

Clinical Article

Clinical Outcome in Gamma Knife Radiosurgery for Metastatic Brain Tumors from the Primary Breast Cancer : Prognostic Factors in Local Treatment Failure and Survival

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Objective : Brain metastases in primary breast cancer patients are considerable sources of morbidity and mortality. Gamma knife radiosurgery (GKRS) has gained popularity as an up-front therapy in treating such metastases over traditional radiation therapy due to better neurocognitive function preservation. The aim of this study was to clarify the prognostic factors for local tumor control and survival in radiosurgery for brain metastases from primary breast cancer.

Methods : From March 2001 to May 2011, 124 women with metastatic brain lesions originating from a primary breast cancer underwent GKRS at a tertiary medical center in Seoul, Korea. All patients had radiosurgery as a primary treatment or salvage therapy. We retrospectively reviewed their clinical outcomes and radiological responses. The end point of this study was the date of patient's death or the last follow-up examination.

Results : In total, 106 patients (268 lesions) were available for follow-up imaging. The median follow-up time was 7.5 months. The mean treated tumor volume at the time of GKRS was 6273 mm³ (range, 4.5-27745 mm³) and the median dose delivered to the tumor margin was 22 Gy (range, 20-25 Gy). Local recurrence was assessed in 86 patients (216 lesions) and found to have occurred in 36 patients (83 lesions, 38.6%) with a median time of 6 months (range, 4-16 months). A treated tumor volume >5000 mm³ was significantly correlated with poor local tumor control through a multivariate analysis (hazard risk=7.091, $p=0.01$). Overall survival was 79.9%, 48.3%, and 15.3% at 6, 12, and 24 months, respectively. The median overall survival was 11 months after GKRS (range, 6 days-113 months). Multivariate analysis showed that the pre-GKRS Karnofsky performance status, leptomeningeal seeding prior to initial GKRS, and multiple metastatic lesions were significant prognostic factors for reduced overall survival (hazard risk=1.94, $p=0.001$, hazard risk=7.13, $p<0.001$, and hazard risk=1.46, $p=0.046$, respectively).

Conclusion : GKRS has shown to be an effective and safe treatment modality for treating brain metastases of primary breast cancer. Most metastatic brain lesions initially respond to GKRS, though, many patients have further CNS progression in subsequent periods. Patients with poor Karnofsky performance status and multiple metastatic lesions are at risk of CNS progression and poor survival, and a more frequent and strict surveillance protocol is suggested in such high-risk groups.

Key Words : Breast cancer · Metastases · Gamma knife radiosurgery · Prognosis.

INTRODUCTION

Brain metastases, which ultimately develop in 20% to 40% of patients with systemic cancer, have a poor prognosis. The median survival of patients with untreated brain metastasis is estimated to be approximately 4 weeks^{4,15}.

Breast cancer is the second most common cause of CNS metastasis. The incidence of brain metastasis in patients with pri-

mary breast cancer is reported to be between 5% and 20% and the rate is increasing¹. The social cost is assumed to be double in patients with CNS metastasis and it may warrant more worrisome social concerns.

Traditionally, surgical resection and whole brain radiotherapy (WBRT), which are usually well tolerated, have been the mainstay of treatments for brain metastases. Recently, however, stereotactic radiosurgery (SRS), either alone or conjunction with

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other modalities, has emerged as the preferred treatment option for these metastases. In one previous randomized controlled trial, neurocognitive function was compared after SRS alone and SRS plus WBRT. Neurocognitive decline was higher in the SRS plus WBRT group, but the CNS recurrence rate was higher in the SRS alone group⁵. Because of the increased survival of breast cancer patients, neurological deterioration following WBRT is becoming a serious issue. Although SRS can be a better alternative than WBRT with regard to long-term sequelae, the definitive role of SRS in treating the brain metastases of primary breast cancer patients has not been clarified and the prognostic factors remain to be established.

The aim of this study was to clarify the prognostic factors for local tumor control and survival in cases of gamma knife radiosurgery (GKRS) for brain metastases deriving from primary breast cancer.

MATERIALS AND METHODS

Patient's population

From March 2001 to May 2011, 124 women with metastatic brain lesions from primary breast cancer underwent GKRS at the GKRS center in the Asan Medical Center, Seoul, Korea. Double primary cancer patients (e.g., with both lung cancer and breast cancer) were excluded from this study. Breast cancer was confirmed by biopsy or surgical resection.

During the study period, 124 patients (312 lesions) were treated; 18 patients were not available for any follow-up images.

Table 1. Patients' characteristics

Characteristics	No. of patients/lesions (%)
No. of metastases	
1	66 (53.2)
2	17 (13.7)
3	11 (8.8)
Multiple (≥4)	30 (24.1)
Biological type	
HER-2 (+)	73 (70.1)
Luminal type	14 (13.4)
Triple negative	17 (16.3)
KPS score	
≥80	69 (55.6)
<80	55 (44.3)
RPA class	
1	9 (7.2)
2	81 (65.3)
3	34 (27.4)
Pre-GKRS cerebral therapy	
WBRT	25 (20.1)
Surgical resection	14 (11.2)

KPS : Karnofsky performance status, RPA : recursive partitioning analysis, GKRS : Gamma knife radiosurgery, WBRT : whole brain radiotherapy

The median overall survival of these patients was 1 month and most of them died of primary disease progression shortly after the radiosurgery. Therefore, 106 patients (268 lesions) were available for follow-up images. 54 patients had multiple sessions of GKRS. Except for two patients who had the simultaneous diagnosis of brain metastasis and breast cancer as the primary lesion, all patients underwent chemotherapy prior to GKRS. GKRS was performed not only as the primary treatment, but also as the adjuvant therapy in some patients after WBRT or surgery (n=25, n=14, respectively).

The mean age of the treated patients was 48 years (range, 40-53 years). At the time of the radiosurgery, 59 patients (47.5%) were asymptomatic. The median Karnofsky performance status (KPS) score at the time of the radiosurgery was 80 (range, 50-100). When stratified according to the prognostic value of the recursive partitioning analysis (RPA) devised by the Radiation Therapy Oncology Group, 9 patients (7.2%) were in Class 1, 81 (65.3%) in Class 2, and 34 (27.4%) in Class 3.

Hormone receptor data was not available for 10 of the 124 patients and the HER-2 status was recorded in only 104 patients, 70.1% of whom were HER-2 positive. Triple negative type was found in 17 patients (16.3%).

The median interval from the primary site diagnosis to the brain metastases diagnosis was 46.5 months (range, 0-182 months). Two patients had a simultaneous diagnosis of metastatic brain lesions and primary breast cancer.

Eight patients already had leptomeningeal seeding before the radiosurgery. Two of these patients were suspicious of leptomeningeal seeding accompanied by metastatic lesions on initial imaging and were confirmed to have leptomeningeal seeding after the radiosurgery. The other six patients had controlled leptomeningeal seeding with WBRT or intrathecal chemotherapy and their performance status was good enough to plan further active treatment. The median age of these patients was 41.4 years (range, 33-48 years) and the median pre-GKRS KPS score and RPA class were 70 (range, 50-90) and 2 (range, 2-3), respectively. Other characteristics of these patients were similar to those of total cohort in our study. The numbers of treated lesions, treated tumor volume and radiation dose were similar to those of total cohort (median number of treated lesions 2, median treated tumor volume, 5057 mm³, median radiation dose, 22.5 Gy).

Patients' characteristics are summarized in Table 1.

Techniques in GKRS

We used Leksell Gamma knife system with the Leksell Gamma-Plan software from 2001. A Leksell Gamma knife C-model was used until December 2010; from January 2011, a Leksell Gamma knife Perfexion™ (ELEKTA, Sweden) model was used.

The mean treated tumor volume at the time of GKRS was 6273 mm³ (range, 4.5-27745 mm³) and the median dose delivered to the tumor margin was 22 Gy (range, 20-25 Gy) with a median isodose line 50% (range, 40-75%).

We assessed each treated tumor volume and used the summa-

tion value when considering multiple metastatic lesions (≥ 4); the portion of treated tumor volume $< 5000 \text{ mm}^3$, $5000\text{-}10000 \text{ mm}^3$, and $\geq 10000 \text{ mm}^3$ were 89%, 31%, and 43%, respectively.

We performed multiple sessions of radiosurgery with fractionated dose in nine patients who had large volume of brain metastases or significant peritumoral edema and therefore had significant risk of acute brain swelling following usual dose of radiosurgery. The mean treated tumor volume and the median radiation dose at the 1st session were 13142 mm^3 (range, $2800\text{-}17000 \text{ mm}^3$) and 18 Gy (range, 15-20 Gy), respectively. The median interval period between each session was 2 months (range, 1-5 months). On the 2nd session of radiosurgery, the mean treated tumor volume and the median radiation dose were 4700 mm^3 (range, $380\text{-}9100 \text{ mm}^3$) and 12 Gy (10-15 Gy), respectively.

All patient received methylprednisolone for a short period (up to 7 days) to prevent acute brain swelling following radiosurgery. Follow-up images were taken 2 months after the initial radiosurgery and every 3 months thereafter; some patients needed earlier follow-up images, depending on their clinical status.

Radiological response

The radiological response to the GKRS was evaluated by measuring the tumor volume on MRI. Follow-up MRI scans were taken at 2 month intervals and we assessed the radiological response based upon serial changes in follow-up image and the tumor volume on the last follow-up image. In cases of local recurrence, the response was assessed at the last image just before the documented local recurrence. Radiological outcomes were classified as complete remission (complete disappearance of lesions), partial remission ($\geq 50\%$ decrease in tumor volume), stable disease ($< 50\%$ decrease in tumor volume), or progression ($\geq 50\%$ increase in tumor volume). Complete remission, partial remission, and stable disease were considered to indicate local tumor control. New lesions were defined as any newly developed metastatic lesions remotely located from previously treated lesion(s). We assessed local recurrence at least the 4th month or in the 2nd follow-up image after the initial GKRS. When there was an increase in the volume of the enhancing lesions on the initial follow-up MRI, we performed MR spectroscopy and methionine PET (if possible) to discriminate tumor recurrence from radiation necrosis^{21,22,24}. Local recurrence was defined as any secondary increase in tumor volume that had initially responded to the radiosurgery.

The end point of overall survival time was the date of patients' death or the last follow-up examination. Neurological death was defined as a patients' death that was related to a metastatic brain lesion or leptomeningeal seeding.

Statistical analysis

Prognostic factors affecting local tumor control and survival were assessed with Kaplan-Meier plots. Univariate and multivariate analyses were performed with a Cox proportional hazards model with $p < 0.05$ set as the level of significance.

RESULTS

Local tumor control

In total, 106 patients (268 lesions) were available for follow-up images. The median follow-up duration was 7.5 months (range, 1-93 months). The mean number of treated lesions was 2.5 (range, 1-11) and multiple lesions (≥ 4) were treated in a single session of radiosurgery in 30 patients. The mean treated tumor volume at the time of the GKRS was 6273 mm^3 (range, $4.5\text{-}27745 \text{ mm}^3$). The median dose delivered to the tumor margin was 22 Gy (range, 20-25 Gy). The radiological response was classified as one of four classes depending on the calculated volume on the last follow-up images. Neuroimaging studies showed complete disappearance in 61 lesions (22.7%), partial response in 134 lesions (50%), and stable disease in 73 lesions (27.2%). Local tumor control with a reduction in tumor volume was achieved in 195 lesions (72.7%). All metastatic lesions responded to the initial radiosurgery.

The local recurrence was assessed in 86 patients (216 lesions). A greater than 4-month follow-up could not be performed in 38 patients. The median overall survival of this subgroup was three months and most patients died of progression of their primary disease. Local recurrence occurred in 36 patients with 83 lesions (38.6%) and the median time to local recurrence was six months (range, 4-16 months). The mainstay of further treatment for the local recurrence was a second radiosurgery (24 patients with 50 lesions). In five patients, no further treatment was carried out as their general condition was not stable enough to tolerate further therapy. Two patients had surgical tumor resection and another five patients had conventional radiation therapy as salvage therapy.

The treated tumor volume was the only significant prognostic factors associated with local tumor control. A treated tumor volume $\geq 5000 \text{ mm}^3$ was significantly correlated with poor local tumor control with a multivariable analysis [hazard risk (HR)=7.091, $p=0.001$]. A trend of lower local recurrence with a higher radiation dose ($> 20 \text{ Gy}$) was seen (HR=0.845, $p=0.724$). Although HER-2 positive patients showed more local recurrence, this was not statistically significant (HR=1.259, $p=0.644$) (Table 2).

We performed multiple sessions of radiosurgery with fractionated dose in nine patients. The mean treated tumor volume and the median radiation dose at the 1st session were 13142 mm^3 (range, $2800\text{-}17000 \text{ mm}^3$) and 18 Gy (range, 15-20 Gy), respectively. The median interval period between each session was 2 months (range, 1-5 months). On the 2nd session of radiosurgery, the mean treated tumor volume and the median radiation dose were 4700 mm^3 (range, $380\text{-}9100 \text{ mm}^3$) and 12 Gy (10-15 Gy), respectively. After completion of fractionated radiosurgery, only one patient had local recurrence 16 months later the 2nd radiosurgery. Six patients had new metastases with median interval period of 7 months (range, 3-12 months). Local tumor control rate was excellent in this subgroup compared with that of total cohort. And no patients complained of

any side effects related to radiation therapy (e.g., radiation necrosis). Clinical outcomes were also slightly better than total population in current study; the median overall survival was 14 months (range, 3-58 months) and the median progression-free survival was 9 months (range, 2-14 months).

CNS progression

CNS progression was defined as any local recurrence or new metastasis (including leptomeningeal seeding) found on follow-up images. A total of 83 patients (78.3%) showed CNS progression and the median time to CNS progression for these patients was 5 months (range, 0-113 months). Local recurrence occurred in 32 patients, new metastases in 56 patients, and leptomeningeal seeding in 16 patients. In nine patients, both local recurrence and new metastases were noted. Progression-free survival was 49.1% and 19.3% at 6 months and 12 months, respectively.

On multivariable analysis, the following factors were associated with an increased risk of CNS progression; KPS score (HR=1.78, *p*=0.015), pre-GKRS leptomeningeal seeding (HR=6.42, *p*=0.001), pre-GKRS WBRT (HR=1.86, *p*=0.02), and multiple (≥4)

lesions (HR=2.99, *p*<0.001). HER-2 positive patients showed less CNS progression and more local recurrence; these results were not statistically significant however (Table 2).

Of 56 patients who had new metastases, 57.1% had multiple (≥4) metastatic lesions on follow-up images. The median time to new metastases was 5 months (range, 1-18 months). Patients with multiple metastatic lesions at the time of radiosurgery tended to have further new metastases and this trend was statistically significant in both univariate and multivariate analysis (HR=6.33, *p*=0.001) (Table 2).

Patient's survival and neurological death

Of the 124 patients included in our cohort, 18 were alive at the end of the study. The median overall survival was 11 months (range, 6 days-113 months) after radiosurgery. The overall survival was 79.9%, 48.3%, and 15.3% at 6, 12, and 24 months, respectively.

Multivariate analysis showed that the pre-GKRS KPS score, leptomeningeal seeding prior to initial radiosurgery and multiple metastatic lesions were significant prognostic factors for overall

Table 2. Prognostic factors for local recurrence and new metastases

	Local recurrence		New metastases		CNS progression	
	HR	<i>p</i> value	HR	<i>p</i> value	HR	<i>p</i> value
Age (years)						
<40	1		1		1	
≥40	0.996	0.994	1.374	0.532	1.114	0.714
KPS						
<80	1		1		1	
≥80	1.021	0.646	1.116	0.783	0.590	0.017
RPA class						
1	1	0.881	1	0.363	1	0.117
2	1.406	0.625	2.333	0.270	1.615	0.305
3	1.429	0.643	1.410	0.581	2.456	0.072
HER-2 (+)	1.259	0.644	0.782	0.608	0.886	0.643
Pre-GKRS seeding	-	0.321	0.418	0.482	13.11	<0.001
Pre-GKRS WBRT	1.004	0.994	1.087	0.873	1.8622	0.02
Treated volume (mm ³)						
<5000	1	0.001	1	0.543	1	0.047
5000-10000	7.091	<0.001	1.636	0.365	1.688	0.073
≥10000	3.273	0.01	1.500		1.797	0.021
Radiation dose						
<20 Gy	1		1		1	
≥20 Gy	0.845	0.724	1.216	0.684	1.086	0.761
Number of treated lesions						
n=1	1	0.435	1	0.0002	1	0.0003
n=2	1.602	0.346	6.667	0.008	1.499	0.224
n=3	0.582	0.348	16.000	0.012	2.254	0.032
n≥4	1.281	0.636	6.33	0.001	3.126	<0.001
Neurological symptoms (+)	1.191	0.646	1.435	0.362	1.506	0.068

Neurological symptoms include seizure and focal neurologic deficit attributable to corresponding brain metastases. Headache or vomit associated with increased intracranial pressure due to brain metastases was included as neurological symptoms. HR : hazard risk, KPS : Karnofsky performance status, RPA : recursive partitioning analysis, GKRS : Gamma knife radiosurgery, WBRT : whole brain radiotherapy

survival (HR=1.94, $p=0.001$, HR=7.13, $p<0.001$, HR=1.46, $p=0.046$, respectively). The cut-off value of the pre-GKRS KPS score was 80. HER-2 positive patients tended to show a more favorable clinical outcome in survival and neurological death (HR=0.755, $p=0.229$ for death; HR=0.567, $p=0.198$ for neurological death) (Table 3).

Of eight patients with pre-GKRS leptomeningeal seeding, the median overall survival was 2 months (range, 0-5 months) and half of them died of increased intracranial pressure due to leptomeningeal seeding.

When considering the cause of death, 43 patients died of brain metastases and they were defined as having undergone neurological death. The main causes of neurological death were uncontrolled brain metastases and increased intracranial pressure associated with leptomeningeal seeding. The median overall survival and progression-free survival in the patients who had leptomeningeal seeding were 9 and 4 months, respectively, and these outcomes were inferior to those of the overall study population.

A pre-GKRS KPS score <80 and leptomeningeal seeding prior to GKRS were statistically significant prognostic factors associated with neurological death (HR=2.71, $p=0.01$, HR=17.7, $p<0.001$, respectively) (Table 3).

DISCUSSION

With advances in systemic therapies for breast cancer, the life expectancy of breast cancer patients has been prolonged and CNS metastasis has emerged as an important source of mortality and morbidity. Studies have reported that 5% to 20% of patients with breast cancer will develop CNS metastases and CNS metastases tend to occur late in the course of metastatic breast cancer and are associated with poor outcome⁷.

More positively, metastatic brain tumor originating from a breast cancer is known to be susceptible to radiation therapy and both WBRT and SRS have shown satisfactory outcomes in local tumor control. Due to increased concern about the quality of life and neurocognitive deterioration after radiation therapy, SRS has become a more popular upfront therapeutic modality than WBRT⁵.

Several studies have already described the effectiveness of SRS in local tumor control. Kondziolka et al.¹⁴ reported a 90% local tumor control and 71% progression-free survival in SRS-treated patients at 12 months. In that study, 10% of treated lesions had progression after

SRS and 65% of lesions showed local tumor control with volume reduction. Matsunaga et al.¹⁶ achieved up to a 97% local tumor control rate with 78% progression-free survival at 12 months. In present study, we had no progression in treated lesions after the initial SRS and achieved local control with volume reduction in 72.7% of our subjects. Compared with previous studies, we had more patients in our cohort with a poor general condition (low KPS score, high RPA class) and used SRS as both the primary treatment and as salvage therapy without differentiating the patients into subgroups. Although these factors might explain our inferior outcomes compared with other reports, our study has revealed more relevant outcomes concerning the broader indications of salvage radiosurgery in real clinical practice.

In previous several studies, tumor volume and radiation dose were well demonstrated as significant prognostic factors in local tumor control. In current study, the treated tumor volume was the only significant prognostic factors associated with local tumor control. We set the value of treated tumor volume >5000 mm³ as a significant cut-off value correlated with poor local tumor control (HR=7.091, $p=0.001$). Although there was a trend of lower local recurrence with a higher radiation dose, this was

Table 3. Prognostic factors for patients' survival

	Death		Neurological death	
	HR	<i>p</i> -value	HR	<i>p</i> -value
Age (years)				
<40	1		1	
≥40	0.81	0.382	0.731	0.455
KPS				
<80	1		1	
≥80	0.526	0.001	0.369	0.010
RPA class				
1	1	0.013	1	0.096
2	1.564	0.262	1.270	0.751
3	2.692	0.018	2.908	0.172
HER-2 (+)	0.755	0.229	0.567	0.198
Pre-GKRS seeding	7.965	<0.001	17.763	<0.001
Pre-GKRS WBRT	2.251	0.001	2.854	0.016
Treated volume (mm ³)				
<5000	1	0.62	1	0.778
5000-10000	0.787	0.363	0.687	0.490
≥10000	1.001	0.996	0.950	0.901
Radiation dose				
<20 Gy	1		1	
≥20 Gy	0.952	0.842	1.112	0.818
Number of treated lesions				
n=1	1	0.089	1	0.089
n=2	0.620	0.141	0.279	0.224
n=3	1.094	0.803	0.5543	0.556
n≥4	1.496	0.084	2.086	0.061
Neurological symptoms (+)	1.233	0.283	1.685	0.174

HR : hazard risk, KPS : Karnofsky performance status, RPA : recursive partitioning analysis, GKRS : Gamma knife radiosurgery, WBRT : whole brain radiotherapy

not statistically significant in this study.

We performed multiple sessions of radiosurgery with fractionated dose in cases with larger tumor volume or severe peritumoral edema which were at risk of acute brain swelling following radiosurgery with usual radiation dose. With lowered radiation dose and large tumor volume, we achieved relatively excellent local tumor control (only one patient had local recurrence) and, more positively, no patient had any evidence of radiation necrosis. Thus, applying multiple sessions of radiosurgery with fractionated dose can be an effective and safe alternative when treating the large tumor volumes which are traditionally amenable to conventional radiation therapy.

CNS progression after radiosurgery has been documented in over 50% of patients with metastatic CNS lesions from primary breast cancer and several prognostic factors associated with local failure or new distant metastases have been suggested^{8,12}. In our present study, 78.3% of patients had CNS progression and 38.4% had local recurrence (with a median time of 6 months), even though all treated lesions showed at least a partial radiological response after the initial radiosurgery. Although previous studies have demonstrated outstanding outcomes in local tumor control (up to 97%)^{14,16}, it is notable that many of these cancers finally had progression (local recurrence or new metastases) in subsequent periods. The treated tumor volume and the radiation dose are the most significant prognostic factors found for local tumor control in both the current and previous studies^{12,16}.

Whether the omission of WBRT prevents further CNS progression in patients with metastatic breast tumor is still being debated. Although there was no impact found previously from using WBRT in addition to SRS on survival in patients with breast cancer metastases⁹, several series have reported that there was an increased risk of developing new brain metastases in patients managed initially with SRS alone^{2,18,20}. Other studies have demonstrated that WBRT decreases the rate of tumor recurrence². However, the use of WBRT is also associated with a risk of CNS progression⁸. In our present study, omitting WBRT was associated in univariate analysis with an increased risk of CNS progression, poor overall survival, and neurological death. To interpretate this outcome, it is important to consider a metastatic brain tumor as a systemic progression rather than a local pathological condition.

It has been shown in several studies that extracranial disease status important in predicting overall patient survival^{8,17}. Although we did not assess this in our current study, the KPS score and RPA class indirectly reflect this systemic condition. Those patients who had already undergone WBRT prior to radiosurgery usually had an advanced disease status and tended to have larger metastatic tumor volumes, which might act as a selection bias when interpreting the actual result.

The breast cancer subtype has shown to be associated with CNS progression in several studies, and HER-2-positive and triple-negative tumors are most likely to develop brain metastases^{8,10,13,23}. We found a non-significant trend toward less CNS

progression in HER-2 positive compared with HER-2 negative patients. HER-2 positive breast cancer has demonstrated an increased predilection for CNS metastases^{6,11,19} and several studies have described a better survival outcome in patients with HER-2 positive disease treated with trastuzumab compared with HER-2 negative disease^{3,6}. Interestingly, Dawood et al. reported similar survival times between patients with HER-2 negative and HER-2 positive disease who did not receive trastuzumab, and suggested that the course followed by these two groups after the development of CNS metastases may no longer be governed by the HER-2 status. That study also demonstrated a significantly superior median survival outcome in patients with HER-2 positive disease who only received trastuzumab at the time of the CNS metastases in comparison with patients with HER-2 negative disease. This indicates the importance of improved extracranial disease control at all time points during the natural course of metastatic breast cancer. In our present study, the use of systemic therapy before and after radiosurgery was not well characterized despite the fact that nearly every patient had chemotherapy prior to developing a CNS metastasis. Previous reports suggest that the receipt of systemic therapy after CNS recurrence is an important predictor of survival. In addition to the local factors, such as tumor volume and radiation dose, the extracranial disease status possesses a more powerful prognostic significance in predicting further CNS progression.

Most of the brain metastases in our current cohort showed at least a partial response to the initial radiosurgery, although many of these cases eventually experienced local recurrence. There is a limitation in interpreting an increased enhancing lesion on follow-up images because radiation necrosis may also present as an enhancing lesion. It is important therefore to differentiate between true tumor recurrence and radiation necrosis because any misinterpretation may interfere with the planning of the treatment strategy. We used MR spectroscopy or methionine PET to differentiate tumor recurrence from radiation necrosis. Most lesions that were suggestive of tumor recurrence had some degree of radiation necrosis and further treatment was planned if the portion of the viable tumor was larger than the radiation necrosis on MR spectroscopy or methionine PET. Although MR spectroscopy and methionine PET are known to be effective in discriminating tumor recurrence from radiation necrosis, defined cut-off values remain to be determined and vary among previous studies. Further research is needed to connect histological results with imaging findings and thereby determine the value of imaging studies defining radiation necrosis.

With advances in chemotherapy for primary breast cancer, the life expectancy of breast cancer patients is increasing and brain metastases are causing significant morbidity and mortality in these patients. In present study population, brain metastases developed with a median interval period of 46.5 months after the diagnosis of breast cancer. If treated by radiosurgery, the median progression-free survival was 6 months and patients

with a poor performance status (KPS <80), pre-GKRS WBRT, pre-GKRS leptomeningeal seeding, and multiple metastatic lesions were at high risk of CNS progression. These factors were also prognostic factors for poor overall survival outcomes.

There is no current consensus regarding the follow-up protocol for brain metastases from primary breast cancers. We assessed each patient every two months after radiosurgery. We recommend earlier surveillance for CNS metastases after primary breast cancer diagnosis. Because most brain metastases have shown local recurrence or new metastases with a median time of 5-6 months in several studies, including our present series, frequent follow-up with an interval of 2-3 months after the initial radiosurgery is also indicated in our opinion. A stricter follow-up should also be mandatory in groups at high risk of CNS progression who have a poor performance status, pre-GKRS leptomeningeal seeding, pre-GKRS WBRT, or multiple metastatic lesions.

The limitations of our current study derived from its retrospective nature and the fact that we did not assess the extracranial disease status or characterize the chemotherapy regimen in any detail. Further studies that evaluate the validity of MR spectroscopy and methionine PET are also desirable.

CONCLUSION

GKRS has shown to be an effective and safe treatment modality for brain metastases deriving from primary breast cancer. Most metastatic brain lesions of this type respond to radiosurgery initially, though many of these patients (up to 40%) have further CNS progression at later periods. Patients with a poor KPS score and multiple metastatic lesions are at a high risk of CNS progression and poor survival. We suggest earlier surveillance of brain metastases in primary breast cancer patients and frequent follow-ups with advanced imaging modalities including MR spectroscopy or methionine PET after radiosurgery.

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