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Surgery for brain metastases

Kurt Andrew Yaeger, M. Nathan Nair

Department of Neurosurgery, Georgetown University School of Medicine, Washington DC 20007, USA

E-mail: Kurt Andrew Yaeger - kurtyaegs@gmail.com; *M. Nathan Nair - Nair.nathan@gmail.com
*Corresponding author

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Abstract

The use of surgery in the treatment of brain metastases is controversial. Patients who present certain clinical characteristics may experience prolonged survival with resection compared with radiation therapy. Thus, for patients with a single metastatic lesion in the setting of well-controlled systemic cancer, surgery is highly indicated. Stereotactic radiosurgery (SRS) alone can provide a similar survival advantage, but when used as postoperative adjuvant therapy, patients experience extended survival times. Furthermore, surgery remains the only treatment option for patients with life-threatening neurological symptoms, who require immediate tumor debulking. Treatment of brain metastases requires a careful clinical assessment of individual patients, as different prognostic factors may indicate various modes or combinations of therapy. Since surgery is an effective method for achieving tumor management in particular cases, it remains an important consideration in the treatment algorithm for brain metastases.

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INTRODUCTION

Metastatic brain cancer represents a growing problem in neurological care. Between 10% and 30% of individuals with systemic cancer will eventually present with brain metastases.[18] As survival from these cancers improves with technical and pharmaceutical advances, the incidence of brain metastases will increase.[25] The presence of metastatic brain lesions was historically considered a very poor prognostic factor for patients with systemic cancer, leading to irreparable neurologic deficits and eventually death.[23] Recently, however, better systemic therapies and more aggressive treatment modalities have allowed better symptom control and increased overall survival for patients with brain metastases.[10] Yet even with these clinical improvements, median survival remains 4 months,[32] and 2-year survival is less than 6%.[26] The current treatment paradigm for intracranial metastases depends heavily on individual patient characteristics, and may utilize some combination of surgery and radiation, in an effort to control both local and widespread metastatic disease progression.[35] With ongoing efforts to enhance the precision of surgical techniques and imaging studies, surgery will play an increasingly vital role in the treatment of metastatic brain cancer.

Brain metastases outnumber primary brain lesions 10 to 1, and as a result, are the most prevalent intracranial tumor.[40] Most often, these metastases are derived from primary lung tumors (40-50%) and primary breast tumors (20-30%).[19] Other common primary cancers include melanoma, renal, colorectal, and uterine, while more than 5% of cases are caused by a primary tumor of unknown etiology.[52] The incidence of brain metastasis depends on primary tumor histology, and can be as high as 20% for individuals with lung cancer, 7% for melanoma and renal cancer patients, and more than 5% for patients with breast cancer.[4]

The pathophysiology of metastatic spread involves a series of discrete steps, through which a cancer cell must survive in order to gain a foothold at a distant site. Initially, a cancer cell must escape the region of primary tumor and enter systemic circulation through blood, lymph, or cerebrospinal fluid (CSF). The cell consequently undergoes migration to the target site, extravasation, and finally, proliferation within the target tissue. However, survival at each of these steps is constrained by cancer cell genetic and epigenetic alterations, and only 0.01% of cells that make it to circulation will eventually form metastases.[24] For the case of brain metastasis, primary tumor cells tend to arrest and undergo extravasation in "watershed" zones of the narrowing cerebral microvasculature. Thus, reflecting cerebral blood flow, 80% of brain metastases occur in the hemispheres, 15% in the cerebellum, and 5% in the brainstem.[13] Complete invasion into the brain parenchyma requires stable tumor cell attachment to extracellular matrix, proteolytic degradation of the surrounding matrix, and derivation of a novel blood supply.[18] Metastatic growth depends greatly on the formation of this blood supply, either by recruitment of the surrounding circulation or by induction of neovasculature (angiogenesis). Tumor angiogenesis usually results in aberrant vessels, with a larger lumen and thicker basement membrane, that can prevent efficient exchange between circulation and tissue, result in areas of hypoperfusion, and serve as a barrier to effective drug delivery.[16]

Typically, patients present with brain metastases after a primary tumor has been diagnosed. It is not uncommon, however, to have synchronous presentation of both a primary and metastatic lesion, or even presentation of the metastasis alone, without an obvious primary lesion. Only two-thirds of patients with brain metastases experience significant neurological symptoms in their lifetimes, the rest being identified as a result of incidental imaging or autopsy studies.[14] For patients with a history of a primary cancer, new onset neurological symptoms may indicate the presence of brain metastases, and thus warrant appropriate follow-up. Such symptoms include, cognitive impairment, hemiparesis, seizures, gait ataxia, aphasia, and visual disturbances.[25] The primary diagnostic step should be magnetic resonance imaging (MRI) with and without contrast; this provides high enough resolution to visualize small metastatic lesions that may be missed by computed tomography (CT).[3] Physiologic positron emission tomography (PET) and MR sequences, such as proton MR spectroscopic and dynamic susceptibility contrast-enhanced perfusion-weighted imaging, may add pertinent diagnostic information to more ambiguous lesions. For patients harboring suspected metastases without an obvious primary tumor, stereotactic biopsy may be indicated in order to histologically classify and grade the suspected cancer.[8]

Treatment of brain metastases depends on several prognostic factors. A worse disease outcome is expected in older patients (≥65 years), worse functional status at diagnosis (Karnofsky Performance Score (KPS) <70), more than one metastatic lesion, and an uncontrolled primary cancer, among others.[17] Based on these characteristics, several prognostic indices have been developed and validated, including the Recursive Partitioning Analysis (RPA)[17] and the Graded Prognostic Assessment (GPA).[40] However, due to the variable nature of metastatic progression, the patient population is highly heterogeneous and thus prognostic assessment should be carefully considered at the individual level, prior to establishing treatment options.

The goal in treating metastatic brain cancer is to maximize survival and functional state while limiting deficits to neurologic status. Currently, much debate is centered on the practice of surgical resection versus stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT) for the treatment of brain metastases. Regardless of controversy, however, surgery remains an important consideration in the therapeutic repertoire for metastatic brain cancer, especially for patients with a specific clinical profile.

INDICATIONS FOR SURGERY

Classically, surgical resection of brain metastases has been limited to palliative care. Recently, however, several prospective studies have described a subset of patients for which surgery is highly indicated and results in a prolonged survival.[48] These patients most often have a single, surgically accessible metastatic lesion, absent or well-controlled systemic disease, good functional status (KPS), intact neurological function, and absence of leptomeningeal infiltration.

In 1990, Patchell *et al*. compared surgical resection and postoperative WBRT to needle biopsy and radiotherapy for the treatment of a single brain metastasis.[34] In this seminal work, the authors described surgically treated individuals as having a longer survival period (40 weeks, compared with 15 weeks), greater functional independence, and decreased incidence of recurrence within the original metastatic site. A similar study by Vecht *et al*. in 1993 yielded analogous results, but the authors noted that extended survival with surgery only applied to patients with stable extracranial disease.[47] Currently, the presence of a single metastatic lesion in the setting of well-controlled systemic cancer is the best indicator for surgical therapy, and is predictive for prolonged survival following resection. Furthermore, patients who improve functionally after surgery tend to experience better outcomes in response to adjuvant therapy.[30]

For lesions causing significant neurological complications, the role of surgery is definitive: Tumor resection remains the only effective method of providing immediate relief to life threatening symptoms.[28] Surgical extirpation can alleviate symptoms associated with mass effect, intracranial hypertension secondary to CSF obstruction, and peritumoral edema.[45] Patients experiencing medically refractory seizures, as induced by a metastatic lesion, may similarly benefit from surgery.[37] Because large tumors are most likely to cause significant neurological complications, lesion size greater than 3 cm is an indication for surgery.[31] Cerebellar lesions are also a surgical implication, as they often present with brainstem compression and obstructive hydrocephalus, necessitating immediate resection.[31]

For patients with end stage metastatic disease, surgery may represent an effective salvage therapy. Surgical intervention may be required to reduce mass effect or CSF obstruction, and may ameliorate impaired consciousness and improve neurologic function.[39]

A principle contraindication to surgical treatment of brain metastases is the presence of multiple lesions. Although some appropriately selected patients may benefit from aggressive multimodal therapy, surgery may not improve the already short expected survival, and is thus hard to justify.[36] Additionally, the technical difficulties in accessing and resecting multiple lesions limit the potential benefits of surgery. In cases where there exists a large dominant lesion, however, surgery may be indicated to provide symptomatic relief.[31]

Reoperation for recurrent brain metastases may be indicated in certain situations. Bindal *et al*. reported an increased survival time for patients whose recurrent metastases were resected, versus those who did not undergo additional operations (8.6 and 2.8 months, respectively).[6] Patients with well-controlled systemic disease and high performance scores may indeed experience better survival after sequential surgeries for recurrences. Surgical resection is certainly a viable option for treating tumor recurrence after SRS, unless surgery is otherwise contraindicated.[46]

Proceeding with surgery depends entirely on the individual patient's clinical scenario. Patients with a single metastatic lesion and well-controlled primary cancer experience improvements in neurological function and lengthened survival time following resection. Since rates of surgical mortality and neurological morbidity are low (under 2% and 6%, respectively),[33] surgery remains a feasible option for the treatment of brain metastases.

SURGICAL TECHNIQUE

The primary aims for surgical treatment of brain metastases are to improve neurological performance and to prolong overall survival. With the introduction of image-guided and microscopic surgical techniques, these goals have become more readily attainable.[49] As novel methods of localization and resection become available, the surgical repertoire is enhanced, and treatment is greatly improved. However, depending on the clinical course of each individual patient, certain surgical techniques may engender a better outcome than others.

Control of local recurrence is an important aspect in the management of brain metastases. As many as 46% of resected lesions eventually recur.[35] However, the method of resection has significant impact on local recurrence rate. Tumors that were resected in a piecemeal fashion (without violating the tumor capsule) have been found to have a recurrence rate 1.7 times higher than those removed *en bloc* (circumferential resection). The 14% local recurrence rate for *en bloc* resected tumors most likely reflects less intraoperative tumor spillage, compared with piecemeal procedures.[35] *En bloc* resections are particularly useful in resecting posterior fossa metastases and lesions in contact with the CSF pathway, tumors that are highly prone to lemptomeningeal spread following surgery.[1,42] However, piecemeal resection may be unavoidable in some situations, as in cases where the tumor is adherent to or infiltrating eloquent brain regions, or when the lesion is extremely friable.[35] In these situations, it is not uncommon for local recurrence, even with postoperative MRI confirmation of complete tumor removal. Following gross total resections of well-circumscribed brain tumors, microscopic infiltrates are often left on the tumor bed.[43] To prevent this residual cancer, Yoo *et al*. recently suggested a novel technique, microscopic total resection, in which apparently normal-looking parenchyma is suctioned to a depth of 5 mm by ultrasonic aspiration.[51] In their prospective assessment, microscopic total resection led to a decrease in metastatic local recurrence (29% one year local recurrence rate, as compared with 59% after gross total resection, $P = 0.01$).[51] Thus, *en bloc* resection and microscopic total resection techniques are highly effective in limiting local recurrence, and their use should be assessed in applicable clinical scenarios.

STEREOTACTIC RADIOSURGERY

Stereotactic therapies have arisen as an alternative to traditional surgical resection of metastatic brain lesions, providing a method of noninvasive local control. SRS has been implicated for primary treatment as well as recurrent or adjuvant therapies. For patients who are not surgical candidates due to advanced systemic disease, neurological instability, or presence of multiple metastases, SRS can be used to specifically target lesions, prolonging survival and increasing functional status. Treatment consists of multiple, convergent beam irradiation, delivering high doses to a precise target volume.[25] Energy sources include high energy X-rays (linear acceleration), gamma rays (gamma knife), and protons (cyclotron). A rapid fall-off dose prevents radiation damage to regions outside of the tumor margins. In 2004, Andrews *et al*. prospectively assessed the use of SRS in patients with one to three brain metastases. Patients who received SRS with WBRT had prolonged survival (6.5 months, versus 4.9 months with WBRT alone, $P = 0.03$) and were more likely to experience stable or improving functional status.[2] SRS has been traditionally reserved for treatment of smaller (≤3 cm) lesions, as tumors with a larger preoperative tumor volume have been found to have a shorter time to recur. However, overall survival time does not change as a function of preoperative tumor size,[20] and thus SRS should not be definitively ruled out for patients with larger lesions. Patients with recurrent brain metastases treated with salvage SRS following initial WBRT were found to have a median survival of 7.9 months, indicating the utility of SRS in these cases.[7] These data suggest that SRS represents a viable treatment option for specific patients with initial and recurrent brain metastases, especially for those whose comorbidities prevent surgical resection. Indeed, even for many patients who are good candidates for surgery, the need for craniotomy and invasive resection is low; that is, survival is similar for patients either treated with SRS or surgery.[50]

The role of adjuvant SRS in the control of local recurrence following surgical resection is becoming clear. Although WBRT has been traditionally used following surgery, widespread irradiation may cause significant neurotoxicity. Tumor bed SRS has been shown to limit local recurrence and prevent the use of salvage WBRT.[38] Due to the dynamic nature of the tumor cavity, SRS should be performed soon after resection to prevent cavity collapse and collateral tissue injury, and maximize tumor irradiation.[21] Choi *et al*. suggest that surgery and adjuvant tumor cavity SRS are the most effective means of preventing metastatic recurrence.[11] However, unlike WBRT, postoperative SRS has little effect on the growth of metastases distant from the initial site.

Due to the nature of radiation therapy, SRS will not immediately relieve mass effect compression or CSF obstruction as caused by a metastatic lesion. For patients with life-threatening neurologic impairments, surgical debulking remains the only option for prompt relief. Another significant indication for the use of surgery over SRS is presence of radioresistant tumor (renal cell carcinoma, sarcoma, melanoma). Potential complications of SRS include seizures, edema, and radiation necrosis.

The controversy whether to treat metastatic lesions with SRS or surgery is well founded. While one retrospective study[5] concluded that surgery definitively extended survival compared with SRS, two others[27,29] failed to describe significant differences between the two modalities. What is apparent, however, is that each method is particularly suited for different situations. Whereas a large, overtly symptomatic lesion would benefit from rapid surgical excision, smaller, deeply located metastases may be best treated with SRS.

ADJUVANT THERAPY

Although surgery and SRS are effective in maintaining local control of brain metastases, the intracranial spread of these lesions is an issue that may necessitate therapeutic or prophylactic adjuvant therapy. Considering the pathological mechanism of metastatic spread, it is likely that any lesion that may be recognized by CT or MR imaging is not solitary, and there are potentially many micrometastases present. Widespread treatment may be required to eliminate all latent lesions, and has traditionally been given through whole-brain radiation therapy (WBRT). In patients with a limited number of metastases, as treated by either surgery or radiotherapy, follow-up WBRT can reduce the amount of intracranial recurrences and neurologic deaths.[22] However, adjuvant WBRT does not significantly increase overall survival, yet may induce neurological morbidity.[9] It is suggested, therefore, to withhold WBRT at diagnosis, and instead proceed with SRS or resection with close clinical monitoring.[44] WBRT remains the standard of care for patients with widespread metastatic disease or poor functional status.[25]

Although chemotherapeutic treatment for brain tumors may be limited by the blood–brain barrier and initial tumor chemo-resistance, some novel drugs may have some utility in treating extensive brain metastases. Several studies have assessed the impact of intracranial drug delivery following resection. Ewend *et al*. reported a 0% local recurrence rate after resection of a single metastatic lesion, followed by WBRT and placement of intracavity carmustine polymer wafers.[15] Similarly, in a study by Dagnew *et al*., patients who received resection and permanent iodine-125 seeds experienced a 96% control in local metastatic growth.[12] Furthermore, these patients were less likely to need WBRT at follow-up, thus preventing exposure to neurotoxic radiation.

CONCLUSION

Assessing a patient with metastatic brain cancer requires thorough clinical consideration and a multimodal approach to therapy. Local tumor control can be maintained through surgical resection or SRS, alone or in combination. Studies have shown that the best survival outcomes are seen in patients with one metastatic lesion, high functional performance, and well-controlled systemic disease, and thus patients fitting this profile may benefit from an aggressive therapy, such as resection and adjuvant

SRS of the tumor cavity. Although there are few differences in outcome between surgical resection and SRS, surgery remains as essential therapeutic tool, especially in cases requiring immediate relief from neurological symptoms. As imaging modalities and surgical techniques improve, the role of surgery may become an ever-important method of treatment for metastatic brain cancer.

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