Stereotactic Radiosurgery for Brain Metastases

Worldwide, approximately 100,000 patients have undergone stereotactic radiosurgery for a variety of intracranial lesions, of which brain metastases represent the most common treatment indication. This article summarizes the major issues surrounding the management of brain metastases, and also analyzes 21 independent reports of Gamma Knife– or linear accelerator–based radiosurgery, representing over 1,700 patients and more than 2,700 lesions. Variable reporting in the studies precludes a definitive, rigorous analysis, but the composite data reveal an average local control rate of 83% and median survival of 9.6 months, both of which are comparable to results in recent surgical reports. The most important prognostic factors for survival appear to be fewer than three lesions, controlled extracranial disease, and Karnofsky performance score (KPS). The exact impact of dose has not been clarified, but a dose-response relationship, especially for ≥ 18 Gy, is emerging. The role of whole-brain radiotherapy remains unresolved. It may enhance local control but does not convincingly improve survival and, in some series, is associated with an increased risk of late complications. Chronic steroid dependence and increased intracranial edema do not appear to be common problems. This is an opportune time for the completion of ongoing randomized trials to validate these observations. [ONCOLOGY 13(10):1397-1409, 1999]

Introduction

Cancer is the second most common cause of mortality in the United States, accounting for approximately one-quarter of all deaths. Although primary central nervous system (CNS) cancers are relatively rare, the annual estimated incidence of brain metastases in the United States exceeds 100,000 cases. The vast majority of patients with metastatic brain cancer die within a few months of diagnosis, making this one of the most common immediate causes of death in the United States.[1]

The most frequent primary cause of brain metastases is lung cancer, which is responsible for almost half of all secondary tumors of the brain. Other major primary tumors that contribute significantly to the occurrence of brain metastases include breast cancer, melanoma, and colorectal cancer. Less commonly, primary tumors of the kidney, other gastrointestinal neoplasms, lymphomas, sarcomas, gynecologic tumors, and, rarely, prostate cancer also metastasize to the brain. Recent therapeutic advances have led to longer disease-free survival for patients with several types of cancer, thereby increasing the overall population of cancer survivors. Unfortunately, these patients are not truly cured, and their longer disease-free interval places them at higher risk of developing metastatic disease at sanctuary sites, such as the brain, where penetration of traditional cytotoxic therapeutic agents is impaired by the blood-brain barrier. These clinical observations, combined with enhanced utilization of cranial imaging, explain the apparent perception of an increase in the overall incidence of brain metastases.

Conventional External-Beam Radiation Therapy

In 1954, Chao et al first reported on the value of external-beam radiation in the treatment of brain metastases.[2] Because of its simplicity and ease of delivery as an outpatient modality, with little morbidity, low cost, and minimal disruption of quality of life, external-beam radiation rapidly became the most commonly used strategy in the management of patients with brain metastases. The Radiation Therapy Oncology Group (RTOG) has conducted several sequential studies exploring a variety of different fractionation schedules.[3,4] Four major conclusions were drawn from these studies: (1) Median survival improves to 15 to 21 weeks, a slight improvement over steroids only. (2) A radiation dose of 30 Gy in 10 fractions is as efficacious as more prolonged regimens or higher doses. (3) No significant survival advantage is afforded by prolonged fractionation or higher doses (up to 50 Gy), implying the lack of a dose-response relationship in this range. (4) Prognostic criteria that predict for slightly improved survival include age < 60 years, Karnofsky performance score.
Based on the RTOG trials, the standard treatment for most patients with brain metastases for the last 2 decades has been conventional external-beam radiation (30 Gy in 10 fractions) delivered to the whole brain. The fact that this is, indeed, the most widely practiced community standard was confirmed in the Patterns of Care palliation survey conducted in the 1980s.[6] Accelerated Hyperfractionated Schedules

In the older RTOG studies, one-third to one-half of the patients died from neurologic deterioration. One might logically assume that if such deterioration could be controlled, survival might be enhanced. In order to test this hypothesis, a recent RTOG study evaluated the role of dose-escalation using accelerated hyperfractionation (1.6 Gy twice daily to total doses ranging from 48 to 70.4 Gy). This study demonstrated that higher doses significantly improve survival and neurologic function, suggesting that control of intracranial disease may be related to dose and that such control may translate into a neurologic improvement and survival advantage.[7]

Although this phase I/II RTOG report suggested a potential benefit from an altered fractionation regimen in patients with limited metastatic disease and good KPS or neurologic function, a randomized trial failed to conclusively demonstrate any improvement in survival with accelerated hyperfractionated radiotherapy (1.6 Gy twice daily to a total dose of 54.4 Gy), as compared to a conventional regimen of 30 Gy in 10 fractions.[8] The results of this phase III trial notwithstanding, the fact remains that relatively low doses, on the order of 30 Gy, cannot successfully diminish tumor growth or control it for a sustained period. The need for a higher dose to improve tumor control is one of the central reasons for considering radiosurgical boost.

Role of Surgical Resection

The role of surgery in the treatment of brain metastasis remains controversial. Clear indications for resection include craniotomy or stereotactic biopsy to establish the diagnosis, when it is in doubt, and removal of the tumor mass when such therapy is likely to provide immediate palliation. Such indications lead to a very high level of selectivity in surgical series. It is common practice in some institutions to select patients with a single brain metastasis who are otherwise clinically stable for surgical resection.

Resection Plus Whole-Brain Radiation

Retrospective data suggest that, in patients undergoing craniotomy without external-beam radiation, the relapse rate approaches 85%.[9] In a recent prospective, randomized trial, the addition of whole-brain radiation therapy to surgical resection improved intracranial progression-free survival.[10] Several retrospective series suggest that, in highly selected patients, surgical resection followed by whole-brain radiotherapy may prolong survival from a median of 16 to 26 months.[11] To establish whether improved intracranial control would reduce morbidity, improve quality of life, prolong survival, and alter mortality patterns, three, small, randomized trials have compared surgery plus whole-brain external-beam radiotherapy to radiotherapy alone in patients with single brain metastases. Two of the trials showed an improvement in median survival, to 43 and 40 weeks, respectively, with the addition of surgery.[12,13] These two trials also demonstrated that functional independence, as defined by maintenance of KPS at or above a level of 70 following therapy, was sustained for a longer duration in patients undergoing surgery. These findings therefore established resection as a new standard for selected patients with single brain metastases. These results lend credence to the notion that aggressive management strategies directed at improving local control are beneficial for selected patients with brain metastases. However, a more recent and slightly larger randomized trial addressing this issue failed to identify a survival benefit from the addition of surgery: Median survival was 6.3 months in the radiation-alone group, as compared with 5.6 months in the resection group.[14]

Radiosurgery

Radiosurgery involves the delivery of a high single dose of radiation to a discrete tumor volume. Three radiosurgical technologies are currently used: high-energy photons produced by linear accelerators; the Gamma Knife; or, less frequently, charged particles, such as protons, produced by cyclotrons or synchrotrons.

Rationale for Use in Patients With Brain Metastases

The use of radiosurgery for the treatment of brain metastases is supported by the following
Observations:

1. The vast majority of brain metastases are pseudospherical and, therefore, are ideal targets for radiosurgery, since spherical dose distributions can be generated very easily by most radiosurgery systems.

2. The grey-white matter junction, an area of the brain often thought to be relatively "noneloquent," is a common location for these lesions, thus permitting the delivery of a single large fraction of radiation without excessive toxicity. Even complex, large lesions in such a location can be treated radiosurgically, using multiple isocenters.

3. With modern diagnostic techniques, most brain metastases are detected while still relatively small, ie, less than 3 cm in diameter. Such volumes can be targeted relatively easily by radiosurgical techniques. The limited treatment volumes help reduce long-term morbidity.

4. Many brain metastases remain pseudoencapsulated without substantial microscopic peripheral spread, thus permitting the use of "tight" margins.[15]

5. It has now clearly been established that achieving local control in the brain improves survival. Randomized data, such as those reported by Patchell et al[12] and Noordijk et al[13] support this observation.

6. A dose-response relationship of radiation therapy for local control of brain metastases may exist, as suggested by RTOG study 85-28[7] and also by nonrandomized results reported by Nieder et al.[16] However, this issue has not been validated in the randomized RTOG 9104 study.[8]

Clinical Experience

The earliest report of the use of radiosurgery in patients with brain metastases was published by Sturm et al in 1991. In their initial pilot study, these researchers reported marked clinical improvement in 12 of 12 patients and a major radiographic response rate of 5 (71%) of 7.[17] These data were subsequently updated to include an additional 54 lesions in 39 patients.[18] A mean dose of 18 Gy was utilized, and in the 28 patients for whom follow-up information was available, a major response rate of 86% was documented.

A comprehensive search of all English language studies published from 1987 to 1998 revealed a total of 21 distinct, nonoverlapping radiosurgery reports, including 1,783 patients and > 2,700 lesions. Several institutions have published multiple manuscripts, and in some instances, multi-institution reports have included patients reported in other single-institution publications. To eliminate this duplication as much as possible, this review includes only the largest published series from single institutions (excluding all reports with fewer than 20 patients). Multi-institution studies provide valuable information regarding prognostic variables, and these data are also presented. A brief summary of these 21 series, including treatment parameters, local control, and survival, is presented in Table 1.[17,19-38]

Overall, just over 1,750 patients treated with radiosurgery for brain metastases have been reported in the literature. Because of divergent definitions, response rates vary from 33% to 92%, local control rates range from 25% to 99%, and median survival durations vary from 6 to 15 months. There is a significant variety of patients included in these reports, ranging from those with newly diagnosed to recurrent lesions, single or multiple lesions, varying primary histologies, and a wide range of tumor size, performance status, and other variables. Such a wide spectrum of underlying variables makes it difficult to adequately assess the reported results in a meaningful fashion, or to compare them with other reports of alternative management strategies.

This point is well illustrated by a recent recursive partitioning analysis of 1,200 patients with brain metastases treated in three consecutive nonradiosurgery RTOG studies, which revealed that underlying prognostic factors substantially affect outcome.[39] This report identified three major prognostic classes of patients with varying survival. The most favorable category, class 1, included patients with a KPS > 70, age < 65 years, a controlled primary tumor, and no extracranial metastases; these patients had a median survival of 7.1 months. In contrast, class 3 patients had a KPS < 70, leading to a median survival of only 2.3 months. Class 2 patients had a median survival of 4.2 months. We have recently completed an analysis of 472 patients from 9 institutions treated with
radiosurgery and stratified by recursive partitioning analysis class; the median survival for classes 1, 2, and 3 is 13.6, 9.4, and 8.4 months, suggesting that even when balanced for recursive partitioning analysis class, radiosurgery appears to provide a survival advantage. Therefore, although a comprehensive literature review provides a broad overall picture of the efficacy of radiosurgery, specific conclusions regarding improvement in local control and/or survival have to be carefully interpreted.

**Does Radiosurgery Improve Local Control?**

A review of the 21 series in Table 1 reveals local control rates varying from 25% to 99% and response rates (complete plus partial) ranging from 33% to 92%, with a series average of 67%. In comparison, local control rates following whole-brain radiotherapy are generally around 50%, suggesting a possible increase in local control with the addition of radiosurgery. In fact, these local control values of radiosurgery are very comparable to those achieved with surgical resection. Unfortunately, few reports provide actuarial data, and most local control figures represent an assessment at a single point in time.

In the largest review to date, involving 421 lesions in 248 patients, Alexander et al reported 1- and 2-year actuarial local control rates of 85% and 65%, respectively.[19] Similarly, actuarial data from a multi-institution trial by Flickinger et al indicate a local control rate of 67% at 2 years.[25] In a report by Shiau et al, actuarial local control rates (defined as freedom from progression) were 82% and 77% at 6 and 12 months, respectively. These data substantially validate the clinical observation of improved local control following radiosurgery.

**Does Radiosurgery Improve Survival?**

The entire hypothesis of radiosurgery yielding a survival benefit hinges on the paradigm that, despite the high mortality from systemic disease, neurologic deaths contribute substantially to an increase in mortality. Therefore, any strategy that improves local control should have at least some impact on survival.

The validation of this hypothesis awaits the completion of an ongoing prospective, randomized, phase III clinical trial being conducted by the RTOG. This trial is randomizing patients with one to three brain metastases to whole-brain radiation with or without a radiosurgery boost. Pending completion of this trial, only retrospective comparisons are available to address this question. The median survival time following radiosurgery ranges from 5 to 15 months in the patient series reported in Table 1, with a series average of 9.4 months. Considering that this experience reflects a significant proportion of patients with recurrent disease, it is a rather inadequate database from which to derive firm conclusions.

To better address this question, we recently completed a multi-institution analysis of the radiosurgery databases from four centers; from these databases, we selected patients with a single, newly diagnosed brain metastasis and a KPS > 70%. Computed tomographic (CT) criteria for single lesions were acceptable, and radiosensitive histologies were excluded.[40] This group of 122 patients was compared with a similar group of 54 patients receiving whole-brain radiotherapy alone, selected from two recent randomized trials.[12,13]

Table 2 shows the median survival and rates of local control in these two groups. Although retrospective in nature, this comparison strongly suggests that incorporation of a radiosurgery boost provides a survival advantage in selected patients with a single brain metastasis. This survival gain is achieved by reducing local failure and, hence, neurologic deaths. The >13 month median survival seen in the patients treated with radiosurgery is almost twice that noted for the class I patients in the recent RTOG recursive partitioning analysis.

Flickinger et al reviewed the results of brain metastases treated with the Gamma Knife from five institutions. Of the 116 patients with solitary brain metastases included in this multi-institution report, 39% had tumors that recurred after prior whole-brain radiation therapy. The median survival time in these patients was 11 months. For the patients with newly diagnosed brain metastases, median survival duration was 14 months.[25]

A recent report from the University of California, San Francisco, also analyzed the survival of patients comparable to those in the series of Patchell et al and found a rather impressive median survival of 16 months.[41]

**Prognostic Factors for Response, Local Control, and Survival**

Prognostic factors for response, local control, and survival following radiosurgery are still being delineated. Our group recently defined some of the most important of these variables in a multi-institution analysis. They are presented below. In addition, a few recent single-institution
Factors From the Multi-institution Analysis—In our multi-institution report, with a median follow-up of 123 weeks, the overall local response rate was 59% (complete response rate, 25%; partial response rate, 34%). In-field local recurrence, including progressive disease, was noted in 17 patients (14%), for an overall local control rate of 86%.[40] Intracranial recurrence outside of the radiosurgery volume occurred in 27 patients (22%).

A univariate analysis of potential predictors of response to radiosurgery was performed on the following factors: age; time interval from diagnosis of the primary tumor to detection of the brain metastases; gender; baseline KPS; site of the primary tumor; radiosurgery dose; tumor volume; and the presence of non-CNS metastasis. Only the site of the primary tumor was a statistically significant predictor of local response (P = .047). Patients with breast cancer showed the highest response rate (complete response rate, 38%; partial response rate, 31%). Colorectal cancer patients had the poorest response (complete response rate, 0%; partial response rate, 33%).

The same factors were analyzed as predictors of in-field tumor recurrence. For this end point, the presence of non-CNS metastasis was significantly associated with a lower risk of in-field recurrence (P = .02). This was believed to be due to the increased risk of early death from systemic progression occurring prior to the development of local failure.

Melanoma and renal cell carcinoma, generally considered to be more radioresistant tumors, showed remarkable local control (only 1 failure in 27 patients, for a 96% control rate). Breast cancer patients and the few patients with unknown primary tumors also achieved excellent local control (92% in breast cancer patients, 100% in those with an unknown primary).

We also performed both univariate and a multivariate analyses of predictors of survival, as well as predictors of quality survival (defined as KPS ≥ 70). The following factors were evaluated: age; time interval from diagnosis of the primary tumor to detection of brain metastases; gender; baseline KPS; site of primary tumor; location of the metastases; in-field and out-of-field brain recurrence.

In the univariate analysis, the most significant predictor of survival and functional independence was baseline KPS (P < .0001). For patients with a baseline KPS of 100, median survival had not been reached with a follow-up > 123 weeks. For patients with a KPS of 90, median survival was 54 weeks, whereas for those with a KPS of 70 to 80, median survival was only 28 weeks.

In the multivariate analysis, baseline KPS remained the strongest predictor of survival. The only other factor that reached statistical significance in the multivariate model was the presence of extracranial metastases at the time of radiosurgery, which carried a relative risk of death of 1.96 (median survival 78 weeks if absent vs 42 weeks if present; P = .008). Primary site showed a trend for predicting survival that did not reach statistical significance (P = .13).

Breast cancer patients had the longest survival, with a relative risk of dying of 0.42 compared to all other patients and a median survival of 115 weeks. The shortest median survival times were noted in patients with lung cancer (47 weeks) and renal cell cancer (29 weeks).

The status of the primary tumor was a significant predictor of survival on univariate analysis. Patients who had active disease at the primary site showed a relative risk of dying of 2.74 (P = .04), compared to patients with a controlled primary tumor. However, this factor lost significance on multivariate analysis. Gender was a significant predictor in the univariate model, but lost significance in the multivariate model because of the covariance with breast cancer.

Factors From Other Studies—Some of the more recent and larger studies have attempted to perform more detailed univariate and multivariate analyses of prognostic factors. The results of these studies, as well as our multi-institution trial, are summarized in Table 3.[19,22-29,34,40-42]

Number of Intracranial Metastases—Three of the more recent trials consistently found that patients with one or two lesions fare equally well, but those with three or more metastases have a uniformly poor survival.[19,22,29] The presence of three or more metastases at the time of radiosurgery was associated with significantly decreased survival, (relative risk, 1.69) in a conducted study by Alexander et al.[19]

In a study from Stanford, a multivariate analysis was performed to test the independence of the number of metastasis (one or two vs three or four) as a prognostic factor.[29] The best-fit model showed that the number of lesions was an independent significant predictor of survival (P = .0001).

In addition, this study showed that patients treated with stereotactic radiosurgery for two brain metastases identified on computed tomography (CT) or magnetic resonance imaging (MRI) had a median survival time identical to that of patients with a solitary lesion.

Similarly, Breneman et al found that patients with one or two lesions had identical survival after radiosurgery (44 weeks), but patients with more than two lesions had significantly shorter survival (P = .02).[22]
Active Extracranial Disease] Of the nine studies summarized in Table 3, one did not analyze active extracranial disease, five found that its presence was a negative prognostic factor for survival, and, in the remaining two, it reached borderline significance. These data suggest that active extracranial disease is probably one of the more important variables to consider.

In the study by Alexander et al,[19] the presence of known systemic disease at the time of radiosurgery was a markedly unfavorable prognostic factor for survival, carrying a relative risk of death of 4.43. Breneman et al[22] found that patients without active extracranial disease at the time of radiosurgery had superior survival (45 vs 35 weeks; P = .03). In a study by Shirato et al,[34] the actuarial survival rate was higher in patients with no active extracranial diseases compared to those with active disease (P = .0411). In a study by Shu et al from the University of California, San Francisco (UCSF),[41] the absence of known extracranial disease at the time of radiosurgery was the second most significant factor associated with an improvement in overall survival (P = .006). In a recent study outlining radiosurgery results in 77 lung cancer patients, Kim et al found that the median survival of patients with active systemic disease was 2 months, as compared with 12 months for patients with stable disease at the time of radiosurgery (P < 10^-4; log-rank test).[42]

Karnofsky Score In the Stanford report by Joseph et al, when several clinical factors potentially associated with prolonged survival after radiosurgery were examined by univariate and multivariate analyses, pretreatment KPS ≥ 70 was significant as a continuous variable.[29] This is in keeping with our finding in the multi-institution analysis.[40] In the UCSF study, decreasing KPS was the third most important predictor of decreased survival (P = .009).[41] In contrast, Kim et al did not find that pretreatment KPS was a significant prognostic factor for survival on univariate or multivariate testing.[42]

Histologic Type Although conventional wisdom categorizes tumors into radiosensitive vs radioresistant malignancies, no significant differences in survival were seen with respect to the primary tumor in any of the major trials. There was initially some speculation that radioresistant tumors, such as melanoma, would be less responsive. Indeed, in a volumetric analysis, Voges et al demonstrated that the mean relative volume reduction was 23% for melanoma, 27% for renal cell cancer, 53% for breast cancer, 60% for adenocarcinomas, and 77% for squamous cell carcinomas.[18]

An earlier trial by us evaluated complete response rates in terms of histology. This trial showed that whereas 100% of lymphomas responded completely, the complete response rates for other histologies were 67% for melanoma/sarcoma, 50% for non-small-cell lung cancer, 33% for breast cancer, and 11% for renal cell carcinoma.[32]

A more detailed analysis of this phenomenon shows some intriguing results. Exquisitely radiosensitive tumors, such as small-cell lung cancer, indeed demonstrate marked radiographic regression in comparison to radioresistant tumors, such as melanoma, that are typically slower to respond and tend not to undergo complete radiographic resolution. The better response rates of the radiosensitive tumors do not necessarily correlate with local control, however. In fact, it appears that the so-called radioresistant tumors may be better controlled than the radiosensitive lesions. In a report from Pittsburgh, Somaza et al reported 32 melanoma metastases in 23 patients treated radiosurgically, with local control achieved in 31/32 (97%) lesions, despite an imaging response rate of 13/32 (41%).[43]

In the series of Breneman et al, melanoma remained locally controlled in all 12 patients throughout the duration of the study.[22] Loeffler et al reported a local control rate of 94% for 330 metastatic brain lesions in 217 patients.[44] The so-called radioresistant tumors in this study actually had higher local control rates. In the more recent update by Alexander et al from the same institution, this trend was maintained but did not reach statistical significance.[19]

When analyzed by univariate and multivariate methods, no significant differences in survival were seen with respect to histologic type of the primary tumor in the Stanford study reported by Joseph et al,[29] the study by Shirato et al,[34] or the study by Breneman et al.[22] In contrast, the multi-institution report by Flickinger found breast histology to be the only significant predictor for survival (P = .0002). Patients with breast cancer had a median survival of approximately 18 months, in comparison to < 12 months for other histologic types. In terms of local control, however, multivariate analysis revealed improved control for melanoma and renal cell carcinoma, as opposed to other histologies (P = .0006).[25]

Age and Gender The only trials that have demonstrated age to be a significant predictor of survival were those of Alexander et al[19] and Shu et al,[41] although in the latter trial, the P value was only .041. Age greater than 60 years at the time of radiosurgery was significantly associated with decreased survival, with a relative risk of 1.18 per decade.
No significant differences in survival with respect to age were seen in any of the other major series. Similarly, gender has not been found to be a prognostic factor in any of the trials. 

**Radiation Dose** Intuitively, one would expect dose to have a major influence on local control and, possibly, survival. However, there is no uniform agreement about the dose to be used for lesions of various sizes. In general, larger tumors are treated with lower dose, resulting in some size-dependent loss of local control.

Alexander et al reviewed the impact of dose and found that it did not influence local control.[19] Similarly, Shirato et al reported no impact of dose on survival.[34] The report by Flickinger et al also did not find a correlation between dose and survival.[25] In contrast, Breneman et al showed significant improvement in local control with a radiation dose ≥ 1,800 cGy (median time to failure, 52 weeks with a dose ≥ 1,800 cGy vs 25 weeks with < 1,800 cGy; P = .008).[22] The RTOG has completed a phase I dose-seeking trial and recommends dose prescription based on tumor size as follows: 24 Gy for ≤ 20-mm tumors, 18 Gy for 21- to 30-mm tumors, and 15 Gy for 31- to 40-mm tumors.[45]

In a separate analysis of the UCSF data, Shiau et al specifically evaluated the impact of dose. They found that an increased dose led to improved local control and freedom from progression, with lesions treated to ≥ 18 Gy being controlled for substantially longer periods than those treated to < 18 Gy.[33]

**Lesion Size** A volumetric analysis of 54 recurrent and newly diagnosed brain metastases treated with linear accelerator-based stereotactic radiosurgery in one of our earlier studies sheds some light on the relationship between size and response.[32] As expected, a dramatic decline in complete response was noted with increasing tumor size. The overall response rate was 78% for tumors < 2 cm³ but dropped to 50% for lesions > 10 cm³ (Table 4). Kida and colleagues from Japan also noted that smaller tumors tend to respond faster than do larger tumors.[30]

In a multivariate analysis, Alexander et al found that tumor volume > 3 cm³ approached borderline significance with regard to local control.[19] In the studies of Shirato et al[34] and Flickinger et al,[25] no significant differences in survival were seen with respect to primary tumor size. However, Shu et al found tumor volume to be the most important predictive factor for survival (P = .0005).[41] Likewise, a multivariate analysis performed by Kim et al showed that tumor volume < 2 cm³ significantly affects survival (P = .009; log-rank test).[42]

Therefore, whereas smaller tumors may be more effectively controlled, there are conflicting data concerning the effect of lesion size on survival.

**Whole-Brain Radiotherapy** The impact of whole-brain radiotherapy on survival remains contentious. This issue has only recently been addressed in a prospective, randomized fashion. In older, nonrandomized studies, a small minority of patients did not receive whole-brain radiation, and these patients were compared to the remaining cohort, with indeterminate conclusions. For example, in the Stanford report, the 20 patients who did not receive whole-brain radiotherapy were compared with the 100 patients who did; there was no difference in survival between the groups.[29]

Shirato et al recently reported on a series of 44 patients with single metastases treated with single-fraction or fractionated radiosurgery, without whole-brain radiation.[34] The intra-cranial relapse rate outside of the radiosurgical volume was 39%. All of the patients who received salvage whole-brain irradiation did not require further therapy, but 36% of those who underwent repeat radiosurgery needed additional treatment. These findings indicate that some patients with single metastases may be treated without whole-brain radiation, but with the expectation of a high rate of intracranial relapse.

The nonrandomized study conducted by Flickinger et al included 51 patients treated with radiosurgery alone who were compared with 65 patients treated with radiosurgery plus fractionated radiation.[25] In their multivariate analysis, these investigators found that the actuarial local control rate at 24 months was 50% following radiosurgery alone, as compared with 80% after radiosurgery plus fractionated radiotherapy (P = .011). However, this improvement in local control did not translate into a survival advantage, possibly because of a mix of recurrent and newly diagnosed tumors.

The issue of delaying or withholding whole-brain radiotherapy is currently being assessed by the Eastern Cooperative Oncology Group (ECOG) in a phase II trial. Patients with one to three brain metastases from melanoma, sarcoma, or renal cell carcinoma are being treated with radiosurgery only in an attempt to define the short- and long-term intracranial relapse patterns. This trial is expected to lead to a phase III, randomized trial to evaluate the role of whole-brain radiotherapy. Recently, Patchell et al completed a randomized phase III evaluation of the role of whole-brain...
radiotherapy following surgical resection in patients with single metastases. Their findings demonstrate a significant improvement in freedom from intracranial progression when whole-brain radiotherapy is utilized.[10]

**Radiosurgery vs Surgery**

The median survival of well-selected patients with single brain metastases treated with whole-brain irradiation and resection or radiosurgery is comparable, although a randomized trial of these two modalities has not been completed. Such a trial is, in fact, underway at the M. D. Anderson Cancer Center.[F. Lang, personal communication, 1999]

The observation that linear accelerator radiosurgery produces median survival comparable to that achieved with whole-brain irradiation is supported by a major multi-institution analysis of outcome and prognostic factors previously reported by our group.[40] We reviewed the stereotactic radiosurgery databases of four institutions and identified so-called surgical patients, as defined by the criteria used by Patchell et al.[12] Patients had to be 18 years of age, have a single brain metastasis (by CT or MR), a lesion located in a surgically resectable area, KPS ≥ 70, nonradiosensitive histology, and no prior cranial surgery or whole-brain radiotherapy. We identified 122 patients who met these criteria. These patients were compared with similar patients enrolled in the surgical arms of two recently reported randomized trials.[12,13] The patients in the radiosurgery category received a median of 37.5 Gy whole-brain radiotherapy followed by a median radiosurgery boost of 17 Gy.

With a potential median follow-up of 123 weeks for all patients, the actuarial median survival with radiosurgery was 56 weeks. In comparison, the median survival times in the two surgical arms were 43 and 40 weeks, respectively. Pending firm evidence from randomized trials, these data, as well as the 23-patient subset analysis reported by Shu et al (selecting only those patients who met Patchell’s criteria) support the contention that aggressive management of well-selected patients yields superior survival; the data show no remarkable differences between surgery and radiosurgery (Table 5).[41]

**Cost-Effectiveness and Cost-Utility Analysis**

In this era of cost-containment, it is imperative that health care professionals make fiscally prudent decisions. The present environment necessitates a critical appraisal of apparently equally efficacious therapeutic modalities. Within this context, we recently performed a cost-effectiveness and cost-utility analysis of radiosurgery vs resection for single brain metastases.[46]

Survival and quality-of-life data for radiation alone or combined with surgery were obtained from the above-mentioned two randomized trials, and radiosurgical results were obtained from our multi-institution analysis, and were limited to data on linear accelerator radiosurgery. Cost-analysis was performed from a societal viewpoint, and the relative cost ratios of resection and radiosurgery were compared using the Wilcoxon rank sum test. The cost-effectiveness of each modality was defined as the cost per year of median survival. The cost-utility of each modality was defined as the cost per quality year (KPS ≥ 70) of median survival.

Our analysis showed that both resection and radiosurgery yielded superior survival and functional independence, compared to whole-brain radiotherapy alone; resection resulted in a 1.8-fold increase in cost, compared to radiosurgery. These data, presented in Table 6, strongly suggest that radiosurgery is the more cost-effective modality, with an average cost per week of survival of $270, compared to $310 for radiotherapy alone and $524 for resection plus radiation therapy.

**Complications of Radiosurgery**

**Acute Complications**

Very few significant acute complications are observed within the first week following radiosurgery. Loeffler and Alexander reported nausea in 22 (11.2%) of 196 patients during the first 24 hours (all of these patients received > 2.75 Gy to the area postrema). They also noted seizures in 12 patients (6.1%) within 24 hours and transient motor weakness in 4 patients (2%) within 36 hours, all 4 of whom had motor cortex lesions.[44]

An update of these data by Alexander et al suggests that in order to reduce or eliminate radiosurgery-induced nausea/vomiting, all patients who are being irradiated with more than 375 cGy to the area postrema should receive antiemetic therapy prior to treatment.[19] Ten of the patients experiencing post-radiosurgery seizures had a history of seizure disorder and, in retrospect, had subtherapeutic levels of anticonvulsants. Since 1990, the Boston group recommends that all patients
with cortical lesions receive antiseizure prophylaxis before the radiosurgery procedure, regardless of their seizure history.

Breneman et al reported an 8.3% (7/84) acute complication rate.[22] Three patients experienced transient worsening of their neurologic symptoms within the first 2 weeks after radiosurgery that resolved after a short course of steroids. Three patients with lesions in the motor cortex experienced grand mal seizures within the first 72 hours after radiosurgery. Parenthetically, all of these patients had subtherapeutic anticonvulsant levels.

Joseph et al reported a low incidence of severe headaches or nausea, and a 2.3% (3/120) incidence of seizures within 12 hours of completing radiosurgery.[29] Each of these patients was also found to have a subtherapeutic anticonvulsant level at the time of treatment.

Shiau et al observed complications in 100 evaluable patients. They found that six patients (6%) experienced acute deterioration of preexisting neurologic deficits, such as aphasia or hemiparesis, within 2 weeks of radiosurgery; in five of the six, this deterioration responded to steroids.[33]

Fukuoka et al described several episodes of acute toxicity in 130 evaluable patients treated with Gamma Knife stereotactic radiosurgery. In one case, a 9-cm³ metastatic lesion in the cerebellar hemisphere was treated with 30 Gy to the tumor margin. The lesion subsequently swelled and the preexisting perifocal edema increased, requiring surgical resection the day after Gamma Knife therapy. In another case, a patient with a 1.4-cm³ lesion developed hemiplegia 3 days after Gamma Knife therapy (30 Gy to the tumor margin) due to intratumoral bleeding. However, this patient recovered with minimal hemiparesis. In a third case, a massive perifocal hematoma was surgically removed 14 days after Gamma Knife therapy for a 19-cm³ metastatic lesion from thyroid cancer (30 Gy to the tumor margin). It is possible that the high doses to the tumor margin used in these cases may have contributed to these acute toxic episodes.[26]

Therefore, it is prudent to consider premedicating patients with lesions near the posterior fossa with antiemetics and to routinely check serum anticonvulsant levels in those with a seizure history. In addition, we do not use doses in the 30-Gy range, even for small lesions.

Subacute Complications

Complications occurring within the first 6 months are considered subacute. The data from the major trials suggest the following as possible subacute complications:

1. In the Joint Centers for Radiation Therapy (JCRT) series, alopecia developed in 11 patients (5.6%), all of whom received at least 4.4 Gy of radiation to the scalp.[19]

2. Steroid reinstitution and/or continuation was necessary in 21% of survivors at 6 months in the JCRT series, probably reflecting vascular change rather than tumor recurrence.[19] In the multicenter report of Flickinger et al, steroids had to be reinitiated at < 6 months in < 3% of patients.[25]

3. The UCSF series reported six cases of neurologic deterioration between 2 weeks and 3 months after radiosurgery, including 4 cases of increased hemiparesis and/or confusion treated with steroids, and 2 cases of necrosis documented by magnetic resonance (MR) spectroscopy or autopsy.[33] In the Japanese experience, reported by Fukuoka et al,[26] perifocal edema developed in 19 of 130 patients (45 single, 85 multiple lesions) treated with Gamma Knife stereotactic radiosurgery. Among the 19 cases with edema, transient hemiparesis developed in 7 cases, and disappeared within 1 week to 1 month. Permanent deficits developed in four patients (hemiparesis in three and mental status change in one).

Chronic Complications

The major chronic complications of radiosurgery are radiation necrosis, cranial nerve palsies, and chronic steroid dependence.

Radiation Necrosis

In the JCRT experience, symptomatic radiation necrosis developed in 17 (8%) of 217 patients from 2 to 22 months following therapy; all of these patients eventually required resection.[19,44] Ten of these patients had also received methotrexate, which may have contributed to the necrosis.

Breneman et al reported worsening of neurologic symptoms associated with increasing mass effect in 2 (2.3%) of 84 patients after radiosurgery; these patients required surgical decompression.[22] Both of these patients were found to have radiation necrosis.

Delayed local necrosis within the treated volume was the major complication in 16.6% (20/120) of patients in the Stanford study.[29] The risk of necrosis was a function of tumor volume and prior or
concurrent whole-brain irradiation. Symptomatic and pathologically confirmed necrosis with no viable tumor developed in 1 of 116 patients 11 months after radiosurgery in the report by Flickinger et al, yielding a 2-year actuarial risk of developing necrosis of 4%. However, reoperation was required in 10 patients (8.6%) because of hemorrhage, necrosis, or recurrence.[25] In the UCSF report, four late complications occurred > 3 months after radiosurgery. This included one case of increased hemiparesis, one case of increased confusion, and two cases of brain necrosis documented by positron emission tomography (PET).[33] In the study by Kim et al, two patients demonstrated delayed intratumoral hemorrhage and underwent craniotomy and resection. One additional patient underwent surgical resection for necrosis.[42] In a report of 40 patients with 41 metastatic lesions, Alleyne et al noted the development of seizure activity and MRI evidence of temporal lobe necrosis in 1 patient 12 months after radiosurgery.[20] Cranial Nerve Palsies[25]Only about 1% of patients (2/196) in the JCRT series developed permanent cranial nerve palsies.[44] This phenomenon was observed at 7 and 8 months, respectively, following treatment. One palsy involved the fifth nerve, which received 16.5 Gy, and the other involved the eighth nerve, which received 15 Gy.

Chronic Steroid Dependence[30]One of the potential complications ascribed to radiosurgery is persistent edema requiring chronic steroid usage, with all of its attendant complications. In the University of Wisconsin experience, the need for steroids beyond 6 months was documented in 4 (7%) of 54 of patients. This figure is quite comparable to the 8% rate of steroid dependence at 12 months noted in the JCRT experience.[32,44] Flickinger and colleagues reported a 2-year actuarial rate of developing delayed symptomatic edema of 10.8%.[25] In our experience, in several cases, radiosurgery results in dramatic resolution of edema, rather than persistence of this phenomenon. Further confirmatory evidence is provided by the study of Jokura et al, who found dramatic improvement of perifocal edema with regression of tumors.[28]

Conclusions

Based on a review of the literature, the following general conclusions can be drawn about the treatment of brain metastases:

1. In general, the natural history of brain metastases is very poor. If left untreated, patients with these metastatic brain lesions have a median survival of only 1 month.
2. This natural history can be altered somewhat by the use of steroids and external-beam radiotherapy. However, neither the fractionation scheme nor the total dose seem to have much of an effect in the older RTOG studies.
3. Predictors for favorable outcome include age < 60 years, KPS > 70, a controlled primary tumor, the brain as the only site of metastasis, and fewer than three metastatic lesions.
4. Radiosurgery has been employed in over 1,750 patients, with local control rates of nearly 70%.
5. The morbidity of radiosurgery is low. The most serious risks are radiation necrosis and cranial nerve damage, both of which occur in relatively small percentages of patients (4% and 1%, respectively). Treatment volume and prior radiation therapy may be important predictors for late damage; a very high dose appears to be related to the development of acute toxic episodes.
6. Retrospective comparisons suggest that radiosurgery produces results comparable to those of surgical resection and is probably more cost-effective.
7. The role and sequencing of whole-brain radiation are not clearly defined. Shirato et al have reported a very high failure rate if whole-brain radiation is not used, but this does not appear to compromise survival.[34] Flickinger et al have found an improvement in local control but not in survival when whole-brain radiation is used in conjunction with radiosurgery.[25]
8. Clinical trials of radiosurgery for brain metastases are underway and need to be actively supported. These include an RTOG phase III study testing the value of a radiosurgery boost in addition to whole-brain radiation therapy in patients with one to three metastases; an ECOG phase II study attempting to define intracranial relapse patterns following radiosurgery alone for radioresistant tumors; an M. D. Anderson study comparing resection to radiosurgery; and a recently opened RTOG trial evaluating the radiosensitizer RSR-13 in conjunction with radiosurgery.

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