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Outcomes and Prognostic Factors of Women with 1–3 Breast Cancer Brain Metastases Treated with Definitive Stereotactic Radiosurgery

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Abstract

Background—As the utilization of definitive stereotactic radiosurgery (SRS) continues to increase for patients with limited brain metastases (BM), clinicians need more specific prognostic tools. We investigated clinical predictors of outcomes in patients with limited breast cancer BM treated with SRS alone.

Methods—We identified 136 patients with breast cancer and 1–3 BM who underwent definitive SRS for 186 BM between 2000 and 2012. The Kaplan-Meier method was used to assess overall survival (OS), regional failure (RF), and local failure (LF). Associations between clinical factors and outcomes were tested using Cox regression. Point scoring system was used to stratify patients based on OS, and the predictive power was tested with concordance probability estimate (CPE).

Results—Median OS was 17.6 months. The 12-month RF and LF rates were 45% and 10%, respectively. On multivariate analysis, >1 lesion (HR=1.6, $p=0.02$), triple negative (TN) disease (HR=2.0, $p=0.006$), and active extracranial disease (ED) (HR=2.7, $p<0.0001$) were significantly associated with worse OS. Point score system was defined using proportional simplification of the multivariate Cox proportional hazards regression function. The median OS for patients with 3.0–

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Conflict of Interest: None

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4.0 points ($n=37$), 4.5–5.5 (28), 6.0–6.5 (37), and 8–8.5 (34) were 9.2, 15.6, 25.1, and 45.1 months ($p<0.0001$, CPE=0.72). Active ED (HR=2.4, $p=0.0007$) was significantly associated with RF. Higher risk for LF was significantly associated with larger BM size (HR=3.1, $p=0.0001$).

Conclusion—Patients with >1 BM, active ED, and TN had the highest risk of death after SRS. Active ED is an important prognostic factor for OS and intracranial control.

Keywords

Brain Metastasis; Stereotactic Radiosurgery; Breast Cancer; Prognostic Factors

INTRODUCTION

Breast cancer is the second most common cause of brain metastases (BM), a growing clinical problem that affects approximately 30% of all women with metastatic disease [1,2]. Among patients with metastatic human epidermal growth factor receptor type-II (HER2) amplified or triple negative disease (TN, estrogen receptor (ER), progesterone receptor (PR), and HER2 negative), over a third of patients will develop BM [3–5]. The incidence of BM appears to be increasing, likely due to earlier diagnosis and prolonged survival with contemporary treatments [6]. In general, BM do not respond well to systemic agents and are managed by radiation therapy (RT), surgery, or both [7–9]. For patients with multiple BM, whole brain radiation therapy (WBRT) remains the standard of care [10]. In patients with limited metastases, stereotactic radiosurgery (SRS) has emerged as a preferred definitive modality as it offers excellent local control, is associated minimal acute and long-term toxicity, and does not significantly interfere with systemic therapy schedules [11–13].

The prognosis of patients with breast cancer BM is poor, with median survival of 4–7 months after WBRT [14–16]. It is imperative for clinicians to have accurate prognostic methods in order to recommend treatments that maximize benefits and minimize toxicities. In 1997, a prognostic index (recursive partitioning analysis, RPA) based on 1,200 patients from three Radiation Therapy Oncology Group (RTOG) trials was created, stratifying patients with BM into three outcome groups [17]. An updated index with 2,000 patients from five trials (graded prognostic assessment, GPA) was published in 2008 [18]. While useful, neither of these indices were specific to a primary diagnosis and only provided general prognostic information independent of histology. Given the unique prognosis of patients with BM of certain primary histologies, a breast cancer-specific GPA (breast-GPA [19]) was created in 2012 with four prognostic groups based on Karnofsky performance status (KPS), age, and receptor subtypes. While this represented a significant advancement in the management of breast cancer patients with BM, the treatments patients received in the breast-GPA analysis varied widely, including WBRT, SRS, surgery, or combinations of the above, potentially confounding clinical outcomes.

In addition to providing excellent intracranial disease control in patients with limited BM, SRS also allows patients to continue on systemic therapy with minimal interruption in order to maximize extracranial disease control due to its single-fraction or hypofractionated nature. In some patients, continuing on systemic treatments without significant delay may be crucial in improving survival. As the utilization of definitive SRS continues to increase for patients

with limited BM, there is a need for better understanding of which patients would most likely benefit from SRS. The hypothesis of this study is that definitive SRS is associated with unique prognostic factors that are different from the factors concluded from the breast-GPA analysis. Clinical factors associated with survival and intracranial disease control after definitive SRS for 1–3 breast cancer BM were investigated.

MATERIALS AND METHODS

Study Population

Patients with 1–3 breast cancer BM treated with SRS alone as the initial definitive therapy from 2000 through 2012 at our institution were eligible. Institutionally, we use a cutoff of 3 BM with each lesion being less than 4cm in maximum diameter in selecting patients for single-fraction SRS as the initial definitive therapy. Patients with >3 BM generally received WBRT, and patients with >4cm BM often received partial brain RT or WBRT. Patients with prior cranial RT, leptomeningeal disease, or with more than one primary malignancy at BM diagnosis were excluded. All patients had histologically confirmed adenocarcinoma of the breast in the primary and/or a metastatic site. Approval of the Institutional Review Board was obtained. Medical records were reviewed and the RPA class and breast-GPA score were calculated for each patient. The standard followup consisted of MR imaging at 6–8 weeks post-SRS and then every 2–3 months thereafter. Accelerated MR-based followup was performed at shorter intervals if clinically warranted.

SRS

A post gadolinium-enhanced T1-weighted MRI with 2-mm slices was obtained before SRS and reviewed by a board-certified neuroradiologist prior to treatment. Patients were immobilized in a Brown-Roberts-Wells (BRW) frame (Integra Radionics, Burlington, MA). On the day of treatment, a 2-mm sliced computed tomography (CT) study was acquired with intravenous contrast. The CT images were transferred to the treatment planning system (BrainLAB, Feldkirchen, Germany) and fused to the T1-weighted MRI for target delineation. The gross target volume (GTV), defined as the contrast-enhancing lesion, was delineated on T1-weighted MRI and on the planning CT (contrast enhancement on MRI and CT). The planning target volume (PTV) was defined as a three-dimensional median 2-mm margin around the GTV. The radiation treatment plans consisted of 8–12 non-coplanar static fields using the micro-multileaf collimator with 3-mm leaves for field shaping. The plans were developed such that the 80% isodose line (IDL) encompassed the PTV in the most conformal manner possible, and the determined dose was prescribed to the 80% IDL. Treatment dose and quality criteria including dose homogeneity and conformation index followed RTOG guidelines [20,21].

Statistical Analysis

Survival time, local failure (LF), and intracranial regional failure (RF) rates were measured from the date of SRS to the date of event or to last clinical follow up for patients without event. LF was defined as progression of disease within the SRS targets and was determined both radiographically and clinically by the treating physicians' consensus at our institutional SRS tumor board involving radiation oncology, neurosurgery, and neurology. The utilization

of advanced imaging modalities (PET-CT brain and MRI perfusion) was allowed based on physician preference. RF was determined radiographically and was defined by the development of new brain metastasis outside the treated SRS target(s).

Time to progression and overall survival (OS) were estimated using the Kaplan-Meier method. Prognostic factors for OS, LF, and RF were analyzed by univariate and multivariate Cox proportional hazards regression analysis. Univariate analyses for OS and RF were based on patients and performed selecting from the following factors: age, RPA class, KPS (≥ 80 vs. <80), number of BM (1 vs. 2–3), extracranial disease status (active vs. absent/stable), extracranial disease status (present vs. absent), active systemic therapy (systemic treatments within 30 days before and/or after SRS, yes vs. no), breast-GPA score, and receptor subtypes assigned as: HR+ (hormone receptor positive, ER and/or PR positive)/HER2– vs. HR+/HER2+ vs. HR–/HER2+ vs. TN (HR–/HER2–). Active extracranial disease was defined as evidence of new or progressing systemic disease on imaging within 3 months of SRS. Presence of extracranial disease was defined as with evidence of extracranial distant metastasis, which could be either active or stable, at the time of SRS. Univariate analysis for LF was based on lesions and performed selecting from the following factors: age (continuous and dichotomized at median age of 58 yrs), RPA class, KPS, number of BM, extracranial disease status, active systemic therapy, receptor subtypes, tumor maximal dimension, RT dose, margin around GTV, and location of the tumor. Variables with a p value ≤ 0.10 on univariate analysis were considered candidates for the stepwise multivariate analysis. Chi-square test was used to compare salvage therapy methods based on patient's extracranial disease status. A p value <0.05 is considered statistically significant.

A point score system as a proportional implication of the multivariate Cox proportional hazards regression prediction function was generated for overall survival. The point scoring system was constructed based on the hazard ratios (HR) of the prognostic factors in the multivariate analysis model. We assigned 1 point to the reference level which has the highest risk and greater points were given to the comparison levels that have lower risks according to HR for each prognostic factor proportionally. For example, patients with active extracranial disease had 3 times higher risk of death after SRS compared to patients with stable/absent extracranial disease based on HR, therefore, 3 points were given to patients with stable/absent extracranial disease and 1 point was given to patients with active extracranial disease. A total score for each patient was generated based on points scored by clinical characteristics, and patients were then classified into 4 categories according to the quartiles. The predictive power the point score system on OS was assessed using concordance probability estimate (CPE) [22]. Concordance probability ranges between 0 and 1, where 1 indicates perfect prognostic power. Further pairwise comparison using Kaplan-Meier survival function and Log-rank test was performed. CPE analysis was also performed using the breast-GPA and RPA scores. Comparison between CPEs was performed using bootstrap resampling method.

RESULTS

Patient characteristics

The study population comprised of 136 patients with 186 treated lesions. The median follow-up time for survivors was 23.4 months (2.3–140.2 months). The median age of patients was 58 years, and the majority of patients (89%) had KPS ≥ 80 . Eighty patients (59%) were treated to 1 BM, and 63 (46%) had absent/stable extracranial disease. When stratified by receptor subtypes, 32% of patients had HR+ disease, 42% had HER2+ disease, and 26% had TN disease. Similar distribution was observed in the 186 lesions. Detailed patient and lesion data are presented in Table 1.

Overall survival

At the time of assessment, 32 patients (24%) were alive. The median OS was 17.6 months (95% CI=15.4–23.0 months). OS was 65% (95% CI=57–73%) at 12 months and 41% (95% CI=32–49%) at 24 months. On univariate analysis, the factors associated with highest risk for death were: KPS <80 (HR=2.5, $p=0.002$), >1 lesion at presentation (HR=1.7, $p=0.009$), TN disease (vs. HR+/HER2–, HR=1.8, $p=0.02$), active extracranial disease (HR=3.0, $p<0.0001$), not on active systemic therapy (HR=1.5, $p=0.049$), and RPA class <1 (HR=2.1, $p=0.01$). Interestingly, while active extracranial disease was highly associated with OS, the presence of extracranial disease (can be either active or stable) was not found to be significantly associated with OS ($p=0.12$). On multivariate analysis, >1 lesion at presentation (HR=1.6, $p=0.02$), TN disease (vs. HR+/HER2–, HR=2.0, $p=0.006$), and active extracranial disease (HR=2.7, $p<0.0001$) remained significantly associated with worse OS (Table 2).

Using proportional simplification of the multivariate regression model, each significant factor was assigned a point from 1–4, with 1 representing predictive clinical variables associated with worse OS, and 4 representing variables associated with best OS based on hazard ratios. Patients were then classified into 4 categories according to quartiles of point scoring system. OS differed significantly among the 4 groups ($p<0.0001$). The median OS for patients in Group 4 (8–8.5 points) was 45.2 months, compared to 25.1 months for patients in Group 3 (6–6.5 points, $p=0.004$ by log-rank test). Group 2 patients (4.5–5.5 points, median OS=15.6 months) had significantly worse OS when compared to Group 3 ($p=0.005$), and significantly better when compared to Group 1 (3.0–4.0 points, median OS= 9.2 months, $p=0.02$). Table 3 shows the scoring system in detail; a graphic representation is shown in Figure 1. A high concordance probability estimate (CPE=0.715, 95% CI=0.675–0.755) was observed, indicating the robust predictive power of the risk groups derived. The prognostic power of the SRS-specific point scoring system was also found to be significantly greater than the breast-GPA (CPE=0.658, 95% CI=0.614–0.702, $p=0.0003$) and the RPA (CPE=0.558, 95% CI=0.515–0.600, $p<0.0001$).

Regional failure

Seventy (51%) patients demonstrated regional failure. The 12 months and 24 months RF rates were 45% (95% CI=36–54%) and 57% (95% CI=48–67%), respectively. The median time to RF was 14.8 months (95% CI=10.2–27.0 months). On univariate analysis, the factors

associated with RF were: >1 lesion at presentation (HR=1.7, $p=0.03$), active extracranial disease (HR=2.4, $p=0.0007$), not on active systemic therapy (HR=1.9, $p=0.02$), and RPA class >1 (HR=1.9, $p=0.04$). On multivariate analysis, active extracranial disease (HR=2.4, $p=0.0007$) and not on active systemic therapy (HR=1.9, $p=0.01$) remained significantly associated with RF. Of the 70 patients who developed RF, 21 (30%) received additional SRS (median time to SRS= 6.8 months), 24 (34%) received WBRT (median time to WBRT=6.4 months), 5 (7%) received partial brain RT (PBRT, median time to PBRT= 9.4 months) as the first salvage therapy, and 40% of patients were symptomatic prior to salvage RT. Of the patients who received salvage therapy, 26 patients had active extracranial disease at SRS, and 65% of these patients received WBRT as the first salvage treatment for RF, while only 29% of the 24 patients who had absent/stable extracranial disease at SRS underwent salvage WBRT ($p=0.01$). Moreover, only 27% of patients with active systemic disease received additional SRS as the first salvage therapy for RF, while 58% of patients with absent/stable systemic disease received salvage SRS ($p=0.01$).

Local failure

Thirty-three (18%) lesions demonstrated local failure. The 12-month and 24-month LF rates were 10% (95% CI=6–17%) and 29% (95% CI=21–39%), respectively. The median time to LF was not reached. On univariate analysis, the factors associated with LF were: 1 lesion at presentation (HR=2.9, $p=0.009$), TN disease (vs. HR+/HER2–, HR=3.6, $p=0.03$), larger tumor maximum dimension (HR=3.1, $p=0.0001$), and lower RT dose (HR=1.2, $p=0.01$). On multivariate analysis, larger tumor maximal dimension (HR=3.1, $p=0.0001$) was the only factor that remained significantly associated with LF. When separated into two groups based on median tumor maximal dimension (Figure 2), tumors ≤ 0.9 cm (87 lesions) had local control rates of 94% and 83% at 12 months and 24 months, respectively. Tumors >0.9 cm (99 lesions) had 12 and 24-month local control rates of 85% and 62%, respectively ($p=0.003$). The pathologically confirmed radionecrosis rate, defined as with treatment effect and no tumor present on surgical pathology, was 8.6% (16 lesions).

DISCUSSION

The development of brain metastases (BM) can impact disease outcomes diversely in patients with metastatic breast cancer due to the heterogeneous nature of the disease. Identifying receptor status as a risk factor for developing BM [3,23,24], Sperduto et al. published an updated breast-GPA in 2012 [19] incorporating KPS, receptor subtypes, and age in stratifying patients into 4 groups based on prognosis. It provided a valuable predictive scale for the care of breast cancer patients with BM; nevertheless, the patients included underwent a wide range of therapeutic interventions: 33% of the patients received WBRT, 29% received SRS, and 38% of the patients underwent surgery in combination with RT.

Recently, SRS has emerged as the favored definitive treatment modality for patients with limited BM. It is efficacious in tumor control and is associated with minimal toxicities [12,13,25]. In a retrospective analysis of 198 patients with breast cancer BM, Lee et al. found OS differed significantly between patients treated with SRS and WBRT [26]. While

we must interpret the result cautiously, the study posed the possibility that specific clinical factors are prognostic of survival and intracranial disease control after SRS.

Overall Survival

We observed a median OS of 17.6 months after SRS for breast cancer patients with BM, similar to other published survival times after SRS with or without WBRT [27–29]. On multivariate analysis, progressive extracranial disease was the strongest clinical predictor for death after SRS. The breast-GPA excluded the presence or absence of extracranial status as a variable as the authors did not find it to be a significant prognostic factor in survival [19]. It was speculated that the lack of significance was due to the success in systemic treatments. We demonstrated similar findings. When patients were classified based on active vs. absent/stable extracranial disease, active extracranial disease was highly prognostic of poor survival outcome. However, when patients were classified based on present (can be either active or stable) vs. absent extracranial disease, the presence of extracranial disease was not significantly associated with overall survival. With the improvements made in systemic treatments, increasing numbers of patients with metastatic breast cancer are having protracted survival with controlled systemic disease. This is clearly evident with the introduction of trastuzumab in patients with HER2+ breast cancer [30], while TN breast cancer patients who lack efficacious systemic therapies continue to have the worst OS. This was also observed in our study, with HER2+ status strongly predictive for improved OS and TN status leading to the highest risk of death. The presence of extracranial disease may not be an accurate surrogate for survival after treatment of breast cancer BM as the important distinction actually lies between active versus stable systemic disease.

Using proportional simplification of the multivariate regression model, patients in our study were stratified into 4 groups based on a point scoring system. We identified a low-risk subgroup (Group 4) of patients with HER2+ disease, absent/stable extracranial disease status, and 1–3 BM found to have excellent outcome and a median OS of 45 months after SRS. In contrast, patients in the high-risk subgroup (Group 1) had a median survival of 9.2 months. All Group 1 patients demonstrated active extracranial disease at the time of SRS. As SRS alone is offered more frequently as the definitive therapy in breast cancer patients with limited BM, an SRS-specific risk stratification is instrumental in guiding clinicians in treatment decisions making. Patients with low risk of death benefit the most from upfront definitive SRS alone. In patients with high risk of death after SRS due to progressive systemic disease, the treatment must be individualized by considering the clinical picture. In patients with progressive but limited systemic disease, definitive SRS provides the benefit of minimal systemic therapy interruption, allowing medical oncologists to attempt to optimize extracranial disease control. It may also be reasonable to consider definitive SRS with WBRT in this patient population in order to maximize CNS control prior to starting aggressive systemic treatments.

Intracranial Progression

We observed a median time of 14.8 months to the development of new BM after SRS in 51% of our patients. On multivariate analysis, progressive extracranial disease was the strongest clinical predictor for regional failure after SRS. Extracranial disease status was

also identified as a predictor for regional failure in a large series of SRS as primary and salvage treatment for BM from breast cancer reported by Kondziolka et al. [29]. While we did not find receptor subtype to be associated with RF, it has been reported by Dyer et al. [31] and Akyurek et al. [28]. It is possible that receptor subtype was a surrogate for extracranial disease status but the studies lacked patient numbers to demonstrate its significance.

One important distinction from our investigation and prior breast BM SRS studies examining risk factors for outcomes [28,29,31] is that our strict inclusion of only patients undergoing SRS alone as the upfront definitive therapy. By excluding patients who received prior or adjuvant WBRT following SRS, we eliminated the confounding effect of WBRT in identifying risk factors for regional failure. From our findings, we concluded that patients with progressive extracranial disease not only had the highest risk of death after SRS but also had the highest risk in developing new BM.

Of the patients who developed RF, 71% received salvage therapy 6–9 months after treatment in the form of SRS, WBRT, or PBRT. We demonstrated that patients with active systemic disease at SRS not only are more likely to develop RF, these patients also are more often salvage by WBRT (65% vs. 29% in patients with absent/stable extracranial disease, $p=0.01$), likely due to multiple BM recurrence. Development of new BM can cause morbidities such as neurologic deficits and functional impairment. Due to the high risk of RF, it is reasonable to consider the addition of WBRT, or WBRT alone, in breast cancer patients with limited BM with active extracranial disease. Nevertheless, we also found that WBRT salvage was delayed by a median of 6 months after definitive SRS in these patients. It is, therefore, important to have multidisciplinary input on the most appropriate management for patients with active systemic disease. In these patients, upfront SRS alone can potentially limit delays on the initiation of chemotherapy and will provide a time window for medical oncologists to maximize systemic control until salvage therapy is needed for RF. Our finding provides important information for trials designed to utilize the time window in testing potentially more efficacious therapies for the patients, including targeted or molecular therapy.

We observed excellent local control rate of 90% with lesion-based analysis at 1-year after SRS. Kondziolka et al. reported 90% control rate after SRS with lesion-based analysis [29]. Akyurek et al. reported 1-year local control rate of 79% with patient-based analysis [28]. Both of these series included breast cancer patients with BM treated with SRS in the salvage setting (after WBRT) and more advanced intracranial disease (>3 BM) so it is difficult to make direct comparisons. However, what is consistent among the referenced studies and our series was the association between local control and tumor size, with smaller lesions demonstrating lower likelihood of LF. Using the median maximal dimension of 0.9cm as a cutoff, we observed 1- and 2-year LF probabilities of 6% and 17% with lesions ≤ 0.9 cm, and 15% and 38% in lesions >0.9 cm. This finding argues for the importance of early SRS therapy with the diagnosis of limited BM in patients with metastatic breast cancer.

In summary, we identified extracranial disease status as the most important clinical prognostic factor for survival and intracranial progression after SRS in breast cancer patients

with limited BM. Patients with active extracranial disease, TN disease, and >1 BM on presentation were at higher risks of death after SRS. A breast BM SRS-specific prognostic scoring system was created based on systemic disease status, receptor subtypes, and number of lesions at presentation to guide clinicians in selecting the most appropriate treatment for patients with limited breast BM. Our scoring system functions as a guide for clinicians and is designed to complement multidisciplinary decision making and is valuable in clinical trial design.

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SUMMARY

As the utilization of definitive SRS continues to increase for patients with limited brain metastasis, there is a need for better understanding of which patients would most likely benefit from SRS. We identified multiple clinical factors associated with survival and intracranial disease control after definitive SRS for 1–3 breast cancer brain metastasis, with extracranial disease status found to be the most significant risk factor. We also created a SRS-specific prognostic scale for breast cancer brain metastasis.

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Figure 1. Kaplan-Meier curves for overall survival by patient groups based on point scoring system. Median survival time for Group 1 (3.0–4.0 points)= 9.2 months, Group 2 (4.5–5.5 points)= 15.6 months, Group 3 (6.0–6.5 points)= 25.1 months, and Group 4 (8–8.5 points)= 45.2 months). Log-rank test $p < 0.0001$.

Figure 2.
Kaplan-Meier curves for local control by median tumor maximal dimension (0.9cm).
Tumors $\leq 0.9\text{cm}$ demonstrated significantly better local control compared to tumors $> 0.9\text{cm}$
(log-rank test $p=0.003$).

Table 1

Patient and lesion characteristics and treatment data

Characteristics	Patient Number (n=136, %)	Lesion Number (n=186, %)	Median (range)
Age (yr)			58 (24–84)
KPS			
70	15 (11.0)		
80	121 (89.0)		
Number of lesions			
1	80 (58.8)		
2–3	56 (41.2)		
Extracranial disease			
Absent/stable	63 (46.3)		
Active	73 (53.7)		
Active chemotherapy			
Yes	104 (76.5)		
No	32 (23.5)		
RPA class [17]			
I	28 (20.6)		
II	106 (77.9)		
III	2 (1.5)		
Breast-GPA points [19]			
3.5–4.0 (Group 4)	39 (28.7)		
2.5–3.0 (Group 3)	47 (34.6)		
1.5–2.0 (Group 2)	47 (34.6)		
0.0–1.0 (Group 1)	3 (2.2)		
Receptor Subtypes			
HR+/HER2–	43 (31.6)	63 (33.9)	
HR+/HER2+	35 (25.7)	49 (26.3)	
HR–/HER2+	22 (16.2)	27 (14.5)	
HR–/HER2–	36 (26.5)	47 (25.3)	
Location of lesion			
Supratentorial		128 (68.8)	
Infratentorial		58 (32.2)	
Tumor maximal dimension (cm)			0.9 (0.2–3.4)
SRS dose (Gy)			21 (14–24)
Margin from GTV to PTV (cm)			0.2 (0.0–0.4)

Abbreviations: breast-GPA= breast cancer-specific Graded Prognostic Assessment for brain metastases; GTV= gross target volume; HER2= human epidermal growth factor type-2; HR= hormone receptor; KPA= Karnofsky performance status; PTV= planning target volume; RPA= recursive partitioning analysis; SRS= stereotactic radiosurgery.

Table 2

Univariate and multivariate Cox regression analyses for overall survival

Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (continuous, yr)	1.0 (0.99–1.02)	0.62		
Age (<58 vs. ≥58, yr)	1.1 (0.72–1.57)	0.75		
KPS (<80 vs. ≥80)	2.52 (1.42–4.45)	0.002		
Number of lesions (2–3 vs. 1)	1.7 (1.14–2.52)	0.009	1.61 (1.07–2.42)	0.02
Receptor subtypes				
HR+/HER2–	1.00		1.00	
HR+/HER2+	0.40 (0.23–0.69)	0.001	0.45 (0.26–0.79)	0.006
HR–/HER2+	0.36 (0.19–0.71)	0.003	0.49 (0.24–0.98)	0.045
HR–/HER2–	1.78 (1.11–2.87)	0.02	1.98 (1.22–3.20)	0.006
Extracranial disease (active vs. absent/stable)	3.00 (2.00–4.50)	<0.0001	2.73 (1.80–4.14)	<0.0001
Extracranial disease (present vs. absent)	1.55 (0.89–2.68)	0.12		
Systemic therapy (active vs. no)	0.65 (0.42–0.998)	0.049		
RPA class (2 vs. 1)	2.07 (1.19–3.58)	0.01		
Breast-GPA points [‡]				
1.5–2.0	1.00			
2.5–3.0	0.38 (0.24–0.61)	<0.0001		
3.5–4.0	0.20 (0.12–0.36)	<0.0001		

Abbreviations: HR (95% CI)= hazard ratio (95% confidence interval), all other abbreviations same as Table 1.

[‡]Only 3 patients had breast-GPA score of 0.0–1.0; the cohort is too small to be reliably tested in a regression model and therefore was excluded from analysis. Breast-GPA was not included in the multivariate model.

Table 3

Point scoring system of significant clinical factors and median overall survival by patient group based on the point scoring system.

Predictive Factors	Multivariate Analysis Model HR (95% CI)	Point Scoring System
Number of lesions		
1	1.00	1.5
2–3	1.61 (1.07–2.42)	1
Receptor subtype		
HR+/HER2–	1.00	2
HR+/HER2+	0.45 (0.26–0.79)	4
HR–/HER2+	0.49 (0.24–0.98)	4
HR–/HER2–	1.98 (1.22–3.20)	1
Extracranial disease		
Absent/stable	1.00	3
Active	2.73 (1.80–4.14)	1

Group	Point Scoring	Patient Number (%)	Median OS (months, 95% CI)
1	3.0–4.0	37 (27.2)	9.2 (5.4–13.2)
2	4.5–5.5	28 (20.6)	15.6 (7.9–23.0)
3	6.0–6.5	37 (27.2)	25.1 (14.9–37.2)
4	8.0–8.5	34 (25.0)	45.2 (31.4- not reached)

Abbreviations: OS= overall survival, other abbreviations same as Table 1 and Table 2.