ACR Appropriateness Criteria® Follow-up and Retreatment of Brain Metastases

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Abstract: Multiple options for retreatment are available, which include whole-brain radiation therapy, stereotactic radiosurgery, surgery, chemotherapy, and supportive care. Size, number, timing, location, histology, performance status, and extracranial disease status all need to be carefully considered when choosing a treatment modality. There are no randomized trials examining the retreatment of brain metastases. Repeat whole-brain radiation has been examined in a single-institution experience, showing the potential for clinical responses in selected patients. Local control rates as high as 91% using stereotactic radiosurgery for relapses after whole-brain radiation are reported. Surgery can be indicated in progressive and/or hemorrhagic lesions causing mass effect. The role of chemotherapy in the recurrent setting is limited but some agents may have activity on the basis of experiences on a smaller scale. Supportive care continues to be an important option, especially in those with a poor prognosis. Follow-up for brain metastases patients is discussed, examining the modality, frequency of imaging, and imaging options in differentiating treatment effect from recurrence. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of the current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Key Words: brain metastases, recurrence, appropriateness criteria, radiation therapy, radiosurgery

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SUMMARY OF LITERATURE REVIEW

Introduction/Background

Recent progress in the management of various metastatic cancers has led to the emergence of increasing numbers of patients 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 recent report on 177 patients with surgically staged IIIA non–small-cell lung cancer (NSCLC) found that 34% of them had cancer recurrence 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 to 7 mo; 2-year survival $\leq$10%). Survival rates for patients with brain metastases becomes significant only when extracranial disease is controlled, as pointed out by Tan and Black.[3]

There are now several reports of brain metastasis patients surviving >1 or 2 years after treatment,[4,5] and recently, a single-institution report from the Cleveland Clinic documented the incidence of 5- and 10-year survivors in a series of nearly 1300 patients with brain metastases. Thirty-two patients (2.5%) survived $\geq$5 y, and 15 of them had recurrence of local or distant brain cancer.[6] Thus, as a growing percentage of treated patients may live long enough to experience relapse 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 and the patient's performance status and extent of disease beyond the central nervous system. There seems 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.

Repeat WBRT

Repeat WBRT has not been routinely administered for retreatment after previous WBRT, primarily because of concerns about severe neurotoxicity. However, 1 institution recently reported a retrospective review of its database that involved 72 patients who underwent 2 courses of WBRT for brain metastases.[7] 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. An analysis of the time interval between initial treatment and retreatment with cranial irradiation and of patient age at diagnosis of brain metastases showed that these factors did not affect the survival time after repeat radiotherapy. However, a response to the first course of brain irradiation did significantly affect survival time after reirradiation to the brain. Although toxicity data were limited, this study suggests that there may be a role for WBRT in the retreatment of progressive brain metastases (Table 1).

TABLE 1. A 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 is 80

Treatment	Rating	Comments
Local therapy alone		
Surgical resection alone	3	
Stereotactic radiosurgery alone	6	
WBRT alone		
2000 cGy/5 fractions	3	
3000 cGy/10 fractions	7	
3750 cGy/15 fractions	7	
4000 cGy/20 fractions	1	
Combined therapy		
WBRT and radiosurgery	8	
Surgery and postoperative WBRT	7	Surgical intervention felt to be slightly less appropriate due to advanced age and previous response to radiosurgery
Surgery and postoperative radiosurgery	3	Limited evidence supporting 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.

KPS indicates Karnofsky performance status; WBRT, whole-brain radiation therapy.

Radiosurgery

Radiosurgery for recurrent brain metastases is a viable option if size and number permit. In patients undergoing radiosurgery for recurrence after initial WBRT, Noel et al and Chao et al reported 1-year local control rates of 91% and 68% and 2-year rates of 84% and 58%, respectively.[8,9] Good local control, as high as 90%, has been reported in patients who underwent repeat gamma knife SRS to previously treated or newly developed sites, but risk for radiation necrosis increased with repeat treatments to same areas.[10] Radiographic responses after salvage radiosurgery have been well documented, although evidence for a survival benefit is not strong.[11] This modality is increasingly available at many centers. Moreover, a recent review of 10 series totaling 363 patients treated with surgical excision, followed by radiosurgery as an alternative to WBRT showed crude local control rates of about 79%, with a median survival time of 14.2 months and a 52% rate of new metastasis after SRS.[12] In this cohort, SRS was well tolerated with low rates of necrosis. These data suggest that SRS is one valid approach in managing patients having brain relapses even after prior WBRT and especially if no more than 3 metastatic foci are present (Tables 2, 3).

Surgery

Surgery may be indicated for palliation of mass effect from progressive or hemorrhagic brain metastases,[13] and may also be an important diagnosis 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, Karnofsky performance status >60, and stable or absent extracranial disease.[14] Crude reported local control rates range from 69% to 79%,[13–15] and 1 retrospective study comparing resection to no resection showed a modest survival benefit.[14]

Chemotherapy

Chemotherapy has occasionally been a successful strategy for chemosensitive tumors.[16] Limited evidence suggests that some chemotherapy and biological treatments may be effective in brain metastases. These studies, which are based on smaller experiences, are summarized here. The chemotherapy agents include paclitaxel, cisplatin, carboplatin, docetaxel, etoposide, and topotecan.[17] Temozolomide, capecitabine, and gefitinib have also been reported to be used in treating brain metastases from melanoma, breast cancer, and lung cancer, respectively.[18] The response of brain metastases to antiepidermal growth factor inhibitors such as gefitinib or erlotinib provides some new alternatives for the management of brain metastases.[19] 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.[20] Recent evidence also

TABLE 2. A 60-year-old Man With Renal Cancer History, Status Postsurgical 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 is 90. No Other Signs of Recurrence. No Neurological Symptoms

Treatment	Rating	Comments
Local therapy alone		
Surgical resection alone	8	
Stereotactic radiosurgery alone	8	
WBRT alone		
2000 cGy/5 fractions	1	
3000 cGy/10 fractions	1	
3750 cGy/15 fractions	1	
4000 cGy/20 fractions	1	
Combined therapy		
WBRT and radiosurgery	1	
Surgery and postoperative WBRT	1	
Surgery and postoperative radiosurgery	3	Would reserve SRS for future relapse. Recommend close imaging studies for surveillance
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.

KPS indicates Karnofsky performance status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

TABLE 3. A 44-year-old Woman With Breast Cancer (Negative Estrogen Receptor/Progesterone Receptor, Her2neu Receptors) and Multiple Brain Metastases 9 Months Ago, Status Post WBRT (3000 cGy in 10 Fractions). Now with Recurrence of 2 Asymptomatic Bilateral Anterior Frontal Masses, 1-2 cm in Diameter each. No Extracranial Disease Present. KPS is 80

Treatment	Rating	Comments
Local therapy alone		
Surgical resection alone	2	
SRS alone	9	
WBRT alone		
2000 cGy/5 fractions	1	
3000 cGy/10 fractions	1	
3750 cGy/15 fractions	1	
4000 cGy/20 fractions	1	
Combined therapy		
WBRT and radiosurgery	1	
Surgery and postoperative WBRT	1	
Surgery and postoperative radiosurgery	2	
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.

KPS indicates Karnofsky performance status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

suggests that bevacizumab may be safe and effective in patients with active brain metastasis from NSCLC.[21]

Supportive Care

Best supportive care 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 best supportive care considering their reduced survival rates.

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[22] reported a median time of 8.8 months to new metastasis after initial gamma knife radiosurgery. They recommended close surveillance with a 3-month interval between magnetic resonance imaging (MRI), for identifying new metastasis early in order to facilitate the most effective treatment. They found that patients with 3 or more lesions and cancer histologies other than NSCLC were more likely to have additional future metastasis. These patients may benefit most from close surveillance and additional treatments. The most appropriate frequency and choice of imaging modality after treatment of a patient with brain metastases are matters of debate. Given its wide availability in this country and superior sensitivity over computed tomography, MRI is the preferred imaging modality, especially with newer applications such as spectroscopy, diffusion-weighted imaging, and perfusion-weighted imaging. It is an expensive option, however, and its frequency of use should depend on the likelihood of obtaining useful information that is not otherwise available and that could be acted upon for the patient's benefit.

TABLE 4. Follow-up After Treatment of Brain Metastases. (Assuming that Treatment was Carried Out as Planned in Prior Variants, What is the Frequency and Modality of Imaging in Combination with a Physical Examination?) No Extracranial Disease present. KPS is 90. Follow-up for the First Year

Radiologic Procedure	Rating	Comments
Initial MRI head $\leq$3 mo	8	
Subsequent MRI head every 4-6 mo	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 mo	2	
Subsequent FDG-PET head every 4-6 mo	1	

Rating Scale: 1, 2, 3 usually not appropriate; 4, 5, 6 may be appropriate; 7, 8, 9 usually appropriate.

CT indicates computed tomography; FDG-PET, fluorine-18 fluorodeoxyglucose-positron emission tomography; KPS, Karnofsky performance status; MRI, magnetic resonance imaging.

A not uncommon problem after the treatment of brain metastases is the difficulty of differentiating between tumor recurrence and radiation-induced scar tissue or necrosis. This is particularly vexing in asymptomatic patients with a high performance status. Although invasive pathologic evaluation remains the only definitive test to make this distinction, it is not always practical or feasible. In an attempt to address this problem, several imaging modalities have been investigated, with most data advocating fluorine-18 fluorodeoxyglucose (FDG) and carbon-11 methyl methionine positron emission tomography (PET) scanning for this purpose.[23–25] Ross et al[26] reported on the imaging changes after SRS and found that 22% of 35 metastatic tumors appeared larger on MRI at a mean of 10 weeks after SRS. Eleven had FDG-PET performed for enlarging lesions. Eight of them showed increased brain activity, whereas 3 showed decreased activity. Of the 8, however, 6 were incorrectly predicted on the basis of the patient's subsequent course (alive, mean follow-up of 27 mo). A later study showed that FDG-PET imaging is especially effective in detecting tumor recurrence compared with radiation changes in patients with brain metastases from lung cancer.[25] In addition to the previously mentioned imaging studies, dynamic susceptibility-weighted contrast-enhanced MRI has been suggested to improve the prediction of tumor response after treatment for brain metastases and help distinguish between necrosis or recurrence.[27] These findings suggest that examination of cerebral blood volume ratios can predict tumor recurrence.[28,29] Further research in this arena will likely contribute to better determination of imaging changes after radiation treatments. When recurrence of brain metastasis is confirmed, surgery, and particularly radiosurgery, may be useful in improving disease control (Table 4).[9,30–33]

Summary

The issues regarding postirradiation management and retreatment of brain metastases revolve around 3 concerns:

- First is the need to assess the effects of and manage the treatment of sequelae.
- Second is 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.
- Third is the goal of detecting recurrences before the onset of symptoms, when patients may best tolerate additional treatment, and when the lesion size does not preclude the use of radiosurgery, arguably the most effective option.

REFERENCES

1. Mehta MP, Patel RR. Radiotherapy and radiosurgery for brain metastases. In: Black PM, Loeffler JS., eds. *Cancer of the Nervous System*. 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2005:657–672.
2. Mamon HJ, Yeap BY, Janne PA, et al. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol*. 2005;23:1530–1537.
3. Tan TC, Black PM. Surgery for brain metastases. In: Black PM, Loeffler JS, eds. *Cancer of the Nervous System*. 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2005: 645–656.
4. Pollock BE, Brown PD, Foote RL, et al. Properly selected patients with multiple brain metastases may benefit from aggressive treatment of their intracranial disease. *J Neurooncol*. 2003;61: 73–80.
5. Varlotto JM, Flickinger JC, Niranjan A, et al. Analysis of tumor control and toxicity in patients who have survived at least one year after radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2003;57:452–464.
6. Chao ST, Barnett GH, Liu SW, et al. Five-year survivors of brain metastases: a single-institution report of 32 patients. *Int J Radiat Oncol Biol Phys*. 2006;66:801–809.
7. Sadikov E, Bezjak A, Yi QL, et al. Value of whole brain re-irradiation for brain metastases—single centre experience. *Clin Oncol (R Coll Radiol)*. 2007;19:532–538.
8. Chao ST, Barnett GH, Vogelbaum MA, et al. Salvage stereotactic radiosurgery effectively treats recurrences from whole-brain radiation therapy. *Cancer*. 2008;113:2198–2204.
9. Noel G, Medioni J, Valery CA, et al. Three irradiation treatment options including radiosurgery for brain metastases from primary lung cancer. *Lung Cancer*. 2003;41:333–343.
10. Kwon KY, Kong DS, Lee JI, et al. Outcome of repeated radiosurgery for recurrent metastatic brain tumors. *Clin Neurol Neurosurg*. 2007;109:132–137.
11. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2005;63:37–46.
12. Roberge D, Souhami L. Tumor bed radiosurgery following resection of brain metastases: a review. *Technol Cancer Res Treat*. 2010;9:597–602.
13. Vecil GG, Suki D, Maldaun MV, et al. Resection of brain metastases previously treated with stereotactic radiosurgery. *J Neurosurg*. 2005;102:209–215.
14. Truong MT St, Clair EG, Donahue BR, et al. Results of surgical resection for progression of brain metastases previously treated by gamma knife radiosurgery. *Neurosurgery*. 2006;59:86–97; discussion 86–97.
15. Kano H, Kondziolka D, Zorro O, et al. The results of resection after stereotactic radiosurgery for brain metastases. *J Neurosurg*. 2009;111:825–831.
16. Schuette W. Treatment of brain metastases from lung cancer: chemotherapy. *Lung Cancer*. 2004;45(Suppl 2): S253–S257.
17. Wong ET, Berkenblit A. The role of topotecan in the treatment of brain metastases. *Oncologist*. 2004;9:68–79.
18. Kopf B, De Giorgi U, Zago S, et al. Innovative therapy for patients with brain metastases: oral treatments. *J Chemother*. 2004; 16(suppl 5):94–97.
19. Hotta K, Kiura K, Ueoka H, et al. Effect of gefitinib ("Iressa", ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2004;46:255–261.
20. Sutherland S, Ashley S, Miles D, et al. Treatment of HER2-positive metastatic breast cancer with lapatinib and capecitabine in the lapatinib expanded access programme, including efficacy in brain metastases—the UK experience. *Br J Cancer*. 2010;102: 995–1002.
21. De Braganca KC, Janjigian YY, Azzoli CG, et al. Efficacy and safety of bevacizumab in active brain metastases from non-small cell lung cancer. *J Neurooncol*. 2010;100:443–447.
22. Sheehan JP, Yen CP, Nguyen J, et al. Timing and risk factors for new brain metastasis formation in patients initially treated only with Gamma Knife surgery. Clinical article. *J Neurosurg*. 2011; 114:763–768.
23. Belohlavek O, Simonova G, Kantorova I, et al. Brain metastases after stereotactic radiosurgery using the Leksell gamma knife: can FDG PET help to differentiate radionecrosis from tumour progression? *Eur J Nucl Med Mol Imaging*. 2003;30:96–100.
24. Tsuyuguchi N, Sunada I, Iwai Y, et al. Methionine positron emission tomography of recurrent metastatic brain tumor and radiation necrosis after stereotactic radiosurgery: is a differential diagnosis possible? *J Neurosurg*. 2003;98:1056–1064.
25. Wang SX, Boethius J, Ericson K. FDG-PET on irradiated brain tumor: ten years' summary. *Acta Radiol*. 2006;47:85–90.
26. Ross DA, Sandler HM, Balter JM, et al. Imaging changes after stereotactic radiosurgery of primary and secondary malignant brain tumors. *J Neurooncol*. 2002;56:175–181.

27. Essig M, Waschkies M, Wenz F, et al. Assessment of brain metastases with dynamic susceptibility-weighted contrast-enhanced MR imaging: initial results. *Radiology*. 2003;228: 193–199.
28. Hoefnagels FW, Lagerwaard FJ, Sanchez E, et al. Radiological progression of cerebral metastases after radiosurgery: assessment of perfusion MRI for differentiating between necrosis and recurrence. *J Neurol*. 2009;256:878–887.
29. Mitsuya K, Nakasu Y, Horiguchi S, et al. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. *J Neurooncol*. 2010;99: 81–88.
30. Kamath R, Ryken TC, Meeks SL, et al. Initial clinical experience with frameless radiosurgery for patients with intracranial metastases. *Int J Radiat Oncol Biol Phys*. 2005;61:1467–1472.
31. Koutras AK, Marangos M, Kourelis T, et al. Surgical management of cerebral metastases from non-small cell lung cancer. *Tumori*. 2003;89:292–297.
32. Noel G, Proudhom MA, Valery CA, et al. Radiosurgery for re-irradiation of brain metastasis: results in 54 patients. *Radiother Oncol*. 2001;60:61–67.
33. Sheehan J, Kondziolka D, Flickinger J, et al. Radiosurgery for patients with recurrent small cell lung carcinoma metastatic to the brain: outcomes and prognostic factors. *J Neurosurg*. 2005; 102(suppl):247–254.