The Role of the Gamma Knife in the Treatment of Malignant Primary and Metastatic Brain Tumors

Ronald F. Young, MD

Introduction
In the 1950s, Lars Leksell, a Swedish neurosurgeon coined the term radiosurgery to describe the delivery of a high dose of radiation to a small target within the brain on a single exposure. Leksell developed radiosurgery in an attempt to find a safer, less invasive alternative to direct cranial surgery. After exploring heavy particle systems and the linear accelerator, Leksell settled on gamma rays from cobalt 60 sources, carefully collimated and delivered in conjunction with his stereotactic system, as his preferred method for performing radiosurgery.

The gamma unit or so-called “gamma knife” was used at first to treat benign brain tumors and arteriovenous malformations and to perform “functional” neurosurgery to treat entities such as chronic pain, trigeminal neuralgia, and movement disorders.

More recently, attention has been directed toward the use of the gamma knife to treat both malignant primary and metastatic brain tumors. This article considers the role of the gamma knife in the treatment of both malignant primary and metastatic brain tumors, including patient selection, results of gamma knife treatment, and the place of the gamma knife in the overall management of patients with malignant intracranial tumors. It begins with a brief review of the technical details of the gamma knife.

Technical Aspects of Gamma Knife Treatment

Gamma Unit
Figure 1 shows the external appearance of the gamma knife. The central body houses the 201 60Co sources, which emit gamma rays, and the primary collimator system (Fig 2). The primary and secondary collimator systems result in an array of 201 cylindrical gamma-ray beams.

The basic principle of the gamma knife is that the radiation dose along any single beam is very low, but the dose at the intersection point of all of the beams is very high (approximately 200 times the dose along any single beam.) The secondary collimator helmets are designed so that all gamma-ray beams intersect at the same point. Collimators are available in four sizes, measuring 4, 8, 14, and 18 mm in diameter.

Procedure for Gamma Knife Treatment
The general principle of gamma knife radiosurgery is to place the lesion being treated at the focal point of the gamma ray beams. The lesion is placed with the use of stereotactic principles and a dedicated computer planning system, the GammaPlan. This UNIX-based computer allows multiple imaging sources—such as magnetic resonance (MR) imaging, computed tomography (CT), and angiography—to be used for dose planning. The system is rapid, accurate, and easy to use.

Dr. Young is Medical Director, Northwest Gamma Knife Center, Northwest Hospital, Seattle, WA; and Co-Director, Good Samaritan Hospital Gamma Knife Center, Los Angeles, CA.

This article is also available online at http://www.ca-journal.org.
In practice, the procedure for gamma knife treatment includes the following four basic steps:

1. Application of the stereotactic frame with the patient under local anesthesia
2. An imaging study (usually MR imaging) performed with the stereotactic frame in place
3. Computerized dose planning
4. Delivery of the treatment

The stereotactic frame is removed immediately when the procedure is completed.

The entire procedure requires about 3 to 4 hours and is performed while the patient is under local anesthesia with mild supplementary intravenous sedation. Many centers in the United States have hospitalized patients overnight after treatment, but the trend is toward performing these procedures on an outpatient basis.

The total actual treatment time is dependent primarily on the age of the $^{60}$Co sources, which decay with a half-life of about 5 years. Other factors that affect treatment time include the radiation dose to be delivered, the size of the patient’s head, and the location of the tumor to be treated. Typically, treatment times vary from about 10 to 60 minutes. Irregularly shaped or large tumors may require more than a single gamma knife exposure or “multiple isocenter” treatment. Such complex treatments are easily and rapidly planned with the GammaPlan computer system, and the multiple isocenters are delivered sequentially during a single sitting.

**OTHER DEVICES FOR RADIOSURGICAL TREATMENT**

Two other devices are currently in use to deliver radiosurgical treatment. These are linear accelerator (LINAC)-based systems and systems that use accelerated protons.

Except in rare instances, LINAC-based radiosurgical systems represent the conversion of standard linear accelerators, normally used to deliver radiothera-
py, into units for radiosurgery. Several commercially available LINAC conversion systems are in use, and many other one-of-a-kind systems have been developed at individual institutions. A few institutions use dedicated LINAC-based radiosurgical units. Overall, the reported results of LINAC-based and gamma knife radiosurgical systems for treatment of malignant brain tumors are approximately equivalent.

Only one or two clinically active heavy particle units are currently in clinical use in the United States. Little information is available about the safety or efficacy of such systems in the treatment of malignant brain tumors, although these units have considerable experience in the radiosurgical treatment of other lesions, such as pituitary tumors and arteriovenous malformations.

**Radiobiology of Gamma Knife Treatment**

Because radiosurgery delivers the entire radiation dose during a single sitting, the radiobiologic effects are different from those of conventional fractionated radiotherapy. For instance, a particular dose of radiation delivered with the gamma knife has a biologic effectiveness equivalent to about three times the same dose in fractionated radiation. Gamma knife radiosurgery also involves radiation dose inhomogeneity, in which the dose to the central portion of the treated tumor is about twice as high as that to the periphery of the tumor. A typical gamma knife treatment might deliver 20 Gy to the periphery of a tumor at the 50% isodose line so that the center of the tumor would receive 40 Gy. These doses would be equivalent to about 60 Gy and 120 Gy, respectively, if delivered by conventional radiotherapy methods. In the latter case, however, the maximum safe dose to the brain is about 50 to 60 Gy, which limits the amount of radiation that can be delivered safely.

Gamma knife treatment is primarily limited by size, because the treatment of lesions larger than 3.5 to 4.0 cm in average diameter results in the surrounding normal brain tissue receiving an excessive dose of radiation. The excessive radiation can result in complications caused by radiation necrosis or perilesional changes in white matter. The latter are often classified as "edema" because of their appearance on MR imaging scans. Laboratory studies, however, suggest that much of this response is a glial inflammatory response, which usually subsequently subsides, rather than increased water in the tissue.

The treatment size limit of the gam-
Primary Malignant Brain Tumors

Gamma knife treatment is usually an adjunctive therapy for primary malignant brain tumors. The most common primary malignant brain tumors are glioblastomas and anaplastic astrocytomas. Low-grade gliomas, although usually thought of as benign, progress to more malignant forms in nearly 75% of patients. A few types of low-grade glial tumors (e.g., pilocytic astrocytomas) may at times be cured by surgical resection alone. Both glioblastomas and anaplastic astrocytomas are usually fatal lesions, with median survivals of about 1 year and 2 to 3 years, respectively, with conventional treatment.

TREATMENT

We favor maximal safe surgical resection of most glial tumors. Recent advances in imaging, computerized stereotactic surgery, microsurgery, and intraoperative monitoring have increased the safety of craniotomy for brain tumor resection and have made more lesions amenable to surgical resection.

For nearly all malignant primary brain tumors we recommend fractionated external beam radiotherapy after maximal surgical resection and favor regional radiotherapy, rather than whole-brain radiotherapy, because it keeps complications at a minimum. Recent studies suggest that regional radiotherapy is as effective as and safer than whole-brain radiotherapy for the treatment of malignant primary brain tumors.

ROLE OF GAMMA KNIFE RADIOSURGERY

We recommend gamma knife radiosurgery as a planned “boost” after surgery and radiotherapy (Fig. 3). We do not usually recommend gamma knife radiosurgery instead of radiotherapy because primary malignant brain tumors infiltrate well beyond the tumor margins.
that are apparent on imaging studies.\textsuperscript{9}

Because large tumor volumes cannot be treated safely with the gamma knife alone, we rely on fractionated radiotherapy to treat a wider field. The additional radiosurgical boost is delivered accurately to the smaller region of the tumor that shows contrast enhancement on T1-weighted contrast-enhanced MR imaging scans.

The gamma knife also can be used to treat recurrent primary malignant brain tumors that have been treated previously with surgery, radiotherapy, and chemotherapy. Gamma knife treatment of such recurrent tumors also may be limited or impossible if the tumor is too large. Repeat surgical resection with or without implantation of carmustine-impregnated (Gliadel) wafers may be indicated in such situations to reduce the tumor volume before the patient can be treated with the gamma knife.\textsuperscript{10}

\textbf{RESULTS OF TREATMENT WITH THE GAMMA KNIFE}

Several studies have shown a survival advantage when radiosurgery is added to other forms of treatment of primary malignant brain tumors.

The most recent comprehensive report, by Kondziolka and colleagues\textsuperscript{11} from the University of Pittsburgh, evaluated 64 patients with glioblastoma multiforme and 43 with anaplastic astrocytomas after gamma knife radiosurgery, which was used either as a planned boost to fractionated radiotherapy or at the time of later tumor progression.

The median survival time after initial diagnosis for patients with glioblastoma multiforme was 26 months, approximately twice the median survival time of patients given conventional treatment without radiosurgery. For patients with anaplastic astrocytomas, the median survival after diagnosis was 32 months. The 2-year survival rate was 51\% for glioblastoma multiforme patients and 67\% for anaplastic astrocytoma patients.

These results were compared with those of historical controls provided by the Radiation Therapy Oncology Group (RTOG) and stratified according to several prognostic variables. Survival benefit was improved for both glioblastoma multiforme and anaplastic astrocytoma patients who were treated with gamma knife radiosurgery.

Larson et al\textsuperscript{12} also recently reported a retrospective multicenter study (in which our center participated) of gamma knife radiosurgery for the treatment of gliomas. That study also described an in-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{(A) This patient had a large metastatic brain tumor in the left anterior temporal fossa from carcinoma of the prostate. Mass effect with compression and displacement of the ventricular system can be seen. (B) The same patient is shown 1 year after gamma knife treatment. The lesion has shrunk markedly and the mass effect has resolved. The patient remains alive with normal neurologic function 15 months after treatment. No new cerebral or other distant metastases have been identified.}
\end{figure}
increased survival benefit for patients treated with the gamma knife. Factors favorably affecting outcome in both reports included younger age, smaller tumor volume, and better neurologic performance status. The Larson study also suggested that the degree of malignancy as indicated by the pathological tumor grade was an important prognostic factor, but the Kondziolka study did not.

Several other reports exist concerning radiosurgical treatment of glial tumors. Although they generally support the results of the Kondziolka and Larson studies, some of these reports have shown that little benefit is gained by adding radiosurgery to conventional treatment. Alexander has recently reviewed the approach of the Harvard group to the use of LINAC-based radiosurgery to treat malignant glial tumors and has commented on the Kondziolka report previously described. We agree with his assessment that “radiosurgery for gliomas is often a complex endeavor, with appropriate use of aggressive surgery blended in with radiosurgery for the optimal management of the difficult cases.”

Radiosurgery has also been compared with brachytherapy because these two treatment techniques represent possible adjuncts to surgical resection, fractionated radiotherapy, and chemotherapy. These comparisons suggest that radiosurgery is as effective as brachytherapy but much safer and less expensive. Reoperations after brachytherapy occur in about 40% to 45% of patients, whereas after radiosurgery they occur in about 20% to 25% of patients.

Radiosurgery is certainly not a cure for malignant primary brain tumors, but it does offer an adjunctive form of treatment that is clinically effective, safe, and cost-effective.

Metastatic Brain Tumors
Metastatic brain tumors are probably the most common form of malignant brain
tumors or “brain cancers.” Up to 50% of patients with cancers develop neurologic symptoms resulting from brain metastases, and as many as 150,000 new cases of brain metastases may occur each year.29

The most common sources of brain metastases are cancers of the lung and breast, which in our experience make up about 60% of our total cases.29 Metastases from melanomas and cancers of the colon and kidney added to metastases from the lung and breast account for more than 80% of our total cases.29

Use of Gamma Knife Radiosurgery for Brain Metastases
Cerebral metastases present excellent targets for gamma knife radiosurgery because, unlike primary malignant brain tumors, metastatic tumors are usually spherical, small, and well demarcated from surrounding normal brain tissue. Median survival for patients with cerebral metastases that are untreated or treated with corticosteroids alone (to reduce cerebral edema) is only about 1 month. Fractionated whole-brain radiotherapy improves the median survival to about 3 to 4 months, but death from recurrent or persistent metastatic brain tumors occurs in about 50% of patients treated with whole-brain radiotherapy.

Patchell et al30 showed in a randomized prospective study that the combination of surgical resection plus whole-brain radiation therapy increased the survival rate to a median of 10 months. Several recent reports suggest that radiosurgery with or without the addition of whole-brain radiotherapy is as effective as surgery and whole-brain radiotherapy and at considerably less morbidity and at substantially lower cost; however, not everyone is in agreement.31-46

As with primary malignant brain tumors, lesion size may be a limiting factor in the use of gamma knife radiosurgery for treatment of metastatic brain tumors. The same size limitations (a maximum average diameter of 3.5 cm) generally apply. Large metastatic tumors that are in favorable locations in regard to brain function and are surgically accessible should be treated by surgical resection.29

Poor neurologic performance (a rating of less than 70 on the Karnofsky scale47) is an unfavorable prognostic factor for both gamma knife radiosurgery and surgical resection, but this factor requires further analysis.

Metastatic brain tumors, even small lesions (0.5 to 1.5 cm in diameter), may be associated with extensive peritumoral edema. The latter may cause major neurologic symptoms such as paralysis, visual loss, or speech loss that result in poor neurologic performance. Treatment with corticosteroids often produces prompt and dramatic reduction in peritumoral edema with resolution of associated symptoms and improvement in neurologic performance.

Before a patient is considered unsuitable for treatment of a metastatic brain tumor (or tumors) because of poor neurologic performance, the impact of both the tumor itself and peritumoral edema must be assessed. Improvement in neurologic function resulting from successful treatment of peritumoral edema...
ma often converts a patient who would otherwise be rejected for treatment to a patient very suitable for gamma knife treatment.

**RESULTS OF GAMMA KNIFE RADIOSURGERY**

Gamma knife radiosurgery alone controls more than 90% of metastatic tumors, with a median survival of about 8 to 10 months.\(^2^9\) Control refers to (1) stabilization of the lesion without further growth (which occurs in about 40% of treated lesions), (2) a decrease in lesion size (which occurs in about 30% of treated lesions), or (3) virtual disappearance of the treated lesion (which occurs in about 20% of treated patients). Although not effective immediately, gamma knife radiosurgery often produces tumor shrinkage within 2 to 3 months of treatment (Fig. 4).

Dexamethasone may be required to treat cerebral edema, which is often disproportionately extensive in metastatic tumors during the latency period after gamma knife treatment and before response of the tumor.

Successful local control of brain metastases with radiosurgery reduces the death rate from these lesions from about 50% with whole-brain radiotherapy to about 15%.\(^2^9\) The cause of death in the remaining patients is uncontrolled fatal metastases in sites other than the brain (such as lung, liver, and adrenal glands). Gamma knife radiosurgery in our experience also maintains quality of life, with patients maintaining mean Karnofsky scale scores of about 80 until the last few weeks of life.\(^3^3\)

We have treated as many as 15 metastatic tumors successfully in a single patient without associated radiation toxicity, and we have shown that the number of cerebral metastases is not a predictor of the length of survival. Fortunately, most patients with multiple metastases usually harbor one or two medium-sized lesions (1.5 to 2.5 cm in diameter) and several smaller lesions (less than 1.5 cm in diameter). Patients with multiple large metastases usually present with poor neurologic performance (e.g., Karnofsky score less than 70) and are not good candidates for radiosurgery, although whole-brain radiotherapy may provide some palliation.

**ROLE OF WHOLE-BRAIN RADIOTHERAPY IN TREATMENT OF BRAIN METASTASES**

We have questioned the role of whole-brain radiotherapy in the treatment of brain metastases. We have shown, however, that the median survival after treatment of multiple brain metastases is no different from the survival after treatment of a single metastasis.\(^3^3\) If pretreatment score on the Karnofsky scale is above 70 and if the primary cancer and any nonbrain metastases are controlled, multiple cerebral metastases are not a contraindication to radiosurgery. Our own experience with multiple metastases has now been duplicated in a retrospective analysis of a large number of patients by the Harvard group.\(^3^1\)
brain metastases. 33 Formerly, whole-brain radiotherapy combined, when feasible, with surgical resection was the treatment of choice. 30, 48, 49 As radiosurgery has begun to supplant surgical resection of brain metastases, the role of whole-brain radiotherapy also has been reassessed.

In our experience, the median survival is not significantly different whether whole-brain radiotherapy is combined with radiosurgery or radiosurgery alone is used to treat brain metastases. 33 The Harvard group has also confirmed this finding. 31 A recent reanalysis of our data does indicate that whole-brain radiotherapy reduces the incidence of new brain metastases, but this reduction does not significantly affect the length or quality of survival. 29

Because whole-brain radiotherapy adds to the expense, discomfort, and diminution of quality of life involved with the treatment of brain metastases, we no longer use or recommend it when radiosurgical treatment of brain metastases is feasible. Omitting whole-brain radiotherapy from the treatment of metastatic brain tumors also avoids the long-term complications of whole-brain radiotherapy, particularly cerebral atrophy and associated dementia.

When new brain metastases arise after initial radiosurgical treatment (which occurs in about 25% of patients), another radiosurgical session to treat the new lesions is as effective as an initial treatment and also safe. Using this approach, we have treated more than 20 brain metastases in a single patient in three different radiosurgical sessions over a 2- to 3-year period.

Complications of Gamma Knife Radiosurgery
Two primary types of complications are associated with radiosurgery, namely, radiation reactions and radiation necrosis. These complications may occur after the treatment of either primary or metastatic brain tumors.

Radiation Reactions
Radiation reactions appear on T2-weighted MR imaging scans as hyperintense signal areas surrounding the originally treated lesion. This reaction has the MR imaging signal characteristics of increased water content and is usually characterized as edema, although animal studies suggest that much of this reaction is a type of glial inflammatory response rather than true edema. 5

Because perilesional edema is often prominent with both primary and metastatic brain tumors, difficulty may occur in differentiating radiation reactions from cerebral edema. Such radiation reactions also may be misinterpreted as tumor progression on follow-up MR imaging scans.

Perilesional radiation reactions may or may not be associated with clinical symptoms, depending upon the extent of the reaction and its location. Small reactions in eloquent areas of the brain (e.g., speech areas, internal capsule) may be associated with clinical symptoms, whereas larger reactions in “silent” areas (e.g., nondominant frontal lobe) may not be associated with any clinical symptoms.

Corticosteroids (e.g., dexamethasone) may be used to treat symptomatic perilesional radiation reactions, although in our experience the response to such treatment varies. Our approach is to give a therapeutic trial of dexamethasone, 4 mg four times a day for about 1 week. If symptoms improve significantly, the treatment is continued, usually at a lower dose. If no improvement occurs within a week or so, the dexamethasone is discontinued. Radiation reactions almost always subside over time as far as the scan changes are concerned, but permanent neurologic deficits may rarely accompany radiation reactions, even when the scans revert to normal.

Radiation reactions are generally
dose-dependent, and determination of the treatment doses for radiosurgery according to the “integrated logistic formula” is calculated to result in a serious permanent neurologic complication rate of about 3%.50 A recent evaluation of data from more than 1,000 patients treated with the gamma knife at the University of Pittsburgh suggests that the actual complication rate may be closer to 1.6%.51

**Radiation Necrosis**

Radiation necrosis is a more serious reaction to radiosurgery. It may result from the death of tumor cells and associated reaction in surrounding normal brain, or it may result from the necrosis of normal brain tissue surrounding the previously treated metastatic brain tumor. Such reactions tend to occur more frequently in larger lesions (either primary brain tumors or metastatic tumors). Clinical symptoms are more often associated with radiation necrosis than with a radiation reaction.

Radiation necrosis has been estimated to occur in 20% to 25% of patients treated for primary malignant brain tumors. This rate of radiation necrosis is lower than the 40% incidence usually associated with brachytherapy of primary brain tumors, a form of adjunctive treatment often compared with radiosurgery.

Differentiating between radiation necrosis and tumor progression is often difficult, and radioisotope brain scanning with thallium or position emission tomographic (PET) scanning may help in determining the pathologic basis of such reactions.52,53 In some cases, a stereotactic biopsy may be required to establish the correct pathology, but our own experience in the radiosurgical treatment of primary malignant brain tumors indicates that most of what appears on scans to be radiation necrosis is actually a combination of necrotic tissue and viable tumor cells.

If a severe radiation reaction or radiation necrosis is associated with significant clinical symptoms that fail to respond to corticosteroids, surgical resection of the mass may be the only recourse to improve the quality of the patient’s life.

**Cost of Gamma Knife Radiosurgery**

A single radiosurgical treatment at our center results in about $20,000 in charges. This is significantly less than the cost of a craniotomy but more expensive than whole-brain radiotherapy.

For the treatment of primary brain tumors, radiosurgery represents an additional cost because it generally does not replace conventional treatment. Nevertheless, radiosurgery adds significantly to survival and in some instances may obviate a repeat craniotomy if tumor recurrence can be prevented or delayed. Radiosurgery is also less expensive than brachytherapy, which requires surgical placement of the radioisotope seeds, 5 to 7 days of hospitalization, and a much higher rate of subsequent surgery to treat radiation necrosis.

Recent cost comparisons for the treatment of metastatic brain tumors suggest that radiosurgery is the most cost-effective form of treatment for these lesions based on life/years gained from each of the treatments.54,55 Because of recent reductions in reimbursement for radiosurgery, the charges for this modality continue to decrease. Radiosurgery is now the primary form of treatment for brain metastases; thus, the cost of treating these lesions has been reduced proportionally to the benefit gained.

**Conclusion**

In the treatment of primary malignant brain tumors (mostly gliomas), radiosurgery is a valuable adjunct to surgical resection, radiotherapy, and chemotherapy. The addition of radiosurgery to these accepted primary therapeutic maneuvers significantly prolongs the lives of patients with malignant primary brain tumors.
Radiosurgery has radically altered our approach to metastatic brain tumors. Surgical resection and whole-brain radiotherapy, previously the mainstays of the treatment of brain metastases, are now generally used only when patients are not candidates for radiosurgery, based on tumor size and neurologic function. For most brain metastases, in our opinion, radiosurgery is the treatment of choice and will result in effective tumor control in more than 90% of treated tumors.

References
1. Leksell L: The stereotactic method and radiosurgery of the brain. Acta Chir Scand 1951;102:316-319.
2. Lutz W, Winston KR, Maleki N: A system for stereotactic radiosurgery with a linear accelerator. Int J Radiat Oncol Biol Phys 1988;14:373-381.
3. Frankel KA, Phillips MH, Lyman JT, et al: Treatment planning for stereotactic heavy-charged-particle radiosurgery of the brain, in Steiner L (ed): Radiosurgery: Baseline and Trends. New York, Raven Press, 1992, pp 75-84.
4. Larsson B: Radiobiological fundamentals in radiosurgery, in Steiner L (ed): Radiosurgery: Baseline and Trends. New York, Raven Press, 1992, pp 3-14.
5. Altschuler E, Lunsford LD, Kondziolka D, et al: Radiobiologic models for radiosurgery. Neurosurg Clin N Am 1992;3:61-77.
6. Kleihues P, Burger PC, Scheithauer BW, et al: Histological typing of tumors of the central nervous system, in World Health Organization International Histological Classification of Tumors. Berlin, Springer-Verlag, 1993.
7. Harkova JS, Black PM: Strategies in the surgical management of malignant gliomas. Semin Surg Oncol 1998;14:26-33.
8. Larson DA, Wara WM: Radiotherapy of primary malignant brain tumors. Semin Surg Oncol 1998;14:34-42.
9. Silberfeld DL, Chicoine MR: Isolation and characterization of human malignant glioma cells from histologically normal brain. J Neurosurg 1997;86:525-531.
10. Vanstonen S, Timonen U, Toivanen P, et al: Interstitial chemotherapy with Carmustine-loaded polymers for high-grade gliomas: A randomized double-blind study. Neurosurg 1997;41:44-49.
11. Kondziolka D, Flickinger JC, Bissonette DJ, et al: Survival benefit of stereotactic radiosurgery for patients with malignant glioblastomas. Neurosurgery 1997;41:776-785.
12. Loeffer JS, Alexander E 3rd, Shea WM, et al: Gamma knife for glioma: Selection factors and survival. Int J Radiat Oncol Biol Phys 1996;36:1045-1053.
13. Loeffer JS, Alexander E 3rd, Shea WM, et al: Radiosurgery as part of the initial management of patients with malignant gliomas. J Clin Oncol 1992;10:1379-1385.
14. Masciopinto JE, Levin AB, Mehta MP, et al: Stereotactic radiosurgery for glioblastoma: A final report of 31 patients. J Neurosurg 1995;82:530-535.
15. McDermott MW, Sneed PK, Chang SM, et al: Results of radiosurgery for recurrent gliomas, in Kondziolka D (ed): Radiosurgery. Basel, S. Karger, 1995, pp 102-112.
16. Sarkaria JN, Mehta MP, Loeffer JS, et al: Radiosurgery in the initial management of malignant gliomas: Survival comparison with the RTOG recursive partitioning analysis. Int J Radiat Oncol Biol Phys 1995;32:931-941.
17. Shaw E, Scott C, Souhami L, et al: Radiosurgery for the treatment of previously irradiated recurrent primary brain tumors and brain metastases: Initial report of Radiation Therapy Oncology Group protocol (90-05). Int J Radiat Oncol Biol Phys 1996;34:647-654.
18. Alexander E 3rd, Coffey R, Loeffer JS: Radiosurgery for gliomas, in Alexander E 3rd, Loeffer JS, Lunsford D (eds): Stereotactic Radiosurgery. New York, McGraw-Hill, 1993, pp 207-219.
19. Alexander E 3rd, Loeffer JS: Radiosurgery for primary malignant brain tumors. Semin Oncol 1998;14:43-52.
20. Alexander E 3rd: Discussion of Kondziolka D, Flickinger JC, Bissonette DJ, et al: Survival benefit of stereotactic radiosurgery for patients with malignant glioblastomas. Neurosurgery 1997;41:785-784.
21. Agbi CB, Bernstein M, Laperriere N, et al: Patterns of recurrence of malignant astrocytoma following stereotactic interstitial brachytherapy with iodine-125 implants. Int J Radiat Oncol Biol Phys 1992;23:321-326.
22. Florell RC, Macdonald DR, Irish WD, et al: Selection bias, survival, and brachytherapy for glioma. J Neurosurg 1992;76:179-183.
23. Green SB, Shapiro WR, Burger PC, et al: A randomized trial of interstitial radiotherapy boost for newly diagnosed malignant glioma: Brain Tumor Cooperative Group Trial 8701. Proc Am Soc Clin Oncol 1994:13:174. Abstract.
24. Gutin PH, Leibl SA, Wara WM, et al: Recurrent malignant gliomas: Survival following interstitial brachytherapy with high-activity iodine-125 sources. J Neurosurg 1987;67:864-873.
25. Loeffer JS, Alexander E 3rd, Wen PY, et al: Results of stereotactic brachytherapy used in the initial management of patients with glioblastoma. J Natl Cancer Inst 1990;82:1918-1921.
26. Shrieve DC, Alexander E 3rd, Wen PY, et al: Comparison of stereotactic radiosurgery and
brachytherapy in the treatment of recurrent glioblastoma multiforme. Neurosurgery 1995;36:275-284.
27. Stea B, Rossman K, Kittelson J, et al: A comparison of survival between radiosurgery and stereotactic implants for malignant astrocytomas. Acta Neurochir Suppl (Wien) 1994;62:47-54.
28. McDermott MW, Sneed PK, Gutin PH: Interstitial brachytherapy for malignant brain tumors. Semin Surg Oncol 1998;14:70-78.
29. Patchell RA, Tibbs PA, Walsh JW, et al: A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322:494-500.
30. Moriarty TM, Loeffler JS, Black PM, et al: Long-term follow-up of patients treated with stereotactic radiosurgery for single or multiple brain metastases, in Kondziolka D (ed): Radiosurgery. Basel, S. Karger, 1995, pp 83-91.
31. Aaron TR, Lomand JP, Alexander E 3rd, et al: A multi-institutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. Int J Radiat Oncol Biol Phys 1996;35:27-35.
32. Young RF, Jacques DB, Duma C, et al: Gamma knife radiosurgery for treatment of multiple brain metastases: A comparison of patients with single versus multiple lesions, in Kondziolka D (ed): Radiosurgery. Basel, S. Karger, 1995, pp 92-101.
33. Alexander E 3rd, Moriarty TM, Davis RB, et al: Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87:34-40.
34. Engenhart R, Kimmig BN, Hover KH, et al: Long-term follow-up for brain metastases treated by percutaneous single high-dose irradiation. Cancer 1993;71:1353-1361.
35. Kihlstrom L, Karlsson B, Lindquist C: Gamma knife surgery for cerebral metastases: Implications for survival based on 16 years experience. Stereotact Funct Neurosurg 1993;61(Suppl 1):45-50.
36. Loeffler JS, Alexander E 3rd: Radiosurgery for the treatment of intracranial metastases, in Alexander E 3rd, Loeffler JS, Lunsford LD (eds): Stereotactic Radiosurgery. New York, McGraw Hill, 1993, pp 197-206.
37. Mehta MP, Rozental JM, Levin AB, et al: Defining the role of radiosurgery in the management of brain metastases. Int J Radiat Oncol Biol Phys 1992;24:619-625.
38. Somato S, Kondziolka D, Lunsford LD, et al: Stereotactic radiosurgery for cerebral metastatic melanoma. J Neurosurg 1993;79:661-666.
39. Fuller BG, Kaplan ID, Adler J, et al: Stereotactic radiosurgery for brain metastases: The importance of adjuvant whole brain irradiation. Int J Radiat Oncol Biol Phys 1992;23:413-418.
40. Binder AK, Bindal RK, Hess KR, et al: Surgery versus radiosurgery in the treatment of brain metastases. J Neurosurg 1996;84:748-754.
41. Ott K: Surgery or radiosurgery. J Neurosurg 1997;86:165-166. Letter.
42. Warnke PC, Kreth FW, Ostertag CB, et al: Surgery or radiosurgery. J Neurosurg 1997;86:166-167. Letter.
43. Young RF: Surgery or radiosurgery. J Neurosurg 1997;86:167-168. Letter.
44. Stelzer KJ, Goodkin R, Winn HR: Surgery or radiosurgery. J Neurosurg 1997;86:168-169. Letter.
45. Sawaya R: Surgery or radiosurgery. J Neurosurg 1997;86:169-170. Letter.
46. Karmofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer, in Macleod CM (ed): Evaluation of Chemotherapeutic Agents. New York, Columbia University Press, 1949, pp 191-205.
47. Veelen SS: Whole brain radiotherapy in the treatment of metastatic brain tumors. Semin Surg Oncol 1998;14:64-69.
48. Lang FF, Sawaya R: Surgical treatment of metastatic brain tumors. Semin Surg Oncol 1998;14:53-63.
49. Flickinger JC, Lunsford LD, Kondziolka D: Radiosurgery with the gamma knife, in Steiner L (ed): Radiosurgery: Baseline and Trends. New York, Raven Press, 1992, pp 15-24.
50. Kondziolka D: Complications following gamma knife radiosurgery. Presented at the Eighth International Leksell Gamma Knife Society Meeting; June 1997; Marseille, France.
51. Schwartz RB, Carvalho PA, Alexander E 3rd, et al: Radiation necrosis versus high-grade recurrent glioma: Differentiation by using dual-isotope SPECT with 201TI and 99mTc-HMPAO. AJNR Am J Neuroradiol 1991;12:1187-1192.
52. Schwartz RB, Holman BL, Garada BM, et al: Dual-isotope single-photon emission computerized tomography used for prediction of histology and survival in patients after high-dose radiotherapy for malignant astrocytoma. Neurosurgery Focus 1996;1.
53. Rutigliano MJ, Lunsford LD, Kondziolka D, et al: The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. Neurosurgery 1995;37:445-453.
54. Penar PL, Wilson JT: Cost and survival analysis of metastatic cerebral tumors treated by resection and radiation. Neurosurgery 1994;34:888-893.