New Brain Metastases Treatment Guidelines

Issued by the **American Association of Neurological Surgeons**

& the **Congress of Neurological Surgeons**

Published in the ***Journal of Neuro-Oncology***

December 2, 2009

Editorial Commentary
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0070-7

Introduction
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0065-4

Methodology
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0059-2

Role of Whole Brain Radiation Therapy
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0060-9

Role of Surgical Resection
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0061-8

Role of Radiosurgery
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0073-4

Role of Chemotherapy
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0062-7

Recurrent/Progressive Brain Metastases
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0055-6

The Role of Anticonvulsants
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0056-5

The Role of Steroids
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0057-4

New and Emerging Therapies
http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11060-009-0058-3

Chapter 1 - Role of Whole Brain Radiation Therapy

Question

Should whole brain radiation therapy (WBRT) be used as the sole therapy in patients with newly-diagnosed, surgically accessible, single brain metastases, compared with WBRT plus surgical resection, and in what clinical settings?

Target population
This recommendation applies to adults with newly diagnosed single brain metastases amenable to surgical resection; however, the recommendation does not apply to relatively radiosensitive tumors histologies (i.e., small cell lung cancer, leukemia, lymphoma, germ cell tumors and multiple myeloma).
Recommendation
Surgical resection plus WBRT versus WBRT alone
Level 1 Class I evidence supports the use of surgical resection plus post-operative WBRT, as compared to WBRT alone, in patients with good performance status (functionally independent and spending less than 50% of time in bed) and limited extra-cranial disease. There is insufficient evidence to make a recommendation for patients with poor performance scores, advanced systemic disease, or multiple brain metastases.
If WBRT is used, is there an optimal dosing/fractionation schedule?
Target population
This recommendation applies to adults with newly diagnosed brain metastases.
Recommendation
Level 1 Class I evidence suggests that altered dose/fractionation schedules of WBRT do not result in significant differences in median survival, local control or neurocognitive outcomes when compared with “standard” WBRT dose/fractionation. (i.e., 30 Gy in 10 fractions or a biologically effective dose (BED) of 39 Gy10).
If WBRT is used, what impact does tumor histopathology have on treatment outcomes?
Target population
This recommendation applies to adults with newly diagnosed brain metastases.
Recommendation
Given the extremely limited data available, there is insufficient evidence to support the choice of any particular dose/fractionation regimen based on histopathology.
The following question is fully addressed in the surgery guideline paper within this series by Kalkanis et al. Given that the recommendation resulting from the systematic review of the literature on this topic is also highly relevant to the discussion of the role of WBRT in the management of brain metastases, this recommendation has been included below.
Does the addition of WBRT after surgical resection improve outcomes when compared with surgical resection alone?
Target population
This recommendation applies to adults with newly diagnosed single brain metastases amenable to surgical resection.
Recommendation
Surgical resection plus WBRT versus surgical resection alone
Level 1 Surgical resection followed by WBRT represents a superior treatment modality, in terms of improving tumor control at the original site of the metastasis and in the brain overall, when compared to surgical resection alone.

Chapter 2 - **Role of Surgical Resection**
Question

Should patients with newly-diagnosed metastatic brain tumors undergo open surgical resection versus whole brain radiation therapy (WBRT) and/or other treatment modalities such as radiosurgery, and in what clinical settings?

Target population

These recommendations apply to adults with a newly diagnosed single brain metastasis amenable to surgical resection.

Recommendations

Surgical resection plus WBRT versus surgical resection alone

Level 1 Surgical resection followed by WBRT represents a superior treatment modality, in terms of improving tumor control at the original site of the metastasis and in the brain overall, when compared to surgical resection alone.

Surgical resection plus WBRT versus SRS ± WBRT

Level 2 Surgical resection plus WBRT, versus stereotactic radiosurgery (SRS) plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates. SRS has not been assessed from an evidence-based standpoint for larger lesions (>3 cm) or for those causing significant mass effect (>1 cm midline shift).

Level 3 Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS *alone* may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

Note The following question is fully addressed in the WBRT guideline paper within this series by Gaspar et al. Given that the recommendation resulting from the systematic review of the literature on this topic is also highly relevant to the discussion of the role of surgical resection in the management of brain metastases, this recommendation has been included below.

Question

Does surgical resection in addition to WBRT improve outcomes when compared with WBRT alone?

Target population

This recommendation applies to adults with a newly diagnosed single brain metastasis amenable to surgical resection; however, the recommendation does not apply to relatively radiosensitive tumors histologies (i.e., small cell lung cancer, leukemia, lymphoma, germ cell tumors and multiple myeloma).

Recommendation

Surgical resection plus WBRT versus WBRT alone

Level 1 Class I evidence supports the use of surgical resection plus post-operative WBRT, as compared to WBRT alone, in patients with good performance status (functionally independent and spending less than 50% of time in bed) and limited extra-cranial disease. There is insufficient evidence to make a recommendation for patients with poor performance scores, advanced systemic disease, or multiple brain metastases.

Chapter 3 - **Role of Radiosurgery**

Question

Should patients with newly-diagnosed metastatic brain tumors undergo stereotactic radiosurgery (SRS) compared with other treatment modalities?

Target population

These recommendations apply to adults with newly diagnosed solid brain metastases amenable to SRS; lesions amenable to SRS are typically defined as measuring less than 3 cm in maximum diameter and producing minimal (less than 1 cm of midline shift) mass effect.

Recommendations

SRS plus WBRT vs. WBRT alone

Level 1 Single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumors who have a KPS ≥ 70.

Level 2 Single-dose SRS along with WBRT is superior in terms of local tumor control and maintaining functional status when compared to WBRT alone for patients with 1–4 metastatic brain tumors who have a KPS ≥ 70.

Level 3 Single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2–3 metastatic brain tumors.

Level 4 There is class III evidence demonstrating that single-dose SRS along with WBRT is superior to WBRT alone for improving patient survival for patients with single or multiple brain metastases and a KPS < 70.

SRS plus WBRT vs. SRS alone

Level 2 Single-dose SRS alone may provide an equivalent survival advantage for patients with brain metastases compared with WBRT + single-dose SRS. There is conflicting class I and II evidence regarding the risk of both local and distant recurrence when SRS is used in isolation, and class I evidence demonstrates a lower risk of distant recurrence with WBRT; thus, regular careful surveillance is warranted for patients treated with SRS alone in order to provide early identification of local and distant recurrences so that salvage therapy can be initiated at the soonest possible time.

Surgical Resection plus WBRT vs. SRS ± WBRT

Level 2 Surgical resection plus WBRT, vs. SRS plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates. SRS has not been assessed from an evidence-based standpoint for larger lesions (>3 cm) or for those causing significant mass effect (>1 cm midline shift). Level 3: Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

SRS alone vs. WBRT alone

Level 3 While both single-dose SRS and WBRT are effective for treating patients with brain metastases, single-dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of patient survival advantage.

Chapter 4 - Role of Chemotherapy

Question

Should patients with brain metastases receive chemotherapy in addition to whole brain radiotherapy (WBRT)?

Target population
This recommendation applies to adults with newly diagnosed brain metastases; however, the recommendation below does not apply to the exquisitely chemosensitive tumors, such as germinomas metastatic to the brain.
Recommendation
Level 1 Routine use of chemotherapy following WBRT for brain metastases has not been shown to increase survival and is not recommended. Four class I studies examined the role of carboplatin, chloroethylnitrosoureas, tegafur and temozolomide, and all resulted in no survival benefit. Two caveats are provided in order to allow the treating physician to individualize decision-making: First, the majority of the data are limited to non small cell lung (NSCLC) and breast cancer; therefore, in other tumor histologies, the possibility of clinical benefit cannot be absolutely ruled out. Second, the addition of chemotherapy to WBRT improved response rates in some, but not all trials; response rate was not the primary endpoint in most of these trials and end-point assessment was non-centralized, non-blinded, and post-hoc. Enrollment in chemotherapy-related clinical trials is encouraged.

Chapter 5 - Recurrent/Progressive Brain Metastases

Question
What evidence is available regarding the use of whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases?
Target population
This recommendation applies to adults with recurrent/progressive brain metastases who have previously been treated with WBRT, surgical resection and/or radiosurgery. Recurrent/progressive brain metastases are defined as metastases that recur/progress anywhere in the brain (original and/or non-original sites) after initial therapy.
Recommendation
Level 3 Since there is insufficient evidence to make definitive treatment recommendations in patients with recurrent/progressive brain metastases, treatment should be individualized based on a patient's functional status, extent of disease, volume/number of metastases, recurrence or progression at original versus non-original site, previous treatment and type of primary cancer, and enrollment in clinical trials is encouraged. In this context, the following can be recommended depending on a patient's specific condition: no further treatment (supportive care), re-irradiation (either WBRT and/or SRS), surgical excision or, to a lesser extent, chemotherapy.
Question
If WBRT is used in the setting of recurrent/progressive brain metastases, what impact does tumor histopathology have on treatment outcomes?
No studies were identified that met the eligibility criteria for this question.

Chapter 6 - The Role of Anticonvulsants

Question
Do prophylactic anticonvulsants decrease the risk of seizure in patients with metastatic brain tumors compared with no treatment?
Target population

These recommendations apply to adults with solid brain metastases who have not experienced a seizure due to their metastatic brain disease.

Recommendation

Level 3 For adults with brain metastases who have not experienced a seizure due to their metastatic brain disease, routine prophylactic use of anticonvulsants is not recommended.

Only a single underpowered randomized controlled trial (RCT), which did not detect a difference in seizure occurrence, provides evidence for decision-making purposes.

Chapter 7 - **The Role of Steroids**

Question

Do steroids improve neurologic symptoms in patients with metastatic brain tumors compared to no treatment? If steroids are given, what dose should be used? Comparisons include: (1) steroid therapy versus none. (2) comparison of different doses of steroid therapy.

Target population

These recommendations apply to adults diagnosed with brain metastases.

Recommendations

Steroid therapy versus no steroid therapy

Asymptomatic brain metastases patients without mass effect

Insufficient evidence exists to make a treatment recommendation for this clinical scenario.

Brain metastases patients with mild symptoms related to mass effect

Level 3 Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. It is recommended for patients who are symptomatic from metastatic disease to the brain that a starting dose of 4–8 mg/day of dexamethasone be considered.

Brain metastases patients with moderate to severe symptoms related to mass effect

Level 3 Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. If patients exhibit severe symptoms consistent with increased intracranial pressure, it is recommended that higher doses such as 16 mg/day or more be considered.

Choice of Steroid

Level 3 If corticosteroids are given, dexamethasone is the best drug choice given the available evidence.

Duration of Corticosteroid Administration

Level 3 Corticosteroids, if given, should be tapered slowly over a 2 week time period, or longer in symptomatic patients, based upon an individualized treatment regimen and a full understanding of the long-term sequelae of corticosteroid therapy.

Given the very limited number of studies (two) which met the eligibility criteria for the systematic review, these are the only recommendations that can be offered based on this methodology. Please see “Discussion” and “Summary” section for additional details.

Chapter 8 - **New and Emerging Therapies:**

Question

What evidence is available regarding the emerging and investigational therapies for the treatment of metastatic brain tumors?

Target population

These recommendations apply to adults with brain metastases.

Recommendations

New radiation sensitizers

Level 2 A subgroup analysis of a large prospective randomized controlled trial (RCT) suggested a prolongation of time to neurological progression with the early use of motexafin-gadolinium (MGd). Nonetheless this was not borne out in the overall study population and therefore an unequivocal recommendation to use the currently available radiation sensitizers, motexafin-gadolinium and efaproxiral (RSR 13) cannot be provided.

Interstitial modalities

There is no evidence to support the routine use of new or existing interstitial radiation, interstitial chemotherapy and or other interstitial modalities outside of approved clinical trials.

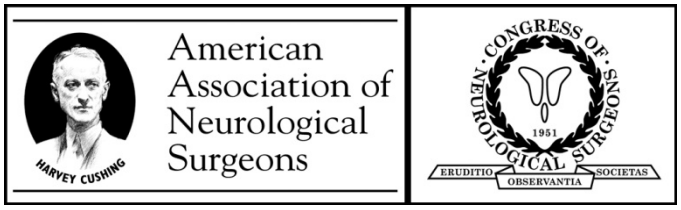
New chemotherapeutic agents

Level 2 Treatment of melanoma brain metastases with whole brain radiation therapy and temozolomide is reasonable based on one class II study.

Level 3 Depending on individual circumstances there may be patients who benefit from the use of temozolomide or fotemustine in the therapy of their brain metastases.

Molecular targeted agents

Level 3 The use of epidermal growth factor receptor inhibitors may be of use in the management of brain metastases from non-small cell lung carcinoma.



*The **American Association of Neurological Surgeons** (AANS), founded in 1931, and the **Congress of Neurological Surgeons** (CNS), founded in 1951, are the two largest scientific and educational associations for neurosurgical professionals in the world. These groups represent approximately 7,600 neurosurgeons worldwide. Neurological surgery is the medical specialty concerned with the prevention, diagnosis, treatment and rehabilitation of disorders that affect the entire nervous system, including the spinal column, spinal cord, brain and peripheral nerves. For more information, please visit www.aans.org or www.cns.org.*