REVIEW

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Current advances in understanding and managing secondary brain metastasis

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Practice Points

- Metastatic brain disease is the most common cause of intracerebral tumors in adults.
- Lung cancer is the most common cause of metastatic brain disease.
- The complex interaction between tumor cells and brain microvascular endothelial cells is responsible for the entry of tumor cells into the secluded brain environment.
- VEGF-mediated vasogenic edema is the most important pathophysiologic mechanism with regard to the symptoms.
- Contrast-enhanced MRI is the investigation of choice.
- Radiation and surgery are the main treatment options for metastatic brain disease.
- Steroid (dexamethasone) is the mainstay of systemic medical treatment.
- Gamma knife and stereotactic radiosurgery are relatively well tolerated and should be considered for selected patients with small oligo-metastatic (e.g., one to three) lesions of the brain. Surgery should also be considered for selected patients with resectable single brain metastasis.
- Venous thromboembolism is a treatment challenge in metastatic brain cancers and needs very close monitoring with anticoagulation treatment.
- Leptomeningeal metastasis is associated with extremely poor prognosis.
- Systemic chemotherapy and radiation sensitizers remain experimental for the treatment of brain metastases.

SUMMARY Metastatic brain tumors are the number one cause of intracranial neoplasms in adults and are associated with higher morbidity and mortality. The frequency of metastatic brain tumors is increasing because of improved survival in cancer patients. The molecular mechanism of brain metastasis is complex and not completely known. Vasogenic edema produced by tumor-derived VEGF is responsible for clinical symptoms. Dexamethasone

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remains the mainstay of medical management with not completely known mechanisms of action. Surgery and radiation are the main treatment modalities for metastatic brain tumors. Systemic chemotherapy has a very limited role in treatment of these tumors. Leptomeningeal metastasis is associated with extremely poor outcome.

Metastatic brain tumors are the number one cause of intracranial neoplasms in adults and are associated with both higher morbidity and mortality [1]. The annual incidence of brain metastasis is believed to be over 170,000 in the USA [2]. The frequency of metastatic brain tumors is increasing due to improvements in cancer management as well as the availability of sensitive imaging techniques.

The incidence of brain metastasis depends on the primary site of cancer. Gramada *et al.* observed that brain metastasis originating from lung cancer represented the most common type (47.39%), followed by those from breast cancer (19.79%), melanoma (8.33%), genitourinary carcinoma (6.30%) and gastrointestinal carcinoma (2.62%) [3,4]. The incidence of brain metastasis was 9.6% in the Metropolitan Detroit Cancer Surveillance System between 1973 and 2001, and was the highest for lung cancer (19.9%). Incidence proportion varies by primary site, race, sex, age at diagnosis of primary cancer and Surveillance, Epidemiology and End Results stage of primary cancer [1]. Approximately 50% of patients have a single brain metastasis [5,6]. Hemispherical metastases preferentially involve the anatomic watershed areas. The site of metastasis also depends on primary tumors. For example, patients with abdominal and pelvic tumors have predominant involvement of the posterior fossa [5,6]. Melanoma and lung cancer are frequently associated with multiple metastases, whereas breast, colon and renal cell carcinoma are associated with single metastasis [5]. Even after extensive investigations in approximately a fifth of cases the primary cancer remains unknown [3]. As identification of the primary cancer site does not affect survival, delaying therapeutic interventions for brain metastasis may not be appropriate [7,8].

Pathophysiology

The molecular mechanism of brain metastasis is very complex and is not completely known. The interaction between brain microvascular endothelial cells, a major constituent of the blood–brain barrier (BBB), and circulating tumor cells is very important for entry of tumor cells into the highly secluded brain environment.

Intercellular tight junctions (TJs) between brain microvascular endothelial cells are responsible for the highly regulated permeability of the BBB. Once the tumor cells have decoded the entry code of the BBB through many complex molecular interactions, they colonize the brain environment, which the immune system and toxins such as chemotherapeutic agents have limited access to [9,10].

Cerebral edema due to metastatic tumor cells plays an important role in determining the neurological symptoms of brain tumors. Edema associated with cerebral tumors is considered to be vasogenic due to an increased vascular permeability in the tumor micro-environment. Metastatic brain tumors produce angiogenic factors that promote capillary formations with ultrastructural abnormalities, such as elongated junctional clefts and increased density of endothelial vesicles [11]. VEGF, originally described as the vascular permeability factor, is a 34–43-kDa dimeric glycoprotein cytokine that appears to be involved in tumorigenesis, neovascularization and edema production by increasing capillary permeability [12,13]. Significant elevation of *VEGF* gene expression was observed in highly vascular and edema-producing brain tumors, such as glioblastomas, meningiomas and metastatic tumors [13,14]. VEGF binds to endothelial cells via transmembrane receptors of the tyrosine kinase family, *flt-1* and *FLK-1/KDR* [15]. Multiple TJ proteins such as occludin, claudin, ZO-1, ZO-2 and ZO-3 have various roles in maintaining the integrity of TJs of brain microvascular endothelial cells. Water channel aquaporin-4 expression may determine the rate of edema fluid clearance. VEGF may cause edema formation by phosphorylation of occludin and opening of TJs [16]. It may also induce fenestrations in venular and capillary endothelium [17,18]. Increased permeability is completely inhibited when VEGF is cleared by immunoprecipitation with anti-VEGF monoclonal antibodies, confirming its significant role in the process [18] and making it a good therapeutic target. Arachidonic acid metabolites, platelet-activating factor and NO have also been implicated in tumor growth and edema formation (Figure 1) [19,20].

Clinical features

Any new neurological symptoms and/or signs in a cancer patient should prompt the physician to investigate for a metastatic lesion in the brain. It is also not uncommon to have an initial clinical presentation with neurological symptoms in many primary malignancies. The signs and symptoms depend on the area of the brain involved. Neurologic signs and symptoms include headache, altered mental status, seizure, paresis, gait disturbance, visual problems, nausea and vomiting.

Management

The investigation of choice for brain metastasis is a contrast-enhanced MRI scan of the brain.

The management for brain metastasis is primarily supportive care and disease-directed treatment. Symptomatic treatment greatly improves quality of life. Medical management with steroids, anticonvulsant medications and other supportive measures are very important initial steps as outlined in the 'Medical management' section of this article.

Specific treatment modalities include surgical resection, whole-brain radiotherapy (WBRT), stereotactic radiosurgery and chemotherapy. The main key in the management of these patients is to stratify them appropriately, depending on the prognosis, and to identify the best treatment to improve their functional status (Figure 2).

The most commonly used prognostic system is the Radiation Therapy Oncology Group recursive partitioning analysis (RPA). According to Gasper *et al.*, optimal survival with a median of 7.1 months was observed in patients less than 65 years of age with a Karnofsky performance status (KPS) of at least 70 and controlled primary tumor with the brain as the only site of metastasis. Based on RPA, patients were divided into three classes: class 1: patients with KPS greater than or equal to 70, age less than 65 years, controlled primary tumor and no extracranial metastasis; class 3: KPS less than 70; and class 2: all others [21]. This classification can help in estimating survival, selecting treatment options and evaluating clinical trials in homogeneous patient groups [22].

A more recent analysis of the Radiation Therapy Oncology Group database of brain metastases led to the development of a revised prognostic scale called the Graded Prognostic Assessment (GPA; which ranges from 0 to 4, with higher scores indicating improved

Figure 1. Role of VEGF in metastatic brain tumors.

survival) based on which prognostic factors varied according to diagnosis of the primary tumor [23]. A multi-institutional retrospective database of 3940 patients with newly diagnosed brain metastases underwent univariate and multivariate analyses of prognostic factors associated with outcomes by primary site and treatment. For lung cancer, prognostic factors were KPS score, age, presence of extracranial metastasis and number of brain metastases, confirming the Lung-GPA. For melanoma and renal cell cancer, prognostic factors were KPS score and the number of brain metastases. For breast cancer, prognostic factors were tumor subtype, KPS score and age. For gastrointestinal cancer, the only prognostic factor was KPS score. The overall median survival time for all patients was 7.16 months, but the median survival time varied from 2.79 to 25.30 months depending on diagnosis and GPA. The lowest average median survival time by histology was in small-cell lung cancer (4.9 months) and the highest was in breast cancer (13.8 months). Subgroups of patients within RPA classes 1 and 2, have a 2-year survival of over 15% and can be candidates for aggressive treatment [24]. Lutterbach *et al.* also observed the survival advantage of a better RPA score in patients treated with radiosurgery only with less than three brain metastases [25]. In general, survival of patients with brain metastasis is low and is expressed in months rather than years even with favorable characteristics [24,25].

■ Surgery

Neurosurgical resection followed by WBRT is the treatment of choice for single brain metastasis in patients with a good performance status and better survival (>3 months) [26]. The goals of surgery are to provide symptom relief and histological confirmation. In a randomized trial, patients with single brain

Figure 2. Simplified treatment outline for metastatic brain cancer in a cancer patient [101].

WBRT: Whole-brain radiotherapy.

metastasis had survival benefit when treated with surgical resection and radiotherapy, with fewer recurrences and a longer functional independence [27]. In a retrospective analysis of 271 patients with single brain metastasis, median survival was 10.6 months after total resection and 17.1 months with stereotactic radiosurgery [28]. This analysis also supported the prognostic significance of RPA classification. Permanent iodine-125 brachytherapy for surgically resected cavities provides good local control but has

increased the risk of radiation necrosis and, therefore, its use remains experimental [29,30]. Surgical techniques using fluorescein sodium and hydrofiber dressing increase the resection rate and improve the local recurrence rate but are not routinely practiced [31,32].

Radiotherapy

The most widely used treatment for patients with multiple metastases is WBRT, especially in surgically inaccessible tumors or if a patient is not a surgical candidate [26]. WBRT causes tumor shrinkage, which correlates with improved survival and neurocognitive functioning [33]. The standard dose is 30 Gy in ten fractions. Accelerated hyper-fractionated radiotherapy (1.6 Gy twice daily) to a total dose of 54.4 Gy did not demonstrate an improvement in survival compared with the conventional regimen of 30 Gy in ten fractions [34].

Stereotactic radiosurgery delivers high-dose radiation by a linear accelerator or gamma knife to targeted regions. It has a lower risk of tumor seeding, infection or hemorrhage, and eliminates the side effects of surgery. In a randomized trial, Kocher *et al.* observed that patients with solid tumors and one to three brain metastases who had surgery or radiosurgery with adjuvant WBRT had reduced neurological deaths and intracranial relapses, but did not have improved overall survival or functional independence [35]. In a multi-institutional review performed by Sneed *et al.*, no survival difference was found between patients treated with radiosurgery alone and radiosurgery with upfront WBRT for newly diagnosed brain metastasis [36]. In patients treated with stereotactic radiosurgery, immediate WBRT improved control at the original site of metastasis (80 vs 52%) and prevented new metastasis (74 vs 48%) at 2 years, but overall survival was only marginally significant [37]. Intracranial failure rates without WBRT were 25.8 and 48.3% at 3 and 6 months, respectively, so routine avoidance should be approached judiciously [38]. WBRT and stereotactic radiosurgery improved KPS and allowed reduced steroid use in all patients, and improved survival in patients with single unresectable brain metastasis in whom it should be the standard treatment [39,40].

The National Comprehensive Cancer Network guidelines divide patients into one to three, or more than three metastatic brain lesions for management purpose. Those patients

with one to three metastatic brain lesions are recommended either surgery or stereotactic brain radiotherapy depending on their performance status and status of their systemic disease. For those with widespread systemic disease with limited treatment options or with very poor performance status, WBRT is recommended as a first-line treatment. For patients with more than three metastatic brain lesions, WBRT is recommended as a first-line treatment. The guidelines also suggest surveillance MRI of the brain every 3 months for the first year and as needed thereafter (Figures 3 & 4) [101].

Recently updated American Society of Radiation Oncology evidence-based guidelines divide patients into single or multiple brain metastases and consider performance status with survival to guide the management (Figure 5) [26].

Radiation sensitizers such as motexafin and efaproxiral have gained attention in recent years. Motexafin gadolinium is a redox mediator that selectively targets tumor cells, where it generates reactive oxygen species and promotes apoptosis. Efaproxiral is an allosteric modifier of hemoglobin that decreases the affinity of hemoglobin binding to oxygen and increases oxygenation of hypoxic tumor cells. Motexafin gadolinium is not US FDA approved for clinical use, while efaproxiral (RSR-13) has not shown any benefit in overall survival in the Phase III ENRICH trial [41].

Medical management

■ Management of cerebral edema

The main treatment for a brain tumor-related edema is corticosteroids. Dexamethasone is commonly used due to its low mineralocorticoid effects [11], and acts by decreasing edema formation within 1 h of administration by reducing capillary permeability. The exact mechanism of action of corticosteroids is still unknown, although it has been shown that they act by reducing the expression of VEGF by tumor cells, or by reducing the response of the vasculature to tumor-derived permeability factors and interfering with its action on target endothelial cells (Figure 1) [42–44]. These effects are mediated by the glucocorticoid receptor, which is markedly reduced by hypoxia in rapidly growing tumor cells [43]. Major concerns about the long-term use of corticosteroids are side effects such as immunosuppression, gastrointestinal problems, weight gain, osteoporosis, myopathy and increased risk of thromboembolism. Also,

dexamethasone could interfere with the efficacy of chemotherapeutic drugs by the inhibition of apoptosis [45]. Due to an increased risk of pneumocystis jiroveci pneumonia, patients on long-term corticosteroids may be started on prophylaxis [46]. Elevation of the head of the bed, fluid restriction, mannitol, diuretics and hyperventilation can be given when there is increased intracranial pressure and mass effect until the corticosteroids take effect or the patient has a debulking procedure.

Other experimental strategies used in small studies for tumor-related edema include boswellic acids (H15), which are phytotherapeutic agents that inhibit edema formation and tumor growth [47]. Human corticotropin-releasing factor reduces water content in tumors and peritumoral tissue in brain models by direct action on tumor vasculature [48]. AZD2171, a multitargeted tyrosine kinase inhibitor, can alleviate edema, a major cause of morbidity in glioblastoma, and is associated with a steroid-sparing effect in these patients [49]. In one study, the selective COX-2 inhibitor SC-236 appeared to be as effective as dexamethasone in prolonging survival in a rat

Figure 3. Simplified treatment outline for metastatic brain cancer without a known cancer diagnosis [101].

Figure 4. Simplified treatment outline for recurrent metastatic brain cancer [101].

brain tumor model [50]. Another selective COX-2 inhibitor, celecoxib, was found to suppress the growth and metastasis of human pancreatic cancer by inhibition of VEGF expression and tumor microvessel formation. It appears to be a consequence of altered Sp1 transcription factor activity [51].

■ Anticonvulsant prophylaxis

Seizures are a common complication of brain tumors. Glantz *et al.* performed a review of 12 studies that showed a 26% (range: 14–51%) incidence of seizures at or before brain tumor diagnosis and a 19% (range: 10–45%) incidence after the diagnosis. In patients with newly diagnosed brain tumors, anticonvulsant medications are not effective in preventing the first seizure and should not be used for prophylaxis [52,53]. There is very limited evidence in the literature for such prophylaxis for brain metastasis in adults. Mikkelsen *et al.* found only one randomized, controlled, underpowered clinical trial in their meta-analysis to give prophylactic anticonvulsant treatment in solid brain metastasis in adults a level 3 recommendation [54]. Phenytoin, phenobarbital and carbamazepine are the most commonly used anticonvulsants, but these drugs need frequent monitoring and have a lot of drug interactions, especially with corticosteroids, which are commonly used in these patients. Also, in patients who are undergoing surgery, anticonvulsants should be tapered and discontinued after the first postoperative week.

Nonhepatic enzyme-inducing medications such as lamotrigine, levetiracetam and gabapentin are good options for these patients [52].

■ Therapeutic anticoagulation

The risk of venous thromboembolism (VTE) is four- to sevenfold higher in patients with cancer [55–57]. The risk is higher in patients with hematological malignancies, brain, lung, gastrointestinal malignancies (pancreas), ovary and liver cancers, especially in the first few months of diagnosis and in those with distant metastasis [55,57,58]. Old age, tumor size and histology, neurological deficits, use of corticosteroids, recent hospitalization or major surgery, active chemotherapy and antiangiogenic therapy, ABO blood type, and presence of central venous catheters increase the risk of VTE [59–61]. Corticosteroids, which are commonly used to treat cerebral edema in patients with brain tumors, increase the levels of factors VII, VIII and XI, and fibrinogen [62]. The most commonly feared complication of anticoagulation in patients with brain tumors is intracranial hemorrhage. The incidence of intratumoral hemorrhage was noted to be higher with malignant melanoma (18%), testicular cancer (18%), renal cell carcinoma (9%) and ovarian cancer (7%) [6]. Owing to the possibility of potential intratumoral hemorrhage and associated high mortality, development of VTE is a challenge to manage in the presence of metastatic brain lesions. Although there are concerning case reports of hemorrhage in brain metastases in patients receiving anticoagulation [63], these events have not been evaluated in prospective clinical trials.

Coumarin anticoagulation is believed to cause an increased risk of intracranial hemorrhage. For this reason, intracaval devices have been preferred as safer alternatives to warfarin for secondary prevention of pulmonary embolism in patients with brain tumors. VTE in patients with cerebral metastasis has been proposed as an indication for inferior vena cava (IVC) filter placement, but as the long-term safety and efficacy of filters is uncertain, use of filters should be restricted to patients in whom anticoagulation is contraindicated [64]. In a review of 50 patients with brain tumors and VTE, Olin *et al.* did not find any differences in overall survival or significant CNS complications between patients treated with either IVC filter or anticoagulation [65]. Schiff and DeAngelis reviewed 51 patients with brain metastasis being treated for VTE

and found that anticoagulation is more effective than IVC filters and safer when maintained in the therapeutic range. Approximately 40% of patients with an IVC filter had recurrent VTE, compared with 12% in those receiving anticoagulation. Systemic bleeding occurred in 19% of patients receiving anticoagulation, but was mostly minor and infrequently required blood transfusion or intervention [66].

Gerber *et al.* has proposed a simple algorithm for the treatment of VTE in patients with brain metastasis. In patients with brain metastasis and symptomatic VTE, the first step is to see whether there is any contraindication to anticoagulate. With recent craniotomy, high-risk histology such as melanoma, renal cell carcinoma, choriocarcinoma and thyroid cancer, or the presence of other contraindications to anticoagulate, IVC filter placement is preferred.

Without such contraindications, intravenous heparin is initiated after a negative noncontrast CT scan for intratumoral hemorrhage. The initial bolus dose of heparin is dependent on the severity of VTE symptoms. Once the patient tolerates 24-h infusion of heparin they are transitioned to low-molecular-weight heparin (LMWH) or warfarin [67]. LMWH monotherapy is preferred in these patients because of its efficaciousness, noninterference with chemotherapy and ease of administration, compared with heparin infusion followed by warfarin [68,69].

■ Prophylactic anticoagulation

The use of anticoagulation in patients with brain tumors is limited owing to concerns regarding intracranial hemorrhage, although this is not supported by review of the literature [70]. Physical methods such as intermittent pneumatic

Figure 5. Simplified treatment outline for metastatic brain cancer [26].

†In a very selective group of patients.

WBRT: Whole-brain radiotherapy.

Figure 6. Simplified management outline for leptomeningeal metastasis [101].
CSF: Cerebrospinal fluid.

compression devices and compression stockings have been preferred over anticoagulant agents, and they provide up to 50% reduction in VTE compared with controls [71]. In a survey of neurosurgeons carried out by Carman *et al.*, 76.2% used only mechanical methods for VTE prophylaxis after brain tumor surgery [72]. In a multicenter, randomized clinical trial carried out in 307 patients undergoing neurosurgery, Agnelli *et al.* found that LMWH combined with compression stockings was more effective than compression stockings alone after elective neurosurgery without increased risk of bleeding [73]. In a meta-analysis of randomized controlled trials performed by Iorio and Agnelli in patients undergoing neurosurgery, heparin prophylaxis resulted in a 45% relative risk reduction of VTE. There was a 50% risk reduction of proximal deep vein thrombosis with the use of LMWH [74].

■ Chemotherapy

The role of systemic chemotherapy for metastasis in the brain is very limited. The tumor cells, once colonized in the brain after decoding the BBB,

are safe from chemotherapy. The limited role of chemotherapy for brain metastasis is because of multiple factors, including tightly regulated and less permeable BBB, and also chemoresistance, concomitant steroid and anti-emetic treatment limiting chemotherapy penetration, and chemotherapeutic substances enhancing efflux of these drugs from the CNS by activating efflux pumps [75]. There are very limited data from comparative clinical trials exploring the role of chemotherapy in brain metastasis to extrapolate any conclusion for clinical guidelines. Mehta *et al.* found variability and various confounding factors in comparative clinical trials, making any definitive treatment decisions difficult. Mature data on various clinical trials on newer therapeutic agents such as temozolomide (an oral alkylator), erlotinib and gefitinib (EGF receptor tyrosine kinases) and bevacizumab (monoclonal antibody against VEGF) in combination with radiotherapy will be helpful to make clinical decisions in the future [76].

Leptomeningeal metastasis

Leptomeningeal metastasis is another complication of systemic neoplasms involving the CNS. Even after aggressive treatment, it is associated with an extremely poor outcome so treatment is aimed at palliation. Malignant cells from various cancers such as solid tumors (carcinomatous meningitis), hematogenous tumors (leukemic meningitis) or lymphomas (lymphomatous meningitis) can seed into leptomeninges. Among the solid tumors, adenocarcinomas are associated with the highest amount of leptomeningeal involvement. The lung, breast, melanoma and hematological malignancies are the major culprits of this complication. The patients with clinical signs and symptoms should be further investigated by MRI and cerebrospinal fluid study, including cytology and flow cytometry. In patients in whom intrathecal chemotherapy is planned cerebrospinal fluid flow analysis and consideration of percutaneous access such as via the ommaya reservoir should be considered. Intrathecal chemotherapy or craniospinal irradiation are the two major modalities for the treatment of leptomeningeal metastasis. Sometimes, systemic chemotherapy is also considered depending on the histology in selected groups of patients in order to target this metastatic site. To date, only two agents are used in intrathecal treatment: methotrexate

and cytosine arabinoside. As there is potential to develop symptomatic arachnoiditis, this treatment is combined with intrathecal steroids. The longer half-life of liposomal cytosine arabinoside is convenient for fewer intrathecal administrations [75,77]. Targeted therapies such as rituximab and trastuzumab [78] are being investigated for their safety and role in treatment.

The National Comprehensive Cancer Network clinical oncology guidelines for the management of leptomeningeal metastasis categorizes patients into poor and good risk categories based on their performance status, neurologic deficit, systemic extent of disease and encephalopathy. For those who are poor risk, craniospinal irradiation is recommended, while for those who are good risk, radiation and intrathecal chemotherapy after assessing cerebrospinal fluid flow are recommended (Figure 6).

Conclusion

Secondary brain metastasis is the number one cause of intracerebral brain tumors. A high index of suspicion can lead to early diagnosis, reducing the associated morbidity and mortality. Early aggressive medical management and early referral to neurosurgery and radiation oncology can

improve prognosis and quality of life in these patients.

Future perspective

The future of cancer treatment is the development of newer biological agents and targeted therapies. Controlling the driver pathway in any cancer would help to control the growth of the tumor and its metastasis. Ongoing clinical trials of these biological agents and targeted therapies, as well as their role in brain metastasis will guide us more in future cancer management. Furthermore, safety and feasibility of these targeted agents using the intrathecal route will help us to take advantage of these therapies in the tightly regulated brain environment.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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