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Role of radiosurgery in the management of central nervous system metastases

Abstract Radiosurgery is being used more routinely to treat patients with inoperable, recurrent, or multiple brain metastases from systemic cancer. Results in >2000 treated patients have been published during the past 8 years. These results indicate that permanent local control can be obtained in >80% of treated lesions with complications in <10% of patients. Success is independent of the histology, ie, melanoma vs adenocarcinoma, of the treated lesion or number of lesions treated. The long-term results of radiosurgery compare favorably with those seen following surgical resection. The cost-effectiveness of radiosurgery compared to surgical resection favors an expanded role for this technology in the treatment of selected patients with brain metastases.

Key words Radiosurgery · Brain metastases · Stereotaxy · Radiotherapy

Introduction

Radiosurgery is an external irradiation technique that utilizes multiple convergent beams to deliver a high single dose of radiation to a small volume. In radiosurgery, multiple, highly collimated beams of radiation are stereotactically directed toward a radiographically discrete treatment site [13]. The hallmark of all stereotactic radiation techniques is the rapid dose fall-off at the target edges. The radiobiologic effects of radiosurgery are associated with small blood vessel thrombosis, and reproductive cell death or growth arrest [8]. The development of pathological and/or clinical radionecrosis is not a required outcome for radiosurgery to be successful [9].

The procedural goals of radiosurgery are 1) to define a small three-dimensional intracranial target volume; 2) to deliver a clinically significant dose of radiation within the target volume; and 3) to avoid delivering a clinically significant radiation dose beyond the target volume [1]. Radiosurgery is currently performed with one of three types of high-energy radiation technologies: high-energy x-rays produced by linear accelerators; the Gamma Knife producing gamma rays; and less frequently, charged particles such as protons produced by cyclotrons [18].

Brain metastases are ideal targets for radiosurgery treatment for the following reasons: 1) lesions are radiographically discrete; 2) the majority of lesions are <3 cm in greatest diameter; 3) brain metastases are rarely invasive; and 4) brain metastases displace normal brain circumferentially, thus leaving little functioning brain within the target volume.

Lessons from surgical resection of brain metastases

To understand the potential benefit of radiosurgery in the treatment of patients with brain metastases, a brief review of surgical trials is necessary. Radiosurgery and surgery are both local therapies, and thus the results with either modality should be viewed in the same context. The most appropriate treatment for patients with a single brain metastasis has been a source of controversy for nearly two decades. There are now two randomized studies evaluating the role of surgery as an adjunct to whole-brain radiotherapy for patients with a single lesion [16, 17]. In designing such studies of surgical resection or radiosurgery, it is essential to consider

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a number of important endpoints including: 1) survival; 2) local control in the central nervous system (CNS); 3) patterns of progression (local, new CNS disease, and systemic progression); and 4) effects of treatment on quality of life. However, it should be noted that any study evaluating various treatment programs for only one site of disease in the presence of other untreated sites is unlikely to have a major impact on overall survival.

Surgery has been used for patients with a single brain metastasis for many years. The undeniable advantage of surgical resection compared to radiosurgery is in immediately relieving neurological signs and symptoms secondary to tumor mass effect. However, uncontrolled retrospective studies of the overall benefit of surgical resection have produced conflicting results. Some of these studies suggested an advantage in local control and quality of life for patients undergoing surgery and whole-brain radiotherapy when compared to treatment with whole-brain radiotherapy alone.

Patchell et al. conducted the first study to address this issue in a well-designed prospective, randomized study [17]. The results of this study of 48 patients demonstrated that patients with or without active systemic cancer and a single brain metastasis treated with surgical resection (documented by a postoperative enhanced computed tomography [CT] scan) combined with whole-brain radiotherapy (36 Gy/12 fractions) lived longer (40 weeks vs 15 weeks), had fewer local recurrences in the CNS (20% vs 52%), and had a better quality of life compared to patients treated with the same dose of whole-brain radiotherapy alone. The median time to recurrence in the surgery and radiotherapy arm was >59 weeks compared to 21 weeks for those patients treated with whole-brain radiotherapy alone. In a multivariate analysis, the factors significant for increased survival were surgical treatment of the metastasis, the absence of extracranial disease, longer time to the development of the brain metastasis, and younger age. All patients in this study underwent magnetic resonance imaging (MRI) to exclude multiple lesions, and those patients who were randomized to radiotherapy alone underwent stereotactic biopsy to confirm the diagnosis of cancer (it is noteworthy that 6/54 [11%] patients at surgical resection or biopsy had a diagnosis other than metastatic disease and were excluded from the study).

Most investigators would have anticipated an advantage in terms of local control in the CNS for patients treated with complete surgical resection and whole-brain radiotherapy compared to patients treated with the same dose of whole-brain radiotherapy alone. That there was also an advantage in survival and quality of life in the surgical arm demonstrated that some patients experienced neurological effects and died from progression of their single brain metastasis. Thus Patchell and coworkers' study has lead to a great deal of debate in the neurooncology community regarding the appropriate therapy for patients with a single brain metastasis [10]. Some have interpreted the data as an indication to recommend surgery for all patients, while others have argued that by using higher doses of radiotherapy results similar to those achieved with surgery and radiotherapy could be obtained.

The second randomized trial evaluated the role of surgery in 66 patients with a single brain metastasis [16]. Similar to the study by Patchell et al., patients were randomized to surgery and whole-brain radiotherapy versus whole-brain radiotherapy alone. The total radiotherapy was 40 Gy in 20 fractions twice a day for a total of 2 weeks of therapy. However, unlike the study by Patchell and colleagues, patients randomized to radiotherapy alone did not undergo stereotactic biopsy to confirm the diagnosis of metastasis (one patient at recurrence was found to have a malignant glioma) nor was routine enhanced MRI done, which might have excluded patients with small, multiple lesions not detected by CT imaging. The major endpoint of this study was overall survival, with an advantage being demonstrated for those patients undergoing surgical resection and whole-brain radiotherapy over those undergoing whole-brain radiotherapy alone (median 10 months vs 6 months, $P = 0.04$). The largest difference in survival was found in the patients with inactive extracranial disease, with median survival of 12 months and 7 months for combined treatment and radiotherapy alone, respectively. In a subset analysis (accepting the potential pitfalls of this statistical method), older patients (>60 years) and patients with active extracranial disease did not appear to benefit from the addition of surgery.

It is not surprising that older patients had decreased survival rates compared to their younger counterparts because it is well known that older age is one of the most important adverse prognostic factors for patients with a wide variety of both primary and metastatic intracranial histologies. In patients with active systemic disease outside the CNS, the competing risk of dying from extracranial causes overwhelms any potential advantage that could be achieved with combined modality therapy for brain metastases.

Radiosurgery results

The results of the two prospective randomized studies discussed above indicate a survival advantage for patients with a single brain metastasis treated with surgery and radiotherapy compared to radiotherapy alone. It is clear that treatment more aggressive than standard whole-brain radiotherapy is warranted in younger patients who present with a single brain lesion without evidence of progressive extracranial disease. Some investigators believe that radiosurgery can serve as a surgical alternative [5, 15]. As stated earlier, the biological and physical characteristics of metastases (radiographically discrete, small, spherical, and noninvasive) appear to make them ideal targets for radiosurgery [11]. The potential advantages of radiosurgery over surgery are reduced morbidity and reduced healthcare costs (Table 1).

Table 1 Advantages and disadvantages of radiosurgery compared to surgery

Advantages
1. Single-day outpatient procedure
2. Ability to treat inoperable lesion(s)
3. Ability to treat multiple lesions in one session
4. Cost-effective
Disadvantages
1. Delayed relief of mass effect
2. Treatment without pathological confirmation
3. Development of delayed radiation necrosis

Table 2 Results of radiosurgery for brain metastases (reproduced, with permission, from Chang et al. [3])

Study	No. of patients	Tumor control (%)	Median follow-up (months)
Flickinger [5]	116	85	7
Kihlstrom [7]	235	94	–
Engenhart [4]	102	94	12
Alexander [1]	248	85	7.5
Joseph [6]	120	96	8

Studies including >100 patients only were considered in this analysis

Results obtained by treating metastases with radiosurgery indicate that local control is obtained in 73–98% of patients, with median follow-up of 5–26 months [13]. In a multiinstitutional trial involving 116 patients treated with radiosurgery for a single brain metastasis using a mean dose of 17.5 Gy, local tumor control was obtained in 99 patients (85%) [5]. The 2-year actuarial tumor control rate for the whole group was 67% $\pm$ 8%, with a plateau in the curve at 18 months. In a multivariate analysis, better local control was obtained in patients who received whole-brain radiotherapy in addition to radiosurgery and in those patients with "radioresistant" histologies (melanoma and renal cell carcinoma).

The results of radiosurgery used for the treatment of 421 metastatic lesions in 248 patients were recently reported by researchers at the Harvard Joint Center for Radiation Therapy, Boston, MA, USA [1]. At the time of radiosurgery, 77 patients had no evidence of systemic disease while 171 patients had stable systemic disease. Of the lesions treated, 126 were classified as "radioresistant" (melanoma, renal cell carcinoma, and sarcoma), with the remaining 295 lesions representing all other histologies. With a median observation period of 26 months, 48/421 (11%) lesions progressed within the radiosurgery volume. The actuarial 1-, 2-, and 3-year local control rates were 85%, 65%, and 65%, respectively, and radioresistant histologies had control rates statistically equivalent to those of other lesions. The median survival for the whole group was 9.4 months measured from the time of radiosurgery treatment. In a multivariate analysis, the absence of systemic disease (RR 4.4, $P = 0.0001$) and age <60 years (RR 1.6, $P = 0.002$) were associated with improved survival. Eighteen patients (7%) required surgery for the development of symptomatic mass effect from 1–22 months following radiosurgery. The development of symptomatic radiation necrosis requiring reoperation for increasing mass effect and steroid dependency occurred in 6% of patients in this series.

In Table 2, the results of 5 studies that included more than 100 patients are presented. The experience with radiosurgery is similar to the surgical results described in the studies by Noordijk et al. [16] and Patchell et al. [17].

A randomized study comparing radiosurgery to surgery in the treatment of single brain metastases in terms of survival, local control, and quality of life was opened at the Harvard Joint Center for Radiation Therapy 5 years ago. However, accrual to this study was poor due to physician and/or patient preference for either surgery or radiosurgery in individual circumstances and the study was closed in early 1995. Radiation Therapy Oncology Group (RTOG) study 95-08 is randomizing patients with 1–3 brain metastases to whole-brain radiotherapy alone versus whole-brain radiotherapy and a radiosurgery boost. Since this study is open to patients with multiple lesions, there is optimism that it will continue to accrue patients acively.

In the absence of a randomized trial comparing radiosurgery to surgery, Auchter and colleagues [2] reviewed the radiosurgery databases of four institutions

Table 3 Comparison of treatments for patients with single brain metastasis (*RS* radiosurgery, *WBRT* whole brain radiotherapy, *S* surgery) (reproduced, with permission, from Loeffler et al. [14])

Treatment	No. of patients	Median survival (weeks)	Functional independent survival (weeks)	CNS death (% of all deaths)	In-field recurrence (%)	30-day mortality
RS + WBRT [2]	122	56	44	25	14	2
S + WBRT						
Patchell [17]	25	40	38	29	20	4
Noordijk [16]	32	43	33	35	–	9
WBRT only						
Patchell [17]	23	15	8	50	52	4
Noordijk [16]	31	26	15	33	–	0

to identify 122 patients who met the following criteria: single brain metastasis; no prior cranial surgery or whole-brain radiotherapy; age >18 years; surgically resectable lesion; Karnofsky performance status >70; and nonradiosensitive histology, e.g., lymphoma and small cell carcinoma. These are the same selection criteria used by Patchell and colleagues in their randomized study [17]. The patients in the study by Auchter et al. received whole-brain radiotherapy (median 37.5 Gy) followed by a radiosurgery boost (median 17 Gy). The overall local control rate was 86% with an actuarial median survival of 56 weeks and a neurologic median survival of Karnofsky performance status >70% of 44 weeks. The patients included in the study had overall survival, functionally independent survival, and local control comparable to the surgical arms of the two randomized studies described above (Table 3) [16, 17].

Complications of radiosurgery

Acute complications of radiosurgery can occur within hours of the treatment and include nausea and vomiting for posterior fossa lesions as well as seizures for cortically based lesions [12]. These complications can be reduced or eliminated with proper use of preradiosurgery antiemetic agents, anticonvulsant drugs, and steroids. Late complications such as the development of symptomatic radiation necrosis requiring either prolonged steroid support or even reoperation occurs in <10% of treated patients [1]. The probability of developing sysmptomatic radiation necrosis is related to dose and volume irradiated as well as prior exposure to radiation and certain chemotherapeutic agents, including methotrexate [8]. Cranial neuropathies can also develop when treating skull base metastases in a situation when cranial nerves receive doses >10 Gy.

Conclusions

In summary, there is compelling evidence to suggest that aggressive local therapy (surgery and radiotherapy) for patients with brain metastasis produces superior survival and quality of life than whole-brain radiotherapy alone. However, the current data suggest that aggressive therapy should be restricted to the minority of patients for whom brain metastases represent the life-threatening site of their disease. For an asymptomatic or mildly symptomatic patient with a small lesion, radiosurgery appears to be an excellent alternative to surgery. While radiosurgery is a noninvasive procedure, the selection criteria considered should be the same as those used for patients undergoing surgical resection [10]. Surgery or radiosurgery cannot be justified as an adjunct to whole-brain radiotherapy in those patients with progressive systemic disease.

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