRS alone would be appropriate.
Whole-Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	3	
30 Gy/10 fractions	7	
37.5 Gy/15 fractions	7	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	8	
Surgery and postop WBRT	7	Surgical intervention is felt to be slightly less appropriate due to advanced age and previous response to SRS.
Surgery and postop SRS	3	SRS may be 1–5 fractions. There is limited evidence supporting this combination.
Chemotherapy only	1	
Supportive care	1	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Follow-up and Retreatment of Brain Metastases**

Variant 2: **60-year-old man with renal cancer history, status post-surgical resection of 2 cerebellar metastases and postoperative WBRT (35 Gy in 14 fractions) 18 months ago. Now with new 3-cm left frontal metastasis without edema. KPS 90. No other signs of recurrence. No neurological symptoms.**

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	5	This treatment may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
SRS alone	8	
Whole-Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	1	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	5	SRS may be 1–5 fractions. Use of this treatment depends on cavity size postoperatively. Given the size (which would limit SRS dose in radioresistant tumor) and the fact that resection alone can have higher rates of local recurrence than SRS alone (see Kocher et al [7]), surgery and postoperative SRS may be appropriate. Additional consideration should be given for postoperative SRS if residual tumor is present in cavity.
Chemotherapy only	1	
Supportive care	1	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Follow-up and Retreatment of Brain Metastases**

Variant 3: **44-year-old woman with breast cancer (negative ER/PR, Her2neu receptors) and multiple brain metastases 9 months ago, status post WBRT (30 Gy in 10 fractions). Now with recurrence of 2 asymptomatic well-separated bilateral anterior frontal masses, 1–2 cm in diameter each. No extracranial disease present. KPS 80.**

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	2	
SRS alone	9	
Whole-Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	1	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	2	SRS may be 1–5 fractions.
Chemotherapy only	1	
Supportive care	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Follow-up and Retreatment of Brain Metastases**

Variant 4: **49-year-old woman with melanoma, status post WBRT (30 Gy in 10 fractions) for multiple metastases 6 months ago. Now with recurrence of one 3.5-cm right parietal metastasis with edema causing weakness. No extracranial disease present. KPS 70.**

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	9	
SRS alone	5	
Whole-Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	1	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	3	SRS may be 1–5 fractions.
Chemotherapy alone	1	
Supportive care	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Follow-up and Retreatment of Brain Metastases**

Variant 5: **73-year-old man with progressing metastatic lung cancer who was previously treated with whole brain radiation for multiple brain metastases 9 months earlier. Now with 3 new slightly symptomatic brain metastasis. KPS 50.**

Treatment	Rating	Comments
Local Therapy Alone		
Surgical resection alone	1	
SRS alone	2	Use of this treatment is size-dependent and also dependent on the patient's clinical response to steroids. SRS is generally not appropriate given low KPS and progressive systemic metastases.
Whole-Brain Radiotherapy (WBRT) Alone		
20 Gy/5 fractions	1	
25 Gy/10 fractions	2	
30 Gy/10 fractions	1	
37.5 Gy/15 fractions	1	
40 Gy/20 fractions	1	
Combined Therapy		
WBRT and SRS	1	
Surgery and postop WBRT	1	
Surgery and postop SRS	1	SRS may be 1–5 fractions.
Chemotherapy alone	2	
Supportive care	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 6: **Follow-up after treatment of brain metastases. No extracranial disease present. KPS 90. Follow-up for 1–2 years.**

Radiologic Procedure	Rating	Comments
Initial MRI head ≤3 months	8	
Subsequent MRI head every 3–6 months	8	
FDG-PET head only if MRI or CT abnormality suggests recurrence after radiosurgery or WBRT	5	Could consider this imaging modality to rule out possible tumor necrosis seen on MRI scans.
Subsequent MRI head when symptomatic on physical examination only	3	
Subsequent CT head every 4–6 months	2	
Subsequent FDG-PET head every 4–6 months	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		