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Management of brain metastases

Abstract Brain metastases occur in 20–40 % of patients with cancer and their frequency has increased over time. Lung, breast and skin (melanoma) are the commonest sources of brain metastases, and in up to 15 % of patients the primary site remains unknown. After the introduction of MRI, multiple lesions have outnumbered single lesions. Contrast-enhanced MRI is the gold standard for the diagnosis. There are no pathognomonic features on CT or MRI that distinguish brain metastases from primary malignant brain tumors or nonneoplastic conditions: therefore a tissue diagnosis by biopsy should be always obtained in patients with unknown primary tumor before undergoing radiotherapy and/or chemotherapy. Some factors are prognostically important: a high Performance Status, a solitary brain metastasis, an absence of systemic metastases, a controlled primary tumor and a younger age. Based on these factors, subgroups of patients with different prognosis have been identified (RPA class I, II, III). Symptomatic therapy includes corticosteroids to reduce vasogenic cerebral edema and anticonvulsants to control seizures. In patients with newly diagnosed brain metastases prophylactic anticonvulsants should not be used routinely. The combination of surgery and whole-brain radiotherapy (WBRT) is superior to WBRT alone for the treatment of single brain metastasis in patients with limited or absent systemic disease and good neurological condition. Complete surgical resection allows a relief of intracranial hypertension, seizures and focal neurological deficits. Radiosurgery, alone or in conjunction with WBRT, yields results which are comparable to those reported after surgery followed by WBRT, provided that lesion's diameter does not exceed 3–3.5 cm. Radiosurgery offers the potential of treating patients with surgically inaccessible metastases. Still controversial is the need for WBRT after surgery or radiosurgery: local control seems better with the combined approach, but overall survival does not improve. Late neurotoxicity in long surviving patients after WBRT is not negligeable; to avoid this complication patients with favorable prognostic factors must be treated with conventional schedules of RT, and monitoring of cognitive functions is important. WBRT alone is the treatment of choice in patients with single brain metastasis not amenable to surgery or radiosurgery, and with an active systemic disease, and in patients with multiple brain metastases. A small subgroup of these latter may benefit from surgery. The response rate of brain metastases to chemotherapy is similar to the response rate of the primary tumor and extracranial metastases, some tumor types being more chemosensitive (small cell lung carcinoma, breast carcinoma, germ cell tumors). New radiosensitizers and cytotoxic or cytostatic agents, and innovative technique of drug delivery are being investigated.

Key words brain metastases · diagnosis · treatment

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Introduction

Brain metastases represent one of the most frequent neurological complications of systemic cancer, being an important cause of morbidity and mortality [99, 111, 127]. Brain metastases are the commonest intracranial tumors, outnumbering primary brain tumors [6]. The frequency of brain metastases has increased over time, probably as a result of advances in neuroimaging procedures and improvements in the treatment of primary tumor and systemic disease, which have led to an increase of survival.

The majority of patients who develop brain metastases have a relatively short survival, despite the fact that initial treatment is often effective. The short survival may be the result of either a progressive systemic disease (more than a half of patients) or an uncontrolled neurological disease. The treatment of brain metastases includes corticosteroids, anticonvulsants, radiotherapy, surgery, radiosurgery and chemotherapy. Although for many patients effective palliation is transient or not possible, other patients with metastastic brain disease do well for prolonged periods with a vigorous therapeutic approach. Based on the knowledge of prognostic factors, i. e. those factors that are recognized to significantly influence the duration of survival, it is crucial to identify at diagnosis subgroups of patients with different life expectancy, who need to be treated with different therapeutic approaches.

Epidemiology and pathophysiology

Brain metastases occur in 20–40 % of patients with cancer, being symptomatic during life in 60–75 % or discovered incidentally on CT/MRI and at autopsy [6].

In adults, lung (36–64 %), breast (15–25 %) and skin (melanoma) (5–20 %) are the commonest sources of brain metastases. Less frequent are cancers from colonrectum, kidney, prostate, testis, ovary and sarcomas; in general any systemic tumor is able to metastatize to the brain. The primary site is unknown in up to 15 % of patients with brain metastases. The propensity of primary tumors to spread to the brain parenchyma ("neurotropism") differs, being high in melanoma (20–45 % of patients), small-cell lung cancer, choriocarcinoma and other germ cell tumors; intermediate in breast cancer, non small-cell lung cancers (being more frequent in adenocarcinomas than in squamous tumors) and renal cancer; low in cancers of the prostate, gastrointestinal tract, ovary, thyroid and sarcomas. Cerebral metastastic disease in children is less frequent than in adults (6–10 %)[16, 54, 123]. The commonest childhood solid tumors that metastatize to the brain are neuroblastomas and a variety of sarcomas, including rhabdomyosarcoma, Wilm's tumor, Ewing's sarcoma and osteogenic sarcoma. In children older than 15 years, germ cell tumors have the highest incidence.

Brain metastases are more often diagnosed in patients with known malignancy and sometimes this is the first evidence of the metastatic disease (metachronous presentation). Less frequently (up to 30 %) brain metastases are discovered in patients at the same time as primary tumour diagnosis (synchronous presentation) or before the evidence of primary disease (precocious presentation).

In the CT era about 50 % of brain metastases were thought to be single, while MRI has revealed that multiple lesions are between two thirds and three fourths [110, 121]. Brain metastases from renal and pelvic-abdominal tumors are often single, whereas malignant melanoma and lung tumors have a greater tendency to produce multiple cerebral lesions.

The overwhelming majority of brain metastases arise from embolisation of tumour cells through the arterial circulation (hematogenous spread). The occurrence of metastases in the different locations is roughly proportional to their relative mass and blood flow: lesions are located in the cerebral hemispheres in at least 80 % of patients, in the cerebellum in 15 %, in the brainstem in 5 %, being very rare in basal ganglia, pineal gland and hypophisis [34]. Brain metastases most commonly are found at the junction of the hemispheric gray and white matter and are overrepresented in "watershed" areas of the brain, consistent with the origin of metastases from tumor cell emboli carried to terminal arterioles. Melanoma is unusual in its predilection to metastasize to the cerebral cortex and basal ganglia rather than to the gray-white matter junction [19, 32]. There are a few circumstancies in which nonspecific hematogenous spread does not explain the observed distribution of brain metastases. For instance, pelvic and abdominal tumors have a predilection to form posterior fossa metastases far in excess of what the proportion of blood flow supply to this region would predict. Dissemination by way of Batson's vertebral venous plexus has long been invoked to explain this phenomenon, but this hypothesis cannot explain why patients with pelvic or abdominal tumors have not a high incidence of spinal and skull metastases as well, as these structures are also drained by Batson's plexus.

The "soil and seed" hypothesis of metastasis formation [42, 43] explains why circulating tumor cells may travel throughout the body, but metastases tend to form in particular organs (as in the brain in absence of lung metastases): the metastasis formation would be the result of the interactions between the organ microenvironment (the "soil") and the adhesive and invasive capabilities of the metastatizing tumor cells (the "seed"). Neoplastic cells with the potential to colonize the brain may express unique molecular determinants and may also respond to brain-derived growth factors, and thus

be able to invade, proliferate and induce angiogenesis [78, 90, 132].

Diagnosis

The clinical presentation of brain metastases is similar to the presentation of any intracranial mass lesion. Headache is a presenting symptom in 40 % to 50 % of patients, is commoner with multiple metastases or with posterior fossa tumors, and may be mild. Papilledema is associated to headache in 15–25 % of patients only. Up to 40 % of patients present with focal neurological deficits, and seizures occur in about 15 % to 20 % of patients. Another 5 % to 10 % of patients have an acute "strokelike" onset of symptoms, due to an intratumoral hemorrhage (especially from melanoma, choriocarcinoma and renal carcinoma). Altered mental status or impaired cognition are frequently seen, particularly in patients with multiple metastases and/or increased intracranial pressure, sometimes resembling a metabolic encephalopathy. The symptoms and signs at presentation are often quite subtle; however, brain metastases should be suspected in any patient with known systemic cancer in whom new neurological findings develop.

Contrast-enhanced MRI is more sensitive than enhanced CT (including double-dose delayed contrast) or unenhanced MRI in detecting brain metastases, particularly lesions in the posterior fossa or multiple punctate metastases [28, 110, 121]. Although T2-weighted images are sensitive in showing vasogenic edema as areas of increased signal intensity, not all metastatic lesions have sufficient edema to be identified. Some studies have reported that triple doses of gadolinium are significantly better than single doses [122, 133]. Metastases 1 cm or greater in diameter were easily seen with standard doses of contrast and generally produce T2 signal abnormality as well; triple-dose gadolinium was slightly better in demonstrating metastases from 5 to 10 mm and was three times as sensitive for demonstrating lesions less than 5 mm [133]. MRI is particularly recommended for patients with an apparently single metastasis on CT, who are candidates for surgical resection, and for patients with limited primary disease (i. e. lung tumors) in whom the demonstration of asymptomatic brain metastases would alter the therapeutic management.

There are no pathognomonic features on CT or MRI that distinguish brain metastases; however 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 history of cancer. A differential diagnosis including primary brain tumors (especially malignant gliomas and lymphomas) and nonneoplastic conditions (abscesses, infections, hemorrhages) must be considered. A tissue diagnosis by biopsy should be obtained in patients with either unknown primary tumor or well-controlled systemic cancer, especially if a long interval has elapsed since the initial cancer diagnosis, or, seldom, in patients with active systemic cancer when the radiographic appearance is atypical: in the age of stereotactic biopsy there is never a justification for irradiating "presumend brain metastases" without an histological diagnosis of cancer.

When a brain mass is discovered on CT or MRI and there is no prior history of cancer, it is difficult to know how far to pursue a systemic investigation. As in most cases of brain metastases the primary tumor is located in the lung [67, 82], a chest radiograph and chest CT are always recommended. CT of the abdomen occasionally shows an unsuspected cancer. Further search for a primary tumor is almost never fruitful without positive features in the patient's history or localizing signs on the physical examination to suggest a specific primary tumor [126].

Regarding brain metastases from an undetected primary site at the first investigations, a recent study has shown that, when performing serial investigations based on CT during the follow-up in asymptomatic patients, the primary tumor (a non small-cell lung carcinoma in the majority) may be discovered in almost all patients, but few of them only benefit in terms of survival from the early detection and treatment [106]. Therefore a costly extensive evaluation for the undetected primary during the follow-up is not appropriate until more effective cancer therapies are available [106, 126]: in this regard the clinical relevance of FDG-PET for detecting the primary tumor in addition to conventional procedures [62] is limited.

In patients with brain metastases, a CSF examination is not indicated, apart from those with symptoms, signs or neuroimaging findings that suggest an associated leptomeningeal carcinomatosis.

Prognostic factors

Several studies have identified the following factors as prognostically favourable in patients with brain metastases: a high Performance Status, a solitary brain metastasis, an absence of systemic metastases, a controlled primary tumor and a younger age (< 60–65 years) [36, 48, 59, 66, 93]. Gaspar [48] utilized RTOG (Radiation Therapy Oncology Group) databases to perform a recursive-partitioning analysis (RPA) on 1200 patients with brain metastases. Based on univariate analysis, the Karnofsky Performance Status (KPS) (Table 1) was the most important prognostic factor and became the first node of a prognostic tree. Among patients with KPS of 70 or greater, status of the primary tumor was the second most important prognostic factor. Age was the third

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

factor and systemic metastases the fourth. The following three prognostic classes were then constructed (Table 2): RPA class I, including patients with KPS of 70 or greater, age 65 years or younger, controlled primary tumor and no systemic metastases, with a median survival of 7.1 months; RPA class II, including all patients not belonging to class I or III, with a median survival of 4.2 months; RPA class III, including patients with KPS less than 70, with a median survival of 2.3 months. In this study 20 % of patients were allocated to class I and 65 % to class II. The validity of this prognostic classification has been confirmed on other databases [23, 49, 92, 130], with two additional findings: class I patients may be very few (3 % only in one study) and class II patients with controlled systemic disease show survival figures similar to those of class I patients. In conclusion, the RPA classes provide significant prognostic information that can be used to select a minority of patients for intensive local treatments (surgery, radiosurgery).

Recently a poor Mini Mental Status Examination (MMSE) has been shown to be prognostically important [87], but it is unknown if MMSE may provide additional prognostic significance to the RPA classes. Not unanimously recognized as favorable prognostic factors are a breast primary, a metachronous presentation, a time interval > 12 months between the diagnosis of primary and the appearance of brain metastasis, the number of brain metastases and the response to steroids [1, 66, 124, 134].

The prognosis is not different between patients with a known and unknown primary tumor [75, 82, 89].

Table 2 Recursive partitioning analysis (RPA) of prognostic factors in patients with brain metastases

RPA class	Criteria	Median survival time (months)
I	Karnofsky Performance Status ≥ 70 < 65 years of age Controlled primary tumor No systemic metastases	7.1
II	Karnofsky performance status ≥ 70 and at least one of the following: ≥ 65 years of age Uncontrolled primary tumor Presence of systemic metastases	4.2
III	Karnofsky Performance Status < 70	2.3

Therapy

General considerations

Therapy of patients with brain metastases can be divided into two areas: symptomatic therapy and definitive therapy. Symptomatic measures are usually instituted immediately and are the same for patients with single or multiple metastases; they include corticosteroids to reduce cerebral edema and anticonvulsants to control seizures. Definitive therapy is directed against the tumor itself and is designed to eradicate or at least diminish the malignancy: surgery, radiosurgery and conventional radiotherapy are the most commonly used treatments.

A critical problem is that of the criteria of evaluation of treatment results. Improvement in neurologic function is a prime goal of treatment but patient's neurological status can be affected by steroid dose and concurrent systemic problems. More objective ways of evaluating a response to a given treatment modality include performing serial imaging studies (CT or MRI) and documenting a decrease in steroid requirements [74]. The duration of survival is an objective and easily measurable way for evaluating treatment efficacy in brain metastases, but its usefulness is limited by the fact that more than a half of patients die from the systemic cancer and not from the neurological disease. Time to neurological deterioration and quality of life have been increasingly used in recent years.

Corticosteroids

Dexamethasone is the corticosteroid of choice, largely because of its minimal mineralocorticoid effect. Its long half-life allows for twice-daily dosing. Most patients are successfully managed with starting doses of 4 to 8 mg per day [111, 129]. Patients with severe headache, focal deficits or somnolence may be started at higher doses (16 mg per day); occasionally patients require higher doses (up to 100 mg/d). Patients with small, completely asymptomatic lesions may not need steroids. Steroids may be useful to reduce the acute side effects of cranial irradiation. Up to 75 % of patients with brain metastases show marked clinical improvement within 24 to 72 hours after beginning dexamethasone [20]: generalized

symptoms such as headache and altered mental status tend to improve more dramatically than focal symptoms. Any corticosteroid is effective if given in equipotent doses. It is advisable to continually attempt to reduce the dose once definitive treatment is underway and patients have stabilized. Patients who respond well can often be completely weaned off steroids within several weeks, whereas approximately 25 % of patients require long-term treatment to maintain neurological function. Side effects from steroids are frequent and can 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-to-6-week median survival of patients who receive no treatment at all. The mechanism of corticosteroid effect in cerebral edema remains unclear, although it is thought to restore the disrupted capillary permeability (partly due to vasoactive substances secreted by tumors).

Anticonvulsants

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 does not support this practice. A large retrospective study of patients with brain metastases revealed that 13 % of patients put on prophylactic AEDs (almost always phenytoin) had late seizures compared with 11 % of patients not getting prophylactic AEDs [26]. A prospective blinded study randomized patients with supratentorial brain tumors (90 % of whom had brain metastases) to receive either valproic acid or placebo [52]. Late seizures occurred in 35 % of the treatment group and 24 % of the placebo group. Phenytoin, carbamazepine and phenobarbital all reduce the efficacy of corticosteroids. Furthermore these anticonvulsants stimulate the cytochrome P450 system, accelerating the metabolism of many chemotherapeutic agents, including nitrosoureas, paclitaxel, cyclophosphamide, topotecan, irinotecan, thiotepa, adriamycin and methotrexate: consequently, inadequate chemotherapeutic dosing of brain tumor patients is a significant problem [41]. The potential immunosuppressive effect of anticonvulsant medications represents an additional risk to this already compromised patient population [88].

Recently the Quality Standards Subcommittee of the American Academy of Neurology has reported on anticonvulsant prophylaxis in patients with newly diagnosed brain tumors [53]. 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. Furthermore, there was no evidence of an effect on the frequency of first seizures, and subtherapeutic levels of anticonvulsants were extremely common. In contrast the severity of anticonvulsants' side effects appeared to be higher (20 to 40 %) in brain tumor patients (because of drug interactions) than in the general population receiving anticonvulsants. Erythema multiforme and Stevens-Johnson syndrome have been reported as apparently rare but life-threatening complications in patients taking phenytoin and tapering doses of dexamethasone during or shortly after receiving cranial radiotherapy [35]. As a consequence the recommendation of the Subcommittee of the AAN [53] is that in patients with newly diagnosed brain tumors prophylactic anticonvulsants should not be used routinely. 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. The efficacy of the newer AEDs has not yet been investigated.

As for patients who underwent a neurosurgical procedure, the efficacy of prophylaxis has not been proven [65]: in this regard the recommendation of the AAN is to taper AEDs 1 week postoperatively in patients placed on prophylactic AEDs for surgery.

Management of venous thromboembolism

Venous thromboembolism is a common complication in patients with brain tumors [56]: the incidence in patients with brain metastases ranges between 1.03 % and 20 % [69, 109]. The two therapeutic approaches include anticoagulation and placement of inferior vena cava filter. The risk of intracranial hemorrhage is often considered an absolute contraindication to anticoagulation of a patient with brain metastasis and venous thromboembolic disease. However, the largest study detected only two serious and one minor intracerebral hemorrhages in 42 patients with brain metastases who underwent anticoagulation whereas four of 10 patients, treated initially with inferior vena cava filters, experienced recurrent venous thromboembolic events [112]. Moreover the risk of long-term filter failure is quite high [33, 70]. As a general rule anticoagulation is not contraindicated as the initial strategy in most patients with brain metastases, apart from those with imminent surgery and/or hemorrhagic lesions.

Treatment of single brain metastasis

Surgery

Surgery has been used in the treatment of single brain metastasis for long time, but its role in improving the prognosis has remained unclear until the last decade. Three randomized studies have compared surgical resection, followed by whole-brain radiotherapy (WBRT), with WBRT alone [83, 95, 128]. The American study [95] and the Dutch study [128] have included mainly patients with controlled or limited systemic disease, and both have reported a significant improvement in survival of patients receiving the combined treatment (median survival 9–10 months) compared with those receiving WBRT alone (median survival 3–6 months). In the American study patients who had surgery displayed a lower rate of local relapses (20 % versus 52 %) and a longer time of functional independence. By contrast the Canadian study [83], which included a higher proportion of patients with an active systemic disease and lower performance scores, failed to show any advantage of surgery plus radiotherapy over radiotherapy alone.

In clinical practice surgery should be considered in any patient with a single brain metastasis in an accessible location, especially when the size is large, the mass effect significant and/or an obstructive hydrocephalus is present. Complete surgical resection allows an immediate relief of symptoms of intracranial hypertension and of seizures, a reduction of focal neurological deficits and a rapid steroid taper in the majority of patients. Several technical factors improve the safety of surgery (by reducing the mortality and morbidity below 3 % and 10 % respectively): at present time frameless stereotaxis, ultrasound guidance, motor strip mapping and advances in neuroanesthesia, in the near future functional and intraoperative MRI. Surgery is more often reserved for patients with limited or absent systemic disease at the time of diagnosis of a brain metastasis, and these patients do far better; however, even patients with disseminated systemic disease may benefit from surgery, especially in terms of quality of life, if their disease is controllable (e. g. bone metastases from breast cancer) or if their primary neoplasm is radioresistant (e. g. renal cancer, melanoma) [31, 131]. The combined resection of a solitary brain metastasis and a primary non small-cell lung carcinoma (stage I and II) yields good results: median survival of at least 12 months with 10–30 % of patients surviving at 5 years [61]. 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 [5, 12].

Stereotactic Radiosurgery (SRS)

In recent years an increasing number of patients with brain metastases have been treated by stereotactic radiosurgery [17]. This procedure allows the delivery of a single high dose of radiation, using multiple cobalt sources (gamma-knife) or a linear accelerator (Linac) through a stereotactic device, to targets of 3–3.5 cm maximum diameter. The dose is inversely related to tumor diameter or volume (between 2 cm and 3 cm median doses of 17–18 Gy). The rapid dose fall-off of SRS minimizes the risk of damage to the surrounding normal nervous tissue. As opposed to primary malignant brain tumors, brain metastases are physically and biologically ideal targets for SRS. They are generally small, spherical, and minimally invasive, with radiographically distinct margins: all these characteristics are favorable for the dose distribution of SRS. In patients with newly diagnosed brain metastases, a rapid decrease of symptoms, local tumor response ("control") rate of 80–90 % and a median survival of 7–12 months have been reported [3, 7, 39, 44, 77, 80, 115, 120]. An homogeneous baseline enhancement and a good initial radiographic response to SRS are good predictors of long-term control [97], whereas a diameter more than 3 cm is a negative prognostic factor [4]. A remarkable finding across SRS series is that metastases from highly radioresistant tumors, like melanoma and renal cell carcinoma, which respond very poorly to fractionated radiotherapy, respond virtually as well to SRS as do tumors far more sensitive to conventional radiation. For example, the median survival for patients with metastatic melanoma treated with the gamma -knife was 8 months, with a 97 % local control rates [71].

SRS offers the potential for treating patients with surgically comorbidities that preclude surgery or with inaccessible lesions. Metastases in the eloquent cortex, basal ganglia, thalamus and brainstem can be treated with relatively low risk. Huang [57] reported a local control rate of more than 90 % and a median survival of 9 months in patients treated with gamma-knife for midbrain and pontine metastases. The type of radiosurgical procedure, gammaknife or Linac-based, does not have an impact on overall survival [18, 108]. Radiosurgery, alone or in conjunction with WBRT, has been reported to be superior to conventional WBRT alone in terms of local control, survival and quality of life [72]. This issue is currently being addressed by the RTOG study 9508, which is comparing in a phase III study WBRT with versus without stereotactic radiosurgery boost for patients with single brain metastasis. Radiosurgery, alone or in conjunction with WBRT, yields results which are comparable to those reported for surgery followed by WBRT [7, 85, 94], with the only exception of the paper of Bindal [13], where patients undergoing surgical resection survived longer and had a better local control. SRS is a pro-

cedure done under local anesthesia in an outpatient setting or with an overnight hospitalisation; consequently, in addition to patient convenience, it offers cost effectiveness advantages over surgery [81, 107]. A randomized trial to compare radiosurgery with surgery would be warranted, but it is difficult to organize. The favourable overall median survival time after SRS in most series is at least partly the result of patient selection with a large percentage of patients free from an active extracranial disease. On the other hand, as brain metastases patients with active extracranial disease have a median survival after SRS of 4–5 months only, the value of the sophisticated SRS in this subgroup is unclear [127, 130], as similar results are reported after conventional WBRT [38].

Radiosurgery is effective for patients with brain metastases that have recurred following conventional WBRT [22, 73, 114].

Acute (early) and chronic (late) complications following radiosurgery are relatively modest after treatment of brain metastases [51, 79]. 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. They are generally reversible with steroids. Chronic complications consist mainly of radionecrosis (5–11 %), requiring a reoperation in no more than 4 % of patients. Radiographically a transient increase in the size of the irradiated lesion, with increasing edema and mass effect, with or without frank radionecrosis, is not distinguishable from a tumor progression [58]. A larger tumor diameter and a higher treatment dose are associated with unacceptable local toxicity [114].

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

A point of controversy, especially after the introduction of MRI, is 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 [84, 118]. Some retrospective studies [30, 117] and one phase III study from USA [96] have reported that adjuvant WBRT after complete surgical resection significantly reduces local and distant CNS relapses (18 % with surgery + WBRT versus 70 % with surgery alone according to Patchell study), without affecting overall survival or functionally independent survival, except for a modest advantage in patients without evidence of extracranial disease. Similarly WBRT in conjunction with radiosurgery improves local control and reduces the risk of new distant brain metastases [24, 47, 72, 103, 116, 118], but most studies support the viewpoint that combined radiosurgery and WBRT does not improve the overall survival [44, 80, 115, 118], except for patients without evidence of extracranial disease [98]. 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-weighted images. A subset of these patients (up to 11 %) have clinical concomitants, that include memory loss progressing to dementia, frontal gait disorders, urinary incontinence [29, 91]. The clinical picture may resemble normal pressure hydrocephalus, but few patients benefit from ventriculoperitoneal shunting [29]. This radiation-induced leukoencephalopathy is a consequence of a damage to microvessels. The risk for this complication increases with hypofractionated schedules of RT (size fraction > 2 Gy): consequently, patients with favourable prognostic factors are optimally treated with conventional fractions of 1.8–2 Gy to a total dose of 40–50 Gy instead of fractions of 3 Gy to a total dose of 30 Gy, as commonly employed in the past. Both the RTOG and the EORTC (European Organization for Research and Treatment of Cancer) are performing phase III trials to investigate the role of WBRT after surgical resection or radiosurgery.

The monitoring of cognitive functions by means of neuropsycological tests should be performed in all clinical trials dealing with the problem of late effects of radiation [102].

In clinical practice there is an increasing tendency to omit adjuvant WBRT in patients with a controlled systemic disease and/or radioresistant lesions, reserving WBRT or radiosurgery as salvage treatments at recurrence. Some centers employ focal RT after surgical resection.

Whole-brain radiotherapy (WBRT) alone

WBRT alone is the treatment of choice for patients with single brain metastasis not amenable to surgery or radiosurgery, especially those with an active and disseminated systemic disease [93]. Median survival after WBRT alone is 3 to 6 months. The neurological improvement, that can be achieved independently from steroids, is not well known [10]: radiosensitive tumors, such as breast cancer, respond better than the radioresistant ones, such as colon and renal cancers or melanomas. The RTOG has demonstrated that different fractionation schedules, ranging from 10 Gy in one fraction to 40 Gy in 20 fractions, yield comparable results [15, 50]. However, very high single fractions, such as 10 Gy, can produce severe neurological side effects during treatment and provide less clinical benefit. Nausea, vomiting, headache, fever and transient worsening of neurological symptoms in the initial phase of therapy may be observed. Therefore WBRT should be delivered quickly

but safely to permit a rapid return home: for these reasons the commonest schedule is 30 Gy/d in 10 fractions. Accelerated hyperfractionated schemes [86] or radiation sensitizers (misonidazole, bromodeoxyuridine) [9] have not been found to improve survival results.

The treatment of multiple brain metastases

WBRT alone has been for a long time the sole treatment, with a median survival of 2–6 months depending on the prognostic factors. Owing to the short life expectancy, hypofractionated treatments are generally employed. In patients with poor prognostic factors one may even question the benefit of radiation therapy: it is our policy to withhold active treatment in bedridden patients (especially with an active systemic disease) and only to provide symptomatic therapy with steroids or anticonvulsants. Radiosurgery may be an alternative to WBRT [39, 113]. Some studies [63, 119] have reported an improved local control after combined SRS plus WBRT. When the number of brain metastases is limited (generally 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 similar results to those for single lesions [11, 94]. The resection of the symptomatic lesion(s) and the radiation treatment of the other ones is of clinical value as well [106].

New approaches in radiotherapy

Fractionated stereotactic radiotherapy (2–3 fractions) has been suggested as being more comfortable for patients and less costly than radiosurgery [76]. Intensity modulation (tomotherapy) and novel radiosensitizers (gadolinium Texaphyrin, RSR 13) are under investigation [21, 60]. In particular gadolinium texaphyrin, a metalloporphyrin with a complex mechanism of radiation sensitization, seems promising. It is detectable by MRI and selectively accumulates in primary and metastatic tumors, without increasing radiation toxicity to normal tissue. A phase II trial of standard fractionated RT (30 Gy in 10 fractions), combined with gadolinium texaphyrin intravenously prior to each radiation fraction, was recently conducted in patients with brain metastases [21]. The radiological response rate was 72 %; median survival was 5.4 months for RPA class 2 patients and 3.8 months for RPA class 3 patients (compared with 4.2 and 2.3 months in the RTOG database). These results have led to a phase III trial of the RTOG, which is ongoing.

The role of chemotherapy

Chemosensitivity is the critical factor for the response of brain metastases to chemotherapeutic agents and some points are well established [68, 100]: brain metastases are as responsive as primary systemic cancer; 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; the response to chemotherapy of brain metastases from mostly chemosensitive tumors (small-cell lung carcinoma, germ cell tumors, breast cancer) is of the same order of that observed after radiotherapy. Response rates to chemotherapy alone are as high as: 21–76 % in small-cell lung carcinoma (SCLC) [55, 64, 101]; 27–50 % in non small-cell lung carcinoma (NSCLC) [46, 104]; 35–60 % in breast cancer [14, 27, 105]. Cisplatin and etoposide seem to be the most effective combination [45]. Among new drugs, topotecan in SCLC [55] and temozolomide in NSCLC and melanoma [2, 25] are promising. The addition of radiotherapy to chemotherapy may improve the response rate, but not the survival [101, 104, 125].

In clinical practice, chemotherapy represents a starting treatment (followed by WBRT) in patients with brain metastases from SCLC and germ cell tumors only, whereas WBRT remains the treatment of choice in symptomatic patients with brain metastases from NSCLC, breast cancer and other solid tumors in the adult.

The blood-brain barrier and the blood-tumor barrier are limiting factors for the response to chemotherapy of micrometastases (< 1 mm in diameter). Innovative techniques of drug delivery are being investigated: blood-brain barrier disruption by hyperosmolar mannitol [37]; blood-brain tumor barrier manipulation by agonists of bradychinin such as RMP–7 [8]; local chemotherapy utilizing BCNU-impregnated biodegradable wafers [40].

Conclusions

Surgery or radiosurgery are now treatments of choice in brain metastasis patients with favorable prognostic factors (RPA class I and a subgroup of class II). After the local treatment of a brain metastasis by either surgery or radiosurgery, survival does not seem to be adversely affected if WBRT is postponed to become salvage treatment at the time of recurrence. In this regard new randomized trials, focusing on the time to neurological deterioration, cognitive defects and quality of life, are needed to better determine the timing of WBRT. How frequently asymptomatic patients need follow-up scans is still controversial.

Biological agents, monoclonal antibodies, gene ther-

apy will be increasingly available in the near future; however, as a general rule, changes in the current management of patients with brain metastases should not be merely based on the availability of advanced techniques or new compounds, but on clinical trials showing a significant improvement of prognosis due to the innovative treatment modalities when compared with the standard ones.

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