CHAPTER 30
Brain metastases

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Objectives

The primary objective has been to establish evidence-based guidelines in regard to the management of patients with brain metastases. The secondary objective has been to identify areas where there are still controversies and clinical trials are needed.

Background

Brain metastases represent an important cause of morbidity and mortality for cancer patients and are more common than primary brain tumours. 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 cancer, being symptomatic during life in 60–75%. In adults, the primary tumours most likely to metastatize to the brain are located in the lung (minimum 50%), breast (15–25%), skin (melanoma) (5–20%), colon-rectum, and kidney, but any malignant tumour is able to metastatize 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 tumour diagnosis (synchronous presentation) or before the discovery of the primary tumour (precocious presentation). High performance status, absence of systemic metastases, controlled primary tumour, and younger age (<60–65 years) are the most important favourable prognostic factors. Based on these factors the Radiation Therapy Oncology Group (US) has identified subgroups of patients with different prognosis (recursive partitioning analysis (RPA) Class I, II, III) [1]. Recently, a new prognostic index, the grade prognostic assessment (GPA), that takes into account the number of brain metastases, in addition to age, KPS, and extracranial metastases, has been proposed [2]. Neurocognitive function is prognostically important as well [3]. The prognosis is similar for patients with both known and unknown primary tumour [4].

Search strategy

We searched: 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,

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Table 30.1 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

Netherlands, Germany, and the UK). Moreover, we performed an investigation (by email questionnaire) regarding the views 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, one medical oncologist).

Method for reaching consensus

The scientific evidence of papers collected from the literature was evaluated and graded according to Brainin *et al.* (2004) [5], and recommendations were given according to the same paper. When sufficient evidence for recommendation A–C was not available, we considered a recommendation to be a 'Good Practice Point' (GPP) if agreed by all members of the task force. When analysing results and drawing recommendations at any stage, the differences were resolved by discussions.

Review of the evidence

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, related to an intratumoural haemorrhage (in particular 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 computed tomography (CT) (including double-dose delayed contrast) or unenhanced MRI in detecting brain metastases, particularly when located in the posterior fossa or very small [6] (Class II). 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 [7] (Class III).

There are no pathognomonic features on CT or MRI that distinguish brain metastases from primary brain tumours such as malignant gliomas and lymphomas or non-neoplastic conditions (abscesses, infections, demyelinating diseases, vascular lesions). A peripheral location, spherical shape, ring enhancement with prominent peritumoural oedema, 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 (DW) MR imaging may be useful for the differential diagnosis of ring-enhancing cerebral lesions (restricted diffusion in abscesses compared to unrestricted diffusion in cystic or necrotic glioblastomas or metastases), but the findings are not specific [8, 9] (Class III). 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 tumour (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 [10] (Class III). Whole-body fluorodeoxyglucose positron emission tomography (FDG PET) is a sensitive tool for detecting a 'probable' primary tumour by visualizing foci of abnormal uptake, more often in the lung [11] (Class III), but the specificity in differentiating malignant tumours from benign or inflammatory lesions is relatively low.

Supportive care

Dexamethasone is commonly used to control cerebral oedema, because of the minimal mineralocorticoid effect

and long half-life. Patients are generally managed with starting doses of 4–8 mg per day [12] (Class II). Up to 75% of patients 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 one month's remission of symptoms and slightly increases the 4–6-week median survival of patients who receive no treatment at all [13].

The need for anticonvulsant medication is clear in patients who have experienced a seizure by the time their brain tumour is diagnosed. The evidence does not support prophylaxis with antiepileptic drugs (AEDs) in patients with brain tumours, including metastases (Class I). Twelve studies, either randomized trials or cohort studies, investigating the ability of prophylactic AEDs (phenytoin, phenobarbital, valproic acid) to prevent first seizures have been examined and none has demonstrated efficacy [14]. Subtherapeutic levels of anticonvulsants were extremely common and the severity of side effects appeared to be higher (20–40%) in brain tumour patients than in the general population receiving anticonvulsants, probably because of drug interactions (Class II). 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 in some subgroups of patients who have a higher risk of developing seizures, such as those with metastatic melanoma, haemorrhagic lesions, and multiple metastases. For patients who underwent a neurosurgical procedure the efficacy of prophylaxis has not been proven [15] (Class II). The efficacy of novel AEDs (levetiracetam, topiramate, gabapentin, oxcarbazepine, lamotrigine) 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) [16] (Class I). LMWH is more effective than oral anticoagulant therapy (warfarin) in preventing recurrent VTE in cancer patients [17] (Class I). 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).

Treatment of single brain metastasis

Surgery

Three randomized trials have compared surgical resection followed by WBRT with WBRT alone [18–20]. The first two studies have shown a survival benefit for patients receiving the combined treatment (median survival 9–10 months versus 3–6 months). In the Patchell study, patients who received surgery displayed a lower rate of local relapses (20% versus 52%) and a longer time of functional independence. The third study, which 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 a brain metastasis can be achieved with lower morbidity using contemporary image-guided systems, such as preoperative functional MRI, intraoperative neuronavigation, and cortical mapping [21]. The combined resection of a solitary brain metastasis and a synchronous non-small-cell lung carcinoma (NSCLC) (stage I and II) yields a median survival of at least 12 months, with 10–30% of patients surviving at 5 years [22] (Class III). In patients with local brain relapse and good performance status, re-operation affords a neurological improvement and prolongation of survival [21] (Class III).

Leptomeningeal dissemination (LMD) can be a complication, especially for patients with posterior fossa metastases [23].

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. Most brain metastases represent an ideal target for SRS, owing to the small size, spherical shape,

and distinct radiographic and pathologic margins [24]. The dose is inversely related to tumour diameter and volume [25]. In patients with newly diagnosed brain metastases, a decrease of symptoms, a local tumour 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 [26] (Class II). Metastases from radioresistant tumours, such as melanoma, renal cell carcinoma, and colon cancer, respond to SRS as well, as do metastases from radiosensitive tumours [27] (Class II). Radiosurgery allows the treatment of brain metastases in almost any location, including brainstem [28]. The type of radiosurgical procedure, gamma-knife or Linac-based, does not have an impact on the results. SRS combined with WBRT (radiosurgical boost) is superior to WBRT alone in terms of survival [29] (Class II). Survival following radiosurgery is comparable to that achieved with surgery [30, 31] (Class II). SRS is less invasive and can be accomplished in an outpatient setting, and thus offers cost-effectiveness advantages over surgery; on the other hand, patients with larger lesions may require chronic steroid administration. Radiosurgery is effective for patients with brain metastases that have recurred following WBRT [25] (Class II).

Acute (early) and chronic (late) complications following radiosurgery are reported in 10–40% of patients, serious complications being rare [32]. Acute reactions (due to oedema) occur more often within 2 weeks of treatment, and include headache, nausea and vomiting, worsening of pre-existent neurological deficits, and seizures. These reactions are generally reversible with steroids. Chronic complications consist of haemorrhage and radionecrosis (1–17%), requiring re-operation in up to 4% of patients. Radiographically, a transient increase in the size of the irradiated lesion, with increasing oedema and mass effect, with or without radionecrosis, cannot be distinguished from a tumour progression: FdG-PET [33] and MR spectroscopy [34] can give additional information .

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). Nausea, vomiting, headache, fever, and transient worsening of neurological symptoms in the initial phase of therapy may be observed.

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

It is still controversial whether adjuvant WBRT, which has a rationale of destroying microscopic metastatic deposits at the original tumour site or at distant 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 [37], whereas the negative impact of central nervous system (CNS) progression on the neurologic and neurocognitive function when omitting initial WBRT, and the uncertainty regarding the value of salvage treatments in reversing the neurologic symptoms and signs are arguments in favour [38]. There are three randomized trials [39–41] showing that the omission of WBRT in patients with newly diagnosed brain metastases after either surgery or SRS results in significantly worse local and distant control in the brain on MRI, though it does not affect overall and functionally independent survival (Class I). 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, hydrocephalus, and hyperintensity of the periventricular white matter in T2 and FLAIR images. Up to 11% of patients receiving hypofractionated schedules of radiotherapy (size fraction of 4–6 Gy) [42] have clinical symptoms such as memory loss progressing to dementia, frontal gait disorders, and urinary incontinence. Overall, aside from the risk of dementia after large fractions of WBRT, the true incidence of cognitive dysfunctions after conventional treatments (i.e. 30 Gy in 10 fractions) is not well understood, even if the deterioration of neurocognitive functions in long-term survivors (up to 36 months) could not be negligible [43].

The identification of patients with different risk of developing brain tumour relapse could be extremely important to define the most appropriate initial management [44].

Local forms of radiotherapy could be an alternative to WBRT after resection of a brain metastasis, because they target the most frequent site of tumour recurrence, that is the resection cavity. SRS to the resection cavity [45] and the Gliasite Radiation Therapy System (an intracavitary high-activity ^{125}I brachytherapy) [46] yield local control and local failure rates and survival in the range

which is expected for patients in RPA Class 1 and 2, treated with either surgery + WBRT or SRS, alone or in association with WBRT. Radiation-induced neurocognitive deficits may result from radiation injury to proliferating neuronal progenitor cells in the subgranular zone of the hippocampus [47]. Conformal avoidance of the hippocampus during WBRT is a novel technique that allows treatment of the majority of the brain to full dose while keeping the radiation dose to the hippocampus relatively lower [48].

The treatment of multiple brain metastases

Median survival after WBRT alone is 2–6 months, with good palliation of neurological symptoms. 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 [29] (Class I). Among new radiosensitizers, associated with WBRT, motexafin-gadolinium has shown a benefit in prolonging time to neurologic/neurocognitive progression in patients with brain metastases from NSCLC [49] (Class II) and efaproxiral has shown a benefit in prolonging survival and quality of life in patients with brain metastases from breast cancer [50] (Class II). When the number of brain metastases is limited (up to three), 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 to those obtained in single lesions [51] (Class III).

Chemotherapy

Chemotherapeutic agents are effectve in the treatment of brain metastases [30] (Class III): brain metastases are often as responsive as the primary tumour and extracranial metastases, but not always the intracranial response parallels the extracranial response; higher response rates are observed when newly diagnosed, chemotherapy-naïve patients are treated; response to chemotherapy of brain metastases from mostly chemosensitive tumours (small-cell lung carcinoma, germ cell tumours, lymphomas) is of the same order as that observed after radiotherapy. Novel cytotoxic drugs, such as temozolomide, capecitabine, and fotemustine, can be useful in brain metastases from lung cancers, breast cancers and melanoma respectively. The combination of radiotherapy and chemotherapy may improve the response rate and/or the progression-free survival, but not the overall survival [52, 53] (Class I).

Local chemotherapy after surgical resection (Gliadel wafers) could reduce the risk of local relapse [54] (Class III).

Targeted therapies

Molecularly targeted therapies have been increasingly investigated in recent years in patients with brain metastases [55]. Brain metastases from NSCLC can respond to the epidermal growth factor receptor (EGFR) inhibitors gefitinib and erlotinib [56, 57] (Class III). As with extracranial disease, the response of brain metastases to EGFR inhibitors appears to depend upon the presence of specific EGFR mutations [58]. The dual EGFR and HER-2 tyrosine kinase inhibitor lapatinib has shown modest activity in a recent phase II study on HER-2 + breast cancer patients with brain metastases following trastuzumab-based systemic chemotherapy and WBRT [59] (Class III).

Recommendations

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 emphasis on the presence/activity of the systemic disease and the general physical condition (estimation of the performance status) are recommended (GPP).
- CT is inferior to MRI (Level B), but it is sufficient when it shows multiple brain metastases.
- Contrast-enhanced MRI is indicated when: (a) surgery or radiosurgery are considered for one or two metastases on contrast-enhanced CT and a KPS ≥ 70; (b) contrast-enhanced CT is negative but the history is strongly suggestive for the presence of brain metastases in a patient with established malignant disease; (c) CT is not conclusive to eliminate non-neoplastic lesions (abscesses, infections, demyelinating diseases, vascular lesions) (GPP).

- Diffusion MRI is useful for the differential diagnosis of ring-enhancing lesions (Level C).
- EEG is indicated where there is suspicion of epilepsy, but there remains clinical uncertainity (GPP).
- Tissue diagnosis (by stereotactic or open surgery) should be obtained when: (a) the primary tumour is unknown; (b) the systemic cancer is well controlled and the patient is a long-term survivor; (c) lesions on MRI do not show the typical aspect of brain metastases; (d) there is clinical suspicion of an abscess (fever, meningism) (Level B). In patients with unknown primary tumour, CT of the chest/abdomen and mammography are recommended, but a further extensive evaluation is not appropriate in the absence of specific symptoms or indications from the brain biopsy (GPP). FDG PET can be useful for detecting the primary tumour (GPP). 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 tumour-specific antigens is useful (GPP).
- CSF cytology and contrast enhanced MRI of the spine are needed when the coexistence of a carcinomatous meningitis is suspected (GPP).

Supportive care

- Dexamethasone is the corticosteroid of choice and twice-daily dosing is sufficient (GPP). Starting doses should not exceed 4–8 mg per day, but patients with severe symptoms, including impaired consciousness or other signs of increased intracranial pressure, may benefit from higher doses (≥16 mg/day) (Level B). An attempt to reduce the dose should be undertaken within 1 week of initiation of treatment; if possible, patients should be weaned off steroids within 2 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 recommendations are Good Practice Points.
- AEDs should not be prescribed prophylactically (Level A). In patients who suffer from epileptic seizures and need a concomitant treatment with chemotherapeutics, enzyme-inducing antiepileptic drugs (EIAEDs) should be avoided (Level B).
- In patients with venous thromboembolism low molecular weight heparin is effective and well tolerated for both initial therapy and secondary prophylaxis (Level A). A duration of the anticoagulant treatment ranging from 3 to 6 months is recommended (GPP). Prophylaxis in patients undergoing surgery is recommended (Level B).

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 (GPP). Surgery is recommended when the systemic disease is absent/controlled and the Karnofsky Performance score is 70 or more (Level A). 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 (GPP). Patients with disseminated but controllable systemic disease (i.e. bone metastases from breast cancer) or with a radioresistant primary tumour (melanoma, renal cell carcinoma) may benefit from surgery (GPP). Surgery at recurrence is useful in selected patients (Level C).
- 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, brainstem, or with comorbidities precluding surgery (Level B). Stereotactic radiosurgery may be effective at recurrence after prior radiation (Level B).
- WBRT 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). For patients with poor performance status supportive care only can be employed (GPP).
- Following surgery or radiosurgery, in case of absent/controlled systemic disease and Karnofsky Performance score of 70 or more, one can either withhold adjuvant 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 (GPP).

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, stereotactic radiosurgery is an alternative to WBRT (Level B), while surgical resection is an option in selected patients (Level C).
- In patients with more than three brain metastases WBRT with hypofractionated regimens is the treatment of choice (Level B), whereas for patients with poor performance status supportive care only can be employed (GPP).

Chemotherapy

- Chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumours, like small-cell lung cancers, lymphomas, germ cell tumours, and breast cancers, especially if asymptomatic, chemo-naïve, or an effective chemotherapy schedule for the primary is still available (GPP).

Targeted therapies

- Targeted therapies can be employed in patients with brain metastases recurrent after radiation therapy (GPP).

Conflicts of interest

None of the members of the task force, including the chairperson, had any form of conflict of interest.

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