Brain metastasis, which is a frequent cause of morbidity and mortality, occurs in 20% of patients with primary breast cancer. This incidence is increasing because of improvements in neuroimaging screening and systemic treatment options, which prolong survival and thus allow for the spread of cancer to the brain. Therefore, the management of brain metastasis is of major concern to further prolong survival and maintain quality of life in these patients.

The primary treatment modality for brain metastasis, particularly for small multiple lesions, has been WBRT, irrespective of the number of lesions. Whole-brain radiation treatment provides effective tumor control and increased patient survival. However, long-term cognitive deficits are a major side effect of this procedure, affecting the quality of life in survivors, and thus, cognitive deficits constitute an emerging issue in the management of brain metastasis from breast cancer. Radiosurgery has become an alternative treatment option for small metastases.
tases; it is effective for tumor control and improved survival.\textsuperscript{1,2,5,8,11,13,16,18,22} The advantages that radiosurgery has over WBRT in the avoidance of cognitive decline are due to targeted radiation dose distributions, but the number of lesions treatable by the initial radiosurgical procedure is unclear, particularly if potential emergence of new lesions in the nonirradiated brain is considered.

Another issue in the management of brain metastasis from breast cancer is the introduction of targeted systemic therapeutic agents such as trastuzumab and lapatinib. The survival of patients with breast cancer is affected by the histological phenotype of the tumor, including expression of hormone receptors and visceral metastasis.\textsuperscript{23,29,31,35,36} These new chemotherapeutic agents have been shown to promote better survival in patients with breast cancer, especially in those harboring tumors expressing HER2.\textsuperscript{4,6,19,26,27,35} However, no similar analysis has been undertaken in patients with brain metastasis from breast cancer.

In this study, we retrospectively assessed the efficacy and prognostic factors of GKS as an initial treatment for local tumor control and survival in patients harboring brain metastases (up to 10 metastases) from primary breast cancer, and we also analyzed the impact of the tumor’s histological phenotype to further assess the efficacy of radiosurgery and new chemotherapeutic agents.

**Methods**

A retrospective review of patients treated by GKS for brain metastasis from primary breast cancer between April 1992 and December 2008 at Yokohama Rosai Hospital identified 101 women meeting the study criteria. The inclusion criteria were the following: up to 10 metastatic tumors in the brain; maximum tumor diameter < 3 cm on axial, coronal, and sagittal MR images; and total tumor volume < 15 cm\(^3\). The exclusion criteria were as follows: pre-GKS KPS score < 70 without a neurofunctional deficit caused by brain metastases; uncontrolled primary breast cancer and/or extracranial metastatic disease; presence of leptomeningeal seeding on Gd-enhanced MR images; prior WBRT and/or resection for brain metastases; and secondary breast cancer. The patients ranged in age from 32 to 83 years (mean 56.6 ± 1.2 years), and 600 metastatic lesions were identified in this cohort of patients.

A histological diagnosis of primary breast cancer had been determined for all patients based on findings from a core needle biopsy or resection of breast tumor. An immunohistochemical analysis of 3 receptors—ER, PgR, and HER2—was performed for all patients, and the patients were grouped into 1 of 3 biological subtypes: HER2-positive (score of 3+ or a gene copy ratio of ≥ 2 for immunohistochemistry or fluorescent in situ hybridization), luminal (ER-positive and/or PgR-positive, HER2-negative), and triple-negative (ER-negative, PgR-negative, HER2-negative). Brain metastases were categorized as the presence of metastatic disease in the brain detected by MR imaging or CT.

Stereotactic radiosurgery was performed using the Leksell Gamma Knife (model B, Elekta AB) and either GammaPlan treatment software or the KULA dose-planning system (Elekta AB) to create the radiosurgery plans based on Gd-enhanced T1-weighted MR imaging with 2-mm slices and no gaps. After the initial radiosurgical procedure, clinical and MR imaging examinations were scheduled every 1–3 months, and documentation of these examinations was received directly or from referring physicians.

The response to GKS was evaluated by measuring the tumor size on follow-up MR images. The first author (S.M.) measured tumor sizes in axial or coronal MR images. The effect of GKS on metastatic lesions was classified as complete remission (complete disappearance of lesion[s]); partial remission (> 50% decrease in tumor size but not lesion disappearance); no change (≤ 50% decrease in tumor size); and progression (> 50% increase in tumor size). Complete remission, partial remission, and no change were considered to indicate tumor growth control.

The end point of overall survival time was the date of the patient’s death or last follow-up examination. Neurological death was defined as patient death related to an uncontrolled progression of brain metastases identified as tumor recurrence or carcinomatous meningitis. A new lesion was considered to be the development of a new parenchymal or leptomeningeal lesion of the brain at a site other than those of lesions present at the initial GKS. Brain metastasis–free interval time was measured from the date of primary breast cancer diagnosis to the date of the first brain metastasis diagnosis.

All statistics were calculated using a statistical software package for predictive analytics (PASW version 17.0, SPSS Inc.). Significant factors affecting tumor growth control were calculated by logistic regression analysis. Overall, new lesion–free, and neurological survival times were estimated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was developed to identify factors influencing these survival times. A p value < 0.05 was considered to be statistically significant.

**Results**

**Patient Population**

The 101 patients underwent a total of 160 GKS procedures (mean 1.6 ± 1.1 procedures, range 1–7 procedures/patient) for a total of 600 lesions (mean 3.1 ± 2.5 tumors/patient), including 354 lesions at the initial treatment and 246 lesions at additional treatments. Patient characteristics at the initial GKS are listed in Table 1 for the entire population and for 2 separate patient groups: 76 patients with 4 or fewer lesions and 25 patients with 5 or more lesions. At the time of GKS, 22 patients had only brain metastases, and 79 patients also had extracranial metastatic disease located in the lung (50 patients), bone (50 patients), liver (25 patients), and other organs (9 patients). Seventy-five patients had neurological symptoms caused by brain metastases; these were usually related to acceleration of intracranial pressure. The KPS score was 70 or higher in 88 patients, 60 in 4 patients, and 50 in 9 patients who had slight hemiplegia or ataxia caused by intracranial disease. The mean brain disease–free interval from
primary tumor diagnosis was 60.5 ± 5.6 months (median 42 months, range 0–300 months). Synchronous brain metastases (those found within 3 months from the diagnosis of primary breast cancer) were found in 2 patients, and metachronous brain metastases (those found > 3 months from the diagnosis of primary breast cancer) were identified in 99 patients.

Local Tumor Control

The mean tumor volume calculated at the time of GKS was 3.7 ± 3.3 cm³ (range 0.016–14.3 cm³). Four hundred forty brain tumors were supratentorial (73.3%), and 160 brain tumors were infratentorial (26.7%). The dose delivered to the tumor margin was 8–30 Gy (mean 19.0 ± 3.4 Gy, median 19 Gy), and the maximum dose was 10.2–55.6 Gy (mean 29.6 ± 6.7 Gy, median 30 Gy). The follow-up period after initial GKS ranged from 1 to 73 months (mean 9.6 months, median 7 months). Neuroimaging studies showed complete remission in 214 tumors (35.7%), partial remission in 280 tumors (46.7%), no change in 88 tumors (14.7%), and progression in 18 tumors (3%). Therefore, the local tumor control rate, which was defined as suppression of tumor growth, was 97%, and the tumor response rate with volume reduction was 82.3%. Follow-up MR imaging showed at least 4 lesions representing a late complication related to GKS; these were identified as radiation necrosis using ²⁰¹Tl Cl single-photon emission CT and were treated with corticosteroid therapy. The prognostic factors for local tumor control included age (≥ 65 or < 65 years), tumor volume (continuous variable), margin dose (continuous variable), tumor location (supratentorial or infratentorial), number of treated lesions (continuous variable), and initial or additional treatment. A univariate analysis indicated that larger tumor volume and lower margin dose were significantly correlated with unfavorable outcome (p = 0.001). Furthermore, these 2 factors were significantly correlated with poor local tumor control using a multivariate analysis (p = 0.001).

Overall Survival

The median overall survival time was 13 months (range 1–126 months) after the diagnosis of brain metastases and initial GKS treatment (Fig. 1), and 73 months (range 8–328 months) after the diagnosis of primary breast cancer. Regarding the number of lesions, a univariate analysis showed that only single metastasis was significant (p = 0.030) (Table 2). The prognostic factors for overall survival after GKS included patient age (≥ 65 or < 65 years), number of brain metastatic lesions at GKS (1 or ≥ 2), total tumor volume (≥ 10 or < 10 cm³), neurological symptom (symptomatic or occult), pre-GKS KPS score (≥ 80 or < 80), extracranial metastases (present or absent), and primary breast cancer phenotype (HER2-positive type or others [luminal and triple-negative types]). A multivariate analysis showed that the presence of extracranial metastatic disease at the time of the initial GKS (p = 0.041) and phenotype other than HER2-positive (p = 0.001) were significantly correlated with adverse overall survival time (Table 3). The “good prognosis group,” consisting of 10 patients with no adverse prognostic factors, had a longer mean duration of survival, 60 months, than the “poor prognosis group,” which consisted of 91 patients with a mean duration of survival of 12 months (p = 0.001).

New Lesion–Free Survival

New brain metastases developed in 47 patients after the initial GKS, and additional WBRT and/or GKS

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**TABLE 1: Patient characteristics at the time of the initial GKS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>101</td>
</tr>
<tr>
<td>age (yrs) mean ± SD</td>
<td>56.6 ± 1.2</td>
</tr>
<tr>
<td>range</td>
<td>32–83</td>
</tr>
<tr>
<td>no. of tumors (mean ± SD)</td>
<td>3.1 ± 2.5</td>
</tr>
<tr>
<td>total tumor volume (cm³) mean ± SD</td>
<td>3.7 ± 3.3</td>
</tr>
<tr>
<td>range</td>
<td>0.016–14.3</td>
</tr>
<tr>
<td>presence of extracranial disease</td>
<td>79 (78.2)</td>
</tr>
<tr>
<td>neurological symptom(s)</td>
<td>75 (74.3)</td>
</tr>
<tr>
<td>brain disease–free interval from primary diagnosis (mos) mean ± SD</td>
<td>60.5 ± 5.6</td>
</tr>
<tr>
<td>range</td>
<td>0–300</td>
</tr>
<tr>
<td>breast cancer phenotype</td>
<td>HER2-positive</td>
</tr>
<tr>
<td></td>
<td>luminal</td>
</tr>
<tr>
<td></td>
<td>triple-negative</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated.
were performed in 39 patients. The median new lesion–free survival time after the initial GKS was 9 months (range 1–48 months) (Fig. 2). Survival rates were 74.8% at 6 months and 52.1% at 1 year. Regarding the number of lesions, patients with 4 or fewer lesions had significantly more favorable outcomes (Table 2). Calculation of the proportional risk of development of new lesions after GKS, using a multivariate analysis, showed that younger patient age (< 65 years; p = 0.008) and larger number of brain metastases (≥ 5; p = 0.007) were significantly correlated with adverse outcome (Table 4). An analysis of the impact of additional radiation therapy on subsequent detection of new brain metastases showed that patients needing additional treatment had significantly longer overall (p = 0.001) and neurological (p = 0.038) survival times after developing new brain metastases than patients who received conservative therapy. Calculation of the risk of subsequent development of new brain metastases affecting overall survival after initial GKS showed no statistical significance (p = 0.175) and no significant difference between patients with 1–4 (p = 0.249) and 5–10 (p = 0.450) brain metastases.

**Neurological Survival**

At the time of the last follow-up, 78 patients had died of brain metastasis. The causes of death were systemic disease in 68 patients and neurological disease in 10 patients. The survival rate at 1 year was 93.9%. An evaluation of prognostic factors for neurological survival showed only lower KPS score (< 80; p = 0.009) was significantly correlated with poor survival. The number of brain metastases had no effect on neurological survival (Table 2). A comparison of 2 groups of patients, patients who died of systemic disease and those who died of neurological disease as an end point, found a significant difference in new lesion–free survival (p = 0.001), with a higher recurrence rate associated with neurological death, but no difference in overall survival after the initial GKS (p = 0.214).

**Breast Cancer Subtype**

The histological types of primary breast cancer included invasive ductal carcinoma in 90 patients, infiltrating lobular carcinoma in 6 patients, and other types in 5 patients. The phenotypes were HER2 positive in 28 patients, luminal in 37 patients, and triple negative in 36 patients (Table 1). Prior chemotherapy and endocrine therapy were performed in all patients with luminal tumors, and all patients with HER2-positive tumors continued to receive chemotherapy with trastuzumab, which is a high-affinity humanized murine monoclonal antibody, before and after diagnosis of brain metastases. Patients whose lesions had the HER2-positive phenotype had longer survival times from detection of the first brain metastasis (median 25 months) than patients whose lesions had the luminal (median 12 months; p < 0.0001) or triple-negative

<table>
<thead>
<tr>
<th>No. of Tumors</th>
<th>Overall Survival</th>
<th>New Lesion–Free Survival</th>
<th>Neurological Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value†</td>
<td>HR</td>
<td>p Value†</td>
</tr>
<tr>
<td>1</td>
<td>0.030‡</td>
<td>4.431</td>
<td>0.011‡</td>
</tr>
<tr>
<td>≤2</td>
<td>0.385</td>
<td>0.718</td>
<td>0.007‡</td>
</tr>
<tr>
<td>≤3</td>
<td>0.665</td>
<td>0.179</td>
<td>0.004‡</td>
</tr>
<tr>
<td>≤4</td>
<td>0.823</td>
<td>0.048</td>
<td>0.001‡</td>
</tr>
<tr>
<td>≤5</td>
<td>0.846</td>
<td>0.036</td>
<td>0.076</td>
</tr>
<tr>
<td>≤6</td>
<td>0.793</td>
<td>0.066</td>
<td>0.181</td>
</tr>
<tr>
<td>≤7</td>
<td>0.268</td>
<td>1.143</td>
<td>0.117</td>
</tr>
<tr>
<td>≤8</td>
<td>0.602</td>
<td>0.257</td>
<td>0.122</td>
</tr>
<tr>
<td>≤9</td>
<td>0.170</td>
<td>1.683</td>
<td>0.845</td>
</tr>
</tbody>
</table>

* HR = hazard ratio.
† Based on the log-rank test.
‡ Significant difference at p < 0.05.
GKS for metastatic brain tumors from primary breast cancer

Discussion

The results of this study showed that radiosurgery is effective for local tumor control (97% control rate). The analyses of prognostic factors for local tumor control showed that smaller tumor volume at the time of GKS and larger delivered margin dose were significant factors, irrespective of the number of lesions up to 10. The number of lesions did not affect patient overall and neurological survival times. New metastatic lesions appeared in approximately 50% of patients at 1 year post-GKS, as expected, but did not affect overall survival because of subsequent salvage radiosurgery. The other major prognostic factors for overall survival were the presence of extracranial disease and tumor phenotype.

The effectiveness of radiosurgery for brain metastasis has been well established, and good tumor control rates have been reported for metastatic lesions from various primary tumors.28,34,37 Because breast cancer is relatively sensitive to radiotherapy, similar control rates would be expected if tumor size and dose planning fulfill the optimal conditions. The major issue for indication for radiosurgery for brain metastasis is how many lesions can be treated as an initial treatment. The number of lesions is not a limiting factor for radiosurgery if each lesion is small and adequate doses can be delivered. The results of this study showed that simultaneous treatment of up to 10 lesions provided good tumor control regardless of the number of lesions. The disadvantage of radiosurgery, compared with WBRT, is the subsequent appearance of new lesions in the nonradiated field. Indeed, approximately 50% of our patients developed 1 or more new metastatic lesions at 1 year. This issue should be thoroughly evaluated when considering radiosurgery for multiple metastatic lesions.

The theoretical justification for WBRT, particularly for multiple brain metastases, is suppression of potential micro-metastatic lesions not identified by neuroimaging. Whole-brain radiation treatment has been considered the treatment of choice for most patients with metastatic brain tumors, regardless of the number of lesions, as well as for salvage treatment to improve neurological symptoms that are present.17,31,35 However, neurocognitive deterioration caused by radiation-induced damage tends to occur during prolonged survival, which has led to the evolution of systemic chemotherapy combined with use of new monoclonal antibodies.7,31,35

In contrast, radiosurgery is unlikely to be effective against potential dissemination of microlesions in the brain. The results of this study showed that new brain le-

![Fig. 2. Graph showing Kaplan-Meier curves for new lesion–free survival after the initial GKS. Median survival time was 9 months.](image-url)
GKS, especially those patients harboring 5 or more lesions, are screened at regular intervals after the initial treatment. Provided that GKS for the initial treatment, patients are expected to dominate incidences of morbidity and mortality. 

Cancer and visceral metastases without brain disease now benefit from radiation therapy, and progression of primary breast cancer has improved because of a reduction in neurogenic death after the expanded use of radiation-induced injury to surrounding normal brain tissue and protected cognitive function. 

However, we showed that, even if new brain metastases were detected after the initial GKS, regardless of the number of tumors treated at the first GKS, the tumor characteristics associated with brain metastasis relapse did not affect overall survival. From this, we infer that detection of new lesions in the early posttreatment stage is desirable so that additional radiation targets can be identified and treated.

The results of this study showed the efficacy of GKS for the initial treatment of multiple brain metastases from breast cancer when there are less than 10 lesions. In addition, the results show that the choice of GKS over WBRT as the initial treatment reduced the long-term risk of radiation-induced injury to surrounding normal brain tissue and protected cognitive function. 

Therefore, we recommend GKS for the initial treatment, provided that patients are screened at regular intervals after the initial GKS, especially those patients harboring 5 or more lesions at the time of the first procedure. We believe that WBRT should be reserved for subsequent treatment. One should note that, with GKS as the initial treatment, diligent screening must be performed for the early detection of new lesions after GKS and selection of appropriate treatment such as salvage WBRT or additional GKS as needed.

The prognosis for patients with brain metastases from progressive breast cancer has improved because of a reduction in neurogenic death after the expanded use of radiation therapy, and progression of primary breast cancer and visceral metastases without brain disease now dominate incidences of morbidity and mortality. In addition, the specific breast cancer phenotype, distinguished by gene expression profiles, is considered to be the most significant factor of survival.

Considering the systemic and neurological statuses of patients in this study, the significant prognostic factors for overall survival were the presence of extracranial disease at the initial GKS and a breast cancer phenotype other than the HER2-positive type. Previous study results indicated that trastuzumab-treated patients with HER2 overexpression had statistically increased survival with a higher rate of occult brain metastases. The lapatinib-based chemotherapeutic regimen has been investigated as the second targeted drug therapy, based on lapatinib’s potential to reduce the risk of development of brain metastases compared with widespread use of trastuzumab. 

Furthermore, the lapatinib-based chemotherapeutic regimen has been investigated as the second targeted drug therapy, based on lapatinib’s potential to reduce the risk of development of brain metastases compared with widespread use of trastuzumab. In this study, we found that the HER2-positive phenotype was associated with favorable prognosis in overall survival compared with the other 2 breast cancer phenotypes. Therefore, we should consider both the patient’s neurological status and the biological subtype of the individual breast cancer before treatment of brain metastases.

The treatment strategy for brain metastases must also consider long-term maintenance of cognitive function. With respect to cognitive function, GKS as the initial treatment of multiple brain metastases from primary breast cancer may be beneficial. However, this study carries a selection bias inherent to a retrospective analysis, and thus a prospective randomized validation study is greatly needed to establish the efficacy of GKS for these patients and the treatment criteria.

Conclusions

We recommend GKS as the initial treatment in patients harboring up to 10 metastatic brain tumors from primary breast cancer. The results of this clinical study show the importance of indications for GKS at first detection of brain metastases. These indications are based on specific parameters, such as the patient’s neurological status, including the number of brain lesions harbored, and the patient’s systemic status, including the breast cancer phenotype. Follow-up examinations for the early detection of new brain metastases after initial GKS are essential, especially in patients with 5 or more brain tumors at the time of the initial GKS, who have a higher propensity for recurrence.
GKS for metastatic brain tumors from primary breast cancer

tend to develop new brain metastases, and in patients whose lesions have a HER2-positive phenotype, in whom there tends to be favorable prognosis in overall survival. We also recommend additional GKS or WBRT for salvage treatment if new brain metastases occur.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Matsunaga. Acquisition of data: Matsunaga, Suenaga, Inomori, Fujino. Analysis and interpretation of data: Matsunaga, Kawahara, Suenaga, Inomori, Fujino. Drafting the article: Matsunaga, Kawahara. Critically revising the article: Shuto, Kawahara. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Matsunaga. Administrative/technical/material support: Shuto, Kawahara. Study supervision: Matsunaga, Kawahara.

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