Brain metastases (BMs) are diagnosed in 10%–40% of all patients with cancer, and the incidence continues to increase along with the number of long-term survivors. When BMs occur, they are often associated with a myriad of symptoms, including neurologic dysfunction and functional decline; both are difficult to manage and can be distressing for patients and their caregivers. Although clinically significant findings have not kept up with the rapid pace of scientific breakthroughs in understanding the mechanisms of BMs, novel approaches that affect the prognosis of patients with BMs have been introduced in clinical practice.

**At a Glance**

- Screening for brain metastases (BMs) is not routinely performed in patients with no neurologic symptoms. However, screening is indicated in lung cancer and possibly in the context of high-risk cancers.
- Individual differences in patients warrant a personalized approach in the management of BMs.
- Whole brain radiation therapy and steroids are considered to be the cornerstones of treatment for BMs.

Brain metastases (BMs) are diagnosed in 10%–40% of all patients with cancer, and the incidence continues to increase along with the number of long-term survivors. When BMs occur, they are often associated with a myriad of symptoms, including neurologic dysfunction and functional decline; both are difficult to manage and can be distressing for patients and their caregivers. Although clinically significant findings have not kept up with the rapid pace of scientific breakthroughs in understanding the mechanisms of BMs, novel approaches that affect the prognosis of patients with BMs have been introduced in clinical practice.

### Clinical Presentation

Generally, healthcare providers do not routinely screen for BMs in patients with cancer who have no neurologic symptoms, with the exception of patients with lung cancer (Gavrilovic & Posner, 2005). However, in the current age of targeted therapies and extended survival, this concept may be in need of comprehensive review. Although the use of screening to detect occult BMs remains controversial, screening may be indicated in the setting of high-risk cancers (e.g., overexpressed or amplified HER2/neu) (Duchnowska et al., 2015).

## Epidemiology

BMs are the most frequently occurring neurologic complications associated with cancer. They are 10 times more common than gliomas and can be observed in as many as 40% of all patients with systemic cancer (Chamberlain, 2010; Lorger & Felding-Habermann, 2010). The most common origins of BMs in men are lung cancer (44%), malignant melanoma (12%), and colorectal cancer (9%). In women, BMs often develop from lung cancer (33%), breast cancer (33%), and colorectal cancer (7%) (American Brain Tumor Association, 2010; Smedby, Brandt, Bäcklund, & Blomqvist, 2009). Table 1 presents the most common sites of origin for BMs.

BMs commonly present metachronously (developing at different times) with known systemic cancer (greater than 80% of all brain metastases), but may also be the first manifestation of cancer (precocious presentation in 5%–10% of all patients); alternatively, they may present synchronously with systemic and intracranial cancer (5%–10% of all patients with brain metastases) (Chamberlain, 2010; Thomas & Dunbar, 2010). Anatomically, the pattern of BMs corresponds to the volume of brain parenchyma and vascular flow (80% presenting within cerebral hemispheres, 15% within cerebellar hemispheres, 5% within brain stem) (Brastianos, Cahill, & Brastianos, 2015; Nabor et al., 2014). About 20%–50% of patients have a solitary lesion, whereas 20%–30% have oligometastatic BMs (two or three metastatic sites), and 30% or more have polymetastatic (four or more metastatic sites) BMs (Chamberlain, 2010; Fink & Fink, 2013).
BMIs may be asymptomatic, discovered incidentally during cranial imaging for cancer staging or as a baseline requirement before the initiation of new cancer therapy. Common symptoms are headaches and focal weakness, which can likely be attributed to mass effect or increased intracranial pressure (Kuo & Recht, 2006); others include nausea, vomiting, mental and gait disturbances, and seizures (reported by 18%–50% of patients). Presenting signs are altered mental status, hemiparesis, hemisensory loss, papilledema, gait ataxia, and aphasia (18%–60% of patients) (Chamberlain, 2010; Fink & Fink, 2013; Khuntia, Mathew, Meyers, Johnson, & Mehta, 2008; Kuo & Recht, 2006). Brain tumor headaches (worsened discomfort in the morning that gradually improves throughout the day) were previously considered to be the classic symptom of brain masses. However, this type of headache is rarely reported in patients diagnosed with BMs.

Neurologic deficit in patients with cancer increases the possibility of development of BMs. Healthcare providers evaluate for BMs using neuroimaging techniques (see Figure 1). Magnetic resonance imaging (MRI) is the preferred diagnostic method (Klos & O’Neill, 2004). Although MRI is more sensitive than computed tomography (CT) in detecting BMs, CT is vital during initial workup and in perioperative management (Fink & Fink, 2013). Advanced MRI techniques can also distinguish BMs from other pathologies.

### Treatment

Despite the grim prognosis associated with the diagnosis of BMs, novel therapeutic modalities have extended life expectancy in subsets of patients. In most cases, the goals of treatment are to palliate symptoms, preserve function, and improve quality of life (QOL) (Klos & O’Neill, 2004; Thomas & Dunbar, 2010). Although cure may be an unrealistic expectation, survival may be extended and QOL enhanced with appropriate therapy (Klos & O’Neill, 2004). When left untreated, the median survival for patients with BMs is estimated at four weeks, which increases to four to six months with treatment (Khuntia et al., 2008; Klos & O’Neill, 2004). Neurologic death ultimately results from edema surrounding the brain lesion, which increases intracranial pressure, leading to cerebral herniation (Klos & O’Neill, 2004). Current trials in BMs, which demonstrated improved local control and decreased progression elsewhere in the brain, failed to show overall survival benefit (Den & Andrews, 2012) because patients succumb to complications of systemic disease.

Table 2 provides several factors that determine treatment options for patients with one or more BMs. The goal of treatment varies within each variable. With solitary tumors, the goal is resection with possible cure, whereas with multiple metastases, the goal is often palliative. Regardless of the goal, treatment must be carefully planned to avoid unnecessary treatment burden and toxicity in the last few weeks of life (Spencer, Hall, & Jain, 2014).

Individual differences among patients provide justification for a personalized approach in the management of BMs. Although no standard clinical practice management criteria has been established, the Response Assessment in Neuro-Oncology (RANO) Metastatic Working Group has proposed a RANO Brain Metastases Criteria, which was modified from the widely used Response Evaluation Criteria in Solid Tumors, a standardized response assessment used in clinical trials (Wen et al., 2014).

**TABLE 1. Characteristics of Common Sites of Origin for Brain Metastases**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Breast</th>
<th>Lung</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of brain metastasis for each primary site (%)</td>
<td>5–16</td>
<td>25–50</td>
<td>10</td>
</tr>
<tr>
<td>Incidence of postmortem brain metastasis diagnoses (%)</td>
<td>20–30</td>
<td>40–50</td>
<td>50–75</td>
</tr>
<tr>
<td>Median time to brain metastasis (months)</td>
<td>30</td>
<td>6.5</td>
<td>30</td>
</tr>
<tr>
<td>Proportion of brain metastasis cases based on primary site (%)</td>
<td>25</td>
<td>60</td>
<td>10</td>
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</tbody>
</table>

*Note. Based on information from Bai et al., 2010; Chamberlain, 2010; Eigentler et al., 2011; Graesslin et al., 2010; Nieder et al., 2011; Oltean et al., 2009; Yamanaka et al., 2011.*

**FIGURE 1. Imaging Techniques and Their Use in Brain Metastases**

*Note. Based on information from Fink & Fink, 2013.*

- **Angiography**
  - No role in the diagnosis of brain metastases
- **Computed tomography (CT)**
  - Nonenhanced computed tomography (NECT) is often the first-line imaging for new neurologic symptoms.
  - NECT is easily obtained, well tolerated, and can promptly rule out life-threatening emergencies (e.g., hemorrhage, hydrocephalus, significant mass effect).
  - NECT alone is not sensitive enough to screen for cerebral metastases.
  - Contrast-enhanced CT (CECT) screens for metastases if magnetic resonance imaging (MRI) is contraindicated or unavailable.
  - CECT is shown to be more sensitive than noncontrast MRI in detecting cerebral metastases.
- **Diffusion weighted imaging/diffusion tensor imaging**
  - May help distinguish high-grade gliomas from metastases in areas surrounding an enhancing tumor
  - May distinguish metastases from pyogenic abscesses
  - Fluorodeoxyglucose positron emission tomography
  - Used in staging, particularly in lung cancer
  - Not as sensitive as MRI in evaluating brain metastases
- **Magnetic resonance imaging**
  - Sensitive screening for brain metastases
  - Can further evaluate mass lesions found on NECT to refine differential diagnosis
  - Magnetic resonance perfusion
  - Difficult to use to differentiate metastases from primary brain tumors
  - May help to differentiate brain metastases and cerebral abscesses, which can appear identical on anatomic imaging
  - Magnetic resonance spectroscopy
  - Can distinguish neoplastic or non-neoplastic brain mass
  - Not reliable to distinguish metastases from high-grade primary glial neoplasm (e.g., glioblastoma)
Surgery

Surgical resection of a solitary metastatic tumor has been standard practice in patients with favorable features (e.g., accessibility of the tumor, good performance status, absent or controlled extracranial disease) (Soffietti, Rudà, & Trevisan, 2008). In addition, the use of stereotactic radiation surgery and novel radiosurgery techniques as part of initial treatment or salvage of recurrent BMs have increased (Karaïskos et al., 2014; Nabors et al., 2014). Additional considerations include the extent of neurologic deficit, time to metastasis, and histology and radiosensitivity of the primary tumor (Armstrong & Gilbert, 2000). Regardless of the extent of surgery (i.e., resection versus biopsy), neurosurgeons must carefully weigh the risk of new-onset or worsening neurologic deficits when treating BMs. Aside from neurologic deficits prompted by surgery, complications can include thromboembolic events, hematoma, and pseudomeningocele formation and infection, as well as local and distant recurrence (Armstrong & Gilbert, 2000).

Radiation Therapy

Whole brain radiation therapy (WBRT) and steroids are considered to be the cornerstones of treatment for BMs (Hall et al., 2014; Mehta et al., 2005; Nabors et al., 2014). In general, patients who tolerate a course of radiation therapy are managed as outpatients and can carry on with their usual activities with only minor disruption (McQuestion & Daniels, 2011). However, with BMs, the indication for radiation therapy is still being defined, and the impact to patients’ QOL can be dramatically different (Tsao, Lloyd, & Wong, 2005; Tsao, Lloyd, Wong, Rakovitch, et al., 2005). Radiation therapy can be attributed to disabling and sometimes life-threatening toxicities, even when the therapy is considered to be palliative treatment and the management goal is definitive local control (Chi, Behin, & Delattre, 2008; Mehta et al., 2005). Therefore, in patients with BMs with whom extended local control is the primary goal, the treatment plan should address maintaining QOL by minimizing symptoms and side effects (Hall et al., 2014; McQuestion & Daniels, 2011; Serizawa et al., 2014).

Systemic Therapy

For patients with BMs, WBRT has historically been the standard of care, with surgery being reserved for selected cases (Cavaliere & Schiff, 2006; Chang, Robins, & Mehta, 2007). The use of systemic therapy in BMs has been fraught with challenges related to heavy pretreatment, issues with blood-brain barrier penetration, and lack of randomized, controlled trials in a diverse, heterogeneous patient population (Brastianos et al., 2015).

However, new developments in systemic therapy are changing practice and are playing an increasing role in the management of BMs. In addition to stereotactic radiosurgery as primary treatment, systemic therapy (e.g., targeted biologic agents, temozolomide, topoisomerase inhibitors, antimetabolites) and treatment sensitizers are moving to the forefront of treatment of BMs (Cavaliere & Schiff, 2006; Ewend, Elbabaa, & Carey, 2005). For example, in patients with multiple small BMs, one potential strategy is to delay WBRT upfront to initiate an effective targeted therapy, particularly when the therapy is part of a clinical trial (Brastianos et al., 2015).

Uncertainties remain, including those regarding the optimal combination and timing of systemic therapy, as well as the appropriate selection of patients for a particular agent. With the established efficacy of aggressive treatment regimens and the corresponding increase in survival, more patients have neurologic complications from chemotherapy that may preclude development of BMs (Dietrich & Wen, 2008).

Supportive Care

Supportive care often preempts definitive treatment for BMs. Unless a contra-indication exists, symptomatic patients with BMs are empirically treated with corticosteroids (Klos & O’Neill, 2004). High-dose dexamethasone provides symptomatic relief by reducing cerebral edema; typical regimens require 16 mg per day for 48 hours that is tapered to a maintenance dose of 2–4 mg per day (Spencer et al., 2014).

In contrast to the almost intuitive addition of corticosteroids to the management of BMs, patients are not treated with anti-epileptic drugs except when they have a history of seizure or when they are used for prophylaxis immediately following surgical resection (Chamberlain, 2010). These supportive care agents are not without

<table>
<thead>
<tr>
<th>TABLE 2. Brain Metastases and Treatment Considerations</th>
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<tbody>
<tr>
<td>Variable</td>
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</tbody>
</table>
| Age, performance status, clinical symptoms, and extent of disease | • Patients aged 65 years or younger with good performance status and controlled or no extracranial lesions have better outcomes.  
• Patients with poor performance status have the worst outcomes.  
• Based on a recursive partitioning analysis (RPA), patients with the best prognosis (RPA class I) have a median survival of seven months. |
| Histology, including radiosensitivity and chemosensitivity of the primary tumor | • Small cell lung cancer has a propensity for early brain metastasis, causing multiple tumors that are often responsive to chemotherapy; therefore, surgical resection, even of a solitary metastasis, is rarely considered.  
• A single brain metastasis occurring synchronously with non-small cell lung cancer is often surgically removed. |
| Number and size of metastases | • Single and two to three lesions are responsive to focal therapy (e.g., surgery, stereotactic radiosurgery).  
• Multiple metastases are often treated with whole-brain radiation therapy.  
• Tumors larger than 3 cm are not good candidates for radiosurgery.  
• A single large tumor may require surgery to relieve symptoms, even in the presence of multiple smaller metastases. |
| Site of metastases | • Tumors in the basal ganglia are not amenable to surgical removal but do respond to radiosurgery.  
• Cerebellar metastases, if removed surgically, increase the risk of developing subsequent leptomeningeal metastases. |

their own toxicities and potential for drug interactions that may interfere with the definitive treatment for the primary cancer or BMs. Therefore, healthcare providers should determine whether each agent prescribed is beneficial and necessary (Kamar & Posner, 2010).

**Conclusion**

BMs in patients with solid malignancies can represent the final stage in the disease process. In addition, BMs can prompt a rapid deterioration of QOL because of progressive neurologic deficits (Kienast & Winkler, 2010). Regardless of the type of BMs or treatment plan, healthcare providers, patients, and caregivers face daunting care challenges accompanied by increasing emotional, psychological, and physical burdens. Optimal care plans take into account epidemiology, clinical presentation, treatment, and supportive care strategies. Patients and the multidisciplinary team should consider all available treatment options, including prospective clinical trials, to select the most appropriate course of action.

**References**


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**Conclusion**

BM...


