Introduction

Metastasis to the brain is a frequent complication of systemic cancers occurring in 10 to 40% of all patients, and is the most common intracranial tumor (approximately 40%) in adults which has an incidence 10 times higher than that of primary malignant brain tumors. The incidence of brain metastasis is rising because of longer survival of cancer patients as a result of the increase in early diagnosis of primary tumors and aggressive management, and improvements in imaging quality and accessibility such as the widespread use of MRI. Lung, breast, melanoma, renal, and colon cancers, in order of decreasing frequency, are the most common primary tumors of brain metastasis in USA.

Brain metastases are an increasingly important cause of morbidity and mortality in cancer patients. The majority of patients with local metastatic brain tumor control expire due to extracranial disease progression, whereas those with uncontrolled brain metastases more often die of neurological causes. Therefore, the local brain tumor control is the primary treatment option to enhance the quality of life and prolong the survival of patients with brain metastases.

Pathophysiology

Metastatic spread to the brain arises from embolization of tumor cells through the arterial blood circulation. Before entering the brain, circulating tumor cells are filtered out in the capillaries of the lung. So patients with symptomatic brain metastasis usually have involvement of the lung in the form of primary tumors or metastases. The site distribution of brain metastases is determined by their relative mass size and blood flow. At least 85% of brain metastases are located in the cerebral hemispheres, 15% in the cerebellum, 5% in the brainstem, being very rare in basal ganglia, pineal gland and hypophysis. Their most commonly found locations in the cerebral hemispheres are at the junction of the hemispheric gray and white matter indicating their origin from tumor cell emboli carried to terminal arterioles, but melanoma is disposed to metastasize to the cerebral cortex and basal ganglia.

Metastasis of cancer cells occurs via the multistep tumor dissemination process, which has been described as the “metastatic cascade” composed of invasion to surrounding tissue, entry into and survival in the bloodstream (intravasation), arrest and/or extravasation at the secondary site, and survival and proliferation. Developments in molecular biology have expanded our knowledge about the mechanisms of this process involving several important molecules such as E-cadherin, catenins, neurotrophins, plasminogen activators and inhibitors of matrix metalloproteases. Recently, several metastasis suppressor genes (MSGs) such as nm23 and CD44 which can spontaneously suppress metastatic growth of any point in the metastatic cascade, have been identified.
Diagnosis

The signs and symptoms of brain metastasis are related to the involved brain area. The most common symptoms are gradual onset of headache, focal weakness, and mental changes. Generalized or focal seizures may also occur in 20% of patients. Hemorrhage into the tumor can result in an acute stroke-like presentation. Hemorrhage is present in 3~14% of metastases and is commonly seen in metastases from melanoma, choriocarcinoma, renal, thyroid, lung, breast, and germ cell tumors. The median latent interval between the initial diagnosis of a primary tumor and diagnosis of brain metastases is 6~9 months for lung cancer and 2~3 years for melanoma, breast, and colon cancer.

CT or MRI can establish the diagnosis of brain metastases, but contrast-enhanced MRI is more sensitive than enhanced CT for determining the presence, location, and number of brain metastases. So gadolinium-enhanced MRI is currently the gold standard of diagnosis for metastatic brain tumors. It is also the best method for detection of leptomeningeal carcinomatosis, which may be seen as abnormal dural enhancement. Metastatic brain tumor lesions are isointense to mildly hypointense on T1-weighted images and hyperintense on T2-weighted images. Hemorrhagic metastases or melanoma lesions are hyperintense on T1-weighted images. T2-weighted images show vasogenic edema surrounding tumor as areas of increased signal intensity. High-dose gadoteridol detects additional smaller lesions when compared to routine-dose contrast. Whole-body 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) for cancer staging can detect intracerebral metastases as areas of increased metabolism, but it is not considered superior to CT or MRI in the initial evaluation of suspected brain metastases currently. 

CT or MRI findings of dura-based metastases may mimic meningioma. Contrast-enhanced MRI of leptomeningeal carcinomatosis may resemble chronic meningitis, images following irradiation, and prior extra-axial hemorrhage. Single or multiple ring-enhanced lesions surrounded with edema may need to be differentiated from infectious diseases such as brain abscess and parasite infections.

Currently, cerebral angiography is not used as a primary diagnostic procedure for metastatic brain tumor. Rarely preoperative angiography and endovascular embolization of large hypervascular metastases using particles or surgical gelatin (Gelfoam) may be useful.

Prognostic factors

The overall prognosis of brain metastasis has improved over the past two decades with the use of combined therapy. Regardless of the histological features of the primary tumor, patients who received only supportive therapy had median survival of 1~2 months. Radiotherapy improved survival by 3~4 months. Among patients with a single metastasis, those who underwent surgical resection with the addition of radiation therapy had a 7- to 9-month increase in median survival.

Gaspar et al utilized RTOG (Radiation Therapy Oncology Group) databases to perform a recursive-partitioning analysis (RPA) on 1,200 patients with brain metastases. The Karnofsky Performance Status (KPS) (70 or greater), status of the primary tumor, age (65 years or younger) and systemic metastases, in order of decreasing importance, were the important prognostic factors. Then they constructed the following three prognostic classes: 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.

Treatment modalities

1. Symptomatic treatment

Symptomatic therapies are usually begun immediately after diagnosis of brain metastases and are the same for the patients with single or multiple metastases. They include corticosteroids to reduce peritumoral edema and anticonvulsants to control seizures.

Dexamethasone is the corticosteroid of choice because of its minimal meralocorticoid effect. Most patients are successfully managed with starting doses of 4 to 8 mg per day. Steroids should be tapered as early as possible to minimize side effects. Side effects associated with corticosteroids include myopathy, hyperglycemia, edema, weight gain, vascular necrosis and psychosis. Patients who respond well can often be completely stopped steroids within several weeks, whereas approximately 25% of patients require longterm administration to maintain neurological function. The mechanisms of corticosteroid effect
in cerebral edema surrounding tumors remain unclear, although it is thought to restore the disrupted capillary permeability partly due to vasoactive substances secreted by tumors.

Use of anticonvulsants is reasonable in patients who have experienced a seizure by the time their brain tumor is diagnosed. Many clinicians routinely prescribe prophylactic antiepileptic drugs to patients with brain metastases, but the evidence does not support this practice. The retrospective and prospective studies revealed that the incidence of late seizures were similar between patients with prophylactic antiepileptic drugs and those without anticonvulsants. Use of non-hepatic enzyme inducing anticonvulsants such as lamotrigine, levetiracetam and gabapentin are recommended to control seizures, as these do not increase the clearance of chemotherapeutic agents via the cytochrome P450 isoenzyme CYP3A system. It is recommended to taper anticonvulsants 1 week postoperatively in patients put on prophylactic anticonvulsants for surgery.

2. Definitive treatment

Definitive therapy is directed against the tumor itself and designed to eradicate or at least diminish the malignancy. Surgery, radiosurgery and conventional radiotherapy are the most commonly used treatment modalities.

(1) Surgery

The primary goal of surgery for the brain metastasis is grossly total or maximal resection of the tumor with minimal surgical morbidity and histological confirmation of the diagnosis. In clinical practice surgery should be considered in any patient with a single symptomatic brain metastasis in an accessible location and/or an obstructive hydrocephalus. Randomized studies revealed survival of patients with single brain metastasis and controlled systemic disease receiving surgical resection followed by whole-brain radiotherapy (WBRT) (median survival 9–10 months) was significantly prolonged compared with those receiving WBRT alone (3–6 months). Even in multiple brain metastases with the limited number of brain metastases (generally up to 3), accessible location, relatively young age in good neurological condition, and a controlled primary tumor, complete surgical resection yields similar results to those for single lesion. The strategy composed of resection of the symptomatic lesion and the radiation treatment of the other ones is clinically valuable as well. In selected patients with local relapse of a single brain metastasis, reoperation affords a neurological improvement and a prolongation of survival.

Several technical factors improve the safety of surgery by reducing the mortality and morbidity. Image-guided surgery has become routinely used in elective resection of metastatic tumors. Frameless stereotactic guidance, intraoperative ultrasound, motor strip mapping, functional and intraoperative MRI are the factors to related to the good results of surgery.

(2) Stereotactic radiosurgery

In recent years an increasing number of patients with brain metastases have been treated by stereotactic radiosurgery (SRS). This procedure allows the delivery of a single high dose of radiation through a stereotactic device to targets of 3–3.5 cm maximum diameter. The dose is inversely related to tumor diameter or volume. The rapid dose fall-off of SRS at the tumor margin minimizes the risk of damage to the surrounding normal tissue.

In patients with newly diagnosed brain metastases, local tumor response rate of 80-90% and a median survival of 7–12 months have been reported. 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 more sensitive to conventional radiation. Local control rate of metastatic melanoma treated with gamma-knife radiosurgery was 97% and the median survival was 8 months.

SRS offers the potential for treating patients not eligible for surgery or patients with metastases located in the eloquent area. 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. However, many papers have reported patients undergoing surgical resection followed by WBRT survived longer and had a better local control than those treated with SRS alone or in conjunction with WBRT. SRS is effective for patients with brain metastases that have recurred following conventional WBRT.

Cerebral edema as early complication following SRS can occur in 7–10% of patients, more often within 2 weeks from treatment. The related symptoms such as headache, nausea, vomiting, and worsening of preexistent neurological deficits are generally reversible with steroids. Main late complication of SRS is radionecrosis (5–11%) which may be associated with a
larger tumor diameter and a higher radiation dose. Radiographically a transient increasing edema and mass effect, with or without frank radionecrosis, may be not distinguishable from a tumor progression.\(^{23}\)

(3) Whole brain radiotherapy

WBRT has been for a long time the treatment of choice for patients with single or multiple brain metastases not amenable to surgery. Median survival after WBRT alone is 2–6 months depending on the prognostic factors. Owing to the short life expectancy, hypofractionated treatments are generally employed (30 Gy/d in 10 fractions).

After the introduction of MRI, it has been a controversy that adjuvant WBRT after complete surgical resection or radiosurgery whose rationale is destroying microscopic metastatic deposits is necessary. Moreover, adjuvant WBRT after complete surgical resection significantly reduces CNS relapses (18% with surgery + WBRT versus 70% with surgery alone) without affecting overall survival.\(^{26}\) Similarly WBRT in conjunction with radiosurgery improves local control and reduces the risk of new brain metastases, but it does not improve the overall survival.\(^{27}\) Recently, there is an increasing tendency to omit adjuvant WBRT in patients with a controlled systemic disease for reserving WBRT or radiosurgery as salvage treatments at recurrence. The monitoring of cognitive functions by means of neuropsychological tests should be performed for dealing with the late effects of radiation.

(4) Chemotherapy

The blood-brain barrier (BBB) can be the limiting factor for the response to chemotherapy of brain metastases. Therefore, treatment efficacy is determined by the sensitivity of tumor cells to chemotherapeutic agents and whether or not these drugs can cross the BBB. Although BBB is disrupted in patients with brain metastases, most water-soluble chemotherapeutic agents may not penetrate sufficiently to attain a therapeutic concentration. Because most patients have already been exposed to the most effective chemotherapeutic agents, the metastatic tumors may be relatively chemoresistant. Newly diagnosed chemotherapy-naïve patients may respond favorably to systemic chemotherapy. Brain metastases from small-cell lung cancer, germ cell tumors and lymphoid malignancies are perhaps the most sensitive to chemotherapy, whereas brain metastases from non-small-cell lung cancer and breast cancer are somewhat less sensitive to chemotherapy.

Although the role of chemotherapy for brain metastases still remains controversial, a new generation drugs such as temozolomide (TMZ) and topotecan that cross the BBB may hold promise. TMZ is a third generation alkylating agent. Chemoradiation studies with TMZ in brain metastases from solid tumor have shown encouraging results with an objective response rate in 96% of patients versus 67% in the WBRT group.\(^{26}\) Topotecan is a semisynthetic camptothecin derivative that selectively inhibits topoisomerase I in the S phase of the cell cycle. The emerging data suggest that systemically administered topotecan can be a first line treatment for newly diagnosed brain metastases in small cell lung cancer particularly in platinum-sensitive patients.\(^{27}\)

Guideline for the treatment of brain metastases

Selection of treatment modalities suitable for each patient is very important. We suggest the evidence-based algorithm in determining the appropriate treatment of patients with brain metastases as summarized in figure.

Conclusion

Advances in systemic cancer management have resulted in a significant increase of patients with brain metastases. Metastatic brain tumors limit the patient’s survival and worsen the quality of life through an increase risk of developing neurological and cognitive deficits. Although the prognosis is still poor, aggressive local treatment can benefit to patients with brain metastases.

REFERENCES


Metastatic brain tumors

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Abstract

The incidence of brain metastasis is increasing because of longer survival of cancer patients as a result of the increase in early diagnosis of primary cancers, aggressive and advanced management, and improvements in imaging quality and accessibility. Contrast-enhanced MRI is now the gold standard for the diagnosis. Good prognostic factors for metastatic brain tumor are a high performance status, a solitary metastasis, an absence of systemic metastases, a controlled primary tumor and young age. The goal of treatment is to palliate local symptoms and prevent consequences of neurological involvement. Management consists of generalized supportive care and tumor directed treatment. Surgical resection is considered the treatment of choice for solitary brain metastasis. Whole brain radiation therapy (WBRT) remains standard treatment for all patients with brain metastases. The combination of surgery and WBRT is superior to WBRT alone. Radiosurgery offers the potential of treating patients with surgically inaccessible metastases. WBRT in conjunction with surgery or radiosurgery improves local control and reduces the risk of tumor relapse, but does not improve the overall survival. Therefore, there is an increasing tendency to omit adjuvant WBRT for reserving salvage treatment at recurrence. Although the role of chemotherapy for brain metastases still remains controversial, a new generation drugs like temozolomide and topotecan have antitumor activity against the brain metastases as well as the primary tumors. New radiosensitizers, cytotoxic or biologic agents and techniques of drug delivery are being investigated.

Key Words : Brain metastases, Surgery, Radiosurgery, Whole brain radiation therapy, Chemotherapy

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