Metastatic Brain Tumors: Current Therapeutic Options and Historical Perspective

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Metastatic brain tumors affect more than 150,000 patients annually in the United States. The therapeutic paradigms for these tumors have evolved over the years and currently encompass numerous modalities implemented by treating physicians across several medical disciplines. The armamentarium of brain tumor treatment involves neurosurgical intervention, whole-brain and focused radiation modalities, chemotherapy, and immunotherapy. Patient selection, however, remains critical to achieve maximal therapeutic benefit and depends on functional status, number and location of lesions, and tissue histologic findings. Best outcomes can be expected with a multidisciplinary approach to patient care where state-of-the-art treatment options are readily available.

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Brain metastases are the most common intracranial tumors in adults, with 150,000 to 170,000 cases annually in the United States as of 2004.[1] Sources of cerebral metastasis may be cancers of the lung, breast, skin (ie, melanoma), colon or bowel (ie, colorectal), or kidney, with 70% of cases annually comprising cancers of the lung or breast.[2] Because of advancements in cancer management, cancer patients are living longer. The increase in overall survival rates, however, has been associated with an increase in the rates of cerebral metastasis. In fact, according to autopsy studies,[3,4] as many as 45% of cancer patients go on to develop brain involvement. Therapeutic options include medical management alone, neurosurgical intervention, radiation treatments, and adjunct chemotherapy. Although previous reports[5,6] have documented independent survival advantage for these options, it is the multitherapeutic approach to cerebral metastasis that has shown to be most beneficial. In the present review, we discuss historical highlights of brain tumor management, as well as current treatment options for this patient population.

History

Surgical intervention for cerebral metastasis has been performed since the late 1800s.[7] However, early attempts often resulted in devastating complications, including infections and high surgical mortality.[8] Even after improvements such as the use of perioperative antibiotics and advances in surgical illumination and magnification, it took several decades for the benefits of surgical intervention to become widely accepted. Regarded as a less invasive therapeutic option, whole-brain radiation therapy (WBRT) was first recognized, to our knowledge, in the 1950s[9] and demonstrated a substantial survival benefit, quickly becoming the standard of care. Over the next several decades, the benefits of surgical resection versus radiotherapy remained a contentious issue secondary to the paucity of literature. Moreover, early treatment with WBRT was hampered by the insufficient resolution of imaging modalities, which rendered brain metastasis essentially an "invisible" problem. Hence, radiotherapy gained acceptance as the standard of care, whereas surgical interventions were reserved for special circumstances.[10] The landscape of brain tumor therapy experienced a major transformation in the early 1970s with the advent of computed tomography and then again in the 1980s with the implementation of magnetic resonance imaging. The ability to better visualize intracranial lesions and evaluate postsurgical results once again sparked interest in surgical resection of brain metastases.

In a randomized controlled trial from 1990, Patchell et al[4] demonstrated longer survival for patients with brain metastasis who underwent surgical resection compared with the survival of patients who underwent radiation alone (median survival times of 40 weeks and 15 weeks, respectively). These findings were later confirmed by other studies using larger patient samples.[11-13] Bindal et al[12] showed that surgical resection increased survival time for patients with 3 or fewer brain metastases and that the prognosis for these patients was similar to that of patients who underwent surgical resection for a solitary lesion. Patchell et al[13] went on to evaluate WBRT as a surgical adjunct in their 1998 prospective trial, demonstrating that postoperative WBRT attenuated metastatic recurrence at the index site of metastasis, as well as at remote brain locations. Interestingly, the study did not show statistically significant differences in length of survival in patients who underwent adjunct radiation compared with those who underwent surgical resection only.

At nearly the same time that Patchell's research was being conducted,[4,13] in 1993 a group of Swedish researchers[14] was the first to report their experience with brain metastases by using gamma-knife (GK) radiosurgery alone. Initial results from this 16-year study were favorable, with a 94% control rate for treated lesions, a 7-month mean survival time, and 13% of patients experiencing radiation-associated adverse events.[14] Other studies using linear accelerator stereotactic radiosurgery achieved results similar to those of the Swedish group.[15,16]

Over the past 2 decades, the treatment of patients with brain metastases has progressed to include a multi-therapeutic approach as standard of care (*Table*). Various combinations of surgical resection, WBRT, and stereotactic radiosurgery are being evaluated to assess which can provide the best available outcomes for this patient population. Patient-specific variables such as age, functional status, and systemic control of primary disease, as well as number, size, and location of metastatic lesions, become increasingly important in guiding treatment recommendations. Although controversy regarding optimal therapeutic avenues still exists, it is essential for physicians to consider all options when treating patients with brain metastasis.

Surgical Intervention

Surgical intervention is still considered the standard of care for patients with 3 or fewer surgically accessible lesions. The goal of surgical intervention is gross total resection, with tumor debulking comprising a small subset of cases. Surgical intervention has been associated with both a statistically significant and a biologically significant survival rate over best medical management or WBRT alone.[17] Although it is the most invasive of treatment options, surgical intervention offers advantages over other modalities, namely, the opportunity to directly access tissue for histologic evaluation. This aspect is especially important for 2 types of patients: those whose systemic cancers with brain lesions that are, in fact, harboring concomitant primary tumors or infections and those in whom no systemic disease is identified. Tissue evaluation can further guide subsequent chemotherapy and radiation options. Surgical resection also attenuates mass effect of intracranial lesions, often resulting in increased functional status to the patient. Moreover, surgical intervention is often the only possible option for instances of a large cerebral lesion with advanced peritumoral edema. Surgical intervention therefore may be preferable to radiation, which is associated with exacerbation of cerebral edema, or chemotherapeutic options, which are devoid of benefit as a standalone treatment.

Despite many advantages, neurosurgical intervention remains an invasive treatment option that necessitates hospitalization, general anesthesia, and skin incision. With the advent of more advanced intraoperative image guidance and microsurgical technique, however, the mortality and morbidity rates for patients undergoing craniotomies for cerebral metastasis have markedly decreased over the years. In fact, Tan and Black[18] found a 3.6% complication rate with no deaths, 3-day average length of hospital stay, and 96% gross total resection in 49 patients treated for brain metastases.

Radiation

In current practice, several radiation choices are available for physicians who treat patients with brain metastases.

One long-accepted therapeutic option is WBRT. In the past few decades, however, it has been reserved mainly as adjunctive (ie, not standalone) therapy. Studies by Patchell et al[13] and Kocher et al[19] suggest that WBRT can be effective in controlling metastasis locally and at inhibiting the development of remote metastatic lesions. Rarely the sole treatment of choice, WBRT nevertheless is used to care for patients with extensive metastatic burden or patients with contraindications to both surgical and radiosurgical alternatives. Still, complications from WBRT can be serious. Irreversible neurocognitive deficits have been demonstrated at 6 months after treatment and may progress to dementia-like symptoms.[20]

Gamma-knife stereotactic radiosurgery has recently acquired momentum as a major therapeutic intervention for brain metastases. Early work with GK for this condition dates back to the 1970s.[10,14] Over the past decade, studies[21-23] emerged on the safety and efficacy of GK radiosurgery, whether used alone, in conjunction with WBRT, or as adjunctive treatment alongside surgical resection. Length of survival was similar between patients who underwent GK and patients who underwent surgical resection.[21-23] A group in Japan[22] examined 4562 lesions in 521 patients and demonstrated favorable outcomes for patients with 10 or fewer lesions who were treated with up-front GK alone. The combination of GK and WBRT has also been studied for both single and multiple lesions, and similarly promising findings have been reported.[23] Most recently, GK was evaluated as an adjunct to surgical resection and was found to facilitate local control.[21]

For many patients, GK is a preferable alternative to surgical resection. Radiosurgery with GK bypasses the potential hazards of hospitalization and cosmetic blemishes associated with surgical intervention, delivering focused radiation to the target while limiting the amount of surrounding brain tissue exposed to radiation.[24] Eliminating the need for general anesthesia, GK is a safe option for patients with medical comorbidities for whom surgical intervention carries an increased complication rate. It is typically performed on an outpatient basis, which allows the patient to be discharged to home on the same day and resume normal activities shortly thereafter.

Unfortunately, targeted treatment with GK is usually restricted to brain lesions less than 3 cm in diameter. Because a small percentage of patients will develop cerebral edema, GK is not an ideal option for patients with extensive swelling before treatment. Moreover, treatment time can increase with size and multiplicity of lesions, making single-session therapy arduous for the patient, as well as for the treating team.

Tissue Histologic Findings

The most profound factor governing the development of intracranial tumors is the type of primary tumor that is developing. The histologic findings dictate the treatment paradigm in cerebral metastatic disease secondary to varying chemotherapeutic and radiation susceptibilities. Furthermore, histologic findings are an important factor for prognosticating outcome. Lung cancer accounts for up to 65% of brain metastases.[25] Breast cancer, melanoma, renal cancer, and colon cancer are, in order of decreasing frequency, the less common tumor types associated with brain metastases.[26-28]

Small-cell lung cancer is universally regarded as the most aggressive type of lung cancer and accounts

Table.
Comparison of 5 Treatment Options for Patients With Metastatic Brain Tumors

Treatment Option	Benefits	Drawbacks
Observation	Least invasive option.	Carries the worst prognosis and is, therefore, reserved for the most advanced cases as a last resort.
Surgery	Standard of care. Alleviates mass effect while providing tissue histologic findings. Gross total resection possible.	Most invasive option requiring general anesthesia and a skin incision. Subject to risks associated with open cranial surgery.
Whole Brain Radiation	Less invasive option. Effective for known lesions and protective against developing remote metastasis. Good option for patients with extensive metastatic burden.	Requires multiple treatment sessions. Carries a lesser survival advantage compared with other options and is mostly used as adjunct therapy. Neurocognitive deficits may develop in long-term survivors.
Radiosurgery	Less invasive option. Provides local control and has been shown to provide a survival time comparable to that of surgery in select patients. Single day, single treatment session is possible.	May require application of head pins under local anesthetic. Does not reduce mass effect and cannot be used for large lesions. No protective advantage against remote metastasis.
Chemotherapy	Adjuvant therapy. Most effective for systemic disease.	Effectiveness determined by tumor histologic findings. No clear survival advantage as a single therapy. Multitude of systemic adverse reactions.

for 13% to 20% of all lung neoplasms in the United States.[29] Small-cell lung cancer has a high predilection for the brain, and as many as 18% of patients will already have intracranial metastasis at the time of diagnosis.[30] In fact, even with aggressive treatment the risk of developing brain metastases is 50% at 2 years after aggressive treatment is initiated.[31,32] The neurologic burden of small-cell lung cancer is so serious that physicians often consider treating patients with prophylactic cranial irradiation, in part because of the highly radiosensitive nature of this tumor's histologic characteristics. In a landmark study, Aupérin et al[33] demonstrated increased long-term survival in patients receiving prophylactic cranial irradiation at 3 years after treatment. Thus, prophylactic cranial irradiation is now considered the standard of care for treatment of patients with small-cell lung cancer. Furthermore, small-cell lung cancer is very chemosensitive, with clinical response in up to 73% of cases.[34] Consequently, surgical intervention for this type of tumor is rarely undertaken, and a combination of radiation and chemotherapy serves as the first-line option.

Non–small-cell lung cancer carries a more positive prognosis than its small-cell counterpart, yet responses to radiation and chemotherapy are somewhat attenuated by the tumor's histologic findings.[35] Therefore, a radical treatment paradigm is often undertaken, especially in patients with 1 or a few lesions. In most cases, primary surgical intervention or radiosurgery (GK or linear accelerator) is recommended, followed by WBRT.[36]

Breast cancer is the second leading source of brain metastases and is the leading cause of leptomeningeal metastasis.[37] One in 8 women develop breast cancer, and the incidence of intracranial spread is 5% at 5 years after primary diagnosis.[38] Age of less than 40 years and negative estrogen receptor status are the highest prognostic factors for the development of brain metastases, at 43% and 38%, respectively.[39] Surgical intervention remains the mainstay of treatment for patients with brain metastases in whom breast cancer is the primary source; adjuvant WBRT is reserved for circumstances of recurrent cerebral metastases or multiple lesions.[39] Radiosurgery (GK or linear accelerator) has been used in patients with breast cancer–derived brain metastases. Increased survival times were demonstrated in younger patients with a single lesion.[39,40] The role of chemotherapy for this type of tumor histologic finding remains unclear and is currently not considered a standard treatment option for patients with breast cancer–derived brain metastases.

Melanoma is the third most common histologic type of metastatic intracranial disease. Early detection is crucial, as distant spread is associated with grave prognosis.[28,41-43] Surgical intervention remains the primary treatment of choice for patients with a single cerebral lesion. Although melanoma cells are inherently more resistant than other cancer cells to radiation therapy, WBRT alone or in conjunction with surgical intervention has demonstrated beneficial effects. A study by Wroński and Arbit[44] suggested that radiation will have the greatest impact on neurologic function and less of an impact on length of survival. Gamma-knife stereotactic radiosurgery demonstrates good outcomes as well, with survival data (eg, survival time, local tumor control, local brain failure, distant brain failure) similar to that of surgical resection.[45-50] Chemotherapy is largely ineffective for melanoma, with rates of either tumor regression or patient survival never measured higher than 20% in multiple studies.[28,43] Immunotherapy with interleukin-2 and interferon agents is currently under investigation as a potential treatment alternative, but results have been equivocal to date.[51]

Conclusion

Metastatic brain tumors present a major medical and socioeconomic strain on our society. Patient screening remains critical to achieving maximal therapeutic benefit. Therefore, patients' needs and care should be assessed on a case-by-case basis. A multitherapeutic approach combined with state-of-the-art treatment options will provide the best outcomes for patients.

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