American Radium Society™ Appropriate Use Criteria: Neurocognition after stereotactic radiosurgery for multiple brain metastases

Expert Panel on Brain Malignancies

Michael T. Milano, MD PhD 1, Veronica L.S. Chiang, MD 2, Scott G. Soltys, MD 3, Tony J. C. Wang, MD 4, Simon S. Lo, MD 5, Alexandria Brackett, MA MLIS 6, Seema Nagpal, MD 7, Samuel Chao, MD 8, Amit Kumar Garg, MD 9, Siavash Jabbari, MD 10, Lia M. Halasz, MD 5, Melanie Hayden Gephart, MD, MAS 11, Jonathan P. S. Knisely, MD 12, Arjun Sahgal, MD 13, Eric L. Chang, MD 14

1 Department of Radiation Oncology, University of Rochester
2 Department of Neurosurgery, Yale School of Medicine, Yale University
3 Department of Radiation Oncology, Stanford University Medical Center
4 Department of Radiation Oncology, Columbia University Irving Medical Center
5 Department of Radiation Oncology, University of Washington
6 Cushing/Whitney Medical Library, Yale School of Medicine, Yale University
7 Department of Neurology, Stanford University School of Medicine
8 Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic
9 Department of Radiation Oncology, University of Texas MD Anderson Cancer Center
10 Department of Radiation Oncology, Sharp Healthcare
11 Department of Radiation Oncology, Stanford University School of Medicine
12 Department of Radiation Oncology, Weill Cornell Medicine, Cornell University
13 Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto
14 Department of Radiation Oncology, University of Southern California

Conflict of Interest Disclosure Statement

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity.

The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work.

Disclosures potentially relevant to the content of this guideline are provided.

- MT M: Galera Therapeutics (Honorarium); Wolters Kluwer (Royalties)
- VLSC: BrainLab (Speaker/Honoraria); Monteris Medical Inc (Consultant/Advisory Board); MRInterventions (Consultant/Advisory Board)
- SGS: Inovio Pharmaceuticals (Consultant), Novocure (Research Support)
- TJW: AbbVie (Consultant/Advisory Board, Research Support); AstraZeneca (Consultant/Advisory Board); Cancer Panels (Consultant/Advisory Board, Speaker/Honoraria); Doximity (Consultant/Advisory Board, Ownership Interest); Elekta (Consultant/Advisory Board, Speaker/Honoraria); Merck (Research Support); Novocure (Consultant/Advisory Board, Speaker/Honoraria); RTOG Foundation (Research Support); Wolters Kluwer (Royalties)
- SSL: Elekta AB (Member, Elekta Gamma Knife ICON Expert Group; Research Support)
- AB: none
- MHG: none
- SN: none
- SJ: none
- LMH: Abbvie (Research Grant)
- SC: Varian Medical Systems (Speaker/Honoraria)
- AKG: none
- JPSK: none
- AS: Advisor/consultant with Abbvie, Merck, Roche, Varian (Medical Advisory Group), Elekta (Gamma Knife Icon), BrainLAB, and VieCure (Medical Advisory Board); Board Member: International Stereotactic Radiosurgery Society (ISRS); Past educational seminars with Elekta AB, Varian (CNS Teaching Faculty), BrainLAB, Medtronic Kyphon; Research grant with Elekta AB; Travel accommodations/expenses by Elekta, Varian, BrainLAB; Belongs to Elekta MR LINAC Research Consortium, Elekta Spine, Oligometastases and LINAC-Based SRS Consortia
Acknowledgements
ARS Appropriate Use Criteria Steering Committee; Andrea Taylor of ARS; Niki Kozak as patient commenter/reviewer

Methodology
An analysis of the medical literature from peer-reviewed journals was conducted from January 1, 1991 to May 20, 2018 (the date of the literature search) using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [1] guidelines to search the OVID Medline, OVID Embase, Web of Science, PubMed, and Cochrane databases to retrieve a comprehensive set of relevant articles. The search strategy was developed based on National Library of Medicine® Medical Subject Headings (MeSH®) with addition of subject-specific keywords. A clinical librarian (Brackett) developed the search strategy after a consultation with Chiang. Brackett received three articles of interest [2-4] that helped formulate the search strategy used with the Yale MeSH Analyzer [5]; these articles along with 20 others were later used to validate the search. The search strategy was then peer-reviewed by another senior librarian. The search strategy used both keywords and controlled vocabulary combining the terms for radiotherapy, brain metastatic tumor, and neurocognition.

The final search found a total of 18,391 records with 11,614 original articles. These results were exported into EndNote, where they were de-duplicated. To exclude studies which were not relevant, the bibliographies of full articles were initially reviewed by Chiang in EndNote, before being screened by in Covidence by Milano, Chang, and Soltys. After initial screening, the articles were divided amongst panel members for dual-screening. The authors screened the methods and results, selecting those studies which could address any of the following key questions:

- KQ1: Is there an advantage or detriment, with respect to neurocognitive and/or QOL outcomes, to treating 2-4 metastases with stereotactic radiosurgery alone versus whole brain radiotherapy alone?
- KQ2: Is there an advantage or detriment, with respect to neurocognitive and/or QOL outcomes, to treating 5 or more metastases with stereotactic radiosurgery alone versus whole brain radiotherapy alone?
- KQ3: After stereotactic radiosurgery alone for multiple brain metastases, what is the impact of brain metastases number on neurocognitive function?
- KQ4: After stereotactic radiosurgery alone for multiple brain metastases, what is the impact of net brain metastases volume on neurocognitive function?

After final screening, there were 12 articles that were used to create this guideline. The literature was reviewed for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of assessments. A well-established methodology (modified Delphi) [6] was used by the expert panel to rate the appropriate use of procedures. The expert panel is composed of multidisciplinary radiation oncologists, neuro-oncologists, and neurosurgeons with expertise in the management of brain metastases. For assessing the appropriateness of various treatment options for the case variants, panelists voted in of 3 consecutive voting rounds.

Summary of Literature Review

Introduction/Background
Brain metastases are the most common intracranial tumor in adults with cancer and an increasingly important cause of morbidity and mortality [7], particularly in recent years during which advancements in systemic therapies (many of which have low or no central nervous system penetrance) have increased patient survival. The incidence of brain metastases is dependent on cancer site, histology and stage [7,8]. In a US population-based study, 2% of all patients with cancer, and 12% of those with metastatic disease, presented with brain metastases at initial diagnosis [7]; these numbers likely are underestimates due to unscreened patients as well as potential under-reporting of brain metastases to population-based registries. Many more patients (with rates dependent on the aforementioned factors) develop brain metastases over the course of their disease after initial diagnosis. It is estimated that over 100,000 patients per year in the US develop brain metastases [8]. A well-cited paper from 1992 estimates ~170,000 U.S. patients develop brain metastases annually [9]. More recent estimates from the American Brain Tumor Association suggest ~200,000-300,000 cases per year [10].

For patients with multiple brain metastases, radiotherapy options include whole brain radiotherapy (WBRT) and/or stereotactic radiosurgery (SRS) in single- or multi-fraction dose delivery. Some patients may undergo surgical resection and/or receive systemic therapy, targeted therapy, or immunotherapy without radiotherapy (treatment paradigms not addressed in this report).

**SRS vs. WBRT+SRS for 1-4 brain metastases: survival and intracranial tumor control**

Five prospective studies [11-15] randomized patients with 1 or a few (3 to 4) brain metastases, treated with resection (n=2 studies) or SRS (n=5 studies), to receive or not receive WBRT (Table 1). Notably, these studies included 48-81% of patients with only 1 brain metastasis. Data from these studies, as well as from recent meta-analyses [2,16] and a systematic review [4], have shown no detriment in overall survival (OS) with the omission of WBRT, though at the expense of greater risk of recurrence of the treated lesions (local recurrence) and development of new metastases elsewhere in the brain (distant brain recurrence).

In an individual patient meta-analysis of 364 patients from 3 of the aforementioned randomized studies [11-13], WBRT with SRS vs. SRS alone reduced the rate of distant brain recurrences from 53% to 34% and rate of local recurrences from 27% to 12%, with no detriment in OS [16]. A 2018 Cochrane review that included 5 studies reported similar quantitative (in terms of hazard ratios) findings [2]. In the individual patient meta-analysis by Sahgal et al. [16], a greater number of brain metastases (1 vs. >1) was associated with significantly worse distant brain control (HR=0.63, 95% CI=0.46-0.88) and survival (HR=0.72, 95% CI=0.57-0.90) and was not a significant factor for local recurrence risk. Among those ≤50 years old, the addition of WBRT was associated with worse OS.

**SRS for multiple brain metastases: lesion number and target volume**

Several studies [17-27] have shown that intracranial tumor burden (i.e. net volume of brain metastases) may be more prognostic for survival outcomes than the number of brain metastases (Table 2), with many of these studies [17,18,23,25-27] including some patients who received SRS for salvage after prior WBRT (accounting for 15-38% of patients in 5 studies) and with one set of analyses [17,18] also including 46% patients who received upfront WBRT in conjunction with SRS. The role of SRS alone in the treatment of patients with more than a few brain metastases is not well-supported with prospective randomized studies, and considered controversial [28]. However, data (discussed below) are emerging on the use of SRS alone for >4 brain metastases [3]. While outcome data for patients with >10 metastases
selected to receive SRS date back to the mid-2000s [17-19,24,26,27,29-36] (with some studies including patients with >20 brain metastases [26,29,30,32,33,36]), most [17,18,26,27,29-35] of these studies included fewer than 100 patients with >10 metastases, and most [17,18,26,27,29-34,36] did not exclude patients who received SRS for salvage after prior WBRT or as a boost with upfront WBRT. Three studies [19,24,35] (discussed in more detail below), in which some patients underwent SRS-alone for >10 metastases, specifically excluded patients with prior WBRT.

**SRS alone for multiple brain metastases – Overall survival**

The largest series of patients treated with SRS alone as initial definitive therapy for multiple brain metastases are from the prospective Japanese JLGK0901 study [22] and retrospective analyses performed to evaluate potential inclusion factors for this prospective study [19,37-39]. A 2010 retrospective study analyzed 1,508 patients who were treated at two Japanese institutions with SRS for 1-10 metastases, with a net tumor volume <15 cc and with the largest lesion <10 cc; 24% of patients had 5-10 metastases [38]. On multivariate analyses in this retrospective analysis, OS was significantly better in patients with 1 vs. 2-4 metastases, though not for those with 2-4 vs. 5-10 metastases. In an even larger 2012 retrospective study from Japan, 2,246 patients were analyzed including 369 (16.4%) with >10 metastases [19]. More than 10 metastases was associated with a significantly greater need for salvage therapy compared to 5-10 metastases (p=0.023), and served as a cutoff for the JLGK0901 trial. Tumor volume was a significant factor for local control, and net tumor volume >15 cc was significantly (p<0.0001) associated with worse OS, neurologic survival (survival without death from neurologic cause) and qualitative survival (survival without impaired activities of daily living). A study that compared outcomes after SRS alone in 1,000 patients with 5-89 metastases vs. 1,553 patients with 1-4 metastases (as well as a case-matched comparison with 1,096 patients) showed no significant difference between these groups in OS, death from progression of brain metastases, neurologic deaths or receipt of salvage therapy [39].

The prospective Phase II JLGK0901 study [22] enrolled 1,194 patients with 1-10 metastases (net tumor volume <15 cc and largest lesion <10 cc). A total of 455 (38.1%), 531 (44.5%) and 208 (17.4%) of patients had 1, 2-4 and 5-10 metastases, respectively. Similar to the retrospective studies from the JLGK0901 authors, OS was significantly better in patients with 1 vs. 2-4 metastases, though not for those with 2-4 vs. 5-10 metastases. Local recurrence of the treated metastases was similar across the 1, 2-4 and 5-10 metastases subgroups (ranging from 10-16%, p=0.78), while distant brain recurrence occurred in 48% of those treated for 1 brain metastasis and >60% for those treated for 2-4 and 5-10 brain metastases. In JLGK0901, the maximum tumor diameter (≥1.6 vs. <1.6 cm) and cumulative tumor volume (≥1.9 vs. <1.9 ml) were adverse factors for OS on univariate but not multivariate analyses.

In a Japanese/Australian study of 5,750 patients treated with SRS alone for 1 to more than 10 (upper limit was not reported) metastases [24], from lung (n=3,745), breast (n=710), gastrointestinal (n=692) and renal (n=321) cancers and melanoma (n=282), 1,753 (30.5%), 1,872 (32.6%), 1,144 (19.9%), and 981 (17.1%) patients had 1, 2-4, 5-10 and >10 metastases, respectively. Significant differences in OS were seen for 1 vs. 2-10 (HR=1.110, p=0.001) and 2-10 vs. >10 (HR=1.128, p=0.002) metastases; however, the authors found these differences to be “modest.” The cumulative intracranial volume was associated with a HR for survival of 1.015 per cc (p<0.001). A significant effect of lesion number on OS was seen for all primary cancer histologies except for breast cancer, for which no significant difference was seen between patients treated for 1, 2-10 and >10 metastases. With the exclusion of breast cancer patients, each increment of 6-7 lesions was associated with a ~4% increase in the hazard of death.
From a multi-institutional study of 2,089 patients (n=1,094 with 2-15 brain metastasis) treated with SRS alone [35], OS among those (n=882) with 2-4 brain metastases was not significantly different from those (n=212) with 5-15 brain metastases (p=0.25); a greater number of metastases (5-15 vs. 2-4) was associated with greater rates of distant brain metastases progression (p=0.01) and developing more new brain metastases over time (6.1 vs 11.7 metastases per year).

A systematic review published in 2017 summarized 10 studies that included only patients with 4 or more metastases treated with SRS alone; an additional 5 studies were discussed though excluded for not reporting distant brain control [3]. The authors described the wide range in reported outcomes, attributable to heterogeneity between studies with respect to histology, extracranial disease status, and definition of outcomes (such local tumor control). They conclude that data from Phase III studies (of which some are accruing) are needed.

Complicating the interpretation of the aforementioned analyses are the many variables which are known to impact OS [2] as well as the development of novel systemic therapies with potential efficacy against cerebral metastases. Adverse factors for OS (other than number and volume of metastases) in the aforementioned Japanese studies included older age, poorer performance status, male sex, presence of neurologic symptoms, higher Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) class, uncontrolled primary cancer, extracranial metastases, and lung cancer primary [22,24,38,39]. The diagnosis-specific graded prognostic assessment (DS-GPA) incorporates many of these factors [40,41], as well as molecular factors [42-44]. For many primary cancers, the DS-GPA considers number of lesions, but only 1 vs. 2-3 vs >3. In the aforementioned multi-institutional study [35], age>65, male sex, widespread vs. oligometastatic vs. no extracranial disease, primary lung cancer and lower prescribed SRS dose were adverse factors for OS on multivariate analyses.

Omission of WBRT for brain metastases – Neurocognition and QOL

Accepting that for multiple (i.e. >1) metastases, the number of lesions seems to have a modest impact on OS after SRS alone, the more clinically significant outcomes in the decision of SRS vs. WBRT are neurocognitive effects and quality of life (QOL) [45]. In general, the potential acute side effects of alopecia, dermatitis, and otitis media that are associated with WBRT are uncommon with SRS, though SRS may expose small areas of the scalp such that a patch of dermatitis or hair loss could occur [46,47]. WBRT also requires more treatment visits, which can be particularly burdensome for those patients and their caregivers who live far away from a treatment facility [48]. From survey data of 104 patients treated at the University of Pittsburgh with SRS vs. WBRT + SRS for brain metastases, the addition of WBRT was associated with greater subjective (i.e. patient-reported) risks of problems with short-term memory (P<0.0001), long-term memory (p=0.03), concentration (p=0.0007), and mood (p=0.0008) [49]. The authors reported that “treatment selection was fairly random with a tendency to use WBRT with increasing numbers of tumors” though did not specify the number of tumors treated in this cohort. Cognitive effects can worsen or develop shortly after starting WBRT, particularly verbal memory, which has been a primary endpoint in several studies discussed below [50,51]. Notably, patients with brain metastases tend to have compromised neurocognitive function at baseline, perhaps related to effects from the tumor(s) (which would be location-dependent), prior receipt of chemotherapy, and/or general functional decline from cancer [51-54].

In order to better characterize the impact of treatment choice on neurocognitive outcomes in patients with multiple brain metastases the ARS Appropriate Use Criteria group for brain malignancies sought to review the literature on neurocognitive outcomes after radiosurgery for
patients with multiple brain metastases. We specifically focused the literature search on neurocognitive outcomes for which recent data suggest SRS alone may afford a significant advantage. The use of hippocampal avoidance with WBRT, via modulated treatment beams, is another strategy that has been used to lower risks of neurocognitive decline (specifically memory and recall) [55,56] though was not included in this literature search, which focused on patients treated with SRS. The panel opted against including hippocampal sparing WBRT in the literature search knowing that: (1) the prospective randomized NRG CC001 trial of hippocampal sparing WBRT vs. standard WBRT would be forthcoming (and is now published as discussed below [55]); and (2) no cooperative group or large single- or multi-institutional prospective studies comparing hippocampal sparing WBRT vs. SRS (the main focus of this report) were published (at the time of the literature search) or immediately forthcoming.

**Multiple sub-centimeter, asymptomatic brain metastases** ((1) at time of initial diagnosis; or (2) at time of extracranial progression while on systemic therapy)
- **2-4 metastases**
- **5-10 metastases**

For patients with 2-4 or 5-10 asymptomatic, <5 mm brain metastases, from NSCLC (without targetable mutations), the panel agreed that SRS alone was appropriate, whether the brain metastases were diagnosed at initial NSCLC diagnosis (case variant 1) or at time of extracranial progression while on systemic therapy (case variant 2).

- **11-15 brain metastases**

For 11-15 brain metastases, most on the panel (11 of 13 votes) felt that SRS alone for case variant 2 may be appropriate, while there was disagreement on SRS alone (7 of 12 voting for may be appropriate) for case variant 1.

- **16-20 brain metastases**

For 16-20 brain metastases, most on the panel (10 of 13 votes) felt that SRS alone for case variant 1 may be appropriate, while there was disagreement on SRS alone for case variant 2 (7 of 12 voting for may be appropriate).

- **>20 brain metastases**

For >20 brain metastases most considered SRS alone usually not appropriate for case variants 1 and 2.

**Discussion**

Compelling single-institution and multi-institution single-arm studies suggest that SRS alone for multiple brain metastases results in low risks of neurocognitive decline, albeit with limited follow-up due to poor OS after treatment for brain metastases. Randomized comparisons of SRS alone vs. SRS+WBRT demonstrate superior neurocognitive outcomes with the omission of WBRT, though studies include a large proportion of patients with single brain metastases, and exclude patients with more than a few (3-4) brain metastases. Data on neurocognitive outcomes after SRS alone for >4 brain metastases are currently lacking though being assessed in ongoing prospective studies.

**Single-arm studies of neurocognition after SRS alone for multiple brain metastases**

A few studies have analyzed factors affecting neurocognitive and QOL outcomes after SRS for brain metastases. In a pilot study of 15 patients treated with SRS alone for brain metastases, 67% of patients had baseline impairment in one or more neurocognitive tests [52]. Brain metastasis volume (>3 cc) was significantly (p=0.05) associated with worse attention at baseline. Among 4 long-term (>200 days) survivors, some measures of neuro-cognitive function improved over time.
In a Dutch study of 97 patients treated with fractionated SRS alone for 1-4 brain metastases (44% with 1 metastasis and 51% with 2-3 metastases), neurocognitive testing was performed before SRS and at regular intervals following SRS [53]. Over a course of 6 months, all seven of the tested neurocognitive domain scores did not significantly change. Larger net tumor volume (defined as >12.6 cc) was associated with worse information processing speed (p=0.069) and verbal memory (p=0.077) at baseline and significantly (p=0.02) worse information processing speed over time (3-6 month). Though it is unclear from this report to what extent, if any, tumor volume contributed to a decline in this measure. QOL measures were also obtained, with significant declines in physical functioning and fatigue demonstrated. Self-perceived cognitive function (a QOL measure) was correlated with Karnofsky Performance Scale (KPS; p=0.029) as well as tumor volume (p=0.045) but not number of metastases. The authors concluded that while “patients with large tumor volumes were impaired in some aspects of health-related QOL and neurocognitive functioning, most scores did not differ significantly from those of patients with smaller tumors.”

In a Norwegian study of 97 patients with 1-6 brain metastases treated with SRS (14 of whom had prior WBRT), QOL was measured over 12 months using the brain cancer subscale (BRCS) of the FACT-BR [57]. For the overall cohort, the QOL scores did not appreciably change over 12 months after SRS. Pre-SRS/baseline factors associated with improved QOL after SRS include, asymptomatic brain metastases (p=0.001), higher KPS score (p=0.017), low RPA class (p=0.049), lack of seizures (p=0.040), and absence of cognitive impairment (p=0.033); the number of brain metastases, total volume of brain metastases, tumor location, primary cancer type and prior WBRT were not significant factors. After SRS, QOL scores were better with local control of brain metastases (p=0.018), improved or stable symptoms from brain metastases (p=0.005), lack of steroid treatment (p=0.003) and absence of extracranial progression (p=0.001), particularly if symptomatic.

This same Norwegian group used the same measure (BRCS) to assess QOL changes in 44 patients treated with SRS for 1-6 brain metastases from lung cancer (some of whom received prior WBRT) [58]. The net tumor volume was the only factor that significantly predicted the slope of the QOL curves after SRS. The BRCS score improved for 32 patients (72.3%) with a total brain metastasis volume ≤5 cc, while it declined in patients with a larger brain metastasis burden (p=0.04). Notably, the presence of pre-SRS symptoms, the rate symptom improvement after SRS, and local control rates were similar between patients with net volume ≤5 vs. >5 cc. Possible differences between QOL score after SRS between these two groups, as postulated by the study authors, may be due to less steroid administration after SRS and/or less extracranial progression in those patients with smaller intracranial tumor burden.

Neurocognition after SRS with vs. without WBRT for multiple brain metastases

The Phase III studies (Table 1 and discussed above), that randomized patients with ≤3-4 brain metastases (from any primary site) to receive or not receive WBRT, also analyzed neurocognitive, neurologic and/or QOL measures, and allowed for comparison between WBRT and no WBRT groups. These are summarized in Table 3, and briefly below.

In the study by Aoyama et al. of SRS +/- WBRT, the mini mental status examination (MMSE) was an optional endpoint, with 92 of 132 having baseline and follow-up exams [11]. The average duration until deterioration of MMSE score was longer in the group that received WBRT, attributed to the adverse effects on cognition from intracranial recurrence, which was more likely in the SRS-alone group. However, beyond 1-2 years, there was an appreciably greater likelihood of preserving MMSE in the SRS-alone group.
In the study of SRS +/- WBRT from M.D. Anderson Cancer Center, the primary endpoint was neurocognitive function as objectively measured by the Hopkins Verbal Learning Test–Revised (HVLT–R) total recall at 4 months [12]. A battery of other tests (listed in Table 3 footnote) were also analyzed. With the interim analysis after 58 patients were enrolled, the WBRT+SRS group were significantly more likely to have had a drop on the HVLT–R total recall; delayed recall and delayed recognition scores were also more compromised with the addition of WBRT.

In the study of SRS or resection +/- WBRT from the European Organization for Research and Treatment of Cancer (EORTC), the primary endpoint was deterioration of World Health Organization (WHO) performance scale (PS) to a score of >2 [13]. The median time to deterioration to a WHO PS >2 was similar in those treated with upfront WBRT vs. those who were not. In a follow-up analysis, health-related QOL was analyzed as a secondary endpoint, with 88% compliance at baseline and 45% compliance at 1 year. Multiple QOL domains (listed in Table 3) were significantly worse among the group that received WBRT [59].

In the North Central Cancer Treatment Group (NCCTG) N0574 study of SRS +/- WBRT [14], the primary endpoint was cognitive deterioration (>1 standard deviation from baseline) on at least 1 cognitive test (listed in Table 3 footnote) at 3 months. The addition of WBRT was associated with a greater risk of cognitive deterioration, and inferior cognitive outcomes on all of the assessments. WBRT was also associated with worse QOL (p=0.002) and functional well-being (p=0.03).

Neurocognition after SRS alone for >4 brain metastases

In a 2017 update of the JLGK0901 study, the rate of maintaining MMSE score did not significantly differ (by competing risk analysis) between patients with 1, 2-4 or 5-10 metastases [60]. None of the randomized studies discussed above separately analyzed neurocognitive outcomes for patients with multiple vs. single metastases, though the results may apply equally to both subgroups. As none of the randomized studies discussed above included patients with >4 metastases, the impact on neurocognitive function of SRS alone vs. WBRT (+/-SRS) in this group of patients is of particular interest. Ongoing studies of SRS alone for multiple brain metastases are summarized in Table 4.

Clinical scenarios that included treatment options that were not specifically addressed in the literature search or evidence tables (which focused on neurocognitive outcomes after SRS for brain metastases) but included in the panel voting to inform future ARS guidelines.

2 asymptomatic brain metastases (including 1 in the brainstem)

The panel mostly agreed that SRS alone, either single- or multi-fraction SRS, is usually appropriate, and all agreed that multi-fraction SRS [61-64] to the brainstem lesion and single-fraction SRS to the frontal lesion is usually appropriate. The panel felt that WBRT [65] is usually inappropriate (9 of 11 votes) for this case (consistent with voting for 2-4 asymptomatic brain metastases), and there was disagreement on the appropriateness of hippocampal sparing WBRT alone [55] or with SRS boost.

Discussion

Among the studies listed in Table 1, only Brown et al. [14] explicitly excluded metastases within the brainstem, whereas the other studies did not specify the exclusion or inclusion of brainstem metastases. Because of concerns about toxicity risks, and because there have been no published randomized studies comparing single-fraction SRS to either multi-fraction SRS or
hippocampal sparing WBRT, the optimal treatment of patients with brainstem metastases is not currently based on level 1 evidence. Nevertheless, the scenarios with multi-fraction SRS as treatment for both or only the brainstem lesion were considered usually appropriate by most of the panelists, while the use of hippocampal sparing WBRT [55] remains controversial if SRS is a viable treatment option.

Notably, the NRG study CC001, published in 2020, randomized 518 patients to standard WBRT vs. hippocampal sparing WBRT (with memantine offered in both arms) [55]. Hippocampal sparing was associated with statistically significantly improved cognitive function, specifically executive function at 4 months and learning and memory at 6 months, and statistically significantly improved patient-reported outcomes of fatigue, memory, speech, impact of neurologic symptoms on daily activities, and cognitive symptoms; there were no differences in survival or intracranial control outcomes between the 2 treatment groups.

3 brain metastases (including 1 that is >2 cm)

For 3 asymptomatic (largest 2.2 cm) brain metastases from melanoma, SRS alone to all sites, or resection of the largest lesion followed by SRS to all sites [66-72], was considered usually appropriate by all and most voters, respectively. WBRT [65] or WBRT with SRS boost [11-14,52,59,73] was considered usually not appropriate by most (11 of 12) panelists (consistent with voting for 2-4 asymptomatic brain metastases); there was disagreement on the appropriateness of resection followed by WBRT [70-72]: considered usually not appropriate (6 of 12) or may be appropriate (6 of 12), with no panelists considering this option as usually appropriate.

Discussion

Emerging data suggest that SRS (single- or multi-fraction) can be safely and effectively delivered to the resected (pre-operatively to the tumor or post-operatively to the surgical cavity) and unresected brain metastases [66-72]. For asymptomatic lesions, resection can be considered to establish diagnosis (not relevant in this case variant) or (for bulkier lesions) potentially minimize risks of post-SRS toxicity.

In the multicenter, randomized, controlled, NCCTG N107C/CEC.3 phase 3 trial of post-operative SRS vs. WBRT for 1-4 brain metastases (n=194 patients), survival rates were similar between the 2 groups, while cognitive-deterioration-free survival (from 6 standardized tests) at 6 months was significantly better in the group not receiving WBRT [70]. While post-operative SRS vs. no radiotherapy lowered risk of local recurrence in a phase 3 study (n=128 patients) from MDACC [72], local control was significantly worse in the SRS arm (vs. WBRT arm) of the NCCTG N107C/CEC.3 phase 3, findings which may be attributable to the complexity of adequately targeting surgical cavities (with appropriate margin) [74] or incorrectly ascribing necrosis to recurrence.

13 brain metastases (including 1 that is symptomatic and >2 cm)

For a patient with newly diagnosed NSCLC, with 13 brain metastases (≤2.5 cm) and new onset right-sided hemiparesis that partially responded to corticosteroids (case variant 5), the panel mostly agreed that resection of the largest lesion (in the pre-motor area) and SRS to all sites or fractionated SRS to the premotor cortex lesion [61-63,75-77] and single-fraction SRS to all other sites were usually appropriate. There was disagreement on the use of WBRT alone or WBRT after resection, single-fraction SRS to all sites or multi-fraction SRS to all sites.

Discussion

For symptomatic brain metastases, resection can potentially improve or reverse symptoms
from mass effect and edema. While symptomatic improvement can occur after SRS (single- or multi-fraction), generally SRS will not alleviate the mass effect immediately, and post-SRS necrosis can exacerbate tumor-related symptoms. Nevertheless, SRS alone may be appropriate in some situations which is reflected in the panel voting.

For >10 metastases, the role of WBRT vs. SRS (for unresected and/or resected lesions) is lacking data to yield consensus on the panel or strong guidelines for treatment.

5-10 brain asymptomatic brain metastases in setting of poor performance status and progressive extracranial disease not amenable to systemic therapy

For a patient with KPS 60 and 6 asymptomatic brain metastases (0.2-1.5 cm) from NSCLC (case variant 6), the panel mostly (9 of 12 votes) agreed that hospice care was usually appropriate [78]; there was disagreement on the appropriateness of standard WBRT alone, hippocampal sparing WBRT alone, SRS for all lesions, or SRS for selected (i.e. largest or critically located) lesions.

Discussion

The disagreements observed in this case’s various treatment scenarios is a reflection of this paucity of data for patients with poor performance status and relatively poor prognosis. Radiotherapy would be considered palliative in this case, though the optimal approach to control the disease while minimizing side effects is unclear. In clinical practice, discussions with the patient on goals of care can help in treatment decision-making.

Summary of Recommendations

Based upon a systematic literature review stemming from key questions on the use of SRS for multiple brain metastases, evaluating the evidence from that systemic review, and voting on appropriateness of select treatment options for specified case variants, the ARS Appropriate Use Criteria group for brain malignancies’ voting determined that:

- For asymptomatic brain metastases in patient with good performance status: SRS alone is usually appropriate for those with 2-10 brain metastases, and usually not appropriate for those with >20 brain metastases. There was disagreement among the panel on the appropriateness of SRS alone for those with newly diagnosed NSCLC and 11-15 brain metastases or progressive NSCLC and 16-20 brain metastases; and the panel agreed that SRS alone may be appropriate for those with newly diagnosed NSCLC and 16-20 brain metastases or progressive NSCLC and 11-15 brain metastases
- Conventional WBRT alone is usually not appropriate for those with 2-4 asymptomatic brain metastases and good performance status.
- There were several areas of disagreement that were not addressed by the literature search, but were presented as treatment options in the clinical scenarios to inform future ARS guidelines. The disagreement of panel members reflects uncertainty in the appropriateness as a result of lack of compelling data. These areas include:
  o The use of hippocampal sparing WBRT for patients with good performance status and 2-4 asymptomatic brain metastases (for whom SRS alone would be a treatment option).
  o The use of WBRT after resection of a brain metastasis in a patient with good performance status whose disease is amenable to SRS.
  o The use of fractionated vs. single-fraction SRS for resected metastases, larger targets and/or brainstem metastases
  o The optimal treatment (WBRT, hippocampal sparing WBRT, SRS to all lesions, SRS to select lesions) for patients with multiple brain metastases, progressive
extracranial disease and poor performance status from the extracranial disease, for which systemic therapy is not an option.

Neurocognition reflects multiple complex outcome measures, and patients with brain metastases are a highly heterogeneous group with respect to age, baseline function, cancer type, extracranial disease status, size and anatomic distribution of brain metastases, other treatment (i.e. resection) for brain metastases, response to treatment, susceptibility to treatment toxicity and many other factors. As such, further study is needed to quantify risks of neurocognitive decline, and the factors that affect those risks. Patients at risk of developing distant brain recurrence shortly after SRS alone may benefit from WBRT; though in those patients with uncontrolled extracranial disease with the potential to seed new brain metastases, upfront WBRT may be disadvantageous as it’s use as salvage therapy would be compromised. Thus, a better understanding of risk and patterns of cancer recurrence, perhaps using tumor and/or host genomics in addition to other clinical and pathologic factors, and a better understanding the factors that affect (in a clinically meaningful way) neurocognition, are needed to optimally guide treatment decision-making.

Summary of Evidence

Of the 12 references cited in the ARS Appropriate Use Criteria Multiple Brain Metastases document, all of them are categorized as therapeutic references including 6 well-designed studies, 6 good quality studies, and no studies that may have design limitations.

There are 2 references that may not be useful as primary evidence. There are no references that are metaanalysis studies.

The 12 references cited in the ARS Appropriate Use Criteria document for Neurocognition after stereotactic radiosurgery for multiple brain metastases were published from 2007 to 2017.

Although there are references (in the text) that report on studies with design limitations, 12 well-designed or good quality studies provide good evidence.
References


Clinical Condition: multiple brain metastases

Variant 1:
- Age: 50
- KPS: 80
- Primary cancer: NSCLC - no targetable mutations
- Extracranial disease: Newly diagnosed, untreated
- # of brain metastases: as below
- Size of brain metastases: all 4 mm maximum diameter, non-eloquent brain
- Systemic therapy: Standard first line agent planned

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS alone for 2-4 brain metastases</td>
<td>A</td>
<td>1 12 9</td>
<td>S</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for 5-10 brain metastases</td>
<td>A</td>
<td>1 2 6 4</td>
<td>M</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for 11-15 brain metastases</td>
<td>M*</td>
<td>1 1 5 4 1 5</td>
<td>X</td>
<td>L ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for 16-20 brain metastases</td>
<td>M</td>
<td>1 1 3 6 1 1</td>
<td>5</td>
<td>L ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for &gt;20 brain metastases</td>
<td>U</td>
<td>1 1 9 1 1</td>
<td>3</td>
<td>L -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rating:**
- A - Usually appropriate;
- M - May be appropriate;
- U - Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text).

**Group median rating is set automatically to 5.**

**Strength of Evidence:**
- S - Strong;
- M - Moderate;
- L - Limited;
- EC - Expert consensus;
- EO - Expert opinion

**Strength of Recommendation:**
- ↑ Strong Recommendation;
- ↓ Weak Recommendation;
- - Additional considerations do not strengthen or weaken the panel's recommendation

---

**KEY:**
- KPS = Karnofsky Performance Status;
- SRS = stereotactic radiosurgery
Clinical Condition: multiple brain metastases

Variant 2:
- Age: 50
- KPS: 80
- Primary cancer: NSCLC - no targetable mutations
- Extracranial disease: progression after 2 prior lines of systemic treatment
- # of brain metastases: as below
- Size of brain metastases: all 4 mm maximum diameter, non-eloquent brain
- Systemic therapy: planned for after treatment of brain (clinical trial)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS alone for 2-4 brain metastases</td>
<td>A</td>
<td>2 3 8</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for 5-10 brain metastases</td>
<td>A</td>
<td>2 4 4 3</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for 11-15 brain metastases</td>
<td>M</td>
<td>2 3 6 1 1</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for 16-20 brain metastases</td>
<td>M*</td>
<td>4 3 3 1 1</td>
<td>5</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for &gt;20 brain metastases</td>
<td>U</td>
<td>2 1 9 1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

KEY: KPS=Karnofsky Performance Status; SRS=stereotactic radiosurgery
Clinical Condition: 2 brain metastases

Variant 3: Age 50, KPS 90, Primary cancer: NSCLC - no targetable mutations, Extracranial disease newly diagnosed, # of brain metastases 2, Size of brain metastases 1.3 cm (pons) and 4 mm (left frontal), Systemic therapy Standard first line agent planned

Prior smoker presents with 2 small brain metastases: a symptomatic pontine lesion (1.3 cm), and an asymptomatic left frontal lobe enhancing lesion (4 mm). Work-up reveals T2N0 adenocarcinoma of pulmonary origin, EGFR, PDL1, ALK, and ROS negative.

### Treatment Options

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional WBRT alone</td>
<td>U</td>
<td>2</td>
<td></td>
<td></td>
<td>S§</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Hippocampal sparing WBRT alone</td>
<td>M*</td>
<td>5</td>
<td>X</td>
<td></td>
<td>S§</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>WBRT (with or without hippocampus-sparing techniques) with planned SRS boost</td>
<td>M*</td>
<td>5</td>
<td>X</td>
<td></td>
<td>S§</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SRS alone for both lesions</td>
<td>A</td>
<td>8</td>
<td></td>
<td></td>
<td>S</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>2-5 fraction SRS alone for both lesions</td>
<td>A</td>
<td>7</td>
<td></td>
<td></td>
<td>M§</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1-fraction SRS for left frontal lesion and 2-5 fraction SRS for brainstem lesion</td>
<td>A</td>
<td>8.5</td>
<td></td>
<td></td>
<td>M§</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**Ratings:**
- A - Usually appropriate;
- M - May be appropriate;
- U - Usually not appropriate

**Strength of Evidence:**
- S - Strong;
- M - Moderate;
- L - Limited;
- EC - Expert consensus;
- EO - Expert opinion

**Strength of Recommendation:**
- ↑ Strong Recommendation;
- ↓ Weak Recommendation;
- - Additional considerations do not strengthen or weaken the panel's recommendation

** KEY:** KPS = Karnofsky Performance Status; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy with or without memantine being prescribed

§ from selected studies (cited in manuscript) from a clinical scenario that was not specifically discussed in the literature review or addressed in the literature search and evidence tables (which focused on neurocognitive outcomes after SRS alone for brain metastases)
**Clinical Condition:** 3 brain metastases

**Variant 4:**
- **Age:** 50
- **KPS:** 90
- **Primary cancer:** Melanoma, 90% PD-L1 positive, no BRAF mutations
- **Extracranial disease:** Controlled
- **# of brain metastases:** 3 (all asymptomatic)
- **Size of brain metastases:** 2.2 x 1.5 cm, 0.8 x 0.7 cm, 0.6 x 0.5 cm with volumes of 3.5 cc, 0.18 cc, 0.11 cc
- **Location of lesions:** Left frontal (2.2 cm), left parietal lesion (0.8 cm), left hippocampal (0.6 cm)
- **Systemic therapy:** newly diagnosed

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional WBRT alone</td>
<td>U</td>
<td>6 3 2 1</td>
<td>1.5</td>
<td>§</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS alone for all lesions (single or multi-fraction)</td>
<td>A</td>
<td>5 7 9</td>
<td></td>
<td>§</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection of left frontal lesion → WBRT</td>
<td>M*</td>
<td>2 1 3 3 2 1</td>
<td>5 X</td>
<td>§</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection of left frontal lesion → SRS to cavity and intact lesion (single or multi-fraction)</td>
<td>A</td>
<td>1 1 2 6 2 8</td>
<td></td>
<td>§</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBRT with planned SRS boost</td>
<td>U</td>
<td>7 1 3 1</td>
<td>1</td>
<td>§</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rating:** A - Usually appropriate; M - May be appropriate; U - Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text).

Group median rating is set automatically to 5.

**Strength of Evidence:** S - Strong; M - Moderate; L - Limited; EC - Expert consensus; EO - Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

---

**KEY:** KPS = Karnofsky Performance Status; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy with or without memantine being prescribed

§ from selected studies (cited in manuscript) from a clinical scenario that was not specifically discussed in the literature review or addressed in the literature search and evidence tables (which focused on neurocognitive outcomes after SRS alone for brain metastases)
**Clinical Condition:** 10-15 brain metastases

**Variant 5:**
- Age: 63
- KPS: 90
- Primary cancer: NSCLC
- Extracranial disease: newly diagnosed: multiple lung nodules and biopsy proven liver metastasis
- # of brain metastases: 13 (one that is symptomatic)
- Size of brain metastases: largest is 2.5 cm
- Location of lesions: largest is in frontal lobe (pre-motor cortex); others are scattered
- Systemic therapy: newly diagnosed

Nonsmoker with new onset right-sided hemiparesis that partially responded to corticosteroids. KRAS-mutated adenocarcinoma.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection pre-motor lesion – then WBRT</td>
<td>M*</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection pre-motor lesion – then SRS to post-op cavity and all additional lesions</td>
<td>A</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBRT alone</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS (single fraction) alone to all lesions</td>
<td>M*</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS (multi-fraction) alone to all lesions</td>
<td>M*</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS (multi-fraction) to premotor lesion and SRS (single fraction) to all other lesions</td>
<td>A</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

**KEY:** KPS=Karnofsky Performance Status; SRS=stereotactic radiosurgery; WBRT=whole brain radiotherapy with or without memantine being prescribed

¶ as WBRT for multiple brain metastases has been a standard of care practice for decades, specific studies on WBRT alone or after resection were not cited in the manuscript or evaluated

‡ while many studies have addressed resection followed by stereotactic radiosurgery, there is a lack of data on this treatment specifically for patients with 10+ brain metastases

§ from selected studies (cited in manuscript) from a clinical scenario that was not specifically discussed in the literature review or addressed in the literature search and evidence tables (which focused on neurocognitive outcomes after SRS alone for brain metastases)
Clinical Condition: 5-10 brain metastases

Variant 6:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>80</td>
</tr>
<tr>
<td>KPS</td>
<td>60</td>
</tr>
<tr>
<td>Primary cancer:</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Extracranial disease progression of disease</td>
<td></td>
</tr>
<tr>
<td># of brain metastases</td>
<td>6 (all asymptomatic)</td>
</tr>
</tbody>
</table>

Size and location of brain metastases:

1. 1.5 cm diameter (2 cc) right frontal metastasis
2. 1 cm diameter (0.5 cc) left thalamus
3. 6 mm diameter (0.1 cc) left posterior temporal lobe
4. 4 mm (.03 cc) right parietal lobe
5. 4 mm (0.3 cc) left side of cerebellar vermis
6. 2 mm (punctate) left anterior frontal lobe

Systemic therapy none planned

Patient with history of Stage III KRAS mutated lung adenocarcinoma, treated definitively with chemoradiation before developing extracranial metastatic disease. She now has progression of extracranial metastases while on immunotherapy, and is no longer a candidate for systemic chemotherapy. Restaging also revealed the aforementioned brain metastases.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospice care</td>
<td>A</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Standard WBRT alone</td>
<td>M*</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hippocampal sparing WBRT alone</td>
<td>M*</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>X</td>
</tr>
<tr>
<td>SRS alone for all lesions (single or multi-fraction)</td>
<td>M*</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>X</td>
</tr>
<tr>
<td>SRS alone for selected (i.e. largest or critically located) lesions (single or multi-fraction)</td>
<td>M*</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>X</td>
</tr>
</tbody>
</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text).
Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

KEY: KPS=Karnofsky Performance Status; SRS=stereotactic radiosurgery; WBRT=whole brain radiotherapy with or without memantine being prescribed

¶ as WBRT for multiple brain metastases has been a standard of care practice for decades, specific studies on WBRT alone or after resection were not cite in the manuscript or evaluated

‡ while many studies have addressed hippocampal sparing whole brain radiation or radiosurgery alone in the setting of 5-10 brain metastases, data are lacking on such treatment for patients with poor performance status and progressive extracranial disease without systemic therapy options.
The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient’s condition are ranked. Other procedures necessary to evaluate or treat 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 procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.