Brain metastases account for the majority of intracranial tumors, and breast cancer is second to lung cancer only as a common source of such tumors. Brain metastasis, a significant cause of morbidity and death, ultimately develops in approximately 20%–40% of patients with cancer. Reported incidences vary from 5% to 10%–20% in clinical series, to as high as 30% in autopsy studies. Incidence appears to be increasing—most likely because of earlier diagnoses, better neuroimaging methods, and longer survival from the primary diagnosis.

Historically, resection and WBRT have been the mainstays of treatment for cerebral metastases. More recently, however, SRS has emerged as the preferred treatment modality either alone or in conjunction with other methods. Radiosurgery can be used to manage surgically inaccessible tumors or multiple tumors in one outpatient session, and it does not interfere with ongoing systemic treatment.

The delayed toxicities of WBRT have prompted many to question its role in the primary management of brain metastases. Authors of previous studies have attempted to clarify the role of SRS with or without WBRT, but few have specifically focused on breast cancer, and the reported experience is limited.

Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer

Clinical article

Douglas Kondziolka, M.D.,1,2,4,5 Hideyuki Kano, M.D., Ph.D.,1,4 Gillian L. Harrison, B.S.,6 Hua-Che Yang, M.D.,1,4,7 Donald N. Liew, M.D.,1,4 Ajay Niranjan, M.Ch., M.B.A.,1,2 Adam M. Bruksky, M.D., Ph.D.,1,4,6 John C. Flickinger, M.D.,1,2,4,6 and L. Dade Lunsford, M.D.1,2,4,5

Departments of 1Neurological Surgery, 2Radiation Oncology, and 3Hematology/Oncology; 4Center for Image-Guided Neurosurgery; 5University of Pittsburgh Cancer Institute; 6University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and 7Department of Neurological Surgery, Taipei Veterans General Hospital, Taipei City, Taiwan

Object. To evaluate the role of stereotactic radiosurgery (SRS) in the management of brain metastases from breast cancer, the authors assessed clinical outcomes and prognostic factors for survival.

Methods. The records from 350 consecutive female patients who underwent SRS for 1535 brain metastases from breast cancer were reviewed. The median patient age was 54 years (range 19–84 years), and the median number of tumors per patient was 2 (range 1–18 lesions). One hundred seventeen patients (33%) had a single metastasis to the brain, and 233 patients (67%) had multiple brain metastases. The median tumor volume was 0.7 cm³ (range 0.01–48.9 cm³), and the median total tumor volume for each patient was 4.9 cm³ (range 0.09–74.1 cm³).

Results. Overall survival after SRS was 69%, 49%, and 26% at 6, 12, and 24 months, respectively, with a median survival of 11.2 months. Factors associated with a longer survival included controlled extracranial disease, a lower recursive partitioning analysis (RPA) class, a higher Karnofsky Performance Scale score, a smaller number of brain metastases, a smaller total tumor volume per patient, the presence of deep cerebral or brainstem metastases, and HER2/neu overexpression. Sustained local tumor control was achieved in 90% of the patients. Factors associated with longer progression-free survival included a better RPA class, fewer brain metastases, a smaller total tumor volume per patient, and a higher tumor margin dose. Symptomatic adverse radiation effects occurred in 6% of patients.

Conclusions. Stereotactic radiosurgery was safe and effective in patients with brain metastases from breast cancer and should be considered for initial treatment. (DOI: 10.3171/2010.8.JNS10461)
Stereotactic radiosurgery for brain metastasis from breast cancer

In the present study, which involves the largest patient population reported on to date, we attempted to clarify the role of SRS and to identify associated factors of prognostic significance.

Methods

The University of Pittsburgh Institutional Review Board approved this retrospective study.

Patient Population

From our database of over 9700 radiosurgical patients, we identified 350 women (median age 54 years, range 29–84 years) who had undergone SRS for 1535 brain metastases between May 1990 and March 2009. The median number of brain metastases per patient was 2 (range 1–18 metastases). Medical or radiation oncologists had referred each patient for radiosurgery consideration. Resection was advocated for larger tumors (> 3 cm in diameter) with mass effect unresponsive to corticosteroid therapy. Patients with 1–4 metastases underwent radiosurgery alone, and those with 5 or more tumors typically received WBRT plus radiosurgery (before 2000) or radiosurgery alone as initial therapy (since 2000). All patients underwent repeat high-resolution MR imaging 8 weeks later. If new tumors were identified, WBRT was then considered if it had not been previously delivered. Medical and radiation oncologists commonly requested radiosurgery alone as initial therapy since it allowed for the continuation of any extracranial cancer care. Patient characteristics are shown in Table 1. The median interval between primary site diagnosis and the diagnosis of brain metastases was 46 months (range 0–305 months).

Ten patients (3%) had brain metastases in the context of no active systemic disease. Forty-six patients (13%) with extracranial metastases had control of that disease at the time of brain tumor management. At the time of SRS, 125 patients (36%) were asymptomatic, 42 (12%) had headache only, 13 (4%) had a seizure only, 161 (46%) had focal neurological deficits, and 9 (3%) had cognitive disorders. The median KPS score was 100% (range 40%–100%). When stratified according to the prognostic value of the RPA devised by the RTOG,18,19 24 (6.9%) were in Class 1, 310 (88.6%) were in Class 2, and 16 (4.6%) were in Class 3.

The HER2/neu status was analyzed via immunohistochemical testing on the primary site specimens with appropriate positive and negative controls using monoclonal antibody 4B5 (Ventana). The HER2 3+ staining (> 30% of cells exhibiting strong perimembranous staining) was considered positive, whereas HER2 2+ staining (weak staining in > 10% of cells) was considered equivocal. The HER2 testing was performed using fluorescence in situ hybridization with a fluorescent DNA probe for HER2 (Vysis, Inc.) and fluorescence microscopy. At least 50 nuclei were counted per specimen. A ratio > 2.2 of the HER2 gene probe/chromosome 17 centromere probe was considered positive. A ratio of 1.8–2.2 was considered equivocally positive, whereas a ratio < 1.8 was considered negative.

Radiosurgery Technique

Our radiosurgical technique has been described in detail in previous reports.14 In brief, patients underwent the application of an imaging-compatible stereotactic head frame while under local anesthesia supplemented with intravenous conscious sedation. High-resolution MR imaging or rarely CT was then performed. The tumor was visualized using 2-mm contrast-enhanced volume-acquisition images supplemented by 3-mm T2-weighted sequences. The SRS target was defined as the contrast-enhanced tumor volume.

The median volume for each individual tumor was 0.7 cm³ (range 0.01–48.9 cm³). The median volume of the largest tumor per patient was 3.2 cm³ (range 0.06–48.9 cm³).
cm³), and the median total tumor volume per patient was 4.9 cm³ (range 0.09–74.1 cm³). A median of 5 isocenters (range 1–34 isocenters) was used for dose planning in each patient. The median prescription dose delivered to the tumor margin was 17.0 Gy (range 8–23 Gy). The maximum dose varied from 18 to 42.5 Gy (median 32.0 Gy). Stereotactic radiosurgery was performed using a Model U, B, C, 4-C, or Perfexion Leksell Gamma Knife (Elekta, Inc.). The addition of the Perfexion Leksell Gamma Knife facilitated single-session treatment in patients with multiple metastases, especially those who had experienced a relapse after prior WBRT. The largest number of metastases treated in a single procedure in this experience was 18.

All patients received a 20- to 40-mg intravenous dose of methylprednisolone after radiosurgery to reduce the risk of early brain swelling. For patients already taking corticosteroids, the medication was tapered over 1–3 weeks. Patients were evaluated and imaging studies were obtained at regular intervals. Typically, we performed MR imaging 2 months after radiosurgery, at 3-month intervals thereafter for the first 2 years, every 6 months until Year 5, and then annually thereafter. Radiological outcome was classified as “tumor progression” if the tumor volume increased by > 25% compared with its size at the time of SRS and as “tumor regression” if a > 25% volume reduction was noted. A tumor was deemed “stable” on follow-up MR imaging if it remained within 25% of its initial volume. We diagnosed continuously enlarging enhancing lesions as tumor recurrences and stable or decreasing enhancing lesions as radiation effects after a temporary course of corticosteroids if symptomatic. Adverse radiation effects were evaluated according to the late radiation morbidity criteria of the RTOG and the EORTC.¹⁰

Statistical Analysis

We constructed Kaplan-Meier plots for survival and the local tumor control rate by using the dates of primary cancer diagnosis, brain metastasis diagnosis, and SRS. The local tumor control rate and OS time were calculated from the day of the first SRS by using the Kaplan-Meier method. Univariate analysis was performed on the Kaplan-Meier curves by using the log-rank statistic and the Cox proportional hazards model, with p < 0.05 set as the level of significance. We performed multivariate analysis using the Cox proportional hazards model, with p < 0.05 set as significant. Standard statistical processing software (SPSS, version 15.0, SPSS, Inc.) was utilized. Univariate and multivariate analyses were performed to assess the prognostic value of different variables relative to tumor response, distant failure, and patient survival. Variables for multivariate analysis were those with statistical significance on univariate analysis.

Results

Patient Survival

At the time of our assessment, 72 patients (21%) were alive and 278 patients (79%) had died. The median follow-up was 9.5 months (range 0.2–145 months). The MST after SRS was 11.2 months (95% CI 9.46–12.88 months). Survival after SRS was 69%, 49%, 26%, and 16% at 6, 12, 24, and 36 months, respectively. The MSTs for RPA Class 1, 2, and 3 were 16.6 (95% CI 3.30–29.84), 11.2 (95% CI 9.46–12.88), and 3.9 months (95% CI 3.01–4.85 months), respectively (Fig. 1). The MST was 18 months (95% CI 15.36–20.18 months) after the diagnosis of brain metastases and 81 months (95% CI 72.64–88.70 months) after the initial primary diagnosis. The MST of patients who had received prior WBRT (227 patients [65%]) was 10.3 months; and for patients without prior WBRT (123 patients [35%]), 14.2 months. The use of WBRT was significantly associated with a greater number of brain metastases (p < 0.0001, Mann-Whitney U-test) as well as a larger total tumor volume (p < 0.0001, Mann-Whitney U-test).

On univariate analysis, factors associated with a longer survival time included controlled extracranial disease (p < 0.0001), lower RPA class (p = 0.0004), a KPS score of 80 or higher (p < 0.0001), < 5 brain metastases (p = 0.049; Fig. 2), no prior WBRT (p = 0.032), lower total tumor volume (as a continuous variable, p = 0.021; or dichotomized to > 8 cm³, p = 0.035), smaller volume of the largest tumor in each patient (continuous variable, p = 0.024), presence of deep (nonlobar) cerebral metastases (p = 0.002), and presence of brainstem metastases (p = 0.002; Table 2). The median survival of those with (227 patients) and without (123 patients) prior WBRT was 10.3 (95% CI 7.87–12.73) and 14.2 months (95% CI 9.53–18.81 months), respectively.

Tumors from 119 (50%) of 240 patients who were evaluated for estrogen receptor status were positive. One hundred fourteen (59%) of 192 patients who were evaluated for HER2/neu status demonstrated overexpression. Estrogen receptor status was not associated with patient survival (p = 0.428). Patients with HER2/neu overexpression had 6-, 12-, 24-, and 36-month OSs of 79%, 59%, 42%, and 31%, respectively. The MST of patients with HER2/neu overexpression was 14.5 months after SRS (95% CI 11.43–17.63 months). Patients without HER2/neu overexpression had a 6-, 12-, 24-, and 36-month OSs of 57%, 45%, 18%, and 7%, respectively, and a median survival of 8.3 months (95% CI 3.03–13.57 months) after SRS. Thus, patients with HER2/neu overexpression lived longer (p < 0.0005; Fig. 3).

On multivariate analysis, factors associated with longer survival times included controlled extracranial disease (p = 0.002, HR = 1.887), KPS score ≥ 70 (p = 0.003, HR = 2.628), smaller total tumor volume (p = 0.002, HR = 1.028), absence of brainstem metastases (p = 0.042, HR = 1.880), and overexpression of HER2/neu (p < 0.0005, HR = 1.932; Table 3).

New Remote Brain Tumors

Follow-up imaging was available for 266 patients, and new brain metastases were found on imaging studies in 125 patients (47%). The survival rate without a new tumor after SRS was 72%, 48%, 34%, and 22% at 6, 12, 24, and 36 months, respectively. The median time free from another tumor was 11.6 months (95% CI 10.12–13.02 months). Fifty-five (59%) of 94 patients who did not receive WBRT had new remote brain metastases, whereas...
Stereotactic radiosurgery for brain metastasis from breast cancer

71 (41%) of 172 patients who did receive WBRT had new remote brain metastases. According to the Fisher exact test, prior WBRT was associated with a lower rate of new brain disease (p = 0.012); however, the median time to the discovery of a new remote tumor was 11.6 or 11.5 months for patients who had no prior or prior WBRT (p = 0.4), respectively.

On univariate analysis, factors associated with a longer time without new brain disease included controlled extracranial disease (p = 0.005), lower number of metastases at the time of SRS (as a continuous variable, p = 0.010; dichotomized to ≤ 3 metastases, p = 0.076; or dichotomized to < 5 metastases, p = 0.011), and absence of lung metastases (p = 0.030; Table 2). The median time free from new brain disease if the presentation was a solitary tumor, 2–4 tumors, and 5 or more tumors before GKS was 15.3, 11.4, and 8.8 months, respectively (Fig. 4).

**TABLE 2: Univariate analyses of patient survival, distant tumor control, and local tumor control**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Survival</th>
<th>Distant Tumor Control</th>
<th>Local Tumor Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient age, ≥ vs &lt;45 yrs</td>
<td>0.495</td>
<td>0.707</td>
<td>0.953</td>
</tr>
<tr>
<td>interval btwn primary disease &amp; brain metastases, ≥ vs &lt;45 mos</td>
<td>0.142</td>
<td>0.400</td>
<td>0.956</td>
</tr>
<tr>
<td>extracranial disease status, active vs controlled</td>
<td>&lt;0.0001</td>
<td>0.005</td>
<td>0.795</td>
</tr>
<tr>
<td>RPA class, 1 vs 2 vs 3†</td>
<td>0.0004</td>
<td>0.219</td>
<td>0.030</td>
</tr>
<tr>
<td>KPS score, 80–100 vs ≤70</td>
<td>&lt;0.0001</td>
<td>0.541</td>
<td>0.048</td>
</tr>
<tr>
<td>no. of metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>continuous no.†</td>
<td>0.004</td>
<td>0.010</td>
<td>0.001</td>
</tr>
<tr>
<td>1 vs ≥2</td>
<td>0.412</td>
<td>0.066</td>
<td>0.025</td>
</tr>
<tr>
<td>1–3 vs ≥4</td>
<td>0.316</td>
<td>0.076</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1–4 vs ≥5</td>
<td>0.049</td>
<td>0.011</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>neurological symptoms at radiosurgery, yes vs no</td>
<td>0.475</td>
<td>0.110</td>
<td>0.450</td>
</tr>
<tr>
<td>prior WBRT, yes vs no</td>
<td>0.032</td>
<td>0.367</td>
<td>0.003</td>
</tr>
<tr>
<td>prior chemotherapy, yes vs no</td>
<td>0.510</td>
<td>0.723</td>
<td>0.561</td>
</tr>
<tr>
<td>total radiosurgery vol, continuous no.†</td>
<td>0.021</td>
<td>0.970</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>largest target vol, continuous no.†</td>
<td>0.024</td>
<td>0.307</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>total radiosurgery vol, ≥ vs &lt;8 cm³</td>
<td>0.035</td>
<td>0.437</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>presence of metastases, yes vs no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deep cerebral</td>
<td>0.002</td>
<td>0.068</td>
<td>0.135</td>
</tr>
<tr>
<td>cerebellar</td>
<td>0.575</td>
<td>0.441</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>brainstem</td>
<td>0.002</td>
<td>0.050</td>
<td>0.100</td>
</tr>
<tr>
<td>lung</td>
<td>0.927</td>
<td>0.030</td>
<td>0.612</td>
</tr>
<tr>
<td>bone</td>
<td>0.081</td>
<td>0.897</td>
<td>0.075</td>
</tr>
<tr>
<td>liver</td>
<td>0.747</td>
<td>0.728</td>
<td>0.211</td>
</tr>
<tr>
<td>ER positive, yes vs no‡</td>
<td>0.428</td>
<td>0.410</td>
<td>0.339</td>
</tr>
<tr>
<td>HER2/neu overexpression, yes vs no§</td>
<td>&lt;0.0005</td>
<td>0.296</td>
<td>0.781</td>
</tr>
<tr>
<td>tumor margin dose, ≥ vs &lt;17 Gy</td>
<td>NA</td>
<td>NA</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>target vol for each tumor, ≥ vs &lt;3 cm³</td>
<td>NA</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* ER = estrogen receptor; NA = not available.
† Using Cox proportional hazard model for the continuous number, but the log-rank test for the other parameters.
‡ In 119 of 240 patients.
§ In 114 of 192 patients.
extracranial disease (p < 0.0005, HR = 2.075), lower number of metastases at the time of SRS (p = 0.007, HR = 1.913; Table 3). Estrogen receptor status and HER2/neu status were not associated with the development of new remote brain metastases.

Local Tumor Control

Two hundred sixty-six patients with follow-up imaging studies had 1115 tumors (managed in a total of 525 radiosurgical procedures). Follow-up imaging occurred at a median of 7.3 months (range 0.4–144 months). The best response obtained was complete disappearance of 217 tumors (19%). Regression was noted in 513 tumors (46%), no change was found in 272 lesions (24%), and progression was documented in 113 (10%). Progression-free survival after SRS was 90%, 71%, 58%, and 50% at 6, 12, 24, and 36 months, respectively.

On univariate analysis, factors associated with longer PFS included a lower RPA class (p = 0.030), fewer metastases at the time of SRS (as a continuous variable, p < 0.0001; dichotomized to solitary metastasis, p = 0.025; or dichotomized to ≤ 3 metastases, p < 0.0001), no prior WBRT (p = 0.003), smaller total tumor volume (as a continuous variable, p < 0.0001; or dichotomized to < 8 cm³, p < 0.0005), smaller volume for the largest tumor in each patient (continuous variable, p < 0.0001), presence of cerebellar metastases (p < 0.0001), margin dose ≥ 17 Gy (p < 0.0005), and each tumor volume < 3 cm³ (p < 0.0001; Table 2).

On multivariate analysis, factors associated with a longer PFS included a KPS score ≥ 70 (p = 0.019, HR = 3.432), no prior WBRT (p = 0.015, HR = 2.053), and smaller total tumor volume (p < 0.0001, HR = 1.053; Table 3).

Clinical Outcomes

Clinical follow-up information was available in 275 patients. Note that this information was unavailable in 75 patients because of the shorter interval between SRS and death. There were no deaths after SRS. Sixteen patients (6%) had symptomatic AREs. Symptoms resolved completely after a temporary course of corticosteroids in 13 patients. Ten of 13 patients had hemiparesis with headache (RTOG/EORTC Grade 3). The remaining 3 patients (1.1%), who had a declined level of consciousness, required a resection (RTOG/EORTC Grade 4); 2 of these patients had confirmed radiation necrosis, and 1 had mixed necrosis and persistent tumor. Asymptomatic AREs were noted in another 14 patients (5%). In total, suspected or confirmed AREs were detected in 11% of patients. Adverse radiation effects were noted at a median of 6 months (range 1.6–74.5 months) after treatment. On univariate analysis, a larger total tumor volume (continuous variable, p = 0.012) and a larger-volume tumor (continuous variable, p < 0.0005) were significantly associated with a higher incidence of AREs. Prior WBRT, patient age, tumor margin dose, number of tumors, and tumor location were not associated with the incidence of AREs.

Preexisting neurological symptoms improved in 54 patients (20%), including headache (8 patients [3%]), focal neurological deficits (43 patients [16%]), and cognitive dysfunction (3 patients [1%]). Neurological symptoms remained unchanged in 83 patients (30%). All 87 patients who had no neurological symptoms at the time of SRS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Survival p Value (HR)</th>
<th>Distant Tumor Control p Value (HR)</th>
<th>Local Tumor Control p Value (HR)</th>
<th>Better Prognosis Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>controlled extracranial disease</td>
<td>0.002 (1.887)</td>
<td>&lt;0.0005 (2.075)</td>
<td>NA</td>
<td>controlled</td>
</tr>
<tr>
<td>KPS score ≥70</td>
<td>0.003 (2.628)</td>
<td>NA</td>
<td>0.019 (3.472)</td>
<td>higher score</td>
</tr>
<tr>
<td>no. of metastases</td>
<td>0.760 (NA)</td>
<td>0.007 (1.040)</td>
<td>0.522 (NA)</td>
<td>larger no.</td>
</tr>
<tr>
<td>no prior WBRT</td>
<td>0.275 (NA)</td>
<td>NA</td>
<td>0.015 (2.053)</td>
<td>no</td>
</tr>
<tr>
<td>total radiosurgery volume</td>
<td>0.002 (1.028)</td>
<td>NA</td>
<td>&lt;0.0001 (1.053)</td>
<td>smaller</td>
</tr>
<tr>
<td>absence of brainstem metastases</td>
<td>0.042 (1.880)</td>
<td>0.243 (NA)</td>
<td>0.076 (NA)</td>
<td>absent</td>
</tr>
<tr>
<td>absence of lung metastases</td>
<td>0.370 (NA)</td>
<td>0.001 (1.913)</td>
<td>NA</td>
<td>absent</td>
</tr>
<tr>
<td>HER2/neu overexpression</td>
<td>&lt;0.0005 (1.932)</td>
<td>NA</td>
<td>NA</td>
<td>yes</td>
</tr>
</tbody>
</table>
remained symptom free afterward. Preexisting neurological symptoms worsened in 51 patients (19%): neurological deterioration due to new brain metastases, 21 patients; local tumor control failure, 26 patients; and AREs, 4 patients. New focal neurological deficits associated with new brain metastases developed in 11 patients with no neurological symptoms at the time of SRS.

**Further Management After Radiosurgery**

After SRS, 11 patients (4%) required craniotomy and resection due to local tumor progression (8 patients) or AREs (3 patients). One hundred eight patients (39%) required additional repeat SRS, which was performed for the management of delayed tumor progression (31 patients [11%]), new brain metastases (69 patients [25%]), or both (8 patients [3%]). Thirty-nine patients (14%) underwent WBRT after SRS because of the development of multiple new brain metastases.

**Discussion**

The development of 1 or more brain metastases in a patient with breast cancer is an ominous event. Treatment options include resection, WBRT, and SRS, either alone or in combination. Historically, breast carcinoma has been considered a relatively radiosensitive tumor. Accordingly, WBRT has been advocated for many patients. More recently, however, the role of WBRT has been called into question because of the risk of delayed neurocognitive dysfunction in longer-term survivors. In the short term, most patients suffer fatigue and hair loss. Systemic treatment with chemotherapy is typically suspended during WBRT. Resection remains of value for tumors with symptomatic mass effect but must be followed by adjuvant WBRT or tumor bed radiosurgery to improve local tumor control. Magnetic resonance imaging as a brain staging tool often detects brain metastases that are small or asymptomatic. Stereotactic radiosurgery has been used with increasing frequency in patients with brain metastases regardless of the histological type. Several retrospective studies have compared outcomes in patients treated using SRS with or without WBRT. Those studies have generally shown that recurrence rates are reduced by adjuvant WBRT, although total survival is not increased. Aoyama et al. compared the results of SRS alone versus SRS plus WBRT. They noted no improvement in survival for patients with 1–4 brain metastases, although intracranial progression occurred more frequently in those who had not received WBRT. Chang et al. compared the neurocognitive results of SRS alone versus SRS plus WBRT in a randomized controlled trial of 1–3 newly diagnosed brain metastases. They found that patients who underwent SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months as compared with the group that had received SRS alone. The authors recommended that radiosurgery alone combined with close clinical monitoring should be the preferred approach in such patients. Surgical salvage should be used for local failures, and SRS or WBRT should be used for distant failures as indicated.

Patients with brain metastases from breast cancer may live longer than patients with other metastatic cancers because of improving responses to extracranial disease management. The longer survival of these patients has necessitated the study of this cohort separately from other cohorts with heterogeneous brain metastases. To date, the overall prognosis of patients with brain metastases from breast carcinoma remains unclear, due in part to vaguely defined selection criteria, insufficient follow-up data, and variations in the treatment regimens.

The unique molecular features of breast cancer allow for tailored therapeutic approaches that might improve the response of both extra- and intracranial disease manifestations (using agents such as trastuzumab, lapatinib, and aromatase inhibitors).

**Patient Survival**

Median survival times varying from 8 to 19 months have been reported by other centers after SRS with or without WBRT in patients with brain metastases from breast carcinoma (Table 4). Muacevic et al. documented 151 patients with 620 brain metastases. The MST after SRS was 10 months. A KPS score > 70 and an RPA Class 1 were related to prolonged survival. Patients with RPA Class 1, 2, and 3 survived 35, 9, and 8 months, respectively. The reason for such a large difference between RPA Class 1 and Class 2 patients is unclear. In our series, the median survivals were 17 months for RPA Class 1 and 11 months for Class 2 patients. In a recent series, Kased et al. described their results for 176 patients with breast cancer metastases. The MST was 16.0 months for 95 patients with newly diagnosed disease and 11.7 months for 81 patients with recurrent brain metastases. Longer survival was associated with an age < 50 years, a KPS score ≥ 70, primary tumor control, estrogen receptor positivity, and HER2/neu overexpression. In our series,
HER2/neu overexpression was also significantly associated with longer survival (p < 0.0005, HR = 2.025). D’Amico et al.11 reported that HER2/neu overexpression was associated with longer patient survival and a longer time to brain metastases than HER2/neu-negative disease.

DiLuna et al.12 described their results in 334 patients with intracranial brain metastases from a variety of primary cancer origins. In that series, 16% of patients had breast cancer. In the entire series, survival was significantly better in patients who had 1–3 metastases (MST = 8.5 months) as compared with those who had > 4 metastases (MST = 6.3 months; p = 0.03). In our study, patient survival was significantly longer in those who had < 5 brain metastases (MST = 12.2 months) compared with patients who had > 5 metastases (MST = 10.8 months; p = 0.049).

In our series, a larger total tumor volume per patient and an increased volume of the largest tumor were significantly associated with worse patient survival. Akyurek et al.1 also found that a smaller target volume significantly prolonged survival in patients with recurrent breast cancer metastases, but not in patients with newly diagnosed disease. The possibility that smaller tumors were treated with higher doses may be a confounding variable. Perhaps, not surprisingly, prior WBRT was significantly associated with shorter patient survival given the likelihood that patients who received WBRT had both a greater number of brain metastases (p < 0.0001) and a larger total tumor volume (p < 0.0001). Whenever possible, we treated patients with more favorable prognoses by using SRS alone and reserving WBRT for patients with multiple metastases (typically > 4). There is current interest in using SRS alone in all patients regardless of the number of tumors. Patients undergo repeat MR imaging at 2 months. If new tumors are found, WBRT or salvage SRS can be offered. Since many patients are living longer and are at risk for late leptomeningeal carcinomatosis (for which WBRT is the preferred treatment), we prefer to save WBRT for a time when it is truly required. A randomized prospective study may help to define the role of WBRT in patients with brain metastases from breast cancer, emphasizing survival, tumor control, complications, and the risk of neurocognitive dysfunction.

**Distant Tumor Control**

New brain metastases developed after SRS in 47% of the patients in our series. We found that prior WBRT was associated with a lower risk of new brain metastasis, although new disease requiring management still developed in 42% of patients. Factors associated with the development of distant new brain tumors were active extracranial disease and a higher number of brain metastases at the time of SRS, perhaps related to more active systemic disease from the onset. Akyurek et al.1 reported that active primary disease, a younger age, and negative estrogen receptor status was associated with the development of distant new brain metastases. In our series, estrogen receptor status and HER2/neu overexpression were not associated with distant new brain metastases; however, we did find that the presence of lung metastases was significantly associated with distant new brain metastases (p = 0.001, HR = 1.93). Patients with lung metastases from breast cancer had 2 times the risk of distant new brain tumors as compared with patients without them. Prior WBRT was as-

### TABLE 4: Literature review of studies on radiosurgically treated brain metastases from breast cancer*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients (Treatment)</th>
<th>MST (mos)</th>
<th>PFS</th>
<th>Survival Prognostic Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendola et al., 2000</td>
<td>68 (GKS)</td>
<td>7.8</td>
<td>94%</td>
<td>none</td>
</tr>
<tr>
<td>Firlik et al., 2000</td>
<td>30 (GKS)</td>
<td>13</td>
<td>93%</td>
<td>smaller tumor volume, solitary metastases</td>
</tr>
<tr>
<td>Lederman et al., 2001</td>
<td>60 (LINAC)</td>
<td>7.5</td>
<td>NA</td>
<td>≤2 brain metastases, no other metastatic disease, better functional status</td>
</tr>
<tr>
<td>Muacevic et al., 2004</td>
<td>151 (GKS)</td>
<td>10</td>
<td>94%</td>
<td>KPS &gt;70, RPA Class 1, age ≥65 yrs</td>
</tr>
<tr>
<td>Combs et al., 2004</td>
<td>62 (LINAC)</td>
<td>15</td>
<td>9 mos†</td>
<td>age &lt;40 yrs, SRS alone</td>
</tr>
<tr>
<td>Goyal et al., 2005</td>
<td>43 (GKS)</td>
<td>13</td>
<td>10 mos†</td>
<td>solitary metastasis, high KPS score, high SIR, active visceral disease</td>
</tr>
<tr>
<td>Akyurek et al., 2007</td>
<td>49 (LINAC)</td>
<td>19</td>
<td>1-yr: 78%; 2-yr: 48%</td>
<td>KPS score ≥90, SIR ≥6, postmenopausal status, ER positive</td>
</tr>
<tr>
<td>Kased et al., 2009</td>
<td>95 (GKS)‡</td>
<td>16.0</td>
<td>1-yr: 90%; 2-yr: 83%</td>
<td>KPS score ≥70, primary control, ER positive, HER2/neu overexpression</td>
</tr>
<tr>
<td>present study</td>
<td>350 (GKS)§</td>
<td>11.2</td>
<td>1-yr: 71%; 2-yr: 58%</td>
<td>controlled extracranial disease, low RPA class, high KPS score, smaller no. of brain metastases, smaller total brain tumor vol, smaller largest tumor vol, presence of deep cerebral or brain-stem metastases, HER2/neu overexpression</td>
</tr>
</tbody>
</table>

*LINAC = linear accelerator; SIR = standardized incidence ratio.
† Median.
‡ Newly diagnosed.
§ Recurrent.
Stereotactic radiosurgery for brain metastasis from breast cancer

associated with a lower rate of new brain disease, although it did not affect the interval between GKS and new brain disease.

Local Tumor Control

Sustained local tumor control was achieved in 90% of tumors and 75% of patients. Progression-free survival after SRS was 90% at 6 months and 71% at 1 year. According to previous reports, 1-year PFS varies from 73% to 90%. We found that factors associated with a longer PFS included a better RPA class and fewer metastases at the time of SRS. Progression-free survival is better in patients who have not undergone prior WBRT. Patients without prior WBRT have a significantly larger number of brain metastases (p < 0.0001, Mann-Whitney U-test) and a larger total tumor volume (p < 0.0001, Mann-Whitney U-test) than patients with prior WBRT. These outcomes might have made prior WBRT a predictor of longer PFS.

Adverse Radiation Effects

Adverse radiation effects were detected on follow-up imaging in 11% of patients, one-half (6%) with neurological symptoms. A larger total tumor volume (p = 0.012) and the volume of the largest tumor (p < 0.0005) were significantly associated with a higher incidence of AREs. Kased et al.22 also reported that symptomatic radiation effects occurred in 6% of patients, and half of these cases required resection. Mucavevic et al. described symptomatic radiation effects after SRS in 11% of patients and asymptomatic AREs in 9%. In the present study, neurological symptoms remained stable or improved in 82% of the patients, and 64% of patients were gradually weaned from corticosteroids after SRS if they had been using them beforehand.

Conclusions

Stereotactic radiosurgery is an effective management option for primary and recurrent brain metastases from breast cancer. Radiosurgery provides early and safe brain tumor management for the majority of presenting patients and allows extracranial management to continue uninterrupted. Note, however, that total survival is related to the control of extracranial disease. The current role and timing of WBRT for breast cancer brain metastases remains unclear. A prospective study is needed to better define the benefit and risks of WBRT in patients with brain metastases from breast cancer.

Disclosure

Drs. Kondziolka, Niranjan, and Lunsford are consultants for, and Dr. Lunsford is a stockholder in, AB Elekta. The work described herein was funded by a grant from the Osaka Medical Research Foundation for Incurable Diseases (H.K.).

Author contributions to the study and manuscript preparation include the following. Conception and design: Kondziolka, Kano, Bruksy, Lunsford. Acquisition of data: Kano, Harrison, Yang, Liew. Analysis and interpretation of data: Kano. Drafting the article: Kondziolka, Kano, Harrison, Yang, Bruksy, Lunsford. Critically revising the article: Kondziolka, Kano, Bruksy, Flickinger, Lunsford. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Kano. Study supervision: Kondziolka, Kano.

References