Current treatment of patients with multiple brain metastases

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The management of patients with multiple brain metastases remains a difficult challenge for neurosurgeons. This patient population has a poor prognosis when compared with those harboring a solitary brain metastasis, and historically treatment has generally consisted of administering whole-brain radiotherapy once the diagnosis of multiple brain metastases is made. Resection can be useful in a subset of patients with multiple metastases in whom one or two of the lesions are symptomatic, as this may provide rapid reduction of mass effect and edema. Furthermore, the authors of recent studies have shown that stereotactic radiosurgery can be used in certain patients with multiple brain metastases as part of the treatment regimen. In this review the authors outline the treatment options and indications as well as a management strategy for the treatment of patients with multiple brain metastases.

KEY WORDS • multiple brain metastases • radiosurgery • radiotherapy • stereotactic surgery

Multiple brain metastases are a common occurrence in patients with cancer, with an incidence of 12 to 35% in this population.^{3,26} The American Cancer Society estimates that 170,000 cancer patients develop cerebral metastases each year in the United States,²⁵ and many of these patients harbor two or more metastases.¹² The prognosis in this patient population is poor; mean survival is approximately 6 months, even after the provision of WBRT.²⁴ Although many patients with multiple brain metastases receive WBRT alone, the authors of several recent reports have shown that the addition of either tumor resection or stereotactic radiosurgery in a subset of these patients is associated with improved outcome.^{4,18,20,21,29} In this review we discuss our current recommendations for the treatment of patients with multiple brain metastases.

PRETREATMENT EVALUATION

Proper pretreatment evaluation is important in determining the optimum treatment strategy for patients with multiple brain metastases. By the time most patients with brain metastases have been referred to a neurosurgeon, the extent and control of systemic disease has usually been established. In patients in whom systemic disease has not been fully evaluated, an appropriate staging of the disease should be pursued prior to treatment of the intracranial disease. This typically includes examination by CT scanning of the chest, abdomen, and pelvis, as well as obtain-

ing a radionuclide bone scan. The extent of intracranial disease should be determined based on MR imaging with and without administration of gadolinium, as this study is more sensitive than postcontrast CT scanning of the brain in detecting smaller metastases and, thus, determining the total number of visible brain lesions. The primary exception to a complete pretreatment evaluation is patients suffering rapid deterioration in neurological function due to mass effect from their intracranial disease; such patients often benefit from immediate tumor resection prior to staging of their disease.

Several factors have been shown to determine the benefit of surgical and/or radiosurgical intervention in patients with multiple metastases. First, and of greatest importance, is the extent of systemic disease. In numerous studies it has been shown that the presence of advanced or progressing systemic disease is a poor prognostic factor of the patient's survival.^{8,28,29} In such patients, whose survival may be 2 months or less,³⁵ the addition of surgical resection or radiosurgery in addition to WBRT has little impact on final patient outcome. On the other hand, extended survival on the order of several years has been shown for patients with stable systemic disease in whom intracranial tumor control has been achieved.²⁴

The KPS score has been used as a major predictor of survival in patients with multiple brain metastases.^{8,24,28,29} It is generally accepted that patients with a KPS score of 70 or greater may benefit from either resection and/or radiosurgery, it has been shown that patients with higher KPS scores experienced prolonged survival compared with those with a score lower than 70.^{8,24} A lower KPS score often reflects widespread systemic disease or the

Abbreviations used in this paper: CT = computerized tomography; KPS = Karnofsky Performance Scale; MR = magnetic resonance; WBRT = whole-brain radiation therapy.

presence of brain metastases in critical regions of the brain (that is, regions that are less likely to be amenable to resection). Patient age has also been shown to be a predictor of survival length.^{8,29}

The number of brain metastases also affects survival. It has been shown that the probability of tumor control after surgery and WBRT or radiosurgery decreases from 64% for one intracranial metastasis, to 51% for two tumors, and to 41% for three lesions.²⁴ This remains the primary reason that patients with more than four brain metastases are not optimum candidates for surgical resection or stereotactic radiosurgery.

ALGORITHM FOR PATIENTS WITH MULTIPLE BRAIN METASTASES

Although treatment is tailored to each patient, a fairly well-established algorithm for treating patients with multiple brain metastases is followed at Stanford University Medical Center. For patients with progressive systemic disease, poor performance status, or more than four lesions, radiotherapy is the preferred treatment. Patients with multiple lesions who undergo conventional radiotherapy and in whom there is a neuroimaging-documented reduction in the number of metastases may be candidates for a stereotactic radiosurgical boost to the residual tumors if the number of lesions is four or fewer. Patients with stable systemic disease and a good performance status but in whom mass effect has been created by one or more tumors are considered candidates for resection of their symptomatic lesions, and radiosurgery or radiotherapy is used to treat the remaining smaller tumors. Patients with stable systemic disease, a good performance status, and no mass effect related to their brain metastases (four or fewer tumors) are considered optimum candidates for stereotactic radiosurgery. At our institution, most patients in whom radiosurgery is performed to treat multiple brain metastases additionally undergo conventional radiotherapy, whereas patients with a single brain metastasis often undergo radiosurgery alone, conventional radiotherapy being reserved for tumor recurrence/progression and new brain tumors associated with a poor performance status or progressive systemic disease. Unlike conventional brain radiotherapy, radiosurgery can be repeated for metachronous lesions months to years after initial treatment.

SURGICAL TECHNIQUE

Historically, the presence of multiple metastases has been considered a contraindication to surgery,^{17,27} even when the tumors are surgically accessible. However, some authors have shown that patients with two to four metastases may benefit from surgery.⁴ In latter series, in patients with multiple metastases who underwent resection of all their lesions, a longer survival length (median 14 months) was found as compared with those with multiple metastases not resected (median 6 months) ($p = 0.003$). Other neurosurgical centers reserve surgery for symptomatic lesions,³ treating asymptomatic lesions with radiosurgery. For patients considered candidates for resection of one or more of their multiple brain metastases, the following protocol is used at our institution.

Preoperative Preparation

Corticosteroid medication is routinely used in the pre- and postoperative period in patients undergoing brain tumor resection because cortical edema is often present prior to resection and may transiently worsen in the perioperative period. Patients with a prior history of seizures are maintained on their anticonvulsant agents, and prophylactic antibiotic medications are administered at the start of the operative procedure. General anesthesia with judicious control of blood pressure is induced, and patients undergo surgery under normotensive conditions.

Operative Exposure

The surgical approach is chosen according to the location of the metastasis. In most surgical cases, a frameless stereotactic method is used to allow precise localization of the tumor under the scalp and bone, thus allowing for a small craniotomy to be performed via a linear incision. Intraoperative stereotaxis also helps localize portions of the deeper metastases not presenting directly to the cortical surface. Following a sterile surgical scrub, the skin incision is made using a No. 10 blade, and bipolar coagulating forceps are used to cauterize any bleeding scalp vessels. Dissection is carried through the subcutaneous tissue, galea, and/or muscle by using a No. 15 blade or electrocautery, and retractors are used to expose the bone. A perforator and craniotome are used to perform the craniotomy. Bone wax is used to control bleeding along the bone edges, dural tack-up sutures are placed, and Surgicel is used to line the bone-dural interface. The dura is opened using dural forceps and a No. 15 blade.

Microsurgical Technique

A cortical incision is then made using the bipolar irrigating coagulation forceps, and dissection carried down to the tumor. Once identified, the metastasis is resected in a systematic fashion. Microsurgical resection is conducted under high-power magnification by using the bipolar forceps, and meticulous hemostasis is maintained throughout the resection. Unlike intrinsic brain tumors, a distinct plane invariably exists between the metastatic tumor and the adjacent normal brain. Care should be taken to identify this plane while performing circumferential dissection around the tumor. Small cotton micropaddies can be placed on the normal brain within the dissection plane to minimize trauma sustained by the cortex. Once the tumor is removed, the resection bed should be inspected to ensure that no residual tumor remains and that hemostasis is achieved. Transient induced mild hypertension is used to test hemostasis, and the resection bed is then lined with Surgicel.

Closure Technique and Postoperative Management

The dura is closed in the standard fashion using No. 4-0 nylon suture, and the bone is replaced to complete the craniotomy. The muscle and/or scalp incision is closed in layers by using No. 3-0 Dexon sutures, and the skin is closed with staples. Upon completion of the procedure and during the period when the patient is awakening from the anesthetized state, the patient's arterial blood pressure should be controlled to avoid any hypertensive episodes,

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TABLE 1

Summary of results of radiosurgical treatment for metastatic brain tumors in series with more than 100 patients

Authors & Year	No. of Patients	Tumor Response (%)		Median Follow Up (mos)
		Decrease/ Disappeared	Increase/ Recurred	
Engenhart, et al, 1993	102	96 (94)	6 (6)	12
Kihlstrom, et al., 1993	235	221 (94)	14 (6)	—
Loeffler & Alexander, 1993	282	265 (94)	17 (6)	9
Alexander, et al., 1995	248	211 (85)	37 (15)	7.5
Joseph, et al., 1996	120	115 (96)	5 (4)	8

— = median follow up not calculated.

particularly during extubation. In the intensive care unit, normotension should be maintained during the first 24 hours. Coagulation studies should be performed and corrected if abnormal findings are revealed. Any changes in neurological status require that the patient undergo emergency CT scanning for evaluation.

RADIOSURGERY

Stereotactic radiosurgery has emerged as a treatment for patients with metastatic brain disease either with or without WBRT, and an 85 to 95% control rate has been observed (Table 1). Median survival time after radiosurgery (range 6.4–10 months)^{9,13,15,19,21,22,32,36} is comparable with that demonstrated after resection followed by conventional fractionated radiotherapy (survival range 4–13) months,^{14,34} with good local control.^{9,13,19,21,22,31–33,36} In recent studies investigators have shown that patients undergoing radiosurgery for one or two brain metastases experience an equivalent, prolonged survival length similar to that observed in patients in whom the metastases have been resected.^{2,15,18} Furthermore, the effect of stereotactic radiosurgery combined with WBRT in patients harboring two to four metastases has recently been shown to be superior to WBRT alone in the control of metastatic brain disease.²⁰

At our institution stereotactic radiosurgery is performed either using a conventional frame-based linear accelerator system or the Cyberknife (Accuracy, Inc., Sunnyvale, CA), a frameless image-guided robotic stereotactic device. For frame-based treatments, the radiosurgical frame is placed optimally to ensure the surgeon’s ability to treat all the lesions without the need for repositioning of the frame or repeated neuroimaging. Axial T₁-weighted MR images with gadolinium contrast and 2-mm slice thickness are obtained and transferred over the hospital network to the treatment planning workstation. Isocentric-based treatment planning is used to achieve conformal dose plans. The treatment dose to the tumor margin typically is between 15 to 20 Gy and is based on tumor size, location, history of prior radiotherapy, and dose overlap from the treatment of other radiosurgical metastases. On completion of the procedure, the stereotactic frame is removed, and patients receive prophylactic dexamethasone. An antiemetic agent is also administered if one or more of the metastases treated is located in the posterior fossa.

The Cyberknife is used to treat cases in which the brain

metastases are complex in shape or are present in locations that are difficult to treat using frame-based systems. Instead of using skeletal fixation for localization, target position is continually updated using radiographic image-to-image correlation. The precision of localization (< 0.3 mm) is comparable with that which can be achieved by frames, and performance with treatment fields less than 7 cm is similar to much larger medical linear accelerators. The benefits of this instrument include: 1) precision targeting, comparable with skeletal fixation; 2) fractionated radiosurgical treatment of tumors adjacent to critical structures, such as the anterior visual pathways; 3) improved dosimetry by using nonisocentric treatment planning for complex nonspherical treatment volumes; and 4) radiosurgical treatment of central nervous system metastases outside the head.

Patients with brain metastases treated with the Cyberknife undergo construction of an AquaPlast mask that immobilizes the head without using a metal stereotactic head frame. Thin-sliced contrast-enhanced CT scans are then obtained and can be used alone or fused with MR images for treatment planning. The Cyberknife treatment planning software allows the use of either isocentric, or in many cases non-isocentric based treatment planning. As with frame-based radiosurgery, the treatment dose targeted at the tumor margin typically is between 15 to 20 Gy and is based on volume, location, and history of prior WBRT. Patients receive prophylactic dexamethasone prior to treatment, and if one or more of the metastases treated is located in the posterior fossa, an antiemetic agent is administered.

WHOLE-BRAIN RADIATION THERAPY

Whole brain radiation therapy is widely available and has been used for decades in the treatment of patients with multiple brain metastases. Patients with poor (low) KPS scores and progressive systemic disease often receive WBRT alone. In patients with good (high) KPS scores and stable disease, WBRT is often considered if there are new or recurrent metastases following tumor resection or radiosurgery. Based on results obtained from the Radiation Therapy Oncology Group trials,⁶ current radiation doses are either 20 Gy in five fractions or 30 Gy in 10 fractions. In patients with longer expected survival (that is, 1 year or more), a prolonged fractionation regimen of 40 Gy in 2-Gy fractions may decrease radiation-induced morbidity.^{5,10,11}

WBRT COMBINED WITH STEREOTACTIC RADIOSURGERY

The ability of stereotactic radiosurgery to be used in the treatment of multiple brain metastases has raised the issue of whether WBRT in conjunction with radiosurgery represents a treatment advantage over radiosurgery or WBRT alone. In a study of 105 patients treated from 1991 to 1997, Sneed, et al.,³⁰ reported that radiosurgery alone was not statistically different from radiosurgery combined with WBRT with respect to freedom from progression (71% and 79%, respectively) and median survival length (11.3 months and 11.1 months, respectively). Schoeggel, et

TABLE 2

*Studies reporting radiation-induced necrosis following stereotactic radiosurgery for brain metastases**

Authors & Year	No. of Patients	No. of Cases of Necrosis (%)	Equipment
Nedzi, et al., 1991	60	2 (3)	LINAC
Adler, et al., 1992	33	6 (18)	LINAC

* LINAC = linear accelerator.

al.,²⁸ concluded in a review of 97 patients treated for two to four brain metastases that stereotactic radiosurgery provided an equivalent rate of survival to patients historically treated with WBRT, but they did not compare a subset of patients treated with radiosurgery alone with those treated with radiosurgery combined with WBRT. Fuller, et al.,¹⁶ have reported a series of 27 patients with 41 metastatic tumors, noting that radiosurgery combined with WBRT was statistically superior than radiosurgery alone with respect to disease control ($p = 0.0007$). Kondziolka, et al.,²⁰ have reported a randomized trial of patients receiving WBRT compared with those treated with radiosurgery and WBRT; they found that combined WBRT/radiosurgery in patients with two to four brain metastases significantly improved the control of brain disease. The 1-year rate of local failure was 8% in patients treated with combined radiosurgery/WBRT as compared with 100% in those who received WBRT alone. The median survival length in the latter group was 7.5 months as compared with 11 months in those treated with combined WBRT/radiosurgery. Whereas the median time to local failure ($p = 0.0005$) and the development of any brain failure ($p = 0.002$) were statistically significant, the median survival between the two groups was not statistically different, perhaps due in part to the relatively small number of patients in the study (27 cases).

POSTTREATMENT CARE

Posttreatment follow-up examination of patients with multiple brain metastases consists of clinical evaluation and MR imaging 1 to 3 months after treatment (surgery or radiosurgery) and then every 3 to 6 months thereafter. Patients receiving corticosteroid medication prior to undergoing tumor resection can often be weaned off of these medications within weeks of treatment to minimize longer-term consequences of prolonged steroid use. Patients who have undergone radiosurgery can also often be weaned off their corticosteroids, although a longer tapering-off period may be required because edema resolves more slowly following radiosurgery than resection. A small subset of individuals treated with radiosurgery will develop radiation-induced necrosis (Tables 2 and 3).⁷ This often can be managed with a course of corticosteroids, although in cases in which there is significant edema and mass effect, a craniotomy may be required to perform systematic relief.

Follow-up MR imaging may identify the presence of new tumors in some cases. In these patients, repeated craniotomy or radiosurgery can be considered provided the patient has stable systemic disease and a high KPS score.

TABLE 3

*Variables associated with increased risk of radiation-induced necrosis**

Variable	p Value
tumor dose inhomogeneity	< 0.00001
maximum tumor dose	< 0.00002
no. of isocenter	0.00002
maximum normal tissue dose	0.00005
tumor volume	0.001

* Data were obtained from the study by Nedzi, et al. Variables not associated with toxicity were mean tumor dose, number of treatment arcs, total degree of arc, tumor location, previous radiotherapy, tumor geometry, pretreatment performance status, collimator size, and patient age.

Patients with new brain metastases who have a low KPS score or progressive systemic disease are treated with WBRT if this has not been previously used.

SUMMARY

Although the treatment of patients with multiple brain metastases remains a challenge for neurosurgeons, the identification of patients with good performance status (high KPS scores) and controlled systemic disease allows surgeons to determine which individuals may benefit from either tumor resection or stereotactic radiosurgery as part of their treatment regimen. We use the aforementioned algorithm in determining the appropriate treatment of patients with multiple brain metastases.

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