

## American College of Radiology ACR Appropriateness Criteria®

### MULTIPLE BRAIN METASTASES

Expert Panel on Radiation Oncology–Brain Metastases: Gregory M. M. Videtic, MD<sup>1</sup>; Elizabeth M. Gore, MD<sup>2</sup>; Jeffrey D. Bradley, MD<sup>3</sup>; Laurie E. Gaspar, MD, MBA<sup>4</sup>; Isabelle Germano, MD<sup>5</sup>; Paiman Ghafoori, MD<sup>6</sup>; Mark A. Henderson, MD<sup>7</sup>; Stephen T. Lutz, MD<sup>8</sup>; Michael W. McDermott, MD<sup>9</sup>; Roy A. Patchell, MD<sup>10</sup>; Samir H. Patel, MD<sup>11</sup>; H. Ian Robins, MD, PhD<sup>12</sup>; Andrew D. Vassil, MD<sup>13</sup>; Franz J. Wippold II, MD.<sup>14</sup>

#### **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 15% of cancer patients, particularly those with lung cancer, breast cancer, and melanoma, who account for 39%, 17%, and 11%, respectively, of patients with brain metastases [2].

Clinical [2], imaging [3], and autopsy [4] series have shown that about half of brain metastases will be solitary and half will be multiple. Solitary metastatic disease refers to one metastasis to the brain in the setting of *no other* extracranial metastatic disease. Single (or singular) metastatic disease refers to one metastasis in the brain in the setting of metastatic disease elsewhere in the body. Multiple metastases refers to multiple lesions in the brain, with some clinicians distinguishing two or three metastases as being more favorable than a higher number. Renal cell and prostate cancer are more likely to manifest a solitary metastasis [2,4], whereas melanoma is more prone to develop multiple metastases [4]. Among patients with multiple lesions, 70% are supratentorial, 26% are supratentorial and cerebellar, 3% are cerebellar, and 1% are located in the brainstem [2]. 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 [2].

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 (available at: [http://www.ctu.mrc.ac.uk/research\\_areas/study\\_details.aspx?s=27](http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=27)). 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 reproducibly in the 4- to 6-month range. Certain clinical prognostic factors are associated with a better or worse outcome. For instance, patients younger than 65 years of age whose Karnofsky performance status (KPS) is  $\geq 70$  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 [5]. Sperduto et al [6] have proposed a new prognostic index for brain metastases patients. They compared it to three other indices — including the Radiation Therapy Oncology Group (RTOG®) recursive partitioning analysis (RPA) classification for such patients — and found it to be the least subjective and most quantitative. In a more recent analysis, Sperduto et al [7] carried out a retrospective analysis of 5,067 brain metastases patients and found that prognosis factors varied by diagnosis, and this resulted in a disease-specific classification of outcomes. Imaging prognostic factors, such as the number of metastases, presence of midline shift, and post-WBRT response, can also influence outcome [8,9].

##### **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.

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These regimens include 1000 cGy in 1 fraction (1000/1), 1200/2, 1800/3, 2000/5, 3000/10, 3600/6, 4000/20, 4000/20 (200 cGy twice daily [BID]), 5000/20, and 5440/34 (160 cGy BID) [10-17]. While 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 [18].

In selecting treatment regimens appropriate for individual patients, clinicians should consider the RTOG<sup>®</sup> RPA brain metastasis classification [5], which supports short-course treatment in poor-risk patients, (ie, poor performance status, elderly, progressive systemic disease.) (See [Variant 1](#).)

In a recently published trial for patients with one to three brain metastases carried out by the RTOG<sup>®</sup>, 3750 cGy in 15 fractions WBRT (ie, 250 cGy per fraction) was used as the standard treatment arm [19] 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 [20]. However, this 1989 retrospective report of dementia in 12 patients with long survival [20] has been highly criticized for its reported radiation total doses and fractionation schemes. Contemporary prospective data have been critical in defining the safety and appropriateness of conventional WBRT. (See [Variant 2](#).)

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) [21]. Impairment was found in >90% of patients at baseline, and the results suggested that only tumor control correlated with NCF [22], suggesting a potential benefit if WBRT conveys more tumor control [23]. Further substantiating the neurocognitive benefits of WBRT was an analysis of the 208 patients in the control arm of this trial [20] which looked at the relationship between NCF and tumor volume regression. Li et al [24] 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 adversely affected NCF more than WBRT dose.

Even though it is common for patients with multiple brain metastases to have active primary and other systemic metastatic disease, progression of brain disease is the cause of death in about half of these patients (range, 26%-70%) [10,12,15].

### **WBRT and Drug Therapies**

Various radiation sensitizers have been added to WBRT without a demonstrated improvement in survival, including lonidamine [25], misonidazole [26], bromodeoxyuridine [27], and the nitrosourea ACNU, either alone or with fluorouracil [28]. The addition of biological modifiers such as efaproxiral [29] and MGd

[21] has not demonstrated survival benefits. A subgroup analysis of the interval to investigator-determined neurologic progression and the interval to neurocognitive progression [21] suggested a trend towards prolongation of time to neurological progression with the early use of MGd, but this finding was not borne out in the overall study population [30]. Phase III studies with biological agents melatonin [31] and thalidomide [32] likewise showed no improvement in overall survival. 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 [28,33,34], chemotherapy with or without concurrent WBRT [35,36], concurrent versus delayed WBRT [37], and chemotherapy followed by WBRT versus WBRT followed by chemotherapy [38].

### **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 [2,39,40], 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 one to three brain metastases showed that WBRT reduced local relapse and neurologic death but did not improve the duration of functional independence or overall survival [41].

Pollock et al [42] used the RTOG<sup>®</sup> 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. Iwamoto et al [43] 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 [44] reported a small randomized trial in which 27 patients with two to four brain metastases  $\leq$ 25 mm in diameter received WBRT alone or with an SRS boost. Local control at 1 year was 92% with SRS versus 0% without SRS. Median survival time was also better with SRS (11 months vs 7.5 months).

RTOG<sup>®</sup> has published the results of its phase III trial (9508) in which 333 patients with one to three brain metastases were randomized to WBRT with or without SRS boost [19]. 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 vs 4.9 months,  $P=0.0393$ ) but not for patients with multiple metastases. Post-hoc subset analysis

suggested a survival benefit with the addition of SRS for RTOG<sup>®</sup> RPA class 1 patients and those with squamous non-small-cell lung cancer histology. Additionally, an improved KPS and decreasing need for steroids were noted in patients treated with WBRT plus SRS, suggesting a role for SRS in select patients with two to three brain metastases. (See [Variant 3](#).)

Aoyama et al [45] recently reported on a study of 132 patients with one to four 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 two or more brain metastases, clinicians need to practice careful selection of patients for this intervention. The RTOG<sup>®</sup> RPA brain metastasis classification may prove useful in making this selection [5]. (See [Variant 4](#).)

A recently reported phase III neurocognition study by Chang et al [46] of SRS compared to SRS plus WBRT for patients with one to three 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 and also 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 vs 5.7 months, 63% vs 21%; P=0.003), remain controversial. (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 from progressive brain disease.
- 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, as demonstrated in the Aoyama et al trial [45].
- 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 functioning before and after treatment as a standard component of the patient's assessment.

### Supporting Document(s)

- [ACR Appropriateness Criteria<sup>®</sup> Overview](#)
- [Evidence Table](#)

### References

1. Posner JB. Management of brain metastases. *Rev Neurol (Paris)* 1992; 148(6-7):477-487.
2. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer* 1996; 78(8):1781-1788.
3. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. *Arch Neurol* 1988; 45(7):741-744.
4. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. *Adv Neurol* 1978; 19:579-592.
5. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997; 37(4):745-751.
6. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 2008; 70(2):510-514.
7. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys* 2010; 77(3):655-661.
8. Nieder C, Berberich W, Schnabel K. Tumor-related prognostic factors for remission of brain metastases after radiotherapy. *Int J Radiat Oncol Biol Phys* 1997; 39(1):25-30.
9. Swift PS, Phillips T, Martz K, et al. CT characteristics of patients with brain metastases treated in RTOG study 79-16. *Int J Radiat Oncol Biol Phys* 1993; 25(2):209-214.
10. Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; 7(12):1633-1638.
11. Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase. *Strahlenther Onkol* 1994; 170(3):155-161.
12. Chatani M, Teshima T, Hata K, Inoue T. Prognostic factors in patients with brain metastases from lung carcinoma. *Strahlenther Onkol* 1986; 162(3):157-161.
13. Haie-Meder C, Pellae-Cosset B, Laplanche A, et al. Results of a randomized clinical trial comparing two radiation schedules in the palliative treatment of brain metastases. *Radiother Oncol* 1993; 26(2):111-116.
14. Harwood AR, Simson WJ. Radiation therapy of cerebral metastases: a randomized prospective clinical trial. *Int J Radiat Oncol Biol Phys* 1977; 2(11-12):1091-1094.
15. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; 7(7):891-895.
16. Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. *Int J Radiat Oncol Biol Phys* 1997; 39(3):571-574.
17. Davey P, Hoegler D, Ennis M, Smith J. A phase III study of accelerated versus conventional hypofractionated whole brain irradiation in patients of good performance status with brain metastases not suitable for surgical excision. *Radiother Oncol* 2008; 88(2):173-176.

18. Millender L, Wara W. Palliative care. In: Hansen EK, Roach M, eds. *Handbook of evidence-based radiation oncology*. New York, NY: Springer; 2007:xi, 536 p.
19. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; 363(9422):1665-1672.
20. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology* 1989; 39(6):789-796.
21. Mehta MP, Rodrigus P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol* 2003; 21(13):2529-2536.
22. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol* 2004; 22(1):157-165.
23. Brown PD, Asher AL, Farace E. Adjuvant whole brain radiotherapy: strong emotions decide but rational studies are needed. *Int J Radiat Oncol Biol Phys* 2008; 70(5):1305-1309.
24. Li J, Bentzen SM, Li J, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys* 2008; 71(1):64-70.
25. DeAngelis LM, Currie VE, Kim JH, et al. The combined use of radiation therapy and lornidamine in the treatment of brain metastases. *J Neurooncol* 1989; 7(3):241-247.
26. Komarnicky LT, Phillips TL, Martz K, Asbell S, Isaacson S, Urtasun R. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). *Int J Radiat Oncol Biol Phys* 1991; 20(1):53-58.
27. Phillips TL, Scott CB, Leibel SA, Rotman M, Weigensberg JJ. Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. *Int J Radiat Oncol Biol Phys* 1995; 33(2):339-348.
28. Ushio Y, Arita N, Hayakawa T, et al. Chemotherapy of brain metastases from lung carcinoma: a controlled randomized study. *Neurosurgery* 1991; 28(2):201-205.
29. Suh JH, Stea B, Nabid A, et al. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. *J Clin Oncol* 2006; 24(1):106-114.
30. Mehta MP, Shapiro WR, Phan SC, et al. Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients with brain metastases: results of a phase III trial. *Int J Radiat Oncol Biol Phys* 2009; 73(4):1069-1076.
31. Berk L, Berkey B, Rich T, et al. Randomized phase II trial of high-dose melatonin and radiation therapy for RPA class 2 patients with brain metastases (RTOG 0119). *Int J Radiat Oncol Biol Phys* 2007; 68(3):852-857.
32. Knisely JP, Berkey B, Chakravarti A, et al. A phase III study of conventional radiation therapy plus thalidomide versus conventional radiation therapy for multiple brain metastases (RTOG 0118). *Int J Radiat Oncol Biol Phys* 2008; 71(1):79-86.
33. Neuhaus T, Ko Y, Muller RP, et al. A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. *Br J Cancer* 2009; 100(2):291-297.
34. Guerrieri M, Wong K, Ryan G, Millward M, Quong G, Ball DL. A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of the lung. *Lung Cancer* 2004; 46(1):107-111.
35. Mornex F, Thomas L, Mohr P, et al. A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Res* 2003; 13(1):97-103.
36. Postmus PE, Haaxma-Reiche H, Smit EF, et al. Treatment of brain metastases of small-cell lung cancer: comparing teniposide and teniposide with whole-brain radiotherapy--a phase III study of the European Organization for the Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol* 2000; 18(19):3400-3408.
37. Robinet G, Thomas P, Breton JL, et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-Cancerologie (GFPC) Protocol 95-1. *Ann Oncol* 2001; 12(1):59-67.
38. Lee DH, Han JY, Kim HT, et al. Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first : result of a randomized pilot study. *Cancer* 2008; 113(1):143-149.
39. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. *J Neurosurg* 1993; 79(2):210-216.
40. Bindal AK, Bindal RK, Hess KR, et al. Surgery versus radiosurgery in the treatment of brain metastasis. *J Neurosurg* 1996; 84(5):748-754.
41. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011; 29(2):134-141.
42. Pollock BE, Brown PD, Foote RL, Stafford SL, Schomberg PJ. Properly selected patients with multiple brain metastases may benefit from aggressive treatment of their intracranial disease. *J Neurooncol* 2003; 61(1):73-80.
43. Iwadate Y, Namba H, Yamaura A. Significance of surgical resection for the treatment of multiple brain metastases. *Anticancer Res* 2000; 20(1B):573-577.
44. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999; 45(2):427-434.
45. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006; 295(21):2483-2491.
46. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; 10(11):1037-1044.

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 four 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
<b>Whole Brain Radiotherapy (WBRT) Alone</b>		
2000 cGy/5 fractions	8	Poor KPS, active extracranial disease, no evidence of dose benefit with respect to symptom control. Longer treatment schedules are difficult to justify in such a patient.
3000 cGy/10 fractions	8	
3750 cGy/15 fractions	6	
4000 cGy/20 fractions	2	
<b>Stereotactic Radiosurgery (SRS)</b>		
SRS alone	2	SRS as a component of therapy is not recommended in view of patient and disease status, without evidence to support benefit.
SRS + WBRT	2	
<b>Surgery Alone</b>		
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	
<b>Radiosensitizer</b>		
Radiosensitizer + WBRT	1	No evidence for any benefit. Can only be done in trial setting.
Observation	6	Not unreasonable given status of patient. Requires best supportive care with optimized medical management.
<b>Rating Scale:</b> 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 six newly diagnosed, asymptomatic, supratentorial brain metastases on MRI (three surgically accessible, three inaccessible). KPS 90. Primary completely resected (T2 N0 adenocarcinoma of lung). No other systemic metastases present.

Treatment	Rating	Comments
<b>Whole Brain Radiotherapy (WBRT) Alone</b>		
2000 cGy/5 fractions	4	
3000 cGy/10 fractions	8	The number of brain metastases in this patient strongly support use of WBRT only. Schedule choice may depend on KPS, although randomized evidence to date does not favor one schedule over others.
3750 cGy/15 fractions	8	
4000 cGy/20 fractions	2	
<b>Stereotactic Radiosurgery (SRS)</b>		
SRS alone	1	Number of lesions and absence of evidence do not support SRS in this patient.
SRS + WBRT	2	
<b>Surgery Alone</b>		
Excise dominant lesion(s)	1	Number of lesions, absence of focal symptoms, and absence of evidence do not support surgery in this patient.
Excise all lesions	1	
<b>Radiosensitizer</b>		
Radiosensitizer + WBRT	1	No evidence for any role. Should only be done in trial setting.
Observation	1	Patient's lack of symptoms and high KPS would preclude this option.
<b>Rating Scale:</b> 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 two newly diagnosed, surgically accessible, supratentorial brain metastases on MRI. KPS 90. One brain metastasis 3 cm in maximum diameter in right frontal area. Other one <1 cm in maximum diameter in lateral cerebellum. No hydrocephalus. Primary completely resected 6 months ago (T2 N0 adenocarcinoma of lung). No other systemic metastases.

Treatment	Rating	Comments
<b>Whole Brain Radiotherapy (WBRT) Alone</b> 2000 cGy/5 fractions	3	
3000 cGy/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.
3750 cGy/15 fractions	7	
4000 cGy/20 fractions	3	
<b>Stereotactic Radiosurgery (SRS)</b> 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.
<b>Surgery Alone</b> Excise dominant lesion(s)	2	Surgery offers no clear benefit in this scenario, given absence of symptoms and multiplicity lesions.
Excise all lesions	1	
<b>Radiosensitizer</b> Radiosensitizer + WBRT	1	No evidence for any role. Can only be done in trial setting.
Observation	1	KPS would preclude this option.
<b>Rating Scale:</b> 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 two 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 measuring 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
<b>Whole Brain Radiotherapy (WBRT) Alone</b>		
2000 cGy/5 fractions	3	
3000 cGy/10 fractions	7	Active extracranial disease at the time of diagnosis of brain metastases. However, age and high KPS may suggest optimizing local brain control with other modalities like SRS.
3750 cGy/15 fractions	7	
4000 cGy/20 fractions	3	
<b>Stereotactic Radiosurgery (SRS)</b>		
SRS alone	6	There is some controversy about indication for SRS alone in a patient with two 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 judged to be an important component in overall brain and lesional control when SRS is to be used.
<b>Surgery Alone</b>		
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 lesional control require addition of WBRT.
<b>Radiosensitizer</b>		
Radiosensitizer + WBRT	1	No evidence for any role. Should only be done in trial setting.
Observation	1	
<b>Rating Scale:</b> 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 two newly diagnosed, asymptomatic, surgically accessible, supratentorial brain metastases <3 cm in size on MRI. KPS 100. Status post wide local excision of Clark's level IV melanoma 1 month ago. No other metastases.

Treatment	Rating	Comments
<b>Whole Brain Radiotherapy (WBRT) Alone</b>		
2000 cGy/5 fractions	2	
3000 cGy/10 fractions	5	Use of WBRT alone in a patient with two melanoma brain metastases is felt by many to be insufficient therapy.
3750 cGy/15 fractions	5	
4000 cGy/20 fractions	2	
<b>Stereotactic Radiosurgery (SRS)</b>		
SRS alone	7	
SRS + WBRT	8	The role of WBRT addition to SRS in the management of a few melanoma brain metastases is controversial given 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.
<b>Surgery Alone</b>		
Excise dominant lesion(s)	2	Since patient's metastases are asymptomatic, there is no need to take surgical risks.
Excise all lesions	2	
<b>Radiosensitizer</b>		
Radiosensitizer + WBRT	1	No evidence for any role. Can only be done in trial setting.
Observation	1	
<b>Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate</b>		