Complete Summary

GUIDELINE TITLE

EFNS guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force.

BIBLIOGRAPHIC SOURCE(S)

Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, Heimans J, Hildebrand J, Hoskin P, Kalljo M, Krauseneck P, Marosi C, Siegal T, Vecht C. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. Eur J Neurol 2006 Jul;13(7):674-81. [44 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

Guidelines will be reviewed and updated at least every 2 years.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Brain metastases

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurological Surgery
Neurology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To establish evidence-based guidelines and identify controversies regarding the management of patients with brain metastases

TARGET POPULATION

Patients with brain metastases

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Medical history and physical examination
2. Computed tomography (CT) or magnetic resonance imaging (MRI)
3. Tissue diagnosis/histopathologic studies (by stereotactic or open surgery) if needed

4. Fluorodeoxyglucose positron-emission tomography (FDG PET) for detecting the primary tumor
5. Electroencephalogram (EEG)
6. CT of the chest/abdomen and mammography
7. Cerebrospinal fluid cytology if indicated

Management/Treatment

1. Surgical resection
2. Stereotactic radiosurgery (SRS)
3. Whole-brain radiotherapy (adjuvant or alone)
4. Chemotherapy
5. Supportive care (dexamethasone, anticonvulsants in patients with seizures, low-molecular-weight heparin (LMWH) in patients with venous thromboembolism (VTE)

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of diagnostic tests
- Effectiveness of treatment in improving median and overall survival, local tumor control, and functional independence and reducing relapse rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Task Force members searched the following databases: the Cochrane Library to date; Medline–Ovid (January 1966 to date); Medline–ProQuest; Medline-EIFL; Embase–Ovid (January 1990 to date); CancerNet; Science Citation Index (ISI). They used specific and sensitive keywords, as well as combinations of keywords, and publications in any language of countries represented in the Task Force. The Task Force members also collected guidelines from national and European multidisciplinary neuro-oncological societies and groups (from Italy, France, Netherlands, Germany, and UK). Moreover, they performed an investigation (by e-mail questionnaire) regarding the attitudes of members of the Task Force on several critical issues, reflecting the different national situations (10 countries) and specializations (11 neurologists, one neurosurgeon, one radiation oncologist, and one medical oncologist).

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The scientific evidence of papers collected from the literature was evaluated and graded according to European Federation of Neurological Societies (EFNS) Guidelines, and recommendations were given according to the same paper (see "Availability of Companion Documents"). When sufficient evidence for recommendations A–C was not available, the Task Force gave a recommendation as a 'Good Practice Point' if agreed by all members of the Task Force. When analyzing results and drawing recommendations, at any stage the differences were resolved by discussions and, if persisting, were reported in the text.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point When sufficient evidence for recommendations A–C was not available, the Task Force gave a recommendation as a 'Good Practice Point' if agreed by all members of the Task Force.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see "Availability of Companion Documents").

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point) are defined at the end of the "Major Recommendations" field.

Diagnosis

When neurological symptoms and/or signs develop in a patient with known systemic cancer, brain metastases must always be suspected. Careful medical history and physical examination with special emphasis on the presence/activity of the systemic disease and the general physical condition (estimation of the performance status) are recommended. All these recommendations are **Good Practice Points**.

Computed tomography (CT) (including double-dose delayed contrast) is inferior to magnetic resonance imaging (MRI), but it is sufficient when shows multiple brain metastases. Contrast-enhanced MRI is indicated when (a) surgery or radiosurgery are considered, one or two metastases on contrast-enhanced CT and a Karnofsky Performance Status (KPS) $\geq$70 (refer to Table 1 in the original guideline document); (b) contrast-enhanced CT is negative but the history is strongly suggestive of the presence of brain metastases in a patient with established malignant disease; and (c) CT is not conclusive to eliminate non-neoplastic lesions (abscesses, infections, demyelinating diseases, and vascular lesions). All these recommendations are **level B**. Diffusion MRI is useful for the differential diagnosis of ring-enhancing lesions (**level C recommendation**). Electroencephalogram (EEG) is indicated in patients who suffer from seizures that cannot be classified as epileptic (**Good Practice Point**) (refer to Table 1 in the original guideline document).

Tissue diagnosis (by stereotactic or open surgery) should be obtained when (i) the primary tumor is unknown, (ii) the systemic cancer is well controlled and the patient is a long-term survivor, (iii) lesions on MRI do not show the typical aspect of brain metastases, and (iv) there is clinical suspicion of an abscess (fever, meningism) (**level B recommendation**). In patients with unknown primary tumor, CT of the chest/abdomen and mammography are recommended by most members of the Task Force, but a further extensive evaluation is not appropriate in the absence of specific symptoms or indications from the brain biopsy (**Good Practice Point**). Fluorine-18-labeled deoxyglucose positron-emission tomography (FDG PET) can be useful for detecting the primary tumor (**Good Practice Point**). The histopathologic studies on the brain metastasis may provide valuable information in indicating a likely organ of origin and guiding further specialized diagnostic work-up: in this regard immunohistochemical staining to detect tissue-, organ-, or tumor-specific antigens is useful (**Good Practice Point**). Cerebrospinal fluid (CSF) cytology is needed when the coexistence of a carcinomatous meningitis is suspected (**Good Practice Point**).

Supportive Care

Dexamethasone is the corticosteroid of choice and twice-daily dosing is sufficient (**Good Practice Point**). In most cases starting doses should not exceed 4 to 8 mg/day, but patients with severe symptoms, including impaired consciousness or other signs of increased intracranial pressure, may benefit from higher doses such as 16 mg/day or even more (**level B recommendation**). An attempt to reduce the dose should be undertaken within 1 week of initiation of treatment; if possible, steroids should be weaned off within two weeks. If complete weaning off is not possible, the lowest possible dose should be looked for. Asymptomatic patients do not require steroids. Steroids may reduce the acute side effects of radiation therapy. All these recommendations are **Good Practice Points**.

Anticonvulsants should not be prescribed prophylactically (**level A recommendation**). In patients who suffer from epileptic seizures and need a concomitant treatment with chemotherapeutics, enzyme-inducing antiepileptic drugs should be avoided (**level B recommendation**).

In patients with venous thromboembolism (VTE), low-molecular-weight heparin (LMWH) is effective and well tolerated for both initial therapy and secondary prophylaxis (**level A recommendation**). A duration ranging from 3 to 6 months is recommended for the anticoagulant treatment (**Good Practice Point**). Prophylaxis in patients undergoing surgery is recommended (**level B recommendation**).

Treatment of Single Brain Metastasis

Surgical resection should be considered in patients with single brain metastasis in an accessible location, especially when the size is large, the mass effect is considerable and an obstructive hydrocephalus is present (**Good Practice Point**). Surgery is recommended when the systemic disease is absent/controlled and the Karnofsky Performance score is 70 or more (**level A recommendation**). When the combined resection of a solitary brain metastasis and a non-small cell lung carcinoma (stage I and II) is feasible, surgery for the brain lesion should come first, with a maximum delay between the two surgeries not exceeding 3 weeks

(**Good Practice Point**). Patients with disseminated but controllable systemic disease (i.e. bone metastases from breast cancer) or with a radioresistant primary tumor (melanoma, renal cell carcinoma, and colon cancer) may benefit from surgery (**Good Practice Point**). Surgery at recurrence is useful in selected patients (**level C recommendation**).

Stereotactic radiosurgery (SRS) should be considered in patients with metastases of a diameter of $\leq$3–3.5 cm and/or located in eloquent cortical areas, basal ganglia, brain stem or with comorbidities precluding surgery (**level B recommendation**). Gamma-knife or linear accelerator (Linac) are equally effective (**level B recommendation**). SRS may be effective at recurrence after prior radiation treatment (**level B recommendation**).

The role of adjuvant whole-brain radiotherapy (WBRT) after surgery or radiosurgery remains to be clarified. In case of absent/controlled systemic disease and Karnofsky Performance score of 70 or more, one can either withhold initial WBRT if close follow-up with MRI (every 3 to 4 months) is performed or deliver early WBRT with fractions of 1.8–2 Gy to a total dose of 40–55 Gy to avoid late neurotoxicity (**Good Practice Point**).

Whole-brain radiotherapy alone is the therapy of choice for patients with active systemic disease and/or poor performance status and should employ hypofractionated regimens such as 30 Gy in 10 fractions or 20 Gy in five fractions (**level B recommendation**). For elderly patients with poor performance status WBRT can be withheld and supportive care only employed (**Good Practice Point**).

The Treatment of Multiple Brain Metastases

In patients with up to three brain metastases, good performance status (KPS of 70 or more) and controlled systemic disease, SRS is an alternative to WBRT (**level B recommendation**), whilst surgical resection is an option when the lesions are in an accessible location (**level C recommendation**). In patients with more than three brain metastases WBRT with hypofractionated regimens is the treatment of choice (**level B recommendation**). In bedridden patients it should be considered to withhold active radiation treatment and restrict therapy to supportive care (**Good Practice Point**).

The Role of Chemotherapy

Chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumors, like small cell lung cancers, lymphomas, germ cell tumors and breast cancers, especially for chemonaive patients or if an effective chemotherapy schedule for the primary is still available (**Good Practice Point**). Radiation therapy, with or without chemotherapy, is still the treatment of choice for patients needing a palliation of neurological symptoms (**Good Practice Point**).

Definitions:

Evidence Classification Scheme for a Diagnostic Measure:

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Good Practice Point When sufficient evidence for recommendations A–C was not available, the Task Force gave a recommendation as a 'Good Practice Point' if agreed by all members of the Task Force.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and treatment of brain metastases

POTENTIAL HARMS

- Side effects from chronic *dexamethasone* administration, including myopathy, are frequent and contribute to disability.
- Subtherapeutic levels of *anticonvulsants* were extremely common and the severity of side effects appeared to be higher (20–40%) in brain tumor patients than in the general population receiving anticonvulsants, probably because of drug interactions. Some antiepileptic drugs stimulate the cytochrome P450 system and accelerate the metabolism of corticosteroids and chemotherapeutic agents and thus reduce their efficacy.
- Acute (early) and chronic (late) complications following *radiosurgery* for brain metastases are relatively modest. Acute reactions (due to edema) occur in 7

to 10% of patients, more often within 2 weeks from treatment, and include headache, nausea and vomiting, worsening of preexistent neurological deficits and seizures. These reactions are generally reversible with steroids. Chronic complications consist of hemorrhage and radionecrosis (1 to 17%), requiring reoperation in up to 4% of patients.

- *Whole-brain radiotherapy (WBRT)* may cause early adverse effects (fatigue, alopecia, Eustachian tube dysfunction) and late neurotoxicity. Long-term survivors after WBRT frequently develop radiographic changes on computed tomography (CT) or magnetic resonance imaging (MRI), including cortical atrophy, ventriculomegaly and hyperintensity of the periventricular white matter in T2 and fluid-attenuated inversion recovery images. Up to 11% of patients have clinical symptoms such as memory loss progressing to dementia, frontal gait disorders and urinary incontinence. The risk of late neurotoxicity is higher with hypofractionated schedules of radiotherapy (size fraction >2 Gy). Nausea, vomiting, headache, fever and transient worsening of neurological symptoms in the initial phase of therapy may be observed.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, Heimans J, Hildebrand J, Hoskin P, Kalljo M, Krauseneck P, Marosi C, Siegal T, Vecht C. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. Eur J Neurol 2006 Jul;13(7):674-81. [44 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Jul

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on the Diagnosis and Treatment of Brain Metastases

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

None of the Members of the Task Force, including the chairperson, had any form of conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

Guidelines will be reviewed and updated at least every 2 years.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from Dr Riccardo Soffietti, MD, Chairperson of the Task Force, Neuro-Oncology Service, Department of Neuroscience and Oncology, University and San Giovanni Battista Hospital, V. Cherasco 15, 10126, Torino, Italy; Phone: ++39 011 6334904; Fax: ++39 011 6963487; E-mail: riccardo.soffietti@unito.it

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.
- Continuing Medical Education questions available from the European Journal of Neurology Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 6, 2007. The information was verified by the guideline developer on May 25, 2007. This summary was updated

by ECRI Institute on June 26, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection.

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