CLINICAL INVESTIGATION

Potential prognostic markers for survival and neurologic death in patients with breast cancer brain metastases who receive upfront SRS alone

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ABSTRACT

Purpose/Objectives: Stereotactic radiosurgery (SRS) is used as a treatment option for breast cancer brain metastases. It is unclear what factors predict neurologic death for these patients.

Materials/Methods: A total of 128 patients with breast cancer brain metastases were treated with upfront SRS alone in this study. Survival was estimated using the Kaplan-Meier method. Clinicopathologic factors evaluated included age, ER/PR status, Her2 status, numbers of brain metastases treated, minimum SRS dose, disease-specific GPA, extracranial disease status and systemic disease burden.

Results: ER or PR positivity was associated with a trend towards decreased neurologic death (subdistribution hazard ratio (sHR) = 0.54, p=0.06). Factors associated with non-neurologic death include extracranial disease status (sHR = 2.02, p=0.02) and dose (sHR = 1.11, p=0.02); Her2-positivity was associated with reduced hazard of non-neurologic death (sHR 0.52, p=0.05).

Conclusions: ER/PR positivity was associated with a trend towards less neurologic death. HER2 positivity was associated with a trend towards less non-neurologic death.

Keywords: breast cancer, brain metastases, neurologic death, prognostic factors, breast cancer metastases

INTRODUCTION

There has been a recent trend within the population of patients affected by brain metastasis from one with large symptomatic brain metastases¹ to one of smaller occult metastases that are detected at time of staging². The implications of this trend are that some prior studies conducted in the former population affected largely by symptomatic metastases may no longer be valid in the current population. In the past, a diagnosis of brain metastasis was one that nearly universally led to a poor prognosis, but due to lead time bias of better screening³ and improved CNS-directed therapies^{4,5}, the likelihood of dying of brain metastases has decreased⁶.

The breast cancer brain metastasis population is one that is unique in many ways. First, these patients generally have a better prognosis than other patients with brain metastasis due to more effective systemic treatment options⁷. Because of the efficacy of many systemic therapies, but suboptimal blood brain barrier penetration, the significance of brain metastases to a patient's clinical course is often great. In addition, these patients have a greater likelihood of ultimately experiencing leptomeningeal metastases⁸.

Although several published studies have outlined the prognostic factors involved in brain metastases from breast cancer^{9–12}, the likelihood of neurologic death in the modern setting has not been described in detail. Furthermore, it is unclear which factors drive the likelihood of neurologic death in this population. The present study is a single institution retrospective report with the aims of exploring the prognostic markers for neurologic death in a cohort that received stereotactic radiosurgery (SRS) as therapy without initial whole brain radiation therapy (WBRT) or surgery.

METHODS

Study Population

Between July 2001 and March 2017, a total of 128 patients with brain metastases from breast cancer were treated with upfront SRS alone. Patients with a history of prior WBRT were excluded from the study as this study aimed to assess outcomes of the upfront SRS paradigm. This study was approved by the Wake Forest School of Medicine Institutional Review Board. Patient electronic medical records were used to obtain patient and cancer characteristics. Clinico-pathologic factors that were abstracted included: age, ER/PR status, Her2 status, numbers of brain metastases treated, minimum SRS dose, disease-specific GPA, extracranial

disease status and systemic disease burden were evaluated as potential predictors of neurologic death. Extent of extracranial disease^{13,14} and disease-specific graded prognostic assessment (DS-GPA)¹⁵ were defined in prior reports. Oligometastatic disease was defined as ≤ 5 brain metastases without diffuse involvement of any one organ. Widespread disease included patients with >5 metastases or diffuse distant organ involvement.

Radiosurgical Technique

Radiosurgery was performed on a Leksell Gamma Knife Model B (years 2000–2004), Model C (2004–2009), and Perfexion (2009–2013, Elekta AB, Stockholm). A stereotactic headframe was applied by a neurosurgeon for immobilization. High-resolution, thin-slice, contrast-enhanced magnetic resonance imaging was performed on the day of treatment using a 3T unit (GE Healthcare, Waukesha, WI). Median minimum dose delivered to the tumor margin was 20 Gy (range: 10–24 Gy). Dose was generally prescribed to the 50% isodose line according to guidelines published by Shaw et al¹⁶.

Response Assessment and Follow Up

Patient survival from time of SRS was determined from the electronic medical record and the Social Security Death Index. A local failure was determined as either: 1) pathologically proven from surgical specimen, or 2) included an increase in 25% of the volume of a lesion with a corresponding increase in perfusion on perfusion weighted MRI, as previously reported¹⁷.

The brain metastasis velocity was calculated as previously reported by Farris et al¹⁸. In brief, the cumulative number of new brain metastases was calculated and divided by the total time (in years) to last follow-up MRI from time of original SRS. Brain metastasis velocity (BMV) was calculated for each patient in the study to measure the aggressiveness of re-seeding the brain with new metastases. Neurologic death was defined as previously reported by Mctyre et al¹⁹. In brief, patient had neurologic death if they died with progressive neurologic decline regardless of the status of extracranial disease. Patients with severe neurologic dysfunction dying of intercurrent disease were also considered to have died of neurologic death.

Statistics

Survival was estimated using the Kaplan-Meier method. Cumulative incidence of distant brain failure, neurologic and non-neurologic death were estimated using competing risk methodology²⁰. Competing risks models were developed to estimate the single variable sub-

distribution hazard ratios (sHR) associated with each predictor of these events. Potential predictors for neurologic death and non-neurologic death entered into the univariate model included age, number of metastases, ER/PR/Her2 status, extracranial disease burden, extracranial disease status, DS-GPA, and minimum margin dose delivered to a brain metastasis (as a surrogate for largest metastasis size). Statistically significant ($p < 0.05$) variables identified on univariate analysis were included in forward stepwise regressions to identify the multivariable models that minimized the Akaike information criterion.

RESULTS

A total of 128 patients were included in the analysis with a median age of 56. Of these patients, 53% were ER/PR-positive, 39% were Her2-positive and 36% had a DS-GPA greater than 2. Median follow-up was 9.9 months (IQR, 2.7-21.6). Patient characteristics are included in Table 1.

Table 1. Patient Characteristics

	n (%)
	Median (IQR)
Total	128
Age	56 (44-65)
Number of Brain Metastases at SRS	2 (1-2)
ER/PR Status	
Positive	64 (53)
Negative	56 (47)
Her2 Status	
Positive	47 (39)
Negative	73 (61)
Extracranial Disease Burden	
None	24 (19)
Oligometastatic	25 (20)
Widespread	55 (43)
Unknown	24 (19)
Disease Status	
Stable	79 (62)
Progressive	27 (21)
Unknown	22 (17)
DSGPA >2	46 (36)
Lowest Margin Dose	19.5 (16.5-22)

Figure 1. Overall survival for the entire patient population. Solid line: Kaplan-Meier estimate for survival; dashed lines: 95% CI

Overall Survival

Median overall survival for the cohort was 16.3 months (95% CI, 10.6-19.2). Figure 1 depicts the rates of overall survival at 1, 3, and 5 years, which were 56%, 18% and 10%, respectively.

Cause of Death

The cumulative incidence of neurologic death using competing risk methodology at 1, 3 and 5 years was 17%, 34%, and 39%, respectively. The cumulative incidence of non-neurologic death was 31%, 48%, and 51% for the same time points, respectively. One-year cumulative incidence of neurologic death was 12% for ER/PR-positive patients and 22% for ER/PR-negative patients (Gray's $p = 0.08$). Cumulative incidence of non-neurologic death at 1-year were 33% and 23% for ER/PR positive and negative patients, respectively (Gray's $p = 0.05$). One-year cumulative incidence of neurologic death and non-neurologic death for Her2-positive and Her2-negative patients were 19% v. 15% (Gray's $p = 0.29$) and 20% v. 34% (Gray's $p = 0.04$). Competing-risk cumulative incidence curves for neurologic and non-neurologic death as stratified by ER/PR and Her2 status are depicted in Figure 2.

Development of New Brain Metastases

Cumulative incidence of distant brain failure at 6, 12 and 24 months for the entire population was 24%, 41%, and 51%, respectively. One year cumulative incidence of distant brain failure was 47% for ER/PR positive

Figure 2. Cumulative incidence of neurologic and non-neurologic death using competing risk methodology, stratified by ER/PR and Her2 status. A: neurologic death by ER/PR status. B: non-neurologic death by ER/PR status. C: neurologic death by Her2 status. D: non-neurologic death by Her2 status.

patients and 38% for ER/PR negative patients (Gray's $p=0.22$). One year cumulative incidence of distant brain failure for Her2 positive and negative patients was 40% and 45%, respectively ($p=0.28$). At first failure, median brain metastasis velocity (BMV) was 4.86 (IQR 1.77-11.4). BMV was not associated with ER/PR ($p=0.93$) or Her2 status ($p=0.97$).

Salvage Therapy

Fifty-four (42%) patients received at least one salvage SRS for new brain metastases at a median time of 18.3 months (95% CI, 13.1-36.6). Eighteen (14%) patients received multiple courses of salvage SRS. Thirty-three (26%) patients received salvage WBRT; median WBRT-free survival was 11.2 months (95% CI, 8.7-16.3). At 1, 2 and 5 years after SRS, 49%, 23% and 9% of patients were alive and free of WBRT. Summary of salvage procedures are found in Table 2.

Predictors of Neurologic and Non-Neurologic Death

Univariate subdistribution hazards analyses for neurologic and non-neurologic death using competing-risks methodology is shown in Table 3. ER or PR positivity was associated with a trend towards decreased neurologic death (sHR 0.54, $p=0.06$). Oligometastatic (sHR 0.25, $p=0.02$) and widespread (sHR 0.38, $p=0.01$) extracranial disease, as compared to none, was also associated with a decreased hazard of neurologic death. Factors associated with non-neurologic death include oligometastatic disease (sHR 5.46, $p<0.01$), widespread extracranial disease (sHR 3.77, $p=0.01$), progressive disease status (sHR 2.02, $p=0.02$) and dose (sHR 1.11, $p=0.02$). Her2-positivity was associated with a trend toward reduced hazard of non-neurologic death (sHR 0.52, $p=0.05$). Number of metastases analyzed as a continuous variable did not significantly affect hazard of neurologic or non-neurologic death. Multivariate analysis of the covariates did not yield any significant findings.

Table 2. Clinical Outcomes and Salvage Therapy

Overall Survival, median (95% CI)	16.30 (10.6-19.2)
DBF, CI (%)	
1-year	41
2-year	51
BMV* at first failure, median (IQR)	4.86 (1.70-12.23)
Salvage WBRT, n (%)	33 (26)
Salvage SRS, n (%)	54 (42)
Number of Salvage SRS, n (%)	
1	36 (28)
2	11 (9)
3	6 (5)
4	-
5	1 (1)
Overall survival post-DBF, median (95% CI)	13.2 (9.7-19.6)
Neurologic Death, CI (%)	
1-year	17
2-year	29
RTOG Toxicity, n (%)	
None	88 (72)
Grade 1	18 (15)
Grade 2	11 (9)
Grade 3	6 (5)
*63 patients with DBF for which calculation of BMV possible	

DISCUSSION

In a large series of over 700 patients of multiple brain metastasis histologies, Mctyre et al found the cumulative incidence of neurologic death at 1 year to be 24%. The cumulative incidence of neurologic death of 17% at one year in the current study is not appreciably different from those findings. Patients with melanoma histology have classically experienced a high rate of neurologic death, predominantly due to hemorrhagic metastases and distant brain failure²¹. The 31% cumulative incidence of non-neurologic death in this series also appears not to be significantly different from the non-neurologic death rate in prior series¹⁹.

The present study shows an association of ER/PR primary positivity with lower cumulative incidence of neurologic death. This may be because HER2+ and triple negative breast cancers (which are not treated

with hormonal therapy) have a greater aggressiveness in seeding the brain with metastases. Moreover, these patients may also have a greater likelihood of leptomeningeal metastases, which is a common cause of neurologic death in the breast cancer population²². While there have been improvements in systemic therapies for breast cancer, the systemic options that cross the blood brain barrier are quite limited^{17,23}. The decreased incidence in non-neurologic death associated with HER2 positive status supports this ability of systemic therapies to control extracranial disease leaving the intracranial compartment to local therapies.

An increased cumulative incidence of neurologic death was associated with a higher BMV, which also portended a poorer overall prognosis. Brain metastasis velocity is a novel metric recently described by Farris et al to predict overall survival and neurologic death in patients who have received SRS without prior WBRT¹⁸. It has been validated using a multi-institutional dataset²⁴. Both datasets identified the cohort of greater than 13 metastases/year as a population with poor prognosis. A possible clinical implication in breast cancer patients with high BMV is that these may be patients that may be better treated with WBRT due to a significant burden of CNS disease.

There are several limitations to the current study. As a retrospective series, it is limited by patient selection bias and the treatment biases of the treating institution. While the size of the series is large for a breast cancer brain metastasis series, it is underpowered to detect factors that make smaller contributions to prognosis for neurologic death. Because of its limitations, the findings of the current study are limited to hypothesis generation. In spite of its limitations, this is the first modern series to assess the factors that affect cause of death in patients with brain metastasis of breast carcinoma. If these data are validated, they provide important prognostic markers for cause of death in breast cancer brain metastasis patients that have the potential to lead to the optimization of management.

CONCLUSION

ER/PR positivity was associated with a trend towards less neurologic death, while HER2 positivity was associated with a trend towards less non-neurologic death. High BMV was associated with both poor prognosis and high rate of neurologic death. If these data can be validated, they would provide important prognostic biomarkers for cause of death in breast cancer brain metastasis patients.

Table 3. Univariate subdistribution hazards analysis for neurologic and non-neurologic death

	Neurologic Death			Non-neurologic Death		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.99	0.96-1.01	0.32	1.02	1.00-1.04	0.03
No. Metastases	1.06	0.92-1.24	0.42	1.03	0.90-1.17	0.68
Extracranial Disease Burden (v. none)						
Oligometastatic	0.25	0.08-0.77	0.02	5.46	1.95-15.3	<0.01
Widespread	0.38	0.18-0.80	0.01	3.77	1.40-10.2	0.01
Disease Status (progressive v. stable)	0.53	0.20-1.41	0.20	2.02	1.12-3.64	0.02
ER/PR positive	0.54	0.29-1.02	0.06	1.79	0.98-3.27	0.06
Her2	1.45	0.78-2.69	0.24	0.52	0.27-0.99	0.05
DSGPA >2	0.70	0.34-1.42	0.32	0.88	0.50-1.57	0.67
Lowest Margin Dose		0.84-1.02	0.11	1.11	1.02-1.21	0.02
0.92						

CI, confidence interval; HR, hazard ratio; NC, not calculated; No., number; WBRT, whole brain radiotherapy

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Authors' disclosure of potential conflicts of interest

The authors have nothing to disclose.

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