Stereotactic interstitial radiosurgery for cerebral metastases

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Object. The Photon Radiosurgery System (PRS) is a miniature x-ray generator that can stereotactically irradiate intracranial tumors by using low-energy photons. Treatment with the PRS typically occurs in conjunction with stereotactic biopsy, thereby providing diagnosis and treatment in one procedure. The authors review the treatment of patients with brain metastases with the aid of the PRS and discuss the indications, advantages, and limitations of this technique.

Methods. Clinical characteristics, treatment parameters, neuroimaging-confirmed outcome, and survival were reviewed in all patients with histologically verified brain metastases who were treated with the PRS at the Massachusetts General Hospital between December 1992 and November 2000. Local control of lesions was defined as either stabilization or diminution in the size of the treated tumor as confirmed by Gd-enhanced magnetic resonance imaging.

Between December 1992 and November 2000, 72 intracranial metastatic lesions in 60 patients were treated with the PRS. Primary tumors included lung (33 patients), melanoma (15 patients), renal cell (five patients), breast (two patients), esophageal (two patients), colon (one patient), and Merkel cell (one patient) cancers, and malignant fibrous histiocytoma (one patient). Supratentorial metastases were distributed throughout the cerebrum, with only one cerebellar metastasis. The lesions ranged in diameter from 6 to 40 mm and were treated with a minimal peripheral dose of 16 Gy (range 10–20 Gy). At the last follow-up examination (median 6 months), local disease control had been achieved in 48 (81%) of 59 tumors. An actuarial analysis demonstrated that the survival rates at 6 and 12 months were 63 and 34%, respectively. Patients with a single brain metastasis survived a mean of 11 months. Complications included four patients with postoperative seizures, three with symptomatic cerebral edema, two with hemorrhagic events, and three with symptomatic radiation necrosis requiring surgery.

Conclusions. Stereotactic interstitial radiosurgery performed using the PRS can obtain local control of cerebral metastases at rates that are comparable to those achieved through open resection and external stereotactic radiosurgery. The major advantage of using the PRS is that effective treatment can be accomplished at the time of stereotactic biopsy.

KEY WORDS • radiosurgery • cerebral metastasis • stereotactic • brain tumor • brachytherapy

Roughly 25% of patients with systemic cancer suffer from brain metastases, accounting for more than 100,000 new cases per year in the US. The results of two randomized trials have demonstrated that survival for patients with a single brain metastasis is markedly lengthened by adding resection to the standard treatment of WBRT.15,17 For lesions that are 3 cm in diameter or smaller, stereotactic radiosurgery performed using a gamma knife or a linear accelerator achieves local control that is comparable to resection and, likewise, permits long-term survival in selected patients.2,8

Interstitial irradiation or “brachytherapy” involves the placement of radioactive isotopes within a tumor and, like radiosurgery, allows the delivery of a high dose of radiation to a well-defined tumor volume with minimal exposure to surrounding tissue. Using standard radioisotopes, interstitial brachytherapy typically requires many hours to several days of exposure to provide adequate irradiation. Although rates of local control are comparable to those associated with surgery and radiosurgery,9,14 the use of brachytherapy for cerebral metastases has been limited because of the special precautions that are required for storage, handling, shielding, and disposal of radioactive sources.

The radiobiology of the PRS and the initial clinical experience with its use have been described previously.5 The PRS is a miniature x-ray generator, which is stereotactically placed inside an intracranial tumor and delivers a single fraction of high-dose radiation over a brief period of time, thereby combining elements of radiosurgery and brachytherapy. In this article we review our institution’s experience with stereotactic interstitial radiosurgery for cerebral metastases and discuss the indications, advantages, and limitations of this form of treatment.

Clinical Material and Methods

Description of the Device

The Photon Radiosurgery System (PRS; Photoelectron Corp., Inc., Lexington, MA) has previously been described in detail.3,5,6,9 In brief, the PRS is composed of a light-weight (2-kg) x-ray generator that provides a point source of low-energy photons. The dose rate in tissue can reach 120 Gy per hour at a 10-mm radius from the tip of the device. The

Abbreviations used in this paper: KPS = Karnofsky Performance Scale; MR = magnetic resonance; PRS = Photon Radiosurgery System; WBRT = whole-brain radiation therapy.

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low-energy x-rays of the PRS differ from high-energy brachytherapy sources in that they are rapidly attenuated in tissue at a dose declining rate that is approximately the inverse of the radius cubed (1/r^3). The resultant 30% dose reduction per millimeter of tissue creates an extremely steep dose falloff, allowing as much radiation as 35 Gy to be administered per hour to a 30-mm-diameter intracranial lesion with a minimal dose to the scalp and only background levels to personnel farther than 2 m away from the patient.

Treatment Technique

Computerized tomography–guided stereotactic biopsy performed using a Cosman-Roberts-Wells (Radionics Inc., Burlington, MA) stereotactic frame was performed in each patient in the standard fashion. Once the findings of the intraoperative histopathological examination verified the diagnosis of metastasis, the biopsy track was expanded slightly with a graduated series of dilators. The PRS was then mounted onto the stereotactic frame, and the probe was advanced along the biopsy track to the center of the lesion. Lesions 2 cm in greatest diameter or smaller were treated with a minimal peripheral dose of 18 Gy to a 2-mm margin beyond the tumor. Lesions larger than 2 cm in greatest diameter were treated with a minimal peripheral dose of 15 Gy to a 2-mm margin beyond the tumor. Once the prescribed voltage and current parameters were entered into the control box, radiation was delivered for the predetermined duration. Radiation treatment monitors attached to the side carriers of the frame were used to keep track of the surface dosage. Following treatment, the probe was removed and the wound was closed.

Clinical Features

We retrospectively reviewed clinical records and neuroimages in all patients with brain metastases who had been treated with the PRS. Twelve of these patients were originally included in a previous report on technique application. Generally, patients were selected for treatment with the PRS if they were undergoing diagnostic biopsy or if the suspected metastasis was unsuitable for resection because of its location in deep cerebral white matter or near eloquent cortex. Patients who had received radiation therapy or chemotherapy within 4 weeks previously were excluded from treatment. Preoperative KPS scores were determined for each patient, as was the pathological diagnosis of the primary disease, if known. Preoperative neuroimages were studied to determine the number, location, and greatest diameter of brain lesions. Surgical and radiation oncology reports were reviewed to determine which intracranial lesion was treated, the dose delivered, the treatment diameter, and the duration of radiation delivery. All patients who had not received WBRT before treatment received it after treatment with the PRS.

Treated lesions were followed to determine disease progression by obtaining MR images with contrast enhancement every 3 months. Local disease control was strictly defined as stabilization or diminution in the size of the enhancing lesion on MR images. Any increase in the size of the treated tumor at any time, irrespective of its subsequent behavior or histopathological diagnosis, was considered a failure of local control.

Each patient’s postoperative KPS score was determined at follow-up outpatient examinations. Patient survival was assessed by reviewing office records and, in the case of US citizens, verifying dates by checking the Social Security Death Index (http://www.ancestry.com). Causes of death were categorized as systemic cancer, neurological progression of disease, unrelated, or unknown. Neurological disease progression was considered the cause of death if the neurological condition of the patient had worsened since PRS therapy regardless of whether deficits were due to the treated lesion. Both survival and local control of treated lesions were assessed by performing a Kaplan–Meier analysis.

Results

Patient and Lesion Characteristics

The PRS was used to treat 60 patients (35 men and 25 women) with brain metastases between December 1992 and November 2000. The age of the patients ranged from 18 to 83 years (median 58 years); 37 patients had a single brain lesion and 23 harbored multiple metastases. The patients’ preoperative levels of function were generally good (mean KPS Score 84, median KPS Score 90), with only three patients having a KPS Score lower than 70. Lung cancer represented the most common primary disease and was identified in 55% of the study participants (35 patients, one with a small cell carcinoma). Notably, a significant percentage of patients suffered from melanoma (15 patients) or renal cell carcinoma (five patients), diseases historically considered to be relatively resistant to fractionated radiotherapy. Other primary lesions included esophageal and breast cancers in two patients each and colon and Merkle cell cancer and malignant fibrous histiocytoma in one patient each.

In these 60 patients, 72 lesions were treated. Eight patients underwent treatment of more than one lesion during the same session, and two patients returned for treatment of new or progressive lesions. The greatest number of lesions treated in a single session was three (two patients); no lesion was treated with interstitial radiosurgery more than once. Most metastases were distributed throughout the cerebral cortex and white matter, with only one lesion in the cerebellum (Table 1).

TABLE 1

Locations of treated lesions*

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>Rt Hemisphere</th>
<th>Lt Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>frontoparietal</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>parietal</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>temporal</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>temporoparietal</td>
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<td>1</td>
</tr>
<tr>
<td>parietooccipital</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>occipital</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>cerebellar</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* Lesions were distributed throughout the cerebral cortex and white matter, roughly correlating with the amount of white matter per lobe. One lesion was identified at the level of the right caudate nucleus, and one was found in the right cerebellar hemisphere.
The mean diameter of the treated lesions was 20.6 mm (range 4–40 mm). Seven lesions larger than 3 cm in diameter were treated. A mean dose of 16 Gy (range 10–20 Gy) was delivered to a 2-mm margin beyond the tumor, resulting in a mean treatment volume of 7.8 cm$^3$ (range 0.3–45 cm$^3$). The mean duration of treatment was 19.4 minutes (range 3.7–75 minutes).

**Patient Outcomes**

Fifty-seven (95%) of 60 patients participated in follow-up review for a median of 6 months (range 5 days–31 months). Serial MR images were available for review in 59 of 72 treated lesions. At the last follow-up examination, MR images demonstrated stabilization or reduction in tumor size in 48 of 59 lesions, providing a local disease control rate of 81% (Fig. 1). Eleven lesions were found to have enlarged on follow-up MR images, providing a treatment failure rate of 19%. In five patients in whom MR imaging revealed a failure of treatment with the PRS, tissue was obtained either by biopsy (one patient, 24 months posttreatment) or during resection (four patients, at 4, 6, 10, and 12...
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months posttreatment). In resected specimens obtained in two patients, a thin rim of viable tumor and central radiation necrosis were demonstrated. In three other specimens, two of which were obtained during total resections, radiation necrosis alone was identified.

The response of radioresistant lesions—melanoma and renal cell carcinoma—was reviewed as a subgroup. Twenty of 25 lesions were followed for a mean duration of 6 months (range 2–25 months). Local control was obtained in 18 tumors, providing a rate of 90%. Local control was achieved in five (71%) of seven tumors with diameters larger than 3 cm (median follow up 6 months, range 2–11 months).

Karnofsky Performance Scale scores could be obtained in 47 patients at the 3-month follow-up examination. The median posttreatment KPS score was 80 (range 20–100).

For all treated patients, regardless of the pathological diagnosis or the number of intracranial lesions, the actuarial analysis yielded a 6-month rate of survival of 63% and a 12-month rate of 34% with a 50% survival rate occurring at approximately 8 months (Fig. 2 upper). For the sake of comparison with the literature regarding other modalities of local treatment of intracranial metastases, survival rates of 67% at 6 months, 48% at 12 months, and 50% at approximately 11 months (Fig. 2 lower).

The causes of death are depicted in Table 2. Fifty-nine percent of all deaths were due to systemic disease and 30% resulted from neurological disease progression. Only four deaths (15%) resulting from neurological disease progression occurred in patients who underwent treatment for single lesions.

Complications of Treatment

Complications were identified in four patients who experienced perioperative seizures that were easily controlled with antiepileptic medication and were not recurrent. Three patients suffered transient neurological deficits associated with the biopsy or treatment-induced cerebral edema. Biopsy-related hemorrhages were identified in two patients, one of whom had no symptoms; the second patient suffered from an homonymous hemianopia but did not require any surgical intervention. Delayed symptomatic radiation necrosis necessitated treatment with long-term steroid therapy and resection in three patients. There was no apparent relationship between the radiation dose and complications (p = 0.34, Student t-test). No treatment-related death, deep vein thrombosis, or wound complication was identified.

Discussion

Historically, patients with cerebral metastases have been treated with WBRT, and, in the most favorable populations (patients with solitary brain metastases and limited systemic disease), survival averages 18 months.10 Resection of solitary lesions yields greater local control, extends patient survival, and improves quality of life. Similar results have been obtained using external stereotactic radiosurgery, which is now widely used in the US. Contentious issues in the treatment of brain metastases include the utility of locally treating more than one brain lesion15 and the necessity of providing up-front WBRT to patients for whom lesions (single or multiple) are locally treated.12,16

The guiding principle of stereotactic radiosurgery is that a single fraction of high-dose radiation is delivered to a precise volume of diseased tissue. For both the Gamma Knife and the linear accelerator, a steep dosing falloff rate allows sparing of surrounding normal tissues. Stereotactic radio-

Fig. 2. Upper: Kaplan–Meier curve depicting survival for all patients with cerebral metastases treated with the PRS. The median duration of survival is 8 months and the survival rate at 1 year is 34%. Lower: Kaplan–Meier survival curve for treated patients with single brain metastasis. The median duration of survival is approximately 11 months and the survival rate at 1 year is 48%.

TABLE 2

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Patients (%)</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>w/ Single Brain Metastasis</td>
</tr>
<tr>
<td>no. of patients</td>
<td>46 (100)</td>
</tr>
<tr>
<td>neurological disease pro-</td>
<td>14 (30)</td>
</tr>
<tr>
<td>gression</td>
<td></td>
</tr>
<tr>
<td>systemic disease</td>
<td>27 (59)</td>
</tr>
<tr>
<td>other</td>
<td>1 (2)</td>
</tr>
<tr>
<td>unknown</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

* Less than one third of all patients died of neurological disease; accordingly, nearly four fifths of patients with a single brain lesion died of progressive systemic disease.
surgery for metastases has largely supplanted interstitial brachytherapy, which provides focal treatment but demands an invasive procedure, has a less predictable dose distribution, and involves the storing and handling of radioactive materials by health care providers.

The technique of “stereotactic interstitial radiosurgery,” performed using the PRS, combines favorable elements of “external” stereotactic radiosurgery with the principles of brachytherapy. The dose distribution of the low-energy x-rays emitted by the PRS falls off at an approximate rate of 1/r^3, which allows greater sparing of normal brain than other radiosurgical modalities. This also allows treatment of lesions larger than 3 cm in greatest diameter. Histological studies of irradiated lesions in animals have demonstrated a sharp demarcation between the irradiated lesion and surrounding normal tissue. In addition, the in vitro radiobiological effectiveness of the PRS is higher than that of high-energy photon beams.

From a technical standpoint, the PRS is straightforward for the neurosurgeon to apply. The target coordinates are chosen as they are for stereotactic biopsy, and the radiosurgery probe follows the track created by the biopsy needle. The PRS provides the unique advantage of allowing diagnosis by stereotactic biopsy and treatment by radiosurgery to occur during the same session. Although some might purport that the neuroimaging-related discovery of a brain mass in a patient with a known malignancy obviates the necessity for tissue diagnosis, up to 11% of cancer patients harbor unrelated brain lesions with alternative pathological characteristics, and such a discovery might alter prognosis and/or treatment. Another advantage of the PRS is that the time for patient recovery from biopsy and interstitial radiosurgery is brief, and otherwise healthy patients are typically discharged on postoperative Day 1. Resection via craniotomy requires several days of hospitalization and a more prolonged postoperative recovery. External radiosurgery requires a return for a second stereotactic procedure following the biopsy. In patients with a limited life expectancy, minimizing hospital stays and interventions are commendable goals of treatment.

A theoretical disadvantage of the PRS is that conformal shaping of the dose is not yet possible. Metastatic brain lesions are well-suited targets, however, because they are typically spherical. Another possible disadvantage is the fact that the dosing falloff is so steep that the accuracy of targeting and delivery is essential. Target coordinates and treatment volumes are determined by examining an image obtained before the patient is positioned in the operating room, leaving open the possibility of brain shift. In part, this is accounted for by delivering the prescribed dose to a 2-mm margin around the lesion.

Using conservative and stringent criteria for the neuroimaging finding of freedom from disease progression, we have demonstrated that the PRS provides local control of metastatic brain lesions at a rate of 81%, which is comparable to resection and external stereotactic radiosurgery. Likewise, radioresistant lesions (melanoma and renal cell carcinomas) were controlled at an even higher rate (90%), a phenomenon previously reported with external radiosurgery.

Stereotactic interstitial radiosurgery can be performed with relatively low rates of morbidity. Delivery of radiation does not appear to increase the risk of hemorrhage when compared with stereotactic biopsy alone. Three patients suffered acute worsening of neurological deficits, but function was fully restored with temporary administration of steroids and the passage of time. Symptomatic radiation necrosis with edema necessitated craniotomy and resection for three lesions (5%). No association between the size of the treated lesion and complications was identified. Seven lesions larger than 3 cm in diameter were treated; one of these required a craniotomy to alleviate a mass effect due to radiation necrosis. Local control of disease was achieved for five of these seven lesions; however, the small number of these lesions makes a meaningful conclusion about the treatment of large lesions difficult.

Conclusions

The goals of therapy for patients with cancer who have cerebral metastases include the prolongation of survival and a sustained high quality of life without progressive neurological deficits. Local treatment of metastatic brain lesions by resection or radiosurgery can prolong survival and maintain quality of life. Based on our experience, we suggest that treatment with the PRS can achieve local control of metastatic lesions that is comparable to that attained using open resection and external stereotactic radiosurgery. Survival rates for patients with solitary lesions is also comparable, and most patients succumb to systemic rather than neurological disease. The unique advantage of stereotactic interstitial radiosurgery, however, is the opportunity to obtain both diagnosis and treatment during the same intervention. Although perhaps limited to patients presenting without a diagnosis and without a more suitable site for biopsy, we believe that the PRS is an efficient complementary therapy for patients with brain metastases.

Disclosure

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References

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