Management of Cerebral Metastases: The Role of Surgery

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In appropriate circumstances, surgical resection may be used to treat both single and multiple brain metastases.

Background: Metastatic brain tumors represent the most common neurological complication in patients with systemic cancer. They are predominantly cerebrally located and constitute a significant source of morbidity and mortality. The overall incidence of brain metastases exceeds that of all other intracranial tumors, and as improved systemic cancer treatments have extended patients' lives, this number is rising.

Methods: The role of surgery in the management of cerebral metastases is reviewed by considering patient selection criteria, surgical approaches to metastases, intraoperative adjuncts, whole-brain irradiation as a postoperative adjuvant, resection of multiple vs single metastases, and the relative roles of stereotactic radiosurgery and conventional surgery.

Results: Surgical resection of single or multiple metastases can be effective management for patients with otherwise good prognoses, providing all the known metastases can be removed without producing significant neurologic deficit. Radiosurgery, an alternate approach, can be used for smaller or inaccessible tumors.

Conclusions: The presence of multiple brain metastases does not automatically contraindicate surgery because in properly selected patients, resection of multiple metastases can extend survival and enhance the quality of life. An awareness of how the modalities of open craniotomy, whole-brain radiotherapy, and stereotactic radiosurgery best complement each other will result in the best outcomes.

Introduction

In patients with systemic cancer, brain metastases constitute a significant source of morbidity and mortality as first reported by Bucholz in 1898. Cerebral metastases are by far the most common intracranial tumors in adults, and their overall incidence is increasing as systemic cancer therapies have improved and thus have extended patients’ lives. Of the many primary cancers able to metastasize to the brain, carcinomas of the lung and breast, melanoma, renal cell carcinoma, and colon cancers are the predominant brain metastasis types seen clinically, whereas those from sarcomas and primary carcinomas of the prostate, ovary, and bladder are infrequently observed.

In the modern era, metastatic brain tumors are treated with high-dose corticosteroids, whole-brain radiotherapy, stereotactic radiosurgery, and open craniotomy. These modalities are most effectively employed when medical oncologists, radiation oncologists, and neurosurgeons are involved equally in clinical decision making. Candidates for surgery are selected according to the clinical status of the patient, the number and location of the brain lesions, and the histology of the primary cancer. The goals of surgical resection are to obtain a histologic diagnosis, to relieve symptoms, and to provide local cure through gross total resection.

Surgical Resection of Single Cerebral Metastases

Background

Two independent randomized prospective clinical trials in the early 1990s showed that surgical resection of single brain metastases followed by radiation therapy was superior to radiotherapy alone in the treatment of patients with single brain metastases. Specifically, patients with single metastases, Karnofsky scores of 70 and above, and limited systemic disease who underwent surgery lived significantly longer, had fewer recurrences, and had a better quality of life than patients receiving only radiotherapy. Though the role of stereotactic radiosurgery needs to be more precisely defined, surgery is generally accepted as the preferred method for treating single brain metastases.

Patient Selection

When choosing patients with single metastases for surgery, consideration must be given to the clinical status of the patient, the surgical accessibility of the tumor, and the histology of the primary cancer. A risk-benefit analysis is formulated from these factors for each patient.

Clinical Determinants: The most important factor influencing survival in a patient undergoing resection of single brain metastases is the status of his or her primary cancer. As many as 70% of patients undergoing surgery for removal of single brain metastases die of progression of the primary disease rather than neurological causes. Consequently, patients with "absent," "controlled," or "limited" primary cancer are expected to survive longer than patients with "uncontrolled" primary disease or with "progressive" widespread end-stage disease. Patients should undergo a thorough preoperative staging workup including computed tomography of the chest, abdomen, and pelvis, as well as a bone scan and appropriate laboratory tests for tumor markers, if indicated. From these data, the clinician can determine the expected
survival in relation to the extent of noncerebral (systemic) disease. At The University of Texas M.D. Anderson Cancer Center, patients who are expected to survive longer than four months are usually considered to be candidates for surgical resection of a single brain metastasis.

The patient’s neurological status is also an important clinical parameter that influences surgical decision making. Shorter postoperative survival is typical of patients with severe neurological deficits relative to patients with minimal deficits.\(^6\) Patients with Karnofsky scores of $> 70$ (independent despite deficits) are usually the best surgical candidates. However, the mere presence of neurological dysfunction does not preclude a surgical option because surgery often radically improves function by relieving pressure on neurons surrounding the tumor and reducing intracranial pressure. Response to preoperative corticosteroid administration can be used to assess a patient’s potential for postoperative neurological recovery. There is a higher chance of postsurgical recovery for patients whose neurological functions improve after receiving preoperative corticosteroids.

Other clinical factors associated with decreased survival include increasing age, male gender, and infratentorial tumor location.\(^8\) Survival is also related to the interval between the diagnosis of the primary tumor and the appearance of the brain metastasis. Patients who present with a cerebral metastasis one or more years after their primary cancer is diagnosed survive significantly longer than those in whom the metastasis was detected within one year after diagnosis of the primary cancer.\(^6\)

Surgical Accessibility: Magnetic resonance imaging (MRI) studies are assessed to determine whether a metastasis can be removed with limited morbidity, ie, whether it is resectable (Fig 1). The essential features are whether the tumor is deep or superficial and whether it is within or outside functionally critical areas of the brain (often referred to as "eloquent" areas) such as the motor cortex, Broca’s speech area, or the brainstem. At present, tumors previously considered unresectable have been rendered resectable by modern surgical techniques such as microneurosurgery, computer-guided stereotaxy, complex skull base exposures, and intraoperative functional mapping (Figs 1 and 2). Nevertheless, lesions that are deep and within eloquent areas are associated with higher surgical morbidity than those within superficial and noneloquent areas. One must consider the potential morbidity associated with surgical removal in relation to the potentially limited survival of patients with systemic cancer. Patients with metastases in the brainstem, thalamus, and basal ganglia are generally rejected from consideration as surgical candidates.

Histological Factors: The radiosensitivity and chemosensitivity of the primary tumor should be considered before proceeding with surgery.\(^9\) Metastases from primary cancers of certain histologic types such as small-cell lung cancer, lymphoma, and germ-cell tumors are especially sensitive to radiation and/or chemotherapy and are likely to respond better to these modalities than to surgery. Conversely, melanoma, renal cell carcinoma, and most sarcomas are essentially resistant to radiation therapy and are better treated surgically. Finally, for brain metastases from non-small-cell lung cancer and breast cancer, which have an intermediate sensitivity to radiation therapy, surgery should be employed as one aspect of a multidisciplinary treatment plan.

Surgical Approaches and Intraoperative Adjuncts

At present, cerebral metastases can be removed successfully and safely due to a better current understanding of the surgical anatomy related to brain metastases and due to advances in microsurgical techniques along with improvements in intraoperative tumor localization and functional cortical mapping. These advancements have reduced the operative mortality and morbidity for this procedure to less than 3% and 10%, respectively.

Surgical Approaches: The least traumatic approach to a cerebral metastasis is determined by the macroscopic location of the tumor, which is usually defined surgically relative to the sulci and gyri adjacent to it.\(^10\)-\(^12\) Thus, an incision at the apex of the sulcus can be used for resection of subcortical lesions (transcortical
approach), whereas lesions in subcortical or subcortical locations are best approached by splitting the sulcus leading to the lesion. For metastases located at the midline, the optimal approach is to split the interhemispheric fissure. The best approach to cerebellar tumors is along the shortest transparenchymal route to the lesion.

**Intraoperative Adjuncts**: Safe resection of cerebral metastases depends on accurately localizing the lesion and avoiding eloquent brain tissue. Several new technologies have improved the surgeon’s ability to locate a tumor, differentiate it from surrounding structures, and safely resect it, even when it is small or deeply located.  

Intraoperative ultrasound permits visualization of tumors below the surface of the brain. Most metastatic tumors are echogenic on ultrasound and can be clearly delineated from surrounding non-echogenic edematous brain. Ultrasound also provides information about the lesion’s relationship to adjacent sulci and to other anatomical landmarks, such as the ventricles. Ultrasound has the advantage of imaging in “real time” so that changes in the tumor and brain can be followed (on a television monitor) as resection proceeds. Disadvantages of ultrasound include its inability to visualize tumors that are not echogenic or to “see through” bone during positioning of patients for craniotomies.

Computer-assisted, image-guided stereotaxis represents the most advanced method of localizing and resecting metastases. With this system, the surgeon uses preoperative imaging studies, often with three-dimensional reconstructions of the operating region, to guide the approach and resection. In this technique, the surgical site is matched to preoperative images from computed tomography and/or MRI so that the surgeon can identify specific areas within the surgical field corresponding to areas seen on the imaging studies. Computer-assisted, image-guided craniotomy allows for smaller cranial and dural openings, minimal exposure of normal brain, predetermined trajectories to deep lesions, and precise identification of the border between the tumor and the surrounding edematous brain. It is more effective than ultrasound because it allows the surgeon to “see through” the bone when planning surgery. However, unlike ultrasound, it does not update the images in “real time.”

Neurological deficit often can be prevented by identifying eloquent brain prior to resection. Intraoperative functional mapping of motor and sensory cortices can be performed by eliciting somatosensory evoked potentials and recording the phase reversal between grid electrodes placed on the cortical surface. After exposure of the cortical surface, a strip electrode is placed on the surface of the brain perpendicular to the long axis of the motor and sensory cortices. Stimulation of the median nerve results in recordable cortical potentials via the strip electrodes. Recordings from the motor cortex produce positive potentials, whereas simultaneous recording from the sensory cortex results in negative potentials. Identification of the electrodes in which this reversal of phase occurs defines the central sulcus. Proximity of the lesion to the functionally identified motor gyrus can then be determined by visual inspection (Fig 2).

**Postoperative Adjuvant Whole-Brain Radiation Therapy**

Postoperative whole-brain radiation therapy (WBRT) is often routinely administered to patients after craniotomy for resection of a cerebral metastasis in an attempt to destroy any residual cancer cells at the surgical site. However, as patients survive longer, the deleterious effects of WBRT (dementia and other irreversible neurotoxicities) become evident. This has raised the question as to whether elective postoperative WBRT should be administered to all patients after resection of a single brain metastasis. Several studies indicate that the risk/benefit ratio of postoperative WBRT may deserve re-examination. Because the use of MRI has improved our ability to verify the extent of tumor resection and to identify recurrences before they become symptomatic, a more selective use of adjuvant WBRT may be possible. At our center, we no longer routinely give WBRT after resection of solitary metastases (although we do in the case of multiple metastases). Decisions are made based on the completeness of resection, the radiosensitivity of the tumor, the extent of noncerebral disease, and the patient’s potential for long-term survival.

**Surgical Resection of Multiple Cerebral Metastases**

**Background**

The presence of multiple brain metastases has traditionally been considered a surgical contraindication, even when all the lesions were deemed surgically resectable and when the patient had good neurological function with no evidence of other systemic metastases. Nevertheless, in 1993, Bindal et al retrospectively analyzed the experience with 56 consecutive patients undergoing surgical resection for multiple brain metastases between 1984 and 1992. These patients were divided into group A (30 patients with multiple tumors who underwent resection of some but not all the lesions) and group B (26 patients in whom all the lesions were resected). These two groups were compared with 26 matched controls who had single brain metastases that were completely resected (group C). Most patients (52%) in groups A and B had two lesions removed, and the largest number of lesions removed from a single patient was three (five patients). There were no differences among the three groups with respect to patient age distribution, man:woman ratio, type of primary tumor, median time to metastasis, Karnofsky score, or percentage having systemic cancer.

Bindal et al found a significantly longer survival (median = 14 months) for patients in whom all metastases were completely resected (group B) than for patients with multiple metastases in whom at least one lesion was left unresected (group A; median = 6 months; P=0.003). In fact, the survival of patients in group B was similar to the survival (median = 14 months) of patients with resected single metastases (group C). This analysis demonstrated that removing multiple metastatic lesions is as effective as resecting single metastases, provided all lesions are removed.

**Patient Selection**

Patients with multiple brain metastases are selected as surgical candidates according to criteria that are similar to those for patients with single brain metastases. For each patient, the clinical features (general medical condition, extent of systemic disease, level of neurological function), the resectability of each lesion, and the sensitivity of the primary tumor to radiation or chemotherapy are carefully weighed. As in the case of single brain metastases, only patients with absent, limited, or controlled systemic disease status are considered for surgery. Patients with multiple brain metastases who have chemosensitive or radiosensitive primaries, such as small-cell lung cancer, are treated with chemotherapy or radiotherapy in the same manner as patients having single brain lesions. Surgical candidates with multiple cerebral metastases typically should not have more than four lesions, all of which should be resectable. Resection of only some lesions provides no survival advantage unless there is considerable mass effect.

**Whole-Brain Radiation Therapy After Resection of Multiple Metastases**

WBRT is typically administered to all patients after resection of multiple cerebral metastases, even when postoperative imaging studies show no evidence of disease. Unlike the situation for patients with single brain metastases, there is a high likelihood of microscopic residual disease at sites distant from the resected tumors in cases of multiple brain metastases. The potential for distant cerebral recurrence warrants treatment with WBRT, despite the potential risk of radiation-induced injury.

**Stereotactic Radiosurgery for Brain Metastases**
Background

Stereotactic radiosurgery employs multiple small, well-collimated beams of ionizing radiation from a linear accelerator or gamma knife to eradicate stereotactically located intracranial lesions. An advantage of this method over conventional surgery is that it can safely treat metastases that are surgically inaccessible such as those that are unreachable without violating eloquent brain. The technique is also minimally invasive as it requires only the placement of a stereotactic headframe while the patient is under local anesthesia. The radiation dose is delivered as a single fraction, resulting in shorter hospital stays.

Nevertheless, radiosurgery is suited only for small lesions, typically with a diameter of less than 3 cm (volume 31:24,25 Other problems arise due to the fact that the effect of radiosurgery is not immediate; thus, neurological deficits and mass effects of the tumor are not relieved immediately as in conventional surgery, thereby necessitating longer treatment with high cortico-steroid doses. Another shortcoming is that radiosurgery is unable to provide histologic verification that a cerebral lesion is truly a metastasis (the same imaging features are seen for abscesses and primary brain tumors). Indeed, 5% to 11% of patients with systemic cancer have been observed to possess a brain lesion that is either an abscess or a primary tumor rather than a metastasis.5,26

Radiosurgery vs Conventional Surgery

Largely due to the ease of performing radiosurgery and the perception that its cost is lower, some have suggested that it should replace conventional surgery for all small metastases (<3 cm). This is currently one of the most controversial issues in the management of single brain metastases, but to date, no prospective randomized trial has compared the effectiveness of surgery relative to radiosurgery for treating brain metastases. There are, however, two studies that have attempted to retrospectively compare these modalities.27,28 At present, these reports represent the best estimates of the relative efficacy of each modality, but they do not resolve the controversy because their conclusions are exactly opposite.

Auchter et al27 compared a group treated for single metastases by radiosurgery (n = 122) who were also deemed eligible for surgery to an historical control group of patients who had undergone surgery followed by WBRT at other hospitals. They obtained an actuarial median survival of 56 weeks for those who had radiosurgery compared with 43 weeks for patients undergoing conventional surgery. Thus, they concluded that radiosurgery plus WBRT was at least as effective as, if not better than, surgery plus WBRT, and they favored the use of radiosurgery rather than surgery for single brain metastases.

At our center, we also reported a retrospective comparison of radiosurgery and conventional surgery.28 This analysis used matched patients, thereby avoiding historical controls, and yielded a median survival of 7.5 months for the radiosurgical group and 16.4 months for the surgical group, a difference that was significant by both multivariate (P=0.0009) and univariate (P=0.0041) analyses. In contrast to Auchter et al,27 this study showed that surgery was superior to radiosurgery. Consequently, our preference is to perform surgery rather than radiosurgery for lesions that are surgically accessible and to reserve radiosurgery for inaccessible tumors or for patients whose advanced systemic disease or other medical conditions remove them from consideration as surgical candidates.

Until prospective, randomized trials are performed to assess the effectiveness of stereotactic radiosurgery relative to conventional surgery for cerebral metastases, it is probably better to view these two treatment modalities as complimentary rather than competing therapies. Radiosurgery has a unique potential for treatment of small, deep lesions with minimal morbidity that is quite distinct from surgery’s ability to rapidly reverse neurological deficit from larger symptomatic lesions. This point has become especially clear during the treatment of patients with multiple brain metastases, for whom we often combine surgery with radiosurgery. Specifically, large metastases are surgically resected, and small inaccessible lesions are treated with radiosurgery.

References


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