Current and Emerging Treatments for Brain Metastases

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Conventional methods for treating brain metastasis, such as surgery, WBRT, and SRS, each compete with and complement one another. A plethora of recent studies have helped define and expand the utility of these tools.

Introduction

Brain metastases affect 9% to 17% of cancer patients[1]; this frequency is fairly proportionate to the relative cardiac output to the brain. Most cancers spread to distant organs through vascular or lymphatic vessels, but the latter do not exist in the central nervous system. Thus, cancer cells travel through the bloodstream either by colonizing a vascular space or by crossing the blood-brain barrier into the parenchyma.

The cancers that most often metastasize to the brain are those that originate in the lung and breast, which is unsurprising given the high incidence of those two diseases (Figure 1). However, the third most frequent type of brain metastasis is melanoma (Table).[1] This suggests a certain selectivity regarding a given tumor’s propensity to metastasize to the brain, as metastatic melanoma accounts for only a small fraction of cancer diagnoses. This selectivity, perhaps secondary to the brain’s microenvironment, is also evident in the inverse relationship between overall incidence of disease and incidence of brain metastasis with testicular and prostate cancer.[2,3]

Most physicians and patients are unlikely to devote much thought to the nuances of metastasis but are instead focused on the simple matter of survival. Without treatment, median survival for a patient with brain metastasis is estimated to be 3 months for a single lesion, although survival time has likely increased recently due to enhanced screening that detects smaller masses.[4] Fortunately, radiation and surgery are usually sufficient for local control of oligometastasis. The poor life expectancy associated with brain metastasis is more often a result of the consequences of widespread visceral metastasis.[5] There are notable exceptions, however, such as with melanoma metastatic to the brain, where the majority of patients will succumb to a neurologic-related death even with treatment.[6] Further, despite satisfactory local control rates with current modalities, the sheer number of total patients with brain metastases results in a substantial number of treatment failures. Thus, improving therapies for metastatic brain tumors is still an unmet need.

Additional advances in the field face the “law of diminishing returns,” since state-of-the-art techniques for the destruction of metastatic brain lesions by surgical or other means are fairly effective. One potential next-generation tool is magnetic resonance (MR)-guided focused ultrasound surgery (MRgFUS). Theoretically, MRgFUS appears to be an appealing and feasible approach due to the noninvasive nature of thermal ablation and its high degree of conformality. However, as with all focal techniques, disease that is diffuse, intermingled with a critical structure, or not clearly visualized with imaging will be challenging to treat. Hence, there remains a great need for effective systemic agents that target mechanisms of chemotherapy resistance unique to metastatic brain lesions.

Key Biologic Concepts of Metastatic Brain Tumors

Metastatic cascade

The metastatic cascade serves as a model for invasion of a secondary site by primary tumor cells. The first step involves invasion through the extracellular matrix and stromal cell layers at the primary site,[7] followed by invasion into the blood vessel lumen, with support for transport through the vasculature. Once the metastatic cells have been transported, they will come to rest in the brain by adhering to the intimal surface. The mechanisms of initial establishment are still obscure, however. The cells either start proliferating in the vascular space, followed by penetration through
the blood-brain barrier, or the reverse occurs. Regardless of the mechanism, at some point there is permeability of the blood-brain barrier that is putatively mediated by vascular endothelial growth factor (VEGF).[8]

**Blood-brain/metastasis barrier**

The resistance of metastatic brain tumors to systemic therapy has historically been attributed to the blood-brain barrier.[9,10] It was previously assumed that the blood-brain barrier was intact in the vessels of the metastatic lesion, thus preventing drug distribution. Recent studies suggest otherwise; however, there has always been some suspicion that the barrier was not intact because almost all nonminiscule metastatic lesions enhance intensely with gadolinium.

On a morphologic level, the neovascularization of renal cell brain metastasis was reported to be similar to its counterpart at the primary extracranial site.[11] Additionally, the recent study by Nduom et al of three metastatic brain lesions (melanoma, adenocarcinoma, and cervical cancer) revealed thin and dysmorphic CD31-positive endothelial cells within the tumor mass, further accentuated by the absence of glial fibrillary acidic protein (GFAP) and aquaporin 4 (AQP4) immunoreactivity adjacent to CD31-positive vessels, findings that are indicative of an absence of the blood-brain barrier.[12] The investigators also noted that upon passing through the tumor/brain interface into normal brain, endothelial morphology and associated immunostaining characteristics immediately normalized. There are also functional differences in the endothelium of metastatic brain tumors compared with normal brain. P-glycoprotein (P-gp), the product of the multidrug resistance 1 (MDR1) gene, is highly expressed in the vascular endothelial cells of the normal brain and performs as a drug efflux pump. However, endothelial cells of metastatic brain tumors demonstrate absent or variable P-gp staining reflective of the vasculature from tumor of origin.[13,14] It is important to note that submillimeter nests of cancer cells may cross the blood-brain barrier without violating its integrity. Therefore, development of oncologic therapies for brain metastasis that can penetrate the blood-brain barrier is still pertinent, although it may be a lower priority than creating treatments for brain metastasis that are visualized on MRI.

**Brain microenvironment**

The data collectively cast significant doubt on the idea of an intact blood-brain barrier within metastatic brain tumors. So what underlies the resistance of brain metastases to systemic agents? Some investigators have speculated that this phenomenon is a result of the interaction between the tumors' cells and the brain's microenvironment. In essence, this concept is Paget's "seed and soil hypothesis," in which cancer stem cells—that is, the "seeds"—metastasize to locations—the "soil"—that are favorable for implantation and growth.[15] To facilitate integration with neural tissues during reimplantation, the circulating tumor cells that have previously undergone epithelial to mesenchymal transition (EMT) may reacquire some of the original epithelial traits by reversing the EMT process.[16]

There are a number of mechanisms by which the brain's microenvironment potentially nurtures the development of treatment-resistant metastasis. One hypothesis is that cells intrinsic to the central nervous system secrete macromolecules that activate pro-survival pathways. For example, astrocytes can promote survival and growth of metastatic tumor cells by secretion of cytokines, growth factors, and neurotrophins.[17,18] Neman et al recently demonstrated that the neurotransmitter γ-aminobutyric acid (GABA) binds to GABA receptors present on breast cancer cells. The GABA is then catabolized into succinate that is used in the GABA shunt, conferring a metabolic advantage.[19] Interestingly, GABAergic pathways have also been shown to be present in testicular and airway epithelial cells, perhaps suggesting a reason for the propensity of cancers derived from those cells to metastasize to the brain.[20,21]

One unexplained aspect of these theories, which propose that the brain parenchyma supplies some type of nutrient or growth factor that vitalizes the metastatic tumor, is that most of the tumor mass is distant from the adjacent brain. Brain metastasis almost invariably grows as a mass with distinct borders composed of reactive astrocytes and microglia.[22] Pro-survival factors would therefore have to diffuse considerable distances, particularly with larger tumors. That effective concentration gradients would be maintained across centimeters is counterintuitive. There is some speculation that the neuronal/astrocytic population may be admixed with metastatic cells; however, this has not been clearly demonstrated.[23] Thus, alternate mechanisms must always be considered, including the possibility that the brain passively selects for harder metastatic tumor cells.

**Current Therapeutic Strategies**
Surgical treatment

Surgery remains a highly successful treatment approach for accessible brain tumors (Figure 2). Its judicious application necessitates an understanding of the limitations and efficacy of various surgical strategies and technologies. The most significant technical advances in surgery over the last decade have arguably occurred in the field of preoperative brain mapping. These advances include functional MRIs with fiber tract mapping and transcranial magnetic stimulation coupled with three-dimensional MRI renderings.[24] More importantly, the advances in systemic therapy and radiation therapy have had the greatest influence on surgical indications. Better systemic therapies have increased the pool of patients eligible for surgery, while enhanced screening and improved radiosurgery techniques are often used to manage smaller lesions, obviating the need for a craniotomy.

Surgery for a single lesion originating from a solid cancer in an accessible location, and in a patient who has very limited or no systemic cancer and an absence of leptomeningeal infiltration, classically results in significant improvements in neurologic function and improved survival.[25,26] Indications are less defined in patients with moderate systemic tumor burden or multiple brain metastases.[27,28] For these patients, especially if radiation has already been attempted, a craniotomy may be the only remedy that can provide rapid relief of symptoms linked to mass effect, such as intracranial hypertension, seizures, obstructive hydrocephalus, or peritumoral edema.[29] Deviation from classical indications for surgery is often considered when the patient has significant extracranial disease but is eligible for other lines of effective systemic therapies. In addition, the role of surgery for multiple metastases is currently being redefined. Because multiple lesions often require separate craniotomies, there is a higher cumulative probability of complications developing as a result of the multiple surgeries.[30] Nevertheless, this risk seems justified, as median patient survival time is 9 to 14 months, which is 3 to 6 months longer than the survival of those who are treated solely with radiation.[30-32] In fact, surgical removal of all lesions in patients with up to three brain metastases can lead to survival comparable to that of patients with a single metastasis.[30]

Surgical technique has been shown to influence local recurrence rates. Tumors resected in a piecemeal fashion, which violates the tumor capsule, have a recurrence rate 1.7 times higher than that of tumors removed with circumferential resection (en bloc).[33] En bloc resection has been shown to be particularly important for lesions of the posterior fossa and those in contact with cerebrospinal fluid pathways.[34] Moreover, piecemeal resections are not always safe because of the size of the lesion or the proximity of eloquent cortex. To reduce the incidence of local recurrence, Yoo et al suggested a microscopic total resection approach in which a 5-mm margin of normal-appearing tissue is removed by ultrasonic aspiration.[35] Compared with standard piecemeal gross total resection without adjuvant therapy, microscopic total resection reduced 1-year local recurrence rates from 59% to 29%.[35] Since most resection cavities are now treated with postoperative stereotactic radiosurgery (SRS), this finding may be most relevant to the resection of metastatic tumors progressing despite radiation or initial surgery for lesions known to have high radioresistance.

Whole-brain radiotherapy

Whole-brain radiotherapy (WBRT) is often utilized for multiple and disseminated metastases and for salvaging stereotactic radiation therapy failures. Studies have shown that 64% to 83% of patients with multiple metastases who undergo WBRT experience significant symptomatic improvement and a mean increase in survival of 2 to 6 months.[36] Combined with surgery, WBRT drastically lowers recurrence rates to 10% to 18%, compared with 46% to 70% with surgery alone.[37] However, the toxicity of WBRT should be considered. Although WBRT was initially found to be minimally toxic, recent studies have shown potential adverse short- and long-term effects, especially in the elderly population.[38,39]

Stereotactic radiosurgery

SRS focuses beams of radiation on the tumor(s). The convergence enhances tumoricidal effect and results in a rapid dose drop-off in normal tissues, allowing for treatment of lesions adjacent to critical structures.[40] The efficacy of SRS for brain lesions is generally encouraging, with local control rates ranging from approximately 64% to 94%.[41-49] Lesions less likely to respond are generally larger than 2 cm³, receive less than 18 Gy of radiation, or have a radiation-resistant histology (eg, melanoma or renal cell carcinoma).
There are overlapping considerations when deciding whether to use SRS alone, as an adjunct to surgery or WBRT, or not at all. One widely used determinant has been lesion number. For single brain metastasis, SRS alone is potentially as effective as surgery with SRS of the resection cavity when the lesion is small and radiosensitive.[50-52] SRS alone is usually a better option than surgery if the lesion is surgically inaccessible, or if the patient has uncontrolled systemic metastasis or is a poor operative candidate due to other medical conditions. In practice, surgery is often performed to resect or cytodn to decrease the amount of cerebral edema. Seven of the eight patients had drastically bevacizumab (Figure 3).[75] The rationale was to use bevacizumab to block VEGF in leakage-prone edema following SRS.[74]. In a small clinical trial, eight patients were treated with CyberKnife and bevacizumab (Figure 3).[75] The rationale was to use bevacizumab to block VEGF in leakage-prone capillaries to decrease the amount of cerebral edema. Seven of the eight patients had drastically improved neurologic functioning, while only one patient suffered bevacizumab-related hypertension.

Chemotherapy and targeted agents

With few exceptions, most notably germ cell tumors and small-cell lung cancer, metastatic brain tumors do not respond to systemic chemotherapy.[26,68] However, molecularly targeted therapies have shown some promise against brain metastases, especially those that are “oncogene addicted.” One such example is seen in non-small-cell lung cancer (NSCLC) that possesses activating epidermal growth factor receptor (EGFR) mutations.[69] Complete and partial response rates to tyrosine kinase inhibitors have been recorded in clinical studies: Rates of response with gefitinib ranged from 10% to 38%, with a median duration of 9 to 13.5 months, and similar findings were documented with erlotinib.[70,71] These treatments also improved overall survival rates.[72]

Also, a remarkable number of patients with human epidermal growth factor receptor 2 (HER2)-positive breast carcinoma have had a favorable response to lapatinib, a tyrosine kinase inhibitor that targets the C-terminus domain of HER2 and EGFR receptors. In a multicenter phase II trial, which included 242 patients who had received prior trastuzumab and cranial radiation treatment, 6% of patients had an objective response and 21% had at least a 20% volumetric reduction with lapatinib alone.[73] In a subgroup of 50 patients who entered an extension of this study, 20% experienced an objective response and 40% experienced at least a 20% volumetric reduction in their brain metastasis with lapatinib plus capecitabine. Although the current efficacy of targeted therapy is modest, these results inspire great hopes for future systemic treatments.

Use of bevacizumab for treatment of malignant brain edema associated with brain metastasis

A treatment also worth noting is a targeted antiangiogenic approach to managing severe cerebral edema following SRS.[74]. In a small clinical trial, eight patients were treated with CyberKnife and bevacizumab (Figure 3).[75] The rationale was to use bevacizumab to block VEGF in leakage-prone capillaries to decrease the amount of cerebral edema. Seven of the eight patients had drastically improved neurologic functioning, while only one patient suffered bevacizumab-related hypertension.
This novel approach warrants further investigation and should be considered for this frequently encountered clinical scenario.

**Emerging Ablative Technologies**

**Laser interstitial thermal therapy**

Laser interstitial thermal therapy (LITT) is a new ablative tool that promises to be useful for the treatment of central nervous system metastasis. LITT is a minimally invasive cytoreductive treatment strategy that utilizes a low-voltage laser inserted through a burr hole to induce hyperthermia to kill tumor cells.[76] LITT differentiates itself from previous ablative technologies by using MR thermography to assess tissue heating in near-real time. Conformality is sufficient, but procedural times are often comparable to that of an actual craniotomy. The use of LITT for treatment of metastatic disease is limited, but in trials that have looked at its use in recurrent glioblastoma multiforme, results show increases in radiographic responses and progression-free survival.[76-79] With its unique approach and encouraging results, LITT potentially fulfills a need for a treatment that can be applied to metastatic brain lesions that have not responded to radiotherapy when surgery is undesirable or unfeasible.

**MRgFUS**

MRgFUS is another fascinating technology that can be used for precise, incisionless, thermal ablation in the brain. A hemispherical phased-array transducer combined with patient-specific treatment planning are implemented based on acoustic models, with feedback control based on MR thermography used to deliver ultrasound energy to a specific focal point.[80,81] MRgFUS has been successfully used as a minimally invasive treatment method to target deep brain structures in a small series of patients with essential tumor.[82] MRgFUS has also been used to treat three inoperable thalamic glioblastomas[81,83]; however, in one of the three inoperable glioblastomas, a serious complication occurred, in which treatment caused an interruption of blood flow. Currently, MRgFUS can only target deep brain structures, although further iterations of the device are expected in the near future that will facilitate its application to brain metastasis.

**Conclusion**

Conventional methods for treating brain metastasis, such as surgery, WBRT, and SRS, each compete with and complement one another. A plethora of recent studies have helped define and expand the utility of these tools, and an enhanced understanding of the biology of metastatic brain tumors and the advent of molecularly targeted therapies have spurred the development of effective systemic therapies. Recently developed ablative technologies—as well as those currently in development—which can be visualized in real-time, promise to further strengthen the neuro-oncologic armamentarium.

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