NCCN Guidelines® Insights

Central Nervous System Cancers,
Version 2.2014

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Central Nervous System Cancers provide multidisciplinary recommendations for the clinical management of patients with cancers of the central nervous system. These NCCN Guidelines Insights highlight recent updates regarding the management of metastatic brain tumors using radiation therapy. Use of stereotactic radiosurgery (SRS) is no longer limited to patients with 3 or fewer lesions, because data suggest that total disease burden, rather than number of lesions, is predictive of survival benefits associated with the technique. SRS is increasingly becoming an integral part of management of patients with controlled, low-volume brain metastases. (*J Natl Compr Canc Netw* 2014;12:1517–1523)

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Central Nervous System Cancers
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Central Nervous System Cancers

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^cConsider surgery to relieve mass effect.

^dSolid brain metastases with systemic non-primary CNS lymphoma are not well defined, but treatment may include systemic treatment, whole-brain radiotherapy, or focal RT.

^eThe decision to resect a tumor may depend upon the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (< 2 cm), deep, asymptomatic lesions may be considered for treatment with SRS versus larger (> 2 cm), symptomatic lesions that may be more appropriate for surgery. (Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S: Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. J Natl Compr Cancer Netw 2008; 6:505-513.)

^fSee Principles of Brain Tumor Surgery (BRAIN-B).

^gSee Principles of Brain Tumor Radiation Therapy (BRAIN-C).

^hChemotherapy may be considered in select patients (eg, patients who have asymptomatic brain metastases that are otherwise small and who have not had prior chemotherapy). Treatment as per the regimens of the primary tumor.

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LTD-2

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Metastases to the brain are the most common intracranial tumors in adults and may occur up to 10 times more frequently than primary brain tumors. Population-based data reported that approximately 8% to 10% of patients with cancer are affected by symptomatic metastatic tumors in the brain.^{1,2} As a result of advances in diagnosis and treatment, many patients improve with proper management and do not die from progression of these metastatic lesions. Primary lung cancers are the most common source, accounting for half of intracranial metastases, although melanoma has been documented to have the highest predilection to spread to the brain. Diagnosis of central nervous system (CNS) involvement is becoming more common in patients with breast cancer as therapy for metastatic disease is improving.³

Nearly 80% of brain metastases occur in the cerebral hemispheres, an additional 15% occur in the cerebellum, and 5% occur in the brainstem.⁴ These

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^aSee Principles of Brain Tumor Imaging (BRAIN-A).
^bConsider a multidisciplinary review in treatment planning, especially once pathology is available (See Principles of Brain Tumor Management [BRAIN-E]).
^cAs part of diagnostic evaluation, neuroimaging modalities such as MRI, DW-MRI, MRI-SPECT, or PET scan may be considered.
^dConsider surgery to relieve mass effect.
^eSee Principles of Brain Tumor Radiation Therapy (BRAIN-C).
^fSRS can be considered for patients with good performance and low overall tumor volume. (Chang WS, Kim HY, Chang JW, et al. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases? J Neurosurg 2010;113 Suppl:73-78).

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See Follow-up and Recurrence (MU-2)
MU-1

lesions typically follow a pattern of hematogenous spread to the gray–white junction, where the relatively narrow blood vessels tend to trap tumor emboli. Most cases have multiple brain metastases evident on MRI scans. The presenting signs and symptoms of metastatic brain lesions are similar to those of other mass lesions in the brain, such as headache, seizures, and neurologic impairment.

Historically, whole-brain radiation therapy (WBRT) and/or surgery were the mainstay of treatment for metastatic lesions in the brain. The advent of stereotactic radiosurgery (SRS) offered a minimally invasive option to treat unresectable lesions.⁵ Compared with WBRT, SRS-related cognitive changes are extremely rare. Although SRS was previously limited to cases with fewer than 3 brain lesions, its use is expanding to patients with more lesions but a low volume of disease to enhance quality of life.

NCCN convened a multidisciplinary panel of leading experts from NCCN Member Institutions

to develop and continually update guidelines for the treatment of CNS cancers, including metastatic brain lesions. The latest full version of these guidelines, which include a complete list of updates, is available on the NCCN Web site (NCCN.org). These NCCN Guidelines Insights highlight recent revisions in the management of brain metastases using SRS.

Stereotactic Radiosurgery

SRS is a technique that delivers a high dose of extremely focused radiation to small lesions, most frequently in a single session, but it can also be delivered in 2 to 5 fractions. It is becoming a desirable option because of reduced side effects and morbidity compared with both surgery and WBRT.

SRS for Multiple Metastatic Lesions

Accumulating evidence suggests that low disease volume is a better selection criterion for SRS than

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a low number of metastatic lesions. A multivariate analysis of 205 patients who received SRS for 4 or more brain metastases showed total treatment volume to be the most significant prognostic factor of survival, whereas the number of metastases did not reach significance.⁶ The same group conducted another analysis that identified a favorable subgroup of patients with a total treatment volume either less than 7 mL and fewer than 7 brain lesions. These patients had significantly prolonged median survival (13 months) compared with other patients (6 months; $P<.00005$).⁷ A cohort study revealed that patients with a total SRS-treated tumor volume of either less than 5 mL or 5 to 10 mL survived longer than those with a total treated volume greater than 10 mL.⁸ No survival difference was observed between patients with a single metastasis or multiple metastases. Another group analyzed patients divided by their number of brain lesions and found no difference in survival times or local control rates among the groups after SRS treatment.⁹ However, patients with more than 15 lesions had a higher risk of developing new lesions and distant disease progression.

Taken together, patients with multiple lesions but a low total volume of disease may be amenable to SRS. Additionally, patients with a favorable histology of the primary tumor (eg, breast cancer) or controlled primary tumors can often benefit from SRS regardless of the number of brain metastases present.^{10,11} Some brain metastases of radioresistant primary tumors, such as melanoma and renal cell carcinoma, have also been shown to achieve good local control with SRS.¹² Other predictors of longer survival with SRS include younger age, good performance status, and primary tumor control.^{6,10,11,13}

SRS Plus WBRT Versus WBRT Alone

The impact of SRS boost in addition to WBRT was evaluated in 2 published randomized controlled studies. The RTOG 9508 multi-institutional trial randomly assigned 333 patients with 1 to 3 brain metastases to WBRT plus SRS or WBRT alone.¹⁴ Despite the inclusion of larger tumors (3–4 cm) that are less favorable to SRS, the authors found a significant survival benefit in the combined arm (6.5 vs 4.9 months; $P=.04$) when treating a single metastasis; this benefit was not observed in patients with multiple (2 or 3) lesions. A much smaller trial of 27 patients with 2 to 4 lesions found no significant difference in survival, although SRS extended time

to local failure (36 vs 6 months; $P=.0005$).¹⁵ Overall, no difference in overall survival was reported between the approaches in a meta-analysis of the 2 trials.¹⁶ However, the addition of SRS to WBRT significantly improved local control and performance status. SRS plus WBRT also prolonged the overall survival of patients with a single brain metastasis compared with those treated with WBRT alone (6.5 vs 4.9 months; $P=.04$).

SRS Plus WBRT Versus SRS Alone

In a randomized Japanese study of 132 patients with 1 to 4 metastatic brain tumors smaller than 3 cm, the addition of WBRT to SRS did not prolong median survival compared with SRS alone (7.5 vs 8.0 months, respectively).¹⁷ However, the 1-year brain recurrence rate was lowered in the WBRT plus SRS arm (47% vs 76%; $P<.001$). Another small randomized trial of 58 patients with 1 to 3 brain metastases was stopped early because of a significant decline in learning and memory function among the group receiving both SRS and WBRT compared with those receiving SRS alone (52% vs 24%).¹⁸ Analysis showed that SRS plus WBRT was associated with a better 1-year recurrence-free survival rate (73%) than SRS alone (27%). A third trial recruited 359 patients with 1 to 3 metastatic brain lesions who underwent surgery or SRS.¹⁹ They were randomized to either adjuvant WBRT or observation. Compared with the observation arm, intracranial relapse rates and neurologic mortality were lower in the WBRT arm, but overall survival and duration of functional independence were similar. A meta-analysis found no improvement in overall survival with the addition of WBRT to SRS.²⁰

SRS Plus WBRT Versus Surgery Plus WBRT

Retrospective comparative studies showed that SRS plus WBRT resulted in equivalent, if not better, survival compared with surgery and WBRT.^{21–23} SRS also conferred a significant improvement in local control, especially for patients with radiosensitive tumors or solitary brain lesions. A prospective observational study of 1194 patients reported no difference in overall survival between patients with 2 to 4 metastatic brain lesions and those with 5 to 10 lesions treated with SRS alone (hazard ratio, 0.97; 95% CI, 0.81–1.18; P noninferiority $<.0001$).²⁴ SRS alone compared with resection plus WBRT was evaluated in a randomized controlled trial by

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Muacevic et al,²⁵ which was stopped prematurely because of poor accrual. In the final analysis based on 64 patients with solitary brain metastases, SRS alone was less invasive and resulted in equivalent survival and local control, but it was associated with a higher rate of distant relapse.

SRS for Recurrence

Several patient series have demonstrated local control rates greater than 70% with SRS in the recurrence setting for patients with good performance status and stable disease who have received prior WBRT.^{26–31}

NCCN Recommendations

SRS has been an option for limited (1–3) metastatic brain lesions (see LTD-2, page 1519). The panel recently added SRS as a primary treatment option for multiple (>3) metastatic lesions, specifically in patients with good performance status and low overall tumor volume (see MU-1, page 1520). Maximum marginal doses of 24, 18, or 15 Gy according to tumor volume are recommended according to the RTOG 9005 protocol.³²

Conclusions

These NCCN Guidelines Insights highlight important updates to the management of metastatic brain cancer with SRS in the NCCN Guidelines for Central Nervous System Cancers. The NCCN Guidelines are updated at least annually, and more often when new high-quality clinical data become available in the interim. The most up-to-date version of these continuously evolving guidelines is available online at NCCN.org. The recommendations in the NCCN Guidelines are based on evidence from clinical data, when available, and expert consensus of the NCCN panel. Independent medical judgment is required to apply these guidelines to individual patients to optimize care. The physician and patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

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Posttest Questions

1. Metastatic lesions in the brain are:
 - a. Relatively uncommon compared with primary brain tumors
 - b. Commonly associated with seizures and cognitive impairment
 - c. Rarely resectable
 - d. All of the above
2. Which of the following is NOT an appropriate indication for SRS?
 - a. Multiple (4) brain metastases with 15 mL total volume, patient performance score of 70
 - b. Single asymptomatic brain metastasis, patient perfor-

mance score of 70

- c. Multiple (6) brain metastases with 6 mL total volume, patient performance score of 80
 - d. Single recurrent brain metastatic lesion, patient performance score of 90
3. Advantages of SRS include:
 - a. Low risk of long-term cognitive deterioration
 - b. Minimal invasiveness
 - c. Avoidance of surgery-related complications
 - d. All of the above