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Controversies in the management of brain metastases

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Abstract

The multidisciplinary management of brain metastases has generated substantial controversy as treatment has diversified in recent years. Debate about the type, role, and timing of different diagnostic and therapeutic strategies has promoted rigorous scientific research into efficacy. However, much still remains unanswered in the treatment of this difficult disease process. This manuscript seeks to highlight some of the controversies identified in previous sections of this supplement, including prognosis, pathology, radiation and surgical treatment, neuroimaging, and the biochemical underpinnings of brain metastases. By recognizing what is yet unanswered, we hope to identify areas in which further research may yield promising results.

Key Words: Brain metastases, biomarkers, chemotherapy, neuroimaging, stereotactic radiosurgery, whole-brain radiation therapy

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INTRODUCTION

The rapid development of multimodal treatments for brain metastases has generated controversy both in practice and in the published literature.[27,45,48] This is due not only to the heterogeneity of patient disease (histological subtype, number and location of brain metastases, and systemic disease burden) but also institutional, regional, and national biases toward what constitutes the "standard of care." Within the constantly evolving field of neuro-oncology, treatment often involves a multidisciplinary team of neuro-oncologists, medical oncologists, radiation oncologists, and neurosurgeons aided by diagnostic radiologists, pathologists, pharmacists, and ancillary support staff.[16,50] This manuscript attempts to summarize some of the current controversies in brain metastases management, and explore future directions for improved patient care.

More than just an advanced stage of systemic cancer, the presence of brain metastases is a harbinger of worsened systemic prognosis. More than two-thirds of cancer patients diagnosed with brain metastases die of systemic disease progression, rather than the brain metastases themselves.[2] Exceptions to this population include patients with significantly invasive or multiple metastases,[26] large metastases causing significant mass effect, brain herniation, hydrocephalus,[50] intractable seizures,[37] and carcinomatous meningitis.[17] These patients are more likely to die from neurological progression, but even in these patients, advanced systemic disease remains an important cause of mortality.[51]

The National Comprehensive Cancer Network (NCCN) attempts to standardize diagnostic and treatment algorithms for oncological care in the United States. Algorithms for oligometastases (1-3 metastases), multiple metastases (>3), and leptomeningeal metastases

have been developed for both initial and recurrent treatment.[33] These algorithms encompass the complexity of treating brain metastases, and vary regarding systemic screening and treatment, surgery, chemotherapy, and radiation. Regardless of modality, many practitioners consider the goal of treatment of brain metastases to be ultimately palliative (rather than curative) in that success is measured not just by moderate lengthening of overall survival, but also by delaying time to local recurrence and improving quality of life by mitigating symptoms.

PROGNOSIS

Multiple factors must be taken into account when determining the prognosis of patients with brain metastases, since prognosis influences treatment decision-making. The most important of these include age, functional status (usually measured by Karnofsky Performance Score [KPS], systemic disease status (including disease burden and progression despite systemic treatment), primary site,[15,46] number of metastases,[44] interval between diagnosis of systemic and metastatic disease, and tumor-specific genetic factors. Patient-specific factors (e.g., weight loss, depression, support system status, persistent smoking) have been shown to impact overall survival, but these are not often objectively evaluated for each patient. Additionally, patient preferences such as goals of care (quality of life versus overall survival) must be taken into account. While several major grading systems based on some of these factors have been developed to quantify prognosis, there is reasonable consistency between systems especially in the significance of KPS in overall survival.[52]

As stated earlier, institutional biases can impact the prognostic estimations of practitioners in specific practice settings, and some indices that employ more subjective grading criteria (such as the Rotterdam scoring system,[20] in which practitioners estimated patient response to treatment) are considered less accurate and reliable than rigorously objective systems. Moreover, the genetic heterogeneity of most cancers[5] (for which targeted small-molecule or antibody therapies are playing an increasingly important role)[43] will require much larger clinical trials to achieve the statistical power necessary for prognostication.

PATHOLOGY

The primary histological subtype of brain metastases is an essential factor in the prognosis and treatment of brain metastases. However, recent advancements in immunohistochemical testing and tumor biomarkers have led some practitioners to reconsider "traditional" treatment paradigms for certain tumor subtypes. For instance, breast cancer biomarkers, which carry significant prognostic and therapeutic implications (such as hormone and HER2 receptor status and p53- and Ki-67 proliferative indices), can vary between primary tumor and brain metastases.[34,32] The success of antibody treatment (such as trastuzumab) against extracranial Her2/Neu-expressing breast cancers has led to a paradoxically higher incidence of brain metastases. This is due to the efficacy of antibody treatment against extracranial disease, combined with its inability to cross the blood–brain barrier (BBB). More patients are thus surviving their primary disease long enough to develop cranial metastases. Newer small-molecule tyrosine kinase inhibitors such as lapatinib have better BBB penetration, and when combined with capecitabine (a DNA synthesis inhibitor) have shown promise in recent trials of patients with brain metastases of HER2-positive breast cancer.[4,23] Similarly, BRAF and MEK, mutations present in approximately 50% of melanomas, have also been targeted by small-molecule chemotherapeutics dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor), which has shown promise against melanoma brain metastases.[13]

Prophylactic chemotherapy in the prevention of brain metastases is more controversial. Some oncologists have proposed prophylactic lapatinib for patients with established extracranial metastases or who are at high risk for brain metastases, though this strategy is unproven.[10] The availability and cost of certain biomarker tests has also caused debate in brain metastasis management,[3] especially in relatively rare mutations such as anaplastic lymphoma kinase (ALK), which occurs in 3-7% of nonsmall cell lung cancers.[41] For this small population, the tyrosine kinase inhibitor crizotinib has shown encouraging results in primary tumor control; however, evidence of central nervous system (CNS) penetration is limited;[9] it is unclear whether this treatment confers any benefit to patients with brain metastases. The determination of biomarker test, chemotherapeutic agent, dosage, and treatment timing will remain one of the great challenges of neuro-oncology.

WHOLE-BRAIN RADIOTHERAPY

Whole-brain radiotherapy (WBRT) is an established treatment for brain metastases, and evolving techniques have improved progression-free and overall survival in many patients.[14] However, WBRT-related effects of contrast enhancement around previously treated brain lesions on posttreatment magnetic resonance imaging (MRI) can lead to diagnostic difficulty. The phenomenon of pseudoprogression, best defined in primary brain tumors, can look very similar with MRI to radiation necrosis or advancement of disease, and if misdiagnosed can lead to changes in treatment strategies.[39,47] Recent studies evaluating the use of advanced imaging (such as MRI-perfusion or -spectroscopy) may aid in pseudoprogression

diagnosis (see below).[6] However, there is no pathologic correlate of pseudoprogression to provide a "gold standard" for this diagnosis. In fact, the diagnosis of pseudoprogression remains an imaging-based diagnosis, which is confirmed when the region of presumed progression decreases with time and incorrect when there is continued progression.

Late cognitive changes have also been associated with WBRT, and have often been considered a significant drawback to the survival benefit conferred by this treatment.[49] However, other studies have posited that disease progression, and prior multimodality therapy (surgery, chemotherapy, immunotherapy, radiosurgery, etc.), rather than radiation-induced changes, are responsible for declining cognition. This remains an unresolved area of study regarding the late toxicity of WBRT.[22]

SURGERY

Surgical treatment for brain metastases has been established as useful tool in certain patient scenarios, especially when limited to a single metastatic lesion in patients with good KPS and controlled extracranial disease. While some cases necessitate urgent surgical intervention (such as hemorrhagic metastases with pending herniation, large posterior fossa metastases with secondary hydrocephalus and brainstem compression), for other cases surgery is contraindicated (multiple metastases not easily accessible with one surgical approach, inoperable locations of metastases, significant medical comorbidities, etc.). It is the large number of cases that fall between these two extremes where treatment becomes controversial. Debate still exists regarding the superiority of surgery versus stereotactic radiosurgery (SRS),[24,31] though some studies have suggested that SRS to the resection cavity after surgical extirpation is superior to surgery or SRS alone.[8,38] It is also unclear whether modifications to surgical technique, including *en bloc* resection,[1] microscopic total resection,[54] and resection cavity brachytherapy,[12] which have shown promise in controlling local recurrence, will become widely adopted.

NEUROIMAGING

The rapid adoption of advanced neuroimaging has improved the diagnosis and surveillance of brain metastases in recent years. However, determination of the classic diagnostic conundrum of whether a solitary enhancing brain mass represents metastases or primary glial neoplasm remains elusive, as both entities can appear identical on even high-resolution contrast-enhanced MRI. MR-spectroscopy[42] and MR-perfusion[7,18] have both been employed in such situations, especially when measuring the presence of metabolically active tumor infiltrate in peritumoral edema, which is often suggestive of primary glial disease. Similarly, diffusion tensor imaging (DTI) may help differentiate primary brain tumors from metastases or lymphoma,[53] leading some researchers to investigate the potential for histological grading based on imaging characteristics alone.[19] However, recent attempts to correlate DTI parameters with tumor histological subtype have been unsuccessful;[11] it is unlikely that neuroimaging will replace pathological examination of biopsy tissue in the near future.

SEED AND SOIL

The CNS is considered fertile "soil" for the "seed" of metastatic disease.[29,35] However, the nature of both the ability for tumors to metastasize to brain (the seed) and how the brain harbors such tumors (the soil) remains elusive. Some authors have suggested that metastases are the result of spread of tumor stem cells[30] though the existence of tumor stem cells is itself debated.[36] Regardless of their origin, circulating metastatic seeds must find hospitable soil in foreign organs, which is thought to occur in only 0.01% of metastatic cells.[29] The biological mechanisms for tumor intra- and extravasation has not been well elucidated, but the potential for disruption of both seed (via induction of differentiation factors in undifferentiated tumor stem cells[21]) and soil (via antiangiogenic and antigrowth factor agents[40] as well as immunomodulators[25]) has been identified as a promising treatment area. As stated earlier, greater understanding of the genetics of tumor cell proliferation (especially in the tyrosine kinase family) has led to the development of promising small-molecule or antibody-based agents. For instance, ipilimumab, which targets the CTLA-4 receptor on normal regulatory T-cells, renders them intolerant of certain immunoevasive mutations found in metastatic melanoma; the ability for these activated T-cells to cross the BBB obviates the need for toxic doses of traditional chemotherapeutic agents and has shown good activity against melanoma metastases to brain.[28] Further developments in chemotherapy tailored to individual patients' tumor genetics (so-called "pharmacogenomics") thus remains a tantalizing area of future research.

CONCLUSION

The treatment of brain metastases remains challenging despite recent advancements in surgery, radiation oncology, and chemotherapeutics. Because most patients with brain metastases succumb to systemic disease progression, treatment of brain metastases does not often provide increased overall survival. In other words, as long as the CNS disease is treated, systemic disease will usually be the primary "driver."

Advancements in neuroimaging, biomarker pathology, genetics, and treatment delivery will continue improve patient outcomes and quality of life, through the generation of new questions and controversies for which further study is developed. The most effective overall treatments require a multidisciplinary team of oncologists, neuro-oncologsts, neurosurgeons, and radiation oncologists. In combination with ancillary support staff, a multidimensional approach will ensure the best tailored therapy for each patient's individual situation, affording patient's clarity of goals, a wider array of options, and sustained hope.

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