

## Metastatic Brain Tumors: Current Therapeutic Options through Surgery and Radiation Therapy

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### Abstract

Metastatic tumours involving the brain overshadow primary brain neoplasms in frequency and are an important complication in the overall management of many cancers. Importantly, advances are being made in understanding the molecular biology underlying the initial development and eventual proliferation of brain metastases. Surgery and radiation remain the cornerstones of the therapy for symptomatic lesions; however, image-based guidance is improving surgical technique to maximize the preservation of normal tissue, while more sophisticated approaches to radiation therapy are being used to minimize the long-standing concerns over the toxicity of whole-brain radiation protocols used in the past. Furthermore, the burgeoning knowledge of tumour biology has facilitated the entry of systemically administered therapies into the clinic. Responses to these targeted interventions have ranged from substantial toxicity with no control of disease to periods of useful tumour control with no decrement in performance status of the treated individual. This experience enables recognition of the limits of targeted therapy, but has also informed methods to optimize this approach. This Review focuses on the clinically relevant molecular biology of brain metastases, and summarizes the current applications of these data to imaging, surgery, radiation therapy, cytotoxic chemotherapy and targeted therapy.

### Introduction

#### History

Surgical intervention for cerebral metastasis has been performed since the late 1800s. However, early attempts often resulted in devastating complications, including infections and high surgical mortality, even after improvements such as the use of perioperative antibiotics and advances in surgical illumination and magnification, and 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<sup>9</sup> 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.<sup>10</sup> 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.

#### Randomized Study Protocol

In a randomized controlled trial from 1990, 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.

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. 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, in 1993 a group of Swedish researchers 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.<sup>14</sup> Other studies using linear accelerator stereotactic radiosurgery achieved results similar to those of the Swedish group.<sup>15,16</sup>

Over the past 2 decades, the treatment of patients with brain metastases has progressed to include a multitherapeutic 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.



## The importance of Angiogenesis

The growth of metastatic brain tumours is critically dependent on angiogenesis, and thus therapies targeting this process might be important in the management of brain metastasis. Disordered angiogenesis results in structural and functional abnormality of tumour-associated blood vessels, characterized by defective endothelial cells, pericyte covering and basement membranes. These abnormalities can directly restrict the delivery of oxygen, leading to intratumoural hypoxia. Impaired efficacy of systemically administered anti-cancer therapeutics and agents used in radiation therapy due to limited perfusion of the cancer tumour bed and thus exposure to the drug, might lead to the establishment of functional sanctuary sites that enable the growth of cancer cells.

## Brain Metastases—Surgical Management

### Historical and current concepts

Advancements in neuroanaesthesia, instrumentation and imaging technologies, as well as improvements in standard tools, such as the operating microscope, now enable neurosurgeons to perform surgery more safely than ever before. Indeed, in 2010, the first evidence-based compendium for the treatment of patients with brain metastases published a level I recommendation for surgical resection combined with radiation therapy to prolong life in relatively young patients with good functional status and a newly diagnosed solitary brain metastasis.

### Surgical decision making

Perhaps the most critical aspect of the surgical management of brain metastasis is the decision to proceed with an operation. Careful patient selection based on the current body of evidence is of paramount importance. Currently, class I evidence is available in support of surgical resection followed by WBRT in patients with a newly diagnosed solitary brain metastasis, without advanced systemic disease, who spend more than 50% of their time out of bed.

## Radiation Therapy

### Whole-brain Radiation Therapy

WBRT has historically been used as the primary non-surgical therapeutic modality for the treatment of brain metastasis (previously reviewed elsewhere). This trend was due, in part, to the limited chemotherapeutic options demonstrated to be efficacious. On the basis of a recursive partitioning analysis of data from patients treated between 1979 and 1993 on previous RTOG protocols, even patients with brain metastasis who had the best prognosis had a median survival of only 7 months after WBRT alone. However, with improvements in systemic therapies for a variety of cancers, patient survival has now increased, even among those with metastatic disease. In this context, WBRT alone is increasingly found to be inadequate in the long-term control of brain metastasis. In addition, with these improved outcomes, many patients in whom control of brain disease is achieved with WBRT are surviving to experience the considerable neurocognitive sequelae and declines in quality of life that are associated with this treatment. The classic neurocognitive toxicity associated with WBRT in adults is a moderate-to-severe dementia that occurs several months to years after treatment. DeAngelis *et al.* observed a 2–5% incidence of severe dementia in populations of patients who had undergone WBRT (with or without surgical resection) for brain metastases, although these authors estimated that a markedly higher incidence of dementia would have been found if less-severe cases of neurological decline were also included. The degree of neuro-cognitive decline in patients with brain metastasis can be further confounded by the effects of metastasis at presentation or recurrence and therapeutic interventions (that is, chemotherapy) on cognitive function.

### Systemic Therapy for Brain Metastases

Patient survival following the development of brain metastasis is typically measured in weeks to months, although considerable variability is observed based on the size, number and location of the metastases, as well as the histological type of cancer involved.

Whereas the overall 2-year survival rate in patients with brain metastasis is 8.1%, 2-year survival after diagnosis of brain metastasis is less than 2% in patients with SCLC, but as high as 24% in patients with ovarian cancer. Contemporary data from patients with oligometastasis to the brain treated primarily with local surgical or radiation therapy reveal a more encouraging median overall survival of 16 months from the time of brain metastasis diagnosis. As mentioned earlier, the proclivity of certain cancer types to spread to the brain is an intriguing phenomenon whose biological mechanisms remain to be clarified. The so-called „seed and soil“ hypothesis implicates key biological mechanisms that permit the development of metastatic tumour deposits in the brain. Signalling through HER2, EGFR, HSPSE and Notch1-related pathways might mediate specific biological processes important to tumour growth and metastatic spread, including angiogenesis, epithelial–mesenchymal transition, anchorage independent growth and resistance to anoikis, as well as resistance to standard therapeutic interventions. Other than the use of antiangiogenic agents, the exploitation of these biological processes for therapeutic intervention in the context of brain metastasis remains mostly limited to preclinical studies.

### Targeted molecular therapy

For several years, the mainstay of therapy for brain metastasis from a chemotherapeutic standpoint has been temozolomide. Subsequent to the discovery of *BRAF* mutations in a majority of melanomas, *BRAF* inhibitors have been increasingly used to treat this disease, as well as associated brain metastases. Initial evidence of the potential promise of *BRAF*-targeted agents in the clinical management of melanoma-related brain metastasis came from early phase clinical trials. In seven patients with brain metastases, a *BRAF* inhibitor induced CNS tumour shrinkage, and complete responses were observed in three patients. In a phase I trial, in which the majority of patients had *BRAF*-mutant melanomas, in addition to other *BRAF* mutant tumours, dabrafenib treatment was associated with a reduction in the size of brain lesions, and four patients achieved complete resolution of all brain lesions. Normal serum lactate dehydrogenase levels seemed to be a predictor of response to dabrafenib. The intriguing observation of intra cranial responses to dabrafenib in this phase I trial led to a prospective open-label phase II trial of dabrafenib in patients with previously untreated brain metastasis or with progressive brain lesions following initial local treatment. Overall disease control in patients with metastases expressing Val600Glu (V600E) *BRAF* was 79%, but complete responses were rare, and the efficacy of this compound was generally decreased in the tumours with the Val600Lys (V600K) *BRAF* mutation subtypes.

## Conclusions

Surgery and radiation therapy have important roles in the management of metastatic brain tumours and, depending on one's definition, could be considered targeted therapies. As such, they remain the „go to“ modalities for the treatment of most metastatic brain tumours, particularly at the time of initial diagnosis. However, these interventions are responsible for well-recognized and substantial adverse events in some cases. Effective strategies to minimize these problems would be of great advantage to the patients with metastatic CNS lesions. The achievable technical improvements possible in surgical and radiation techniques are limited and ultimately medicinal means of management, probably relying on novel systemic targeted therapies, will be necessary to attain this goal and to improve outcomes in patients with brain metastases.

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