

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

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The objectives have been to establish evidence-based guidelines and identify controversies regarding the management of patients with brain metastases. The collection of scientific data was obtained by consulting the Cochrane Library, bibliographic databases, overview papers and previous guidelines from scientific societies and organizations. A tissue diagnosis is necessary when the primary tumor is unknown or the aspect on computed tomography/magnetic resonance imaging is atypical. Dexamethasone is the corticosteroid of choice for cerebral edema. Anticonvulsants should not be prescribed prophylactically. Surgery should be considered in patients with up to three brain metastases, being effective in prolonging survival when the systemic disease is absent/controlled and the performance status is high. Stereotactic radiosurgery should be considered in patients with metastases of 3–3.5 cm of maximum diameter. Whole-brain radiotherapy (WBRT) after surgery or radiosurgery is debated: in case of absent/controlled systemic cancer and Karnofsky Performance score of 70 or more, one can either withhold initial WBRT or deliver early WBRT with conventional fractionation to avoid late neurotoxicity. WBRT alone is the treatment of choice for patients with single or multiple brain metastases not amenable to surgery or radiosurgery. Chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumors.

Background

Brain metastases represent an important cause of morbidity and mortality for cancer patients. Brain metastases are more common than primary brain tumors. The incidence of brain metastases has increased over time as a consequence of the increase in overall survival for many types of cancer and the improved detection by magnetic resonance imaging (MRI). Brain metastases may occur in 20–40% of patients with can-

cer, being symptomatic during life in 60–75%. In adults the primary tumors most likely to metastasize to the brain are located, in decreasing order, in the lung (minimum 50%), breast (15–25%), skin (melanoma) (5–20%), colon–rectum and kidney, but in general any malignant tumor is able to metastasize to the brain. The primary site is unknown in up to 15% of patients. Brain metastases are more often diagnosed in patients with known malignancy (metachronous presentation). Less frequently (up to 30%) brain metastases are diagnosed either at the time of primary tumor diagnosis (synchronous presentation) or before the discovery of the primary tumor (precocious presentation). High performance status (Fig. 1), solitary brain metastasis, absence of systemic metastases, controlled primary tumor and younger age (<60–65 years) are the most important favorable prognostic factors [1,2]. Based on these factors the Radiation Therapy Oncology Group (US) has identified subgroups of patients with different prognosis [Recursive Partitioning Analysis (RPA)

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Classes I, II, and III] [1]. Neurocognitive functions are prognostically important as well [3,4]. The prognosis is similar for patients with both known and unknown primary tumor [5].

Search strategy

We 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). We used specific and sensitive keywords, as well as combinations of keywords, and publications in any language of countries represented in the Task Force. We also collected guidelines from national and European multidisciplinary neuro-oncological societies and groups (from Italy, France, Netherlands, Germany, and UK). Moreover we 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).

Method for reaching consensus

The scientific evidence of papers collected from the literature was evaluated and graded according to EFNS Guidelines [6], and recommendations were given according to the same paper. When sufficient evidence for recommendations A–C was not available, we 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.

Results

Diagnosis

Headache (40–50%), focal neurological deficits (30–40%) and seizures (15–20%) are the most common presenting symptoms. A minority of patients have an acute ‘stroke-like’ onset, more often related to an intratumoral hemorrhage (melanoma, choriocarcinoma and renal carcinoma). Altered mental status or impaired cognition are seen in patients with multiple metastases and/or increased intracranial pressure, sometimes resembling a metabolic encephalopathy. Contrast-enhanced MRI is more sensitive than enhanced CT (including double-dose delayed contrast) or unenhanced MRI in detecting brain metastases, particularly when located in the posterior fossa or very

small [7] (Class II evidence). Double or triple doses of gadolinium-based contrast agents are better than single doses, but increasing the dose may lead to an increased number of false-positive findings [8] (class III evidence).

There are no pathognomonic features on CT or MRI that distinguish brain metastases from primary brain tumors (more commonly malignant gliomas and lymphomas) or non-neoplastic conditions (abscesses, infections, demyelinating diseases, and vascular lesions). A peripheral location, spherical shape, ring enhancement with prominent peritumoral edema and multiple lesions all suggest metastatic disease: these characteristics are helpful but not diagnostic, even in patients with a positive history of cancer. Diffusion-weighted MRI may be useful for the differential diagnosis of ring-enhancing cerebral lesions (restricted diffusion in abscesses compared with unrestricted diffusion in cystic or necrotic glioblastomas or metastases), but the findings are not specific [9,10] (class III evidence). In patients with either histologically confirmed or radiologically suspected brain metastases and a negative history of cancer chest CT is more sensitive than chest radiograph in detecting a synchronous lung tumor (more commonly a non-small cell cancer) (class III evidence). CT of the abdomen occasionally shows an unsuspected cancer. Further investigations are almost never fruitful without positive features in the patient’s history or localizing signs on the physical examination to suggest a primary site [11] (class III evidence). Whole-body FDG PET is a sensitive tool for detecting a ‘probable’ primary tumor by visualizing foci of abnormal uptake, more often in the lung [12] (class III evidence), but the specificity in differentiating malignant tumors from benign or inflammatory lesions is relatively low.

Supportive care

Most neurologists use dexamethasone to control cerebral edema, largely because of its minimal mineralocorticoid effect and long half-life. Patients are generally managed with starting doses of 4–8 mg/day [13] (class II evidence). Up to 75% of patients with brain metastases show marked neurological improvement within 24–72 h after beginning dexamethasone. Any other corticosteroid is effective if given in equipotent doses. Side effects from chronic dexamethasone administration, including myopathy, are frequent and contribute to disability. When used as the sole form of treatment, dexamethasone produces about 1 month’s remission of symptoms and slightly increases the 4- to 6-week median survival of patients who receive no treatment at all [14].

The need for anticonvulsant medication is clear in patients who have experienced a seizure by the time

their brain tumor is diagnosed. Although many clinicians routinely place patients with brain metastases on prophylactic antiepileptic drugs (AEDs), the evidence (class I) does not support this practice. The Quality Standards Subcommittee of the American Academy of Neurology (AAN) has reported on anticonvulsant prophylaxis in patients with newly diagnosed brain tumors, including brain metastases [15]. Twelve studies, either randomized controlled trials or cohort studies, investigating the ability of prophylactic AEDs (phenytoin, phenobarbital, valproic acid) to prevent first seizures, have been examined, and none have demonstrated efficacy. 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 (class II evidence). Phenytoin, carbamazepine, and phenobarbital stimulate the cytochrome P450 system and accelerate the metabolism of corticosteroids and chemotherapeutic agents such as nitrosoureas, paclitaxel, cyclophosphamide, topotecan, irinotecan, thiotepa, adriamycin and methotrexate, and thus reduce their efficacy. The role of prophylactic anticonvulsants remains to be addressed specifically in some subgroups of patients who have a higher risk of developing seizures, such as those with metastatic melanoma, hemorrhagic lesions and multiple metastases. For patients who underwent a neurosurgical procedure the efficacy of prophylaxis has not been proved [16] (class II evidence), and the AAN recommends to withdraw AEDs at 1 week after surgery. The efficacy of novel AEDs (levetiracetam, topiramate, gabapentin, oxcarbazepine, and lamotrigine) in controlling epileptic seizures has not been extensively investigated.

Anticoagulant therapy is the standard treatment for acute venous thromboembolism (VTE) in cancer patients. For initial therapy subcutaneous low-molecular weight heparin (LMWH) is as effective and safe as intravenous unfractionated heparin (UFH) [17] (class I evidence). LMWH is more effective than oral anticoagulant therapy (warfarin) in preventing recurrent VTE in cancer patients [18] (class I evidence). The duration of anticoagulant therapy has not been specifically addressed in cancer patients. A prophylaxis with either UFH or LMWH reduces the risk of VTE in patients undergoing major surgery for cancer (class II evidence).

Treatment of single brain metastasis

Surgery

Three randomized trials have compared surgical resection followed by whole-brain radiotherapy (WBRT) with WBRT alone [19–21]. The first two studies have

shown a survival benefit for patients receiving the combined treatment (median survival 9–10 months vs. 3–6 months). In the Patchell study patients who received surgery displayed a lower rate of local relapses (20% vs. 52%) and a longer time of functional independence. The third study, that included more patients with an active systemic disease and a low Karnofsky performance status, did not show any benefit with the addition of surgery. Therefore there is class I evidence that the survival benefit of surgical resection is limited to the subgroup of patients with controlled systemic disease and good performance status. Surgical resection allows in the majority of patients an immediate relief of symptoms of intracranial hypertension, a reduction of focal neurological deficits and seizures, and a rapid steroid taper. Gross total resection of brain metastasis can be achieved with lower morbidity using contemporary image-guided systems, such as preoperative functional MRI, intraoperative neuronavigation and cortical mapping [22] (class IV evidence). The combined resection of a solitary brain metastasis and a synchronous non-small cell lung carcinoma (stages I and II) is increasingly performed, yielding a median survival of at least 12 months, with 10–30% of patients surviving at 5 years [23] (class III evidence). In selected patients with local relapse of a single brain metastasis and good performance status, reoperation affords a neurological improvement and a prolongation of survival [22] (class III evidence).

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) permits the delivery of a single high dose of radiation to a target of 3–3.5 cm of maximum diameter by using gamma-knife (multiple cobalt sources) or linear accelerator (Linac) through a stereotactic device. The rapid dose fall-off of SRS minimizes the risk of damage to the surrounding normal nervous tissue. In patients with newly diagnosed brain metastases a decrease of symptoms, a local tumor control (defined as shrinkage or arrest of growth) at 1 year of 80–90% and a median survival of 6–12 months have been reported [24,25] (class II evidence). Metastases from radioresistant tumors, such as melanoma, renal cell carcinoma and colon cancer, respond to SRS as well as do metastases from radiosensitive tumors. Radiosurgery allows the treatment of brain metastases in almost any location. The type of radiosurgical procedure, gamma-knife or Linac based, does not have an impact on the results [26]. A randomized trial has shown that SRS combined with WBRT (radiosurgical boost) is superior to WBRT alone in terms of survival [27] (class II evidence). Survival following radiosurgery is comparable with that achieved with surgery [24,25] (class II evidence). SRS is less

invasive than surgery and can be accomplished in an outpatient setting, and thus offers cost effectiveness advantages over surgery, on the other hand, patients with large lesions may require chronic steroid administration. Radiosurgery is effective for patients with brain metastases that have recurred following conventional WBRT [28] (class II evidence). Hypofractionated stereotactic radiotherapy can be an alternative to SRS.

Acute (early) and chronic (late) complications following radiosurgery for brain metastases are relatively modest [29]. Acute reactions (due to edema) occur in 7–10% 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 (1–17%), requiring reoperation in up to 4% of patients. Radiographically, a transient increase in the size of the irradiated lesion, with increasing edema and mass effect, with or without radionecrosis, cannot be distinguished from a tumor progression: FdG-PET [30] and MR spectroscopy [31] can give additional information.

Whole-brain radiotherapy after surgery or radiosurgery (adjuvant WBRT)

It is still controversial whether adjuvant WBRT, whose rationale is that of destroying microscopic metastatic deposits at original tumor site or at distant intracranial locations, is necessary after complete surgical resection or radiosurgery. Time-consuming fractionated treatment, possible long-term neurotoxicity and availability of effective salvage treatments at recurrence are the main arguments against WBRT. Adjuvant WBRT after complete surgical resection significantly reduces local and distant CNS relapses (18% vs. 70%), without affecting overall survival or functionally independent survival [32] (class I evidence). A modest survival benefit for the addition of WBRT has been found in the subset of patients without evidence of extracranial disease [33]. WBRT in conjunction with radiosurgery improves local control and reduces the risk of new distant brain metastases, but most studies (non randomized) support the viewpoint that the combination of radiosurgery and WBRT does not improve the overall survival, except for patients without evidence of extracranial disease [26] (class II evidence). WBRT may cause early adverse effects (fatigue, alopecia, Eustachian tube dysfunction) and late neurotoxicity. Long-term survivors after WBRT frequently develop radiographic changes on CT or 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) [34].

Whole-brain radiotherapy alone

Median survival after WBRT alone is 3–6 months. Different fractionation schedules, ranging from 20 Gy in 1 week to 50 Gy in 4 weeks, yield comparable results [35,36] (class II evidence). Nausea, vomiting, headache, fever and transient worsening of neurological symptoms in the initial phase of therapy may be observed.

The treatment of multiple brain metastases

Median survival after WBRT alone is 2–6 months, with good palliation of symptoms including headache, motor deficits, confusional states, and cranial nerve palsies. Hypofractionated treatments are generally employed, most commonly 30 Gy in 10 fractions or 20 Gy in five fractions. In patients with poor prognostic factors supportive care only is frequently prescribed. Radiosurgery is an alternative to WBRT in patients with up to three brain metastases. WBRT with radiosurgery boost improves functional independence but not survival in patients with two or three lesions [27] (class I evidence). Amongst new radiosensitizers used in conjunction with standard WBRT, motexafin-gadolinium and RSR 13 have shown a benefit in prolonging time to neurologic/neurocognitive progression in patients with brain metastases from lung cancer and in those of RPA class II, respectively [37,38] (class III evidence). When the number of brain metastases is limited (up to 3), the lesions are accessible and the patients are relatively young, in good neurological condition and with a controlled systemic disease, complete surgical resection yields results that are comparable with those obtained in single lesions [39] (class III evidence).

The role of chemotherapy

Chemosensitivity is the critical factor for the response of brain metastases to chemotherapeutic agents [25]: brain metastases are often as responsive as the primary tumor and extracranial metastases; higher response rates are observed when newly diagnosed, chemotherapy-naïve patients are treated; response rate of brain and systemic cancer declines with second- and third-line therapy; response to chemotherapy of brain metastases from mostly chemosensitive tumors (small cell lung carcinoma, germ cell tumors, lymphomas) is of the same order of that observed after radiotherapy. The blood–brain barrier penetration is a limiting factor in

micrometastases and for molecular targeted agents. The combination of radiotherapy and chemotherapy may improve the response rate and/or the progression-free survival, but not the overall survival [40–42] (class I evidence).

Emerging treatments

Emerging treatments of brain metastases, that are still confined to an investigational setting, include both local and systemic approaches.

An innovative modality of postoperative local irradiation is the Gliasite Radiation Therapy System, consisting of an inflatable balloon placed in the resection cavity at the time of tumor debulking and filled with an aqueous solution of Iodine-125. The dose delivered is up to 60 Gy at 1 cm and the device is explanted after 3–6 days of treatment. A multicenter phase II study on single brain metastasis has been completed in the US, and the preliminary analysis indicates that the procedure is relatively safe and the local recurrence rate could be significantly reduced [43]. Local chemotherapy, utilizing BCNU-impregnated biodegradable polymers placed in the resection cavity, has recently entered a clinical trial in the US.

Novel cytotoxic drugs, such as temozolomide, fotemustine, and capecitabine are being investigated, alone or in combination, in brain metastases from different tumor types [25]. Amongst molecular targeted agents, preliminary encouraging results in brain metastases from non-small cell lung cancer have been reported with gefitinib (ZD 1839), an oral epidermal growth factor receptor tyrosine kinase inhibitor [44]. Novel molecular agents, targeting angiogenesis and/or proliferation and/or invasion and/or apoptosis will be available for clinical trials in the next future.

Recommendations and good practice points

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 (including double-dose delayed contrast) is inferior to MRI, but it is sufficient when shows multiple brain metastases. Contrast-enhanced MRI is indicated when (i) surgery or radiosurgery are considered one or two metastases on

Table 1 Karnofsky Performance Status (KPS)

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS 80	Normal activity with effort; some signs or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or to do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death not imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS 0	Death

contrast-enhanced CT and a Karnofsky Performance Status (KPS) ≥ 70 ; (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). EEG is indicated in patients who suffer from seizures that cannot be classified as epileptic (Good Practice Point) (Table 1).

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). 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). 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 4–8 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 VTE, 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 should be considered in patients with metastases of a diameter of ≤ 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 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 3–4 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 chemonaïve 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).

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

Conflict of interest

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

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