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Stereotactic Radiosurgery for Brain Metastases From Breast Cancer

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Background: Stereotactic radiosurgery is an alternative to resection or to radiotherapy alone for patients with brain metastases. Outcomes after radiosurgery for patients with brain metastases specifically from breast cancer have not been defined.

Methods: We retrospectively studied survival and tumor control for all patients with brain metastases from breast cancer who underwent gamma knife stereotactic radiosurgery at the University of Pittsburgh. Univariate and multivariate analyses were used to determine which prognostic factors significantly affected survival.

Results: Thirty patients underwent radiosurgery between 1990 and 1997. A total of 58 metastases were treated. The median length of survival for all patients was 13 months from radiosurgery and 18 months from diagnosis of brain metastases. The tumor control rate on follow-up imaging was 93%. On multivariate analysis, the only factor that correlated with longer survival was the absence of multiple brain metastases. Age, presence of systemic disease, previous whole brain radiation, location, and total tumor volume did not significantly affect survival. Four patients had tumors with evidence of radiation-induced edema after radiosurgery but did not require resection. Two patients underwent delayed resection for tumor growth after radiosurgery.

Conclusions: Stereotactic radiosurgery is an effective treatment for brain metastases from breast cancer and is associated with a low complication rate.

Key Words: Breast carcinoma—Brain metastases—Radiosurgery—Stereotactic surgery.

Breast cancer, along with lung cancer and melanoma, is one of the most common sources of brain metastases and is clinically recognized in approximately 10% of patients with stage IV disease.[1] This rate may be even higher in the present era of advanced neuroimaging. Standard treatments for brain metastases from breast cancer include whole brain radiation, chemotherapy, and conventional surgery. Stereotactic radiosurgery is an alternative option that can be used either alone or in conjunction with other treatment methods. Although radiosurgery has been found to be an effective, noninvasive, and low-morbidity treatment for brain metastases in general,[2–8] no previous study has specifically examined the subgroup of patients with breast cancer. Despite the great numbers of patients with brain metastases from breast cancer, few reports document patient outcomes. As breast cancer is considered to be a radiosensitive tumor with effective systemic treatments, it is logical to examine this histological tumor type apart from other histologies known to be more refractory to treatment. In this study, we examine clinical and radiographic outcomes of patients with brain metastases from breast cancer after stereotactic radiosurgery.

MATERIALS AND METHODS

Patient Selection and Study Design

All patients with brain metastases from breast cancer who were treated with gamma knife stereotactic radiosurgery at our academic medical center were included in the analysis. Patients were not excluded if they received previous whole brain radiation, chemotherapy, or con-

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ventional surgery for their brain metastases. All patients had imaging typical for metastases, a Karnofsky score greater than 50, and a tumor diameter smaller than 3 cm. The treatment period spanned from May 1990 to July 1997. The patient records and follow-up imaging studies were reviewed in a retrospective manner. Medical records were supplemented by telephone calls to the patient, the patient's family, or the referring physician.

Patient Characteristics

Twenty-eight patients were women and two were men. Age varied from 39 to 70 years, with a mean age of 55 years. Clinical presentations at the time of radiosurgery included headache (seven patients), seizures (six patients), hemiparesis (five patients), brainstem syndromes (two patients), visual changes (four patients), and other neurological symptoms (seven patients). Seven patients were asymptomatic.

Fourteen patients had solitary brain metastases at the time of radiosurgery; 16 patients had multiple metastasis. Fifteen patients had active systemic disease at the time of presentation and 15 patients did not. Twenty-six patients received whole brain radiation (21 patients before radiosurgery and 5 patients after radiosurgery). Only four patients did not have whole brain radiation in addition to radiosurgery. Karnofsky performance scores at the time of radiosurgery were not accurately documented for all patients and were, therefore, not included in the analysis. Table 1 summarizes the patient characteristics.

TABLE 1. *Patient characteristics*

Characteristics	No. of patients (n = 30)
Sex	
Women	28
Men	2
Clinical presentation	
Headache	7
Seizures	6
Hemiparesis	5
Visual changes	4
Brainstem symptoms	2
Other neurological	7
Asymptomatic	7
Number of radiosurgery sessions	
1	27
2	2
3	1
Number of tumors treated	
1	14
2	9
3	4
4	2
5	0
6	1
Whole brain radiation	
Yes	26
No	4
Systemic disease at the time of radiosurgery	
Yes	15
No	15

Tumor Characteristics

A total of 58 brain metastases were treated. Forty-four tumors were supratentorial and 14 were infratentorial. Tumor locations included hemispheric (39 tumors), cerebellar (9 tumors), brainstem (3 tumors), basal ganglia (4 tumors), intraventricular (1 tumor), pituitary fossa (1 tumor), and jugular foramen (1 tumor). Tumor volumes varied from 0.1 to 15.1 ml. Thirty-one tumors were more than 1 ml in volume, whereas 27 were smaller than 1 ml in volume.

Radiosurgery

In all patients, radiosurgery was performed with the 201-source cobalt-60 gamma knife (Elekta Instruments, Atlanta, GA), using either enhanced computed tomography or magnetic resonance imaging for localization. Informed consent was obtained from all patients before the procedure. The Leksell Model G stereotactic coordinate frame (Elekta) was placed under local anesthesia, with mild intravenous sedation as needed. Patients received one dose of methylprednisolone at the time of radiosurgery. In general, patients remained in the hospital for a single night after radiosurgery and returned home the next morning.

Twenty-seven patients underwent radiosurgery on only one occasion, two patients underwent treatment on a total of two occasions, and one patient had three procedures. In all patients who had multiple procedures, radiosurgery was performed for new tumors and not for a tumor that previously underwent radiosurgery. The greatest number of metastases treated in one patient in a single procedure was six. The number of months between diagnosis of brain metastasis and radiosurgery varied from 0 to 49 months (mean, 7 months). Radiosurgical doses varied from 12 to 20 Gy to the tumor margin.

Data Analysis

Median survival was calculated with the Kaplan-Meier method.[9] Survival was calculated both from the time of radiosurgery and from the time the brain metastases were discovered. Factors affecting survival were analyzed in a univariate and multivariate fashion with the log-rank and the Cox proportional hazards models,[10] respectively. The factors analyzed were age, presence of systemic disease, presence of multiple brain metastases, previous whole brain radiation, supratentorial vs. infratentorial location of tumor, and tumor volume. Tumor control was defined as the most recent follow-up imaging scan that demonstrated no change, a decrease in size, or complete disappearance of the treated tumor.

RESULTS

Survival

Mean clinical follow-up was 13 months (median, 9 months; range, 1–47 months). All patients had a least one clinical follow-up documented. Although one patient was lost to further follow-up, his date of death was documented by a national registry. Median survival for all patients was 13 months after radiosurgery (95% confidence interval, 9–17 months) and 18 months from the time of diagnosis (Fig. 1). At the time of this report, 10 patients were alive and 20 had died. The longest survival was 47 months from the time of radiosurgery (96 months from diagnosis) in a 70-year-old man with a solitary, 0.3-ml-volume supratentorial metastasis.

On univariate analyses, smaller total tumor volume and the presence of a solitary metastasis correlated with longer survival after radiosurgery. On multivariate testing, however, only the presence of a solitary metastasis was significant. Multiple metastases increased the death rate by a factor of 3.38. Figure 2 shows the Kaplan-Meier plot for patients with solitary metastases compared with those with multiple metastases. Age, the presence of systemic disease, previous whole brain radiation, and tumor location were not significant prognostic factors. Table 2 summarizes these data.

The cause of death was the result of either progression of systemic disease (n = 8), progression of the treated brain tumor (n = 3), development of a new brain tumor (n = 1), or both systemic and brain progression (n = 1). In seven patients, the cause of death was not clearly known.

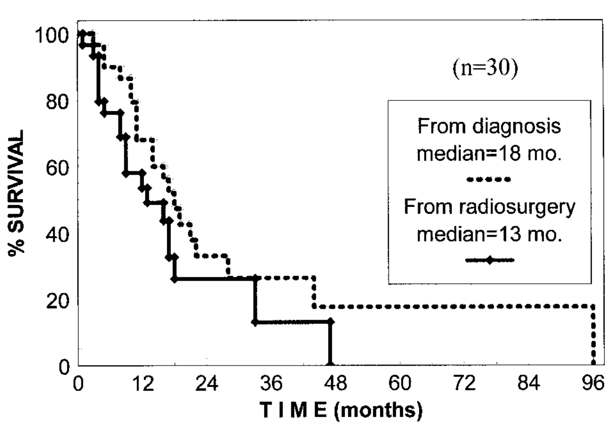

FIG. 1. Survival curve for all patients after stereotactic radiosurgery and after diagnosis of brain metastases (n = 30).

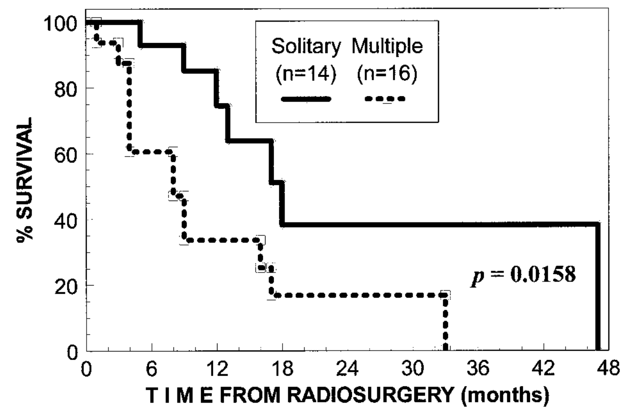

FIG. 2. Survival curve (after radiosurgery) for patients with solitary metastases (n = 14) compared with the survival curve for patients with multiple metastases (n = 16).

Tumor Control

Mean imaging follow-up was 9 months (median, 6 months; range, 1–31 months). A total of 46 of 58 treated tumors had imaging follow-up, using either computed tomography or magnetic resonance imaging. Local tumor control was achieved in 43 of 46 (93%) metastases, based on the most recent follow-up imaging available. Specifically, 7 (15%) tumors completely disappeared (Fig. 3, A and B), 20 (43%) tumors were smaller, 16 (35%) were unchanged, and 3 (7%) had a delayed increase in size. Of the 16 tumors that remained unchanged in size, 4 had evidence of radiation-related edema; none required resection. Nine patients developed new brain metastases (from 1 to 10 new tumors) during the follow-up period (Fig. 3, A and B). Two patients whose treated tumors enlarged eventually required open surgical resections; i.e., one had a cerebellar metastasis with an initial tumor volume of 7.6 ml and the other patient had an occipital metastasis with an initial volume of 2.7 ml.

TABLE 2. *Prognostic variables for survival*

Variable (n = 30)	Univariate (*P*)	Multivariate (*P*)	Tested for favorable status
Age	.60	.57	<55 y
Solitary vs. multiple metastases	.02	.01	Solitary metastasis
Presence of systemic disease radiosurgery	.31	.63	No systemic disease at time of
Whole brain radiation	.20	.09	Whole brain radiation received
Tumor location	.53	.50	Supratentorial only
Total combined tumor volume	.05	.54	<4 ml

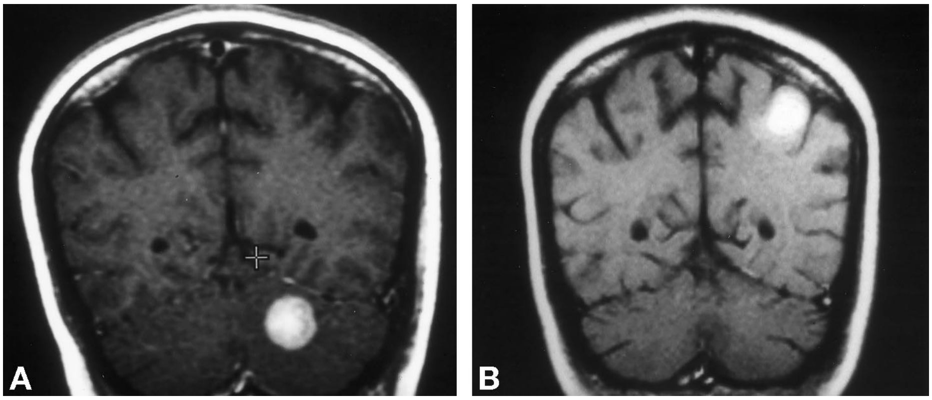

FIG. 3. (**A**) Coronal magnetic resonance imaging scan of a 44-year-old woman with breast cancer and a metastasis to the cerebellum. The patient had already received whole brain radiation. Radiosurgery was performed to deliver 18 Gy to the 60% isodose line. (**B**) Twenty-four months after radiosurgery, the cerebellar metastasis remains gone. The patient developed a new metastasis in the parietal lobe, which was also subsequently treated with radiosurgery.

DISCUSSION

Conventional management for patients with brain metastases from breast cancer includes whole brain radiation, chemotherapy, and resection. Whole brain radiation alone has been reported to be associated with a 3- to 4-month survival in these patients.[1,11–14] Chemotherapy is not widely used to treat metastases to the brain. A small number of available reports, however, cite an approximate 7- to 8-month survival in this population.[15–17] Surgery for brain metastases from any primary cancer is often performed.[18–20] Two large surgical series of patients who underwent craniotomy specifically for breast cancer demonstrated median survivals of 13.9 months[21] and 16 months after surgery.[22] The 16-month figure is the longest reported survival for any treatment method in this population. A single case report describes a 10-year disease-free survival after surgery, radiation, and long-term tamoxifen in a woman with a single brain metastasis from breast cancer.[23]

Stereotactic radiosurgery is a more recently introduced method for the treatment of brain metastases. It can be used in conjunction with, or as an alternative to, other treatment methods.[2–8] Radiosurgery is an appealing option for patients with brain metastases. The procedure requires only a single overnight stay and can even be performed on an outpatient basis. Apart from the stereotactic frame application, which is well-tolerated with local anesthetic and mild intravenous sedation, the procedure is completely noninvasive. Furthermore, patients with significant medical conditions do not face the risk of complications from general anesthesia as they would with conventional surgery. Potential complications attributed to radiosurgery for metastases include local skin complications from the stereotactic frame (rare), failure to control the treated lesion, and the development of radiation-related edema. In the present series, stereotactic radiosurgery failed to control three tumors (7%), two of which eventually required craniotomy for resection. Four tumors (9%), in a total of three patients, had evidence of radiation-related edema and were managed medically without the need for resection.

Radiosurgery Versus Surgery

Although other series of radiosurgery for brain metastases have included small numbers of patients with breast cancer, our report of 30 patients is the first to specifically determine outcomes for this particular subgroup. Given the differences in behavior among different histological types of metastases, it makes sense to examine each type individually. The median survival of 13 months after treatment in our series surpasses the results of whole brain radiation or chemotherapy alone, is similar to the surgical series of Wronski et al.,[21] but falls short of the 16-month survival after conventional surgery reported by Pieper et al.[22] Such simple and direct retrospective comparisons, however, are frought with difficulties.

Because radiosurgery is a noninvasive intervention capable of treating multiple lesions anywhere in the brain, patient selection is not limited to patients with tumors in resectable locations. Direct comparisons with resection, then, must be made carefully. In the surgical series of 63 patients described by Pieper et al.,[22] only 13% had multiple metastases (predominantly, two metastases). In contrast, 53% of patients in our series had multiple metastases, including the 23% of all patients with three or more tumors. In both our series and the surgical series of Pieper et al.,[22] the presence of multiple metastases was significantly correlated with shorter survival.

Another important tumor characteristic that may differentiate surgical series from radiosurgical series is size. In the present group of patients, tumor volume varied from 0.1 to 15.1 ml, and 27 of the 58 metastases were smaller than 1 ml in volume. Despite that our multivariate analysis did not show a statistically significant difference in survival for patients with smaller tumors (combined volume, $<$4 ml), it is at least intuitive that patients with very small metastases who undergo radiosurgery may have an advantage over patients who require open resection for large metastases, all other factors being equal.

All but 2 of the 63 patients in the Pieper et al.[22] surgical series underwent surgery within 2 weeks of the diagnosis of brain metastases. Patients were excluded, in fact, if they had had previous treatment for their brain metastases. In our series, in contrast, mean time period between diagnosis of brain metastases and radiosurgery was 7 months. In many patients, radiosurgery was performed only after whole brain radiation had failed. Many of our patients, therefore, were already several months into their survival with brain metastases before radiosurgery was performed. For some of our patients, this may have meant that they were closer to their expected time of death when they presented for radiosurgery. Alternatively, this intervening time period may have selected for longer-term survivors, because they had already survived for several months before radiosurgery.

Fifty percent of the patients in our series had no evidence of metastases outside of the brain at the time of radiosurgery, whereas in the surgical series, 44% of patients had no other metastases.[22] Although this would seem to give our patients a slight survival advantage, we found that absence of systemic disease did not correlate with longer survival. This may reflect the treatment advantage that breast cancer patients have over patients with other tumor types because of the availability of effective systemic disease treatments such as chemotherapy and hormonal therapy. On the other hand, our relatively small sample size may not have enough statistical power to demonstrate a reliable difference between patients with and without systemic disease.

Tumor location is another important consideration in the comparison of radiosurgery with conventional surgery. Although the surgical series documented that 65% of patients had supratentorial tumors, 35% had infratentorial tumors, and 5% had both, the exact tumor locations were not further detailed.[22] Our series included three brainstem metastases, four basal ganglia metastases, a jugular foramen metastasis, and a pituitary metastasis. Not only do these tumors present a greater threat to the patient than do tumors in more benign locations, but open resection of such tumors may be associated with unacceptable complications, especially in light of the patient's already limited prognosis. Whereas such patients may not be considered candidates for conventional surgery and would not be reflected in a surgical series, they would not be excluded from radiosurgery.

Despite the differences in the nature of the approaches and in patient selection between our radiosurgical series and the conventional surgical series, it is noteworthy that tumor progression (or recurrence after resection) was similar in both series. Of the 63 surgical patients, 11 (17%) had evidence of local recurrence.[22] Of the 30 patients in our series, 3 patients (10%) had progression of the treated tumor, and 3 patients (four tumors) had a transient radiation edema after radiosurgery. Two of our patients eventually required open surgical resection of the enlarged metastases. In the surgical series, although it was stated that no patient required a second operation in the acute postoperative period, no mention was made of whether repeat surgery was performed later for recurrent tumors.

CONCLUSIONS

Stereotactic radiosurgery is a noninvasive, low-morbidity, and effective approach to patients with brain metastases from breast cancer. Radiosurgery is especially appealing for patients with limited life expectancy, because it provides excellent tumor control without the longer hospitalization and distress associated with open resection. In our series of 30 patients, the median survival was 13 months after radiosurgery and 18 months after diagnosis of brain metastases. The tumor control rate was 93%. Retrospective comparisons of radiosurgery with conventional surgery for this population must be performed cautiously, because patient selection criteria are substantially different. Our series includes a large proportion of patients with multiple metastases, small-volume metastases, and tumors in surgically challenging locations.

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