Breast Cancer (2019) 26:147–153
https://doi.org/10.1007/s12282-018-0903-3

ORIGINAL ARTICLE

# Breast cancer patients with brain metastasis undergoing GKRS

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Received: 18 April 2018 / Accepted: 30 August 2018 / Published online: 4 September 2018


## Abstract

**Background** Breast cancer (BC) is the second most common cause of brain metastasis in the United States. Compared to whole brain radiation therapy (WBRT), treatment with gamma-knife radiosurgery (GKRS) offers a better chance at neurocognitive preservation. The goal of our retrospective study is to report the overall survival (OS) in patients receiving GKRS and to identify factors that improve survival outcomes.

**Methods** The records of 80 patients with primary BC treated with GKRS at the Yale Comprehensive Cancer Center between 2000 and 2013 were reviewed. OS was calculated from the date of first GKRS treatment. Other factors studied were age, Karnofsky performance status (KPS), tumor subtype, having WBRT and/or surgical resection pre- or post-GKRS, and number of brain metastases treated with GKRS.

**Results** Median age was 56.2 years. OS from first GKRS was 13.1 months (95% CI 7.6–21.9). On univariate analysis, improved survival was associated with HER-2 subtype ($p=0.026$), KPS score > 80 ($p=0.009$), and good control of systemic disease at time of GKRS ($p=0.020$). Multivariable analysis detected a significantly longer survival with HER-2 positivity (HR 0.22, 95% CI 0.06–0.76, $p=0.017$) and a strong trend in patients with craniotomy prior to GKRS (HR 0.13, 95% CI 0.01–1.11, $p=0.06$).

**Conclusions** GKRS is a promising therapy for treating brain metastasis from BC, particularly in those with HER-2 positivity and high-performance scores even in those patients with > 5 brain metastases. Furthermore, GKRS may also be a useful adjunct to surgical resection in such patients. High rates of neurological death remain from BC brain metastases; however, and need further investigation.

**Keywords** Breast · Cancer · Brain · Metastasis · Gamma-knife · Radiosurgery · Stereotactic

## Introduction

Breast cancer is the most common cancer in females. It represents 14% of all new cancer cases in the US with the majority being diagnosed at an early stage localized to the breast and ipsilateral axilla. However, ~6% of breast cancer patients are found to have distant metastasis at the time of diagnosis with an estimated 26.3% 5-year survival [1]. Common sites of breast cancer metastasis include bone, liver, lung and central nervous system.

Breast cancer is the second most common cause of brain metastasis in women [2]. The current treatment modalities used for the management of brain metastasis include surgical resection, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). The advantage of SRS use is that it offers a higher chance of neurocognitive preservation compared to WBRT. Evidence has shown that younger age and having three or less brain lesions are favorable

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predictors of overall survival (OS) in patients undergoing gamma-knife radiosurgery (GKRS) [3]. Furthermore, Niikura et al. showed that patients with the HER-2 subtype of breast cancer had a significantly longer OS than those with luminal or triple-negative subtypes who underwent GKRS treatment [4]. Additional research efforts are warranted to determine which population of patients would benefit the most from GKRS therapy and to investigate the long-term outcomes of this treatment modality. The purpose of this retrospective study of patients with a diagnosis of brain metastasis secondary to breast cancer, treated at the Yale GKRS Center, is to report the OS of patients from time of GKRS and to identify factors that predict favorable survival outcomes in such patients.

## Methods and materials

### Patients

The medical records of 80 patients with a diagnosis of primary breast cancer treated using GKRS for brain metastases at the Yale Comprehensive Cancer Center between 2000 and 2013 were retrospectively reviewed and included in our analysis. Patients were identified through the Yale GKRS database. All patients had a diagnosis of breast cancer and brain metastases. Estrogen receptor (ER), progesterone receptor (PR) status and HER-2 expression and/or amplification status were collected for patients based on the analysis of primary and/or metastatic breast cancer pathology. Breast cancer subtypes were available for 69 out of 80 patients (86.5%) and included Luminal A (ER+/HER2−), Luminal B (ER+/HER2+), HER-2 (ER−/HER2+) and Basal (ER-/HER2−). Performance status using the Karnofsky scoring system was available for 64 out of 82 (78.1%) patients. Other variables that were included in the analysis were age, craniotomy performed pre- or post-GKRS, WBRT performed pre- or post-GKRS, number of brain metastasis seen on treatment magnetic resonance imaging (MRI), and number of GKRS treatments performed for each patient. We also defined the extent of systemic disease response at the time of GKRS to include extra-cranial breast cancer metastatic disease which continued to respond to treatment including stable disease. OS was calculated as time from GKRS to the date of death or date of last documented contact for living patients.

### Treatment

Patients were treated using institutional standard GKRS techniques for brain metastasis with doses ranging from 16 to 24 Gray (Gy) prescribed to the 40–70% isodose surfaces using the Leksell Gamma-Knife Perfexion.

### Statistical analysis

We performed univariate survival analysis using the Kaplan–Meier estimator to identify clinicopathological patient variables that were significantly associated with overall survival post the GKRS procedure. Multivariate Cox proportional hazards regression analysis was also performed to jointly assess the effect of the covariates on the overall survival of GKRS-treated patients. Significance was assessed at the 5% level in all analyses. Similar univariate and multivariate analyses were performed using neurological death as a secondary outcome. The statistical platform R v 3.2.2 was used in all computations.

## Results

### Demographics

The mean age at which patients underwent GKRS was 56.2 years (range 33–85 years). The Karnofsky performance status (KPS) of the patients ranged from 40 to 100. Forty-one patients (51%) had a score of 90–100 while no KPS score was available for 18 patients (23%). Thirty-eight patients (47.5%) were ER positive, 38 patients (47.5%) were ER negative and the ER status of 4 patients (5%) was unknown. Twenty-eight patients (35%) were PR positive, 46 patients (57%) were PR negative while the PR status of 6 patients was unknown (8%). Thirty-eight patients (47%) were HER-2 positive, 33 patients (41%) were HER-2 negative while the HER-2 status of 9 patients was indeterminate or unknown (12%). Based on the available receptor results, we categorized the breast cancer into the following subtypes, 16 patients (20%) as Luminal A, 19 patients (24%) as Luminal B, 17 patients (21%) as HER-2, 17 patients (21%) as Basal Cell subtypes. The subtype for 11 patients (14%) could not be determined due to missing receptor results. We found that 31 out of the 80 patients (39%) had continued response of systemic disease at time of GKRS (Table 1).

### Treatment

Regarding treatment variables, 14 patients (18%) had a craniotomy prior to undergoing GKRS and twenty-six patients (33%) had WBRT prior to receiving GKRS. The number of brain metastasis noted on treatment MRI ranged from 1 to greater than 5, with 32 out of 80 (40%) patients having $\geq 5$ metastases. While 50 out of 80 patients (62%) received only 1 GKRS treatment, 14 patients (18%) underwent additional 2 or more GKRS treatments as salvage therapy for distant metastases (Table 2). In addition, 9 patients (11%) needed

**Table 1** Patient characteristics

| Characteristics | $N=80$ | Percentage |
|---|---|---|
| Mean age at GKRS (SD) in years | 56.2 (11.5) | |
| Median time of brain metastasis from breast cancer diagnosis (95% CI) in months | 62.8 (46.2–81.6) | |
| Karnofsky performance score | | |
| 40–60 | 8 | 10 |
| 70–80 | 13 | 16 |
| 90–100 | 41 | 51 |
| Unknown | 18 | 23 |
| Estrogen receptor | | |
| Positive | 38 | 47.5 |
| Negative | 38 | 47.5 |
| Unknown | 4 | 5 |
| Progesterone receptor | | |
| Positive | 28 | 35 |
| Negative | 46 | 57 |
| Unknown | 6 | 8 |
| HER-2 status | | |
| Positive | 38 | 47 |
| Negative | 33 | 41 |
| Indeterminate | 3 | 4 |
| Unknown | 6 | 8 |
| Breast cancer subtype | | |
| Luminal A | 16 | 20 |
| Luminal B | 19 | 24 |
| HER-2 | 17 | 21 |
| Basal | 17 | 21 |
| Unknown | 11 | 14 |
| Control of systemic disease (non-CNS) | | |
| Yes | 31 | 39 |
| No | 49 | 61 |

*SD* standard deviation, *CI* confidence interval

craniotomy and 13 patients needed WBRT as salvage after GKRS. Of note, 41 patients (51%) never received WBRT as part of treatment of their brain metastases.

## Overall survival

The median OS for patients calculated from the time of receiving GKRS was 13.1 months (95% CI 7.6–21.9) while the OS for patients calculated from the time of diagnosis of brain metastasis was 18.8 months (95% CI 11.7–23.9).

In univariate analysis, factors associated with longer survival included HER-2 subtype ($p=0.026$) (Fig. 1a), KPS score > 80 ($p=0.009$) (Fig. 1b), good control of systemic disease at time of GKRS ($p=0.020$) (Fig. 2a), and craniotomy performed after GKRS ($p=0.027$) (Fig. 2b). Age, time to brain metastasis from primary diagnosis, number of metastases treated at GKRS, number of GKRS treatments and craniotomy after GKRS did not significantly affect OS. Furthermore, there was no statistically significant effect of receiving WBRT pre- or post-GKRS therapy on survival.

Multivariable analysis, which included 44 patients with complete observations (34 deaths total), detected a significantly longer survival for patients with HER-2 positivity (HR 0.22, 95% CI 0.06–0.76, $p=0.017$). In addition, there was a strong trend, although not statistically significant, towards longer survival in those who had craniotomy prior to receiving GKRS (HR 0.13, 95% CI 0.01–1.11, $p=0.06$).

## Neurological outcome

Of the 80 patients in the study, 21 were lost to follow-up. Therefore, while death data were available for all patients, neurological follow-up was only available for 59 patients. Out of 59 patients, 5 were still alive and free of both brain and systemic disease at end of study, 30 died from systemic progression of disease and 24 died primarily from neurological progression with stable or only slowly progressive systemic disease in 11 of these patients.

Within the group of patients dying of neurological disease, 9 (37.5%) had brain metastases found at original time of breast cancer diagnosis for which they received GKRS treatment only without WBRT. For the remaining 15 patients, time from breast cancer diagnosis to first GKRS treatment ranged from 45 to 638 days.

Overall for the group, the median number of GK treatments for all patients was a single treatment. In patients living longer than 2 years after first GK treatment, however, median number of GK treatments increased to three (range 1–6 treatments) for treatment of development of distant brain metastases. As discussed previously, 13 patients needed WBRT as salvage after GKRS also for distant brain metastases and 9 patients (11%) needed craniotomy as salvage for local recurrence after GKRS. In the 9 post-GKRS craniotomy patients, the original pathologies were Luminal A (2 cases), HER-2 (4 cases) and Basal (2 cases). No patients with Luminal B disease died predominantly of neurological causes. At time of craniotomy after GKRS, pathology showed radiation necrosis in 7 out of the 9 cases with only 2 cases of re-growing tumor.

Uni- and multivariate analysis did not find any specific variables significantly associated with risk of neurological death—specifically including primary breast cancer type, KPS score, systemic control, time from diagnosis to first brain metastasis, prior craniotomy, number of brain metastases treated with GKRS or use of WBRT.

**Table 2** Treatment variables

| Variables | $N=80$ | Percentage |
|---|---|---|
| Craniotomy | | |
| Pre-GKRS | 14 | 18 |
| Post-GKRS | 9 | 11 |
| No surgery | 57 | 71 |
| WBRT | | |
| Pre-GKRS | 26 | 33 |
| Post-GKRS | 13 | 16 |
| No WBRT | 41 | 51 |
| Number of brain metastases noted on treatment MRI | | |
| 1 | 19 | 24 |
| 2 | 12 | 15 |
| 3 | 7 | 9 |
| 4 | 10 | 12 |
| ≥5 | 32 | 40 |
| Number of GKRS treatments | | |
| 1 | 50 | 62 |
| 2 | 16 | 20 |
| 3 | 7 | 9 |
| 4 | 1 | 1.5 |
| 5 | 5 | 6 |
| 6 | 1 | 1.5 |
| Survival range after GKRS relative to number of GKRS treatments | | |
| 1 or 2 GK treatments | 18–1456 days (0.04–4 years) | |
| 3 or more treatments | 176–2531 days (1.4–7 years) | |
| Percent patients with HER-2 positive disease relative to OS from time of GK | | |
| OS < 1 year ($n=42$) | 16 | 38 |
| OS 1–2 years ($n=23$) | 11 | 48 |
| OS > 2 years ($n=15$) | 13 | 87 |

## Discussion

The overall prognosis of patients with brain metastasis from any cancer remains generally poor, with some types of cancers having worse prognoses than others. Currently, the role of GKRS in patients with brain metastasis from breast cancer has shown promising results. Given that breast cancer is the second most common cause of brain metastasis, the need to assess for prognostic factors to predict efficacy of GKRS is necessary to select patients who would benefit the most from this treatment modality. In most cancer patients with brain metastasis treated with WBRT, the overall survival is approximately 4–6 months, [5]. OS in patients receiving only GKRS as first-line treatment for breast cancer brain metastasis, however, has been reported to be as high as 15–19 months [6]. In this study, 51% of patients were treated without WBRT. While a randomized study comparing GKRS alone to GKRS plus WBRT has not been done for breast cancer patients alone, a Phase III trial by Brown et al. looking at patients with 1–3 metastasis from a variety of primary cancers showed that there was no statistically significant difference in overall survival when comparing GKRS alone to GKRS plus WBRT [7]. Our findings support these results making it even more important to delay WBRT where possible to avoid the neurocognitive decline demonstrated by the randomized studies published by Chang et al. (2009) [8] and confirmed by Brown et al.

Number of brain metastases at time of treatment has also been used to determine whether use of WBRT versus GKRS is more appropriate. Yamamoto et al. [9] showed in their prospectively collected observational study that median overall survival in their patients treated with GKRS to 2–4 lesions was no different than those treated for 5–20 lesions. Given that 40% of our study population had 5 or more brain metastases treated, and similar to results found by Matsunaga et al. [10], our findings also suggest that GKRS by itself is a viable option for treating patients with multiple breast cancer brain metastases and that OS is not affected by the number of metastases present at time of GKRS alone.

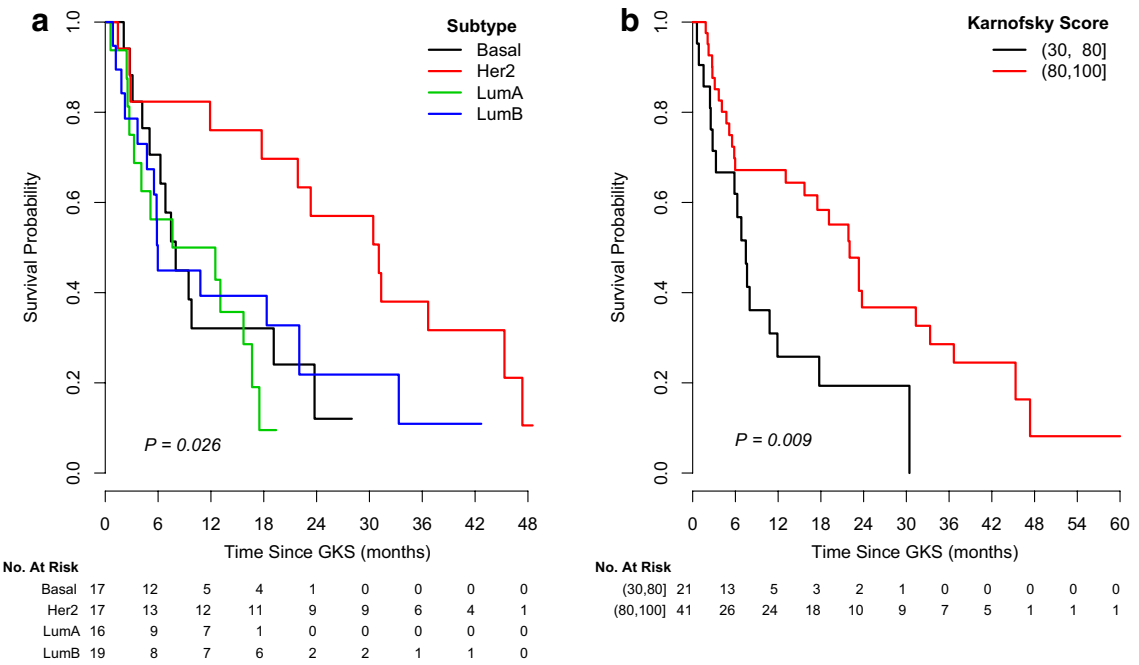


**Fig. 1** Overall survival of patients treated by GKRS by **a** breast cancer subtype and **b** Karnofsky performance score categories. Statistical significance was based on the log-rank test

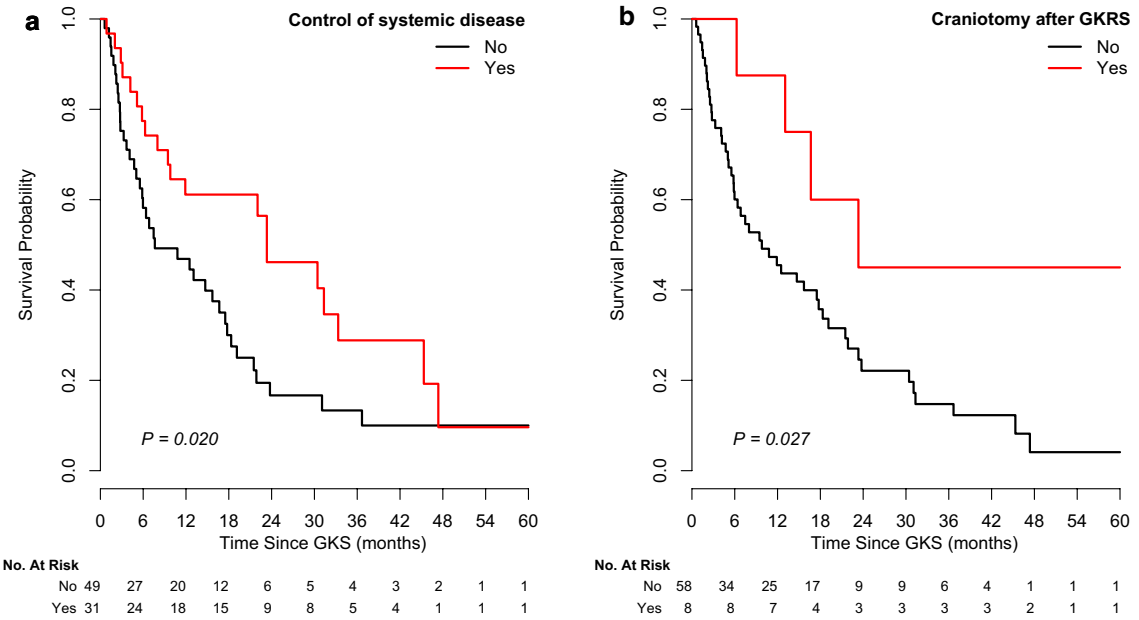


**Fig. 2** Overall survival for patients treated with GKRS stratified by **a** whether patients had good systemic disease control at the time of GKRS treatment, and **b** whether craniotomy was performed post-GKRS. Statistical significance was based on the log-rank test

The median OS in patients in our study was 13.1 months—similar to the 15.7 months reported by Cho et al. [10] and 13 months reported by Matsunaga et al. [11]. In both of these studies, the authors also evaluated which breast cancer subtype confers better prognosis when receiving GKRS and their findings were consistent with ours in that those with HER-2 positive breast cancers appear to have better OS compared to other subtypes. In contrast, Niikura et al. (2014) found that the luminal-HER-2 brain metastasis patients (Luminal B in our study), rather than

those with HER-2 alone had the best survival. Interestingly, while statistically not significant, there were no luminal B patients who died of predominantly neurological causes in our study. HER-2 positive breast cancer patients in general are known to have overall better prognoses but most patients with HER-2 positive breast cancer in our study had also received HER-2 targeted therapy with trastuzumab at some point prior to undergoing GKRS. Although trastuzumab has limited penetration of the blood–brain barrier (BBB), there have been prior studies that have shown its effects were enhanced when compromise of the BBB from radiation, brain metastasis, or meningeal carcinomatosis occurred [12, 13]. These findings may partly explain why patients with HER-2 positive breast cancer had better overall survival compared to other subtypes. Furthermore, patients with HER-2 positive disease have shown to have improved responses and more favorable outcomes with the approval of several HER-2 targeted therapies.

Patients with KPS > 80 had improved OS in our study. This finding is consistent with prior studies showing that those with a better KPS had improved OS when undergoing GKRS [14, 15]. The most commonly used outcome prediction score for brain metastases in the US is the diagnosis-specific Graded Prognostic Assessment (dsGPA) index [16]. In the original study of 4259 patients with brain metastases, the only factor that was found to be important in prediction of outcome for breast cancer patients was the KPS. Since then the dsGPA has been revised to include breast cancer subtype but KPS remains central to the predictive model [17]. Several other outcome scoring systems available for brain metastases patients also include age as one of the key factors in outcome prediction [18]. Our study did not find that age was a significant predictor of survival. In a retrospective study by Kased et al. where 176 patients underwent GKRS for brain metastasis from breast cancer, it was found that those with a KPS ≥ 70 had longer survival times than their counterparts with lower scores [19]. Kased et al. also reported that patients younger than 50 years of age had an improved survival. The lower KPS cutoff of 70 in their study then may suggest that a lower performance status may still correlate with improved OS from GKRS in younger patients. Further, a recent study by Park et al. evaluated scoring systems that predicted survival in elderly patients who received GKRS for brain metastasis, 320 patients over age of 70 were retrospectively analyzed and it was found that KPS ≤ 80 was an independent prognostic factor for short-term survival [20]. This finding in addition to the finding in our study compared to results by Kased et al. may suggest that higher KPS scores > 80 are required in older patients to have a survival benefit from GKRS. Further prospective trials are required to examine this relationship.

In assessing OS in patients receiving GKRS in conjunction with surgical resection, our study found that there was a strong trend on multivariable analysis towards longer survival in those who had surgical resection prior to GKRS. The administration of GKRS rather than WBRT to consolidate surgical resection is currently gaining popularity although the data supporting its use remain controversial [21]. Although radiosurgical hypofractionation alone without surgery for larger lesions allows the avoidance of surgical risk, resection remains the mainstay today in patients with single, large, symptomatic brain metastases. Our study confirms the advantage of surgery and suggests that GKRS is a reasonable adjunct after surgery. Interestingly, on univariate analysis, craniotomy after GKRS was also found to be associated with longer survival. Craniotomy in our institution is offered when follow-up radiological imaging shows persistent an increase in size of lesion after treatment with GKRS. It has been shown by many series that these imaging changes can be seen with either tumor regrowth or a non-neoplastic inflammatory process known as radiation necrosis [22, 23]. Patients who develop radiation necrosis have been shown to have longer survival [24] and in this study 7 of our 9 patients who had craniotomy had pathology confirming radiation necrosis possibly explaining the longer survival in our post-GKRS craniotomy group.

In summary, our retrospective analysis shows that GKRS is a promising therapy for treating brain metastasis from primary breast cancer, particularly in those with HER-2 positivity and high KPS. Of note, 33 (40%) of the patients in our study had 5 or greater number of brain metastasis, and 8 (10%) had 4 or more GKRS treatments. There was no significant difference in OS in those with larger number of brain metastasis present or those needing more GK treatments. Our study suggests that its use may be also beneficial when combined with surgical resection. Furthermore, our findings show that there is no significant improvement in overall survival when GKRS is combined with WBRT. Given the increased chance for neurocognitive preservation with GKRS compared to WBRT, its use for treating brain metastasis should continue to be studied in the context of neurocognition as the primary outcome rather than survival.

## Compliance with ethical standards

**Conflict of interest** James B. Yu: Research funding from twenty-first Century Oncology.

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