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Review Article

Understanding Brain Metastasis: From Molecular Mechanisms to Treatment Advances

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Abstract

Brain cancer metastasis is one of the most common neurological complications associated with various types of cancer, particularly lung cancer, breast cancer, and melanoma. Approximately 20% of cancer patients develop brain metastasis. Current therapeutic strategies are limited and often lack effectiveness, with patient survival typically averaging less than 15 months. As a result, brain metastasis remains one of the leading causes of cancer-related mortality worldwide. Therefore, understanding the mechanisms behind brain metastasis is crucial for improving treatment outcomes. In this review, we provide an overview of the epidemiology, mechanisms, diagnostic approaches, prognostic factors, and treatment strategies associated with brain cancer.

AN OVERVIEW OF BRAIN METASTASIS

Brain metastases are secondary tumors that develop when cancer cells spread from their primary site to the brain. These metastases are commonly associated with cancers of the lung, breast, colon, kidney, and melanoma, making them one of the most frequent neurological complications of primary malignancies. Brain metastasis represents the most common type of brain tumor, affecting approximately 20% of all cancer patients, and they are a leading cause of morbidity and mortality worldwide [1]. Patients diagnosed with brain metastases often experience a range of debilitating symptoms, including headaches, seizures, fatigue, and cognitive deficits, all of which significantly impact their quality of life and daily functioning [2]. Treatment strategies for brain metastasis generally involve a combination of radiation therapy, chemotherapy, immunotherapy, and surgery. Despite these interventions, the overall survival rate remains poor, with most patients surviving less than two years after diagnosis [3]. For this reason, early diagnosis and accurate prognostication are essential for personalized treatment strategies and improved patient outcomes.

EPIDEMIOLOGY

Brain metastases typically occur in patients who have survived primary cancers, often arising as a complication during the advanced stages of the disease. These metastases represent a hallmark of late-stage malignancy, with cancer cells spreading to the brain from other organs. In the United States, approximately 40,000 new cases of brain metastases are reported annually [4]. In countries such as Peru, there is currently no established database to track the annual incidence of brain metastasis cases. However, the most recent study was to determine the characteristics of breast cancer patients with brain metastasis [5].

Epidemiologically, brain metastasis affects 20-40% of adults with malignant neoplasms, while the incidence in pediatric patients ranges from 6-10% [6]. In adults, the most common primary cancers leading to the development of brain metastasis include breast cancer, melanoma, non-small-cell lung cancer (NSCLC), and colon cancer. On the other hand, in pediatric populations, sarcomas, melanomas, and neuroblastomas are more frequently associated with brain metastasis. These differences underscore the distinct malignancies contributing to brain metastasis across age groups [1-7].

Several key factors influence the development of brain metastases, including gender, age, and the stage of the primary disease. Gender plays a notable role: men with lung cancer are most likely to develop brain metastases, while breast cancer is the leading cause in women [2]. Age also significantly affects the likelihood of brain metastasis. Women with breast cancer, especially those aged 20-39, are at a higher risk of developing brain metastases, while lung cancer patients typically present with brain metastasis between the ages of 40-49. For melanoma patients, brain

metastasis most commonly occurs in individuals aged 50-59 years [2].

MECHANISMS

Brain metastasis is a process involving the spread of cancer cells from a primary tumor to the brain. First the cancer cells from the primary tumor have to invade the bloodstream, this process is known as intravasation. The cancerous cells pass through the walls of the blood vessels thanks to factors such as the degradation of the extracellular matrix (ECM) and the influence of matrix metalloproteinases (MMPs). As a result, circulating tumor cells (CTCs) enter the systemic circulation and travel to different organs including the brain [8].

Once in the bloodstream, CTCs must cross the blood-brain barrier (BBB), a highly selective permeability barrier that protects the brain from harmful substances, maintains brain homeostasis and proper neuronal function [9]. The blood-brain barrier is formed by tight junctions (TJs) between endothelial cells, these junctions are transmembrane proteins such as occludin, claudins, tricellulin/marvelD2, marvelD3. These junctions hinder the passage of many substances, including cancer cells [9]. However, certain tumor cells have evolved mechanisms to cross the BBB through endothelial transcytosis, a process in which cancer cells are transported across endothelial cell barriers by vesicle-mediated processes [10]. Once the cancer cells extravasate, when they leave the bloodstream, they penetrate the brain tissue and form micrometastases. Likewise, it has been reported that astrocytes facilitate the migration of circulating cells across the BBB [11,12].

After extravasation, tumor cells face the challenge of establishing themselves in the brain environment. Successful colonization depends on several factors, including the interaction between the tumor cells and the brain microenvironment. However, it is still unclear how brain-tropic cancer cells adapt to the brain's unique microenvironment. It is known that tumor cells undergo various events, such as an angiogenic switch, in which tumors induce the formation of new blood vessels to supply the growing metastatic tumor. Tumor cells secrete angiogenic factors such as vascular endothelial growth factor (VEGF) to promote blood vessel formation within brain tissue [13]. Likewise, the interaction between astrocytes and tumor cells has been demonstrated, where astrocytes supply arachidonic acid (AA, 20:4) and mead acid (20:3) to tumor cells, activating PPARγ signaling and increasing their proliferation in the brain [14]. Additionally, cancer cells may exploit the brain's innate immune responses, sometimes evading immune surveillance and adapting to the immunosuppressive brain environment [15].

After the establishment of cancer cells in the brain, the most common symptoms of brain metastasis are severe headaches, dizziness, seizures as well as movement and speech difficulties.

DIAGNOSIS

Neuroimaging is the primary method for detecting brain metastases, with magnetic resonance imaging (MRI) using gadolinium contrast considered the gold standard. This technique provides superior resolution and sensitivity compared to computed tomography (CT), enabling precise localization of lesions, including their number and size, even those smaller than 5 mm [16].

Advanced MRI techniques, such as diffusion-weighted imaging (DWI), visualize the movement of water molecules within brain tissue. This enables differentiation between various brain lesions, such as gliomas and cerebral infarcts, while also helping assess tumor activity and predict treatment response [17]. Another MRI technique is perfusion-weighted imaging (PWI), which provides information about cerebral hemodynamics, including blood flow and volume. This technique is useful for assessing the vascularity of lesions [18]. Finally, magnetic resonance spectroscopy (MRS) offers biochemical and metabolic insights into brain tissue, aiding in the differentiation between brain metastases and primary tumors such as gliomas [19].

Early and accurate diagnosis of brain metastases relies heavily on advanced imaging and emerging molecular tools.

PROGNOSIS

As mentioned, the prognosis of patients with brain metastases is influenced by multiple factors, including patient age, number of brain lesions, type of primary tumor, and molecular characteristics. One of the most widely used prognostic tools is the Graded Prognostic Assessment (GPA), which incorporates variables such as primary cancer type, patient functional status, and presence of extracranial metastases to generate a personalized score. The GPA ranges from 0 to 4, with 0 indicating the poorest prognosis and 4 the most favorable [20,21].

Another widely used method is Recrudescent Partition Analysis (RPA), originally developed by Gaspar and colleagues using trial data from the Radiation Therapy Oncology Group (RTOG) [22,23]. The RPA stratifies patients based on key clinical factors, such as age (older or younger

than 65 years) and presence of extracranial metastases. Based on these variables, patients are classified into three prognostic classes with different median overall survival rates: Class I (~7.1 months), Class II (~4.2 months) and Class III (~2.3 months). Despite its simplicity and wide adoption, the RPA does not incorporate important prognostic factors such as the number of brain metastases or molecular characteristics of the tumor [22-25].

While traditional prognostic models, such as RPA, have provided a practical framework, newer tools that integrate genomic and treatment response data offer a more nuanced and individualized approach. Thus, accurate prognostic assessment is essential not only to guide therapeutic decisions, but also to inform patients' expectations and optimize their quality of life.

TREATMENTS STRATEGIES

Treatment strategies for brain metastases require a personalized, multidisciplinary approach tailored to the tumor's molecular characteristics, the primary cancer type, and the patient's overall health status. Management typically involves a multimodal regimen that may include systemic therapy, radiation therapy, surgical resection, and supportive care [26].

Systemic therapy, including targeted therapy, immunotherapy, and chemotherapy, has advanced considerably in recent years and now plays a central role in the treatment of brain metastasis, particularly in selected molecular subgroups [27]. Targeted therapies demonstrate tumor-specific efficacy in genetically defined populations. For example, BRAF and MEK inhibitors (such as dabrafenib and trametinib) have significantly improved survival outcomes in patients with melanoma brain metastases, especially when combined with stereotactic radiosurgery (SRS) [28]. Similarly, in HER2-positive breast cancer, HER2-targeted agents such as trastuzumab deruxtecan have shown promising intracranial response rates, including in patients with leptomeningeal involvement [29].

Immunotherapy, particularly immune checkpoint inhibitors targeting PD-1 and CTLA-4 (e.g., nivolumab and ipilimumab), has demonstrated high intracranial response rates and prolonged progression-free survival in patients with melanoma and non-small cell lung cancer (NSCLC) harboring specific mutations. These outcomes are further enhanced when immunotherapy is used in combination with SRS [30].

Although the efficacy of chemotherapy is generally limited by the presence of the blood–brain barrier, it remains a relevant option for chemosensitive tumors such as small cell lung cancer [26].

Radiation therapy remains a cornerstone in the management of brain metastases [31]. Whole-brain radiation therapy (WBRT) has traditionally been employed in patients with multiple brain metastases or leptomeningeal disease. However, WBRT is associated with significant neurocognitive decline, affecting up to 50% of patients within six months of treatment [26]. To address this, advances such as hippocampal-sparing WBRT and the concurrent use of neuroprotective agents like memantine have shown promise in reducing cognitive side effects [32].

Stereotactic radiosurgery (SRS) has emerged as the preferred approach for patients with a limited number of metastases, offering high rates of local tumor control and reduced long-term neurotoxicity [33]. SRS delivers high-dose, targeted radiation to lesions typically less than 3 cm in diameter, and its combination with surgical resection has been shown to improve both survival outcomes and local disease control [34]. For larger lesions, fractionated SRS is increasingly utilized, providing effective tumor management while minimizing radiation-induced toxicity [35].

Surgical resection plays a pivotal role in the management of brain metastases, particularly in patients with a limited number of lesions, large tumors causing significant mass effect, or when histopathological diagnosis is required. It is most beneficial for individuals with a single, surgically accessible metastasis associated with neurological symptoms or elevated intracranial pressure. Tumor removal can provide rapid symptomatic relief from headaches, neurological deficits, or seizures resulting from mass effect.

Outcomes are significantly improved when surgical resection is followed by adjuvant stereotactic radiosurgery (SRS). Studies have shown that this combined approach results in longer median survival (approximately 15.2 months) and lower local recurrence rates, with only 20.5% of patients experiencing recurrence at one year. In contrast, surgical intervention is less commonly recommended for patients with multiple brain metastases, due to increased procedural risk and limited overall survival benefit.

Minimally invasive alternatives, such as laser interstitial thermal therapy (LITT), offer an option for patients with deep-seated, inoperable, or recurrent tumors. LITT employs MRI-guided laser ablation to thermally destroy tumor tissue and has shown promise in select patient populations [36].

Supportive care is a critical component of brain metastases management, aiming to improve quality of life by alleviating symptoms and minimizing treatment-related side effects. Corticosteroids, particularly dexamethasone, are commonly administered to reduce vasogenic edema and intracranial pressure in symptomatic patients. Typical starting doses range from 4–8 mg/day for mild symptoms and up to 16 mg/day for severe presentations. Approximately 75% of patients experience rapid symptom relief within 24 to 72 hours. However, corticosteroids should be tapered as soon as clinically feasible to minimize adverse effects such as hyperglycemia, myopathy, and immunosuppression. Importantly, their use is not recommended in asymptomatic individuals [16].

Antiepileptic drugs represent another essential element of supportive care but are reserved for patients with a documented history of seizures. There is no evidence supporting prophylactic use in seizure-naïve patients, and unnecessary administration may expose individuals to avoidable side effects [16].

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated efficacy in preserving cognitive function in patients undergoing whole-brain radiation therapy (WBRT). It has been shown to slow declines in processing speed and other cognitive domains, contributing to improved neurocognitive outcomes during treatment [37].

Overall, supportive care strategies must be individualized, taking into account tumor burden (number, size, and location of metastases), primary cancer type, and the patient's general performance status.

FUTURE DIRECTIONS IN RESEARCH

Exosomes are a promising area of research in brain metastasis, they represent potential applications in both diagnosis and treatment. These nano-sized extracellular vesicles (30–150 nm), produced by most cells and present in body fluids like blood plasma and urine, are formed through the inward budding of endosomal membranes, resulting in intraluminal vesicles (ILVs) within multivesicular bodies (MVBs), which are then released as exosomes [38].

Once believed to function mainly in cellular waste removal, exosomes are now understood to play a key role in intercellular communication, especially in the spread and development of cancer [39]. In brain metastasis, exosomes help prepare distant organs for tumor colonization by shaping the pre-metastatic niche. Their involvement in tumor signaling makes them valuable as potential therapeutic targets, drug delivery vehicles, and biomarkers. Current research is exploring how these vesicles can be harnessed to develop innovative and more effective treatment strategies for brain metastases [39].

The brain tumor microenvironment (BrTME) is composed of specialized cells, including astrocytes, microglia, and endothelial cells, which interact with metastatic cancer cells to create an immunosuppressive niche that supports tumor growth and survival [40]. Additionally, Tumor cells can manipulate microglia and tumor-associated macrophages, reprogramming them to suppress effective immune responses and helping cancer cells evade immune surveillance within the central nervous system [41]. Emerging research is increasingly focused on disrupting these interactions by modulating microglial activation and enhancing T cell infiltration into the brain. These strategies aim to weaken the protective environment that allows metastases to thrive. Furthermore, immunotherapies such as checkpoint inhibitors are being adapted specifically for brain metastases, offering new possibilities to counteract the unique immune resistance mechanisms of the BrTME [42].

Genomic and molecular profiling has revealed that brain metastases often possess distinct genetic and epigenetic alterations compared to their corresponding primary tumors. These include unique mutations, pathway activations, and copy number variations that may contribute to brain tropism and therapeutic resistance [43]. Studies that had analyzed matched primary and metastatic samples showed that brain metastasis can harbor actionable driver mutations absent in the primary tumor or in extracranial metastases, underscoring the importance of site specific molecular testing for precision oncology [43]. Liquid biopsy approaches, such as the detection of circulating tumor DNA (ctDNA) in cerebrospinal fluid, are expanding the capacity to monitor these alterations non-invasively, allowing for real-time insights into tumor evolution and treatment response [44]. These molecular insights are accelerating the development of brain-penetrant targeted therapies aimed at overcoming resistance mechanisms and addressing the unique challenges posed by the blood–brain barrier.

CONCLUSION

Brain metastasis remains one of the most challenging diseases in the medical field due to its high prevalence, complex biology, and limited therapeutic options. Despite advances in imaging, molecular profiling, and targeted therapies, patient outcomes remain poor, underscoring the urgent need to investigate the mechanisms driving

brain metastasis. The interaction between tumor cells and the brain microenvironment, including the blood-brain barrier and immune components, plays a critical role in metastatic colonization and treatment resistance. Emerging research on exosomes, immune modulation, and genomic alterations offers promising avenues for new diagnostic and therapeutic strategies. Looking ahead, the integration of multidisciplinary approaches—combining precise molecular characterization, innovative systemic therapies, and refined local treatments—will be essential to improving personalized care and increasing survival and quality of life for patients with brain metastases, especially those who are resistant to treatment. The ongoing exploration of the unique biology of brain metastases will ultimately pave the way for more effective and personalized interventions in this challenging clinical setting.

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