Original Article

The Prognostic Contribution of Clinical Breast Cancer Subtype, Age, and Race Among Patients With Breast Cancer Brain Metastases

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BACKGROUND: Brain metastases (BM) arising from triple-negative breast cancer (TNBC) portend a poor prognosis. TNBC is more common in premenopausal and African-American (AA) patients; both of these characteristics also confer a poor prognosis. In a single-institution cohort study, the authors attempted to determine whether the inferior outcome noted with TNBC brain metastases is more reflective of a higher risk population or the subtype itself. **METHODS:** The University of North Carolina Breast Cancer Database identified patients with BC brain metastases who were diagnosed between 1988 and 2008. BC subtype was assigned by immunohistochemistry: hormone receptor (HR) positive (+);(HR, estrogen receptor [ER]+ and/or progesterone receptor [PR]+)/human epidermal growth factor receptor 2 (HER2) negative (-), HR+/HER2+, HR-/HER2+, and TN (ER-/PR-/HER2-). Survival and disease recurrence patterns were evaluated by subtype, patient age (<40 years vs ≥40 years), and race (AA vs non-AA) using the Kaplan-Meier method and Cox regression analysis. **RESULTS:** Among 119 patients with BC brain metastases, 33% were AA and 31% were aged <40 years. BC subtype was confirmed in 98 patients (30% with HR+/HER2-, 21% with HR+/HER2+, 18% with HR-/HER2+, and 31% with TNBC). Survival after BM was found to be impacted by subtype ($P = .002$), and was shortest for patients with TNBC (0.24 years; 95% confidence interval, 0.17 years-0.48 years). There were no age-specific ($P = .84$) or race-specific ($P = .09$) differences in survival noted after brain metastases; stratification of BC subtypes by age and race revealed no difference (all, $P > .1$). The receipt of systemic therapy after BC brain metastases was found to be an important predictor of survival after BC brain metastases (hazard ratio, 0.29; $P = .002$) when adjusted for race, age, number of central nervous system lesions, and BC subtype. **CONCLUSIONS:** TNBC confers a high risk of death after brain metastases regardless of patient race and age, supporting the need for novel agents capable of controlling both intracranial and extracranial TNBC across all races and ages. ***Cancer* 2010;000:000–000.** © *2010 American Cancer Society.*

KEYWORDS: breast cancer, brain metastases, subtype, age, race, triple negative.

Brain metastases are a burgeoning clinical problem that negatively impact approximately 30% of patients diagnosed with advanced breast cancer.[1,2] Despite local and systemic therapeutics, prognosis after a diagnosis of brain metastases arising from breast cancer is quite poor; historically, the 1-year survival rate is approximately 20% across all breast cancer subtypes.[3] Breast cancer is no longer viewed as a homogenous disease process, but rather as a compilation of reproducibly identified intrinsic subtypes as defined by microarray (luminal A, luminal B, basal-like, and human epidermal growth factor receptor 2 [HER2]-enriched subtypes), each characterized by unique clinicopathologic features and a distinct prognosis.[4-6] Moreover, gene expression studies have identified subtype-specific predilection to distant metastatic sites.[7] Endocrine-sensitive tumors are more likely to recur in bone, whereas basal-like and HER2-positive (+) breast tumors are more likely to recur in visceral sites, including the central nervous system (CNS), a site historically difficult to treat because of properties inherent to the blood-brain barrier.[8]

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Building on these observations, several groups have sought to determine the contribution of intrinsic breast cancer subtype to the incidence, behavior, and prognosis of CNS metastases. Studies largely performed in Eastern European and Asian patient populations have suggested a high incidence and aggressive nature of brain metastases arising from basal-like (usually identified as "triple-negative" on clinical assays for HER2 and the estrogen receptor [ER] and progesterone receptor [PR]) breast tumors.[9-12]

Basal-like/triple-negative breast cancer (TNBC) is a subtype of breast cancer commonly diagnosed in premenopausal and African-American (AA) women, clinical factors that have both been correlated with poorer breast cancer outcome.[13-15] To our knowledge, it is not clear whether the inferior outcome of basal-like/TNBC brain metastases is a reflection of a higher risk baseline population or of the subtype itself. To our knowledge, the prognostic interplay of breast cancer subtype, race, and age has yet to be explored in a cohort of racially diverse patients diagnosed and treated for breast cancer and brain metastases.

In this single-institution cohort study, we examined the clinicopathologic characteristics and outcome of breast cancer patients diagnosed with brain metastases who received treatment at the University of North Carolina (UNC) at Chapel Hill between 1988 and 2008. The goals of this study were 1) to evaluate the clinical and pathologic characteristics of both primary breast and metastatic CNS tumors; 2) to report practice patterns (including both local and systemic therapies) among patients diagnosed with breast cancer-related brain metastases; and 3) to determine the contribution and interaction of breast cancer subtype, race, and age on outcomes, particularly after CNS recurrence.

MATERIALS AND METHODS

Patient Population

This retrospective study was approved by the UNC Chapel Hill Office of Human Research Ethics Committee Institutional Review Board (IRB). Using an electronic clinical breast cancer database maintained at UNC Chapel Hill that includes >1400 patients diagnosed with breast cancer between 1988 and 2008 who received a cancer-related treatment at UNC hospitals, 119 patients (25 of whom patients were treated at UNC exclusively for brain metastases) were diagnosed with CNS metastases and were selected for the study. A waiver of consent was granted by the UNC IRB to conduct this study given that all clinical data remained deidentified to study investigators.

The UNC clinical breast cancer database routinely includes clinical, treatment, and outcome data from clinical and translational trial participants and patients treated with preoperative systemic therapy. Disease and vital status are updated yearly. Annual patient follow-up included a chart review of radiology reports, clinical notes, pathology reports, and vital status (via the medical record, Social Security Death Index, and obituaries).

Primary Breast Tumor Characteristics

All 119 patients had a histologic confirmation of invasive breast cancer (with the exception of 2 patients who were initially diagnosed with ductal carcinoma in situ) and an eventual diagnosis of CNS metastases. The majority (92 patients; 77%) of primary breast tumor pathologic specimens were reviewed by breast pathologists at UNC Chapel Hill. The remaining 27 patients (23%) received their initial therapy at outside institutions and therefore did not have pathologic specimens reviewed by UNC breast pathologists. In these cases, pathology data were extracted from the medical record. Clinical variables included patient age, gender, and race; stage of primary breast cancer at diagnosis; primary tumor size; lymph node stage at diagnosis; primary tumor histology, including ER status, PR status, and HER2 status; presence or absence of lymphovascular invasion (LVI) within the primary breast tumor; and treatment history (including local and systemic therapies).

Initial breast cancer staging was coded according to the sixth edition of the American Joint Committee on Cancer (AJCC). Primary tumor histological type (ie, ductal or lobular) and grading of primary breast tumors were classified according to the Nottingham modification of the Scarff-Bloom-Richardson criteria.[16] ER and PR status reported via the clinical breast cancer database was determined by ligand binding assay (until 1993) or immunohistochemistry (IHC) (from 1993-present). HER2 status reported via the clinical breast cancer database was determined either by IHC or fluorescence in situ hybridization (FISH). HER2 was reported as negative if classified as either 0 or 1+ by IHC or nonamplified FISH. HER2 was reported as positive if classified as 3+ by IHC or amplified FISH. In the rare case in which HER2 was classified as 2+ by IHC and FISH data were unavailable, samples were reported as HER2 negative (-) (n = 7).

CNS Metastases-Specific Data

All patients included in the analysis were diagnosed with breast cancer metastatic to the CNS. CNS metastases were defined by the presence of metastatic disease to the brain parenchyma and/or the presence of leptomeningeal

disease. CNS-specific data extracted from the database included the number of CNS metastases and local CNS-specific therapies, including neurosurgical resection, whole-brain radiotherapy (WBRT), and focused brain radiotherapy. The presence or absence of extracranial disease was also recorded. Details regarding systemic therapies in the metastatic setting were extracted from the database.

IHC Assays for ER, PR, and HER2

Archival formalin-fixed, paraffin-embedded tumor tissues were available for 35 of the 119 patients and ER, PR, and HER2 status were repeated via IHC for this subset of patients. Among these 35 patients, both primary breast tumor tissue and brain metastases tissue were available in the UNC Surgical Pathology Archives or Tissue Procurement Facility for 14 patients (matched pairs); brain metastases tissue was available for only 18 patients and primary breast tumor tissue was available for only 3 patients. Approval to study clinically annotated, deidentified tissues was obtained from the UNC IRB.

IHC studies were performed on 5-μm formalin-fixed, paraffin-embedded tissue sections on coated glass slides. A sequential IHC assay was performed on the Dako Autostainer platform (DakoCytomation, Carpinteria, Calif). Respective monoclonal antibodies were applied for 30 to 60 minutes (with the exception of HER2, which was incubated overnight at 4°C). Detection was completed by incubating with a biotinylated link. An avidin-biotin complex (Vectastain Elite Kit 6102; Vector, Burlingame, Calif) was applied followed by diaminobenzidine (Innovex NB314SB; Innovex Biosciences, Richmond, Calif) chromogen for nuclear localized antibodies (ER and PR) and Vector SG Substrate SK-4700 (Vector Laboratories, Burlingame, Calif) for the membrane-localized antibodies (HER2). Signal contrast was maximized by counterstaining in hematoxylin (DakoCytomation Mayer hematoxylin S3309), rinsing in deionized water, and placement in a bluing solution (Richard-Allan Scientific 7301; Richard-Allan Scientific, Kalamazoo, Mich) for the nuclear antibodies (ER and PR) and Vector Nuclear Fast Red H3403 for HER2. The following primary antibodies and dilutions were used: ER: clone 1D5, 1:50 dilution (Dako); PR: clone 16, 1:70 dilution (Vision BioSystems, Norwell, Mass); and HER2: clone CB11, 1:100 dilution (BioGenex, San Ramon, Calif). For each antibody, primary breast tumor tissue was used as a positive control.

ER and PR staining were scored using the Allred scoring system on a scale from 0 to 8 for nuclear staining only.[17] The intensity score and percentage score are added to obtain the Allred score. Allred scores of 0 to 2 were classified as negative and Allred scores of 3 to 8 were classified as positive. HER2 was scored using the current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines.[18] Membranous immunoreactivity was scored (0 and 1+ indicates negative; 2+, indeterminate; and 3+, positive for overexpression) and the percentage of tumor cells staining positive was shown as a raw score ranging from 0% to 100%. For the purposes of this analysis, a score of 0 to 2+ was considered HER2- and a score of 3+ was considered HER2+.

Assignment of Breast Cancer Subtype

Clinical breast cancer subtype was assigned by IHC as previously described: hormone receptor (HR)+ (HR ER+ and/or PR+)/HER2-, HR+/HER2+, HR-/HER2+, and triple-negative (ER-/PR-/HER2-).[13] In the cases in which the ER, PR, and HER2 status of the primary breast tumor were known via both the clinical database and repeat IHC, repeat receptor status via IHC was prioritized over information obtained from the database to assign subtype. If receptor status was unknown for primary breast specimens (via repeat IHC or from the clinical database), available ER, PR, and HER2 status from brain specimens was used to assign subtype, again prioritizing repeat IHC over information obtained from the clinical database. Concordance between clinical database assignment of ER, PR, and HER2 status and that of repeat IHC among breast tumor samples in which both were known was 91% (10 of 11 samples), 73% (8 of 11 samples), and 79% (11 of 14 samples), respectively. Concordance between clinical database assignment of ER, PR, and HER2 and repeat IHC among brain metastases samples in which both were known was 88% (7 of 8 samples), 44% (4 of 9 samples), and 100% (12 of 12 samples), respectively.

Statistical Analysis

The Kaplan-Meier method and log-rank test were used to compare differences among survival curves, and Cox regression analysis was used to evaluate possible predictors in the time-to-event outcomes. Overall survival (OS) was available for all patients included in this retrospective review, and was defined as the time from diagnosis of the primary breast tumor to death or last contact. Time to CNS recurrence (TTCNS) was defined as the time from primary breast tumor diagnosis to date of CNS metastasis; for those patients whose initial distant recurrence included the CNS, this time was the same as the time to distant recurrence. CNS-specific survival (CNS survival) was

Table 1. Patient Demographics and Primary Breast Tumor Characteristics.

Clinicopathologic Characteristics	All Patients	ER-/PR-/HER2- (n=30; 31%)	HR-/HER2+ (n=18; 18%)	HR+/HER2- (n=29; 30%)	HR+/HER2+ (n=21; 21%)	*P*
Age at diagnosis, y	n = 119					
Median (range)	44 (23-83)	48.5 (28-72)	49 (29-63)	41 (29-83)	43 (32-63)	.2
<40	37 (31%)	10 (33%)	4 (22%)	11 (38%)	5 (24%)	.6
≥40	82 (69%)	20 (67%)	14 (78%)	18 (62%)	16 (76%)	
Race	n = 119					.16
Caucasian	74 (62%)	15 (50%)	12 (67%)	18 (62%)	14 (67%)	
African American	39 (33%)	15 (50%)	4 (22%)	8 (28%)	7 (33%)	
Hispanic	3 (2%)		2 (11%)	1 (3%)		
Other	3 (2%)			2 (7%)		
AJCC stage at diagnosis	n = 91					.2
I	3 (3%)			1 (5%)		
II	20 (22%)	6 (25%)	1 (7%)	3 (14%)	7 (44%)	
III	43 (47%)	12 (50%)	7 (47%)	11 (52%)	4 (25%)	
IV	25 (28%)	6 (25%)	7 (47%)	6 (29%)	5 (31%)	
Lymph node status at diagnosis	n = 89					.19
Negative	24 (27%)	8 (32%)	2 (13%)	4 (20%)	7 (47%)	
Positive	65 (73%)	17 (68%)	13 (87%)	16 (80%)	8 (53%)	

ER indicates estrogen receptor; -, negative; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; +, positive; AJCC, American Joint Committee on Cancer.

defined as the time from the date of CNS metastasis to the date of death or last follow-up. Because of missing data, the sample size available for multivariable modeling was limited, such that all variables (from univariable analysis) were not included in a single model. Thus, 4 multivariable models were constructed. The first included triple-negative status with age, race, and >3 brain metastases. The remaining 3 models included those 4 variables with the addition of 1 of the treatments after brain metastases (systemic therapy, neurosurgical resection, or radiotherapy). Statistical analyses were performed with SAS 9.2 statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of the Study Population

The clinical characteristics of the study population are presented in Table 1. The median age at breast cancer diagnosis was 44 years (range, 23-83 years); 31% of patients were aged <40 years. The majority of patients were female (118 of 119 patients; 99%). Approximately 58% (62 of 106 patients) were premenopausal at diagnosis, whereas 42% (44 of 106 patients) were postmenopausal. Among the study population, 62% were Caucasian and 33% were AA.

Clinical and Pathological Characteristics of Primary Breast Carcinomas

The majority of patients (47%) presented with stage III disease and 28% of patients presented with stage IV disease. The median tumor size was 3 cm (range, 0-14 cm [83 assessable patients]) and 90% (78 of 87 patients) of patients had primary breast tumors measuring ≥2 cm. Approximately 73% (65 of 89 patients) of patients with known lymph node status had positive axillary lymph nodes at diagnosis. Approximately 35% (30 of 85 tumors) of breast tumors exhibited LVI. There were no significant differences in primary breast cancer characteristics, including stage at diagnosis, tumor size, lymph node status, presence/absence of LVI, or grade noted by race (AA vs non-AA: all, $P > .05$), age (<40 years vs ≥40 years: all, $P > .05$) or subtype (all, $P > .05$).

Approximately 58% of primary breast tumors (61 of 106 tumors) were ER- and 65% (66 of 102 tumors) were PR-, whereas 40% (38 of 94 tumors) were HER2-; no significant age-specific or race-specific differences with regard to the ER, PR, and HER2 status of the primary breast tumor were noted. All clinical breast cancer subtypes were represented: 30% were HR+/HER2-, 21% were HR+/HER2+, 31% were triple-negative, and 18% were HR-/HER2+ (Table 1). Consistent with prior reports,[13] a higher proportion of younger, AA patients were diagnosed with TNBC (vs non-triple-negative) when compared with older, non-AA patients (64% [9 of 14 patients] vs 29% [14 of 48 patients]; $P = .03$).

Local and Systemic Therapies for Primary Breast Cancer Diagnosis

Because patients included in this analysis were treated either on a clinical trial or with preoperative systemic therapy, the large majority (104 of 117 patients; 89%)

Table 2. CNS-Specific Tumor Characteristics and Therapies

Clinicopathologic Characteritics	All Patients	ER-/PR-/HER2- (n=30; 31%)	HR-/HER2+ (n=18; 18%)	HR+/HER2- (n=29; 30%)	HR+/HER2+ (n=21; 21%)	*P*
Location of CNS metastases	n = 119					.8
Brain parenchyma	105 (88%)	26 (87%)	16 (89%)	24 (83%)	19 (90%)	
Leptomeninges only	10 (9%)	4 (13%)	1 (6%)	3 (10%)	1 (5%)	
Both	4 (3%)		1 (6%)	2 (7%)	1 (5%)	
Sites of disease at initial metastatic presentation	n = 119					.09
Extracranial only	70 (59%)	13 (43%)	13 (72%)	19 (66%)	13 (62%)	
Intracranial only	32 (27%)	8 (27%)	5 (28%)	8 (28%)	6 (29%)	
Intracranial and extracranial	17 (14%)	9 (30%)		2 (7%)	2 (10%)	
No. of metastatic CNS lesions	n = 113					.3
1	48 (43%)	11 (41%)	5 (28%)	16 (57%)	12 (60%)	
2-3	22 (19%)	6 (22%)	6 (33%)	3 (11%)	3 (15%)	
≥3	43 (38%)	10 (37%)	7 (39%)	9 (32%)	5 (25%)	
Chemotherapy in the metastatic setting	n = 107					.2
Yes	80 (75%)	16 (62%)	15 (88%)	22 (81%)	15 (79%)	
No	27 (25%)	10 (38%)	2 (12%)	5 (19%)	4 (21%)	
Lines of chemotherapy in the metastatic setting	n = 80					.15
1	4 (5%)		1 (7%)	1 (4%)		
2-3	37 (46%)	12 (75%)	5 (33%)	9 (41%)	6 (40%)	
≥3	39 (49%)	4 (25%)	9 (60%)	12 (55%)	9 (60%)	

CNS indicates central nervous system; ER, estrogen receptor; -, negative; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; +, positive.

received chemotherapy with curative intent. Approximately half of the patients treated with chemotherapy received both an anthracycline and a taxane (50 of 101 patients; 49.5%). Approximately 19% (22 of 115 patients) received trastuzumab in the neoadjuvant or adjuvant setting, 45% of whom had HR+/HER2+ breast tumors, and 45% of whom had HR-/HER2+ breast tumors. One patient with HR+/HER2- breast cancer and 1 patient with TNBC also received trastuzumab. Approximately 44% (50 of 113 patients) of patients received endocrine therapy. There were no significant differences noted with regard to race or age in primary breast cancer systemic therapies with 1 exception: a higher percentage of AA patients received chemotherapy in the neoadjuvant setting (70% [21 of 30 patients] of AA patients vs 44% [25 of 57 patients] of non-AA patients; $P = .04$). As expected, a higher percentage of patients with HR+ (both HER2- and HER2+) breast tumors received endocrine therapy ($P < .001$), whereas a higher percentage of patients with HER2+ (both HR- and HR+) breast tumors received trastuzumab ($P < .001$).

Characteristics and Treatment of CNS and Non-CNS Metastatic Disease

Among the 119 breast cancer patients with CNS metastases, 88% (105 patients) of CNS lesions were parenchymal, 9% were leptomeningeal, and 3% were both (Table 2). At the time of metastatic presentation, 59% of patients were diagnosed with extracranial disease only, 27% were diagnosed with intracranial disease only, and 14% were diagnosed with both. Approximately 43% of patients presented with a solitary brain metastasis whereas 38% presented with >3 CNS metastatic lesions. There were no age-specific, race-specific, or subtype-specific differences noted with regard to the number of CNS lesions or the site of initial disease recurrence (all $P > .05$).

Among the 118 patients for whom information regarding CNS local therapy was available, 42% received WBRT, 10% underwent surgical resection, 8% underwent radiosurgery, 13% underwent surgical resection and WBRT, 7% underwent radiosurgery and WBRT, and 20% received other treatment. Numerically, a higher percentage of patients with HR+/HER2+ breast cancer underwent neurosurgical resection (Table 3). There were no age-specific, race-specific, or subtype-specific differences noted with regard to receipt of intracranial radiation (all, $P > .05$).

In the metastatic setting, 75% (80 of 107 patients) of patients received chemotherapy, of whom 95% (76 patients) received >1 line of chemotherapy (median, 3 lines of chemotherapy). Although no age-related differences were noted, a lower percentage of AA patients received

Table 3. Systemic, Surgical, and Radiation Treatments After CNS Recurrence by Subtype, Race, and Age

	All Patients	Subtype				Race[a]		Age, Years[a]	
		ER-/PR-/HER2- (n=30; 31%)	HR-/HER2+ (n=18; 18%)	HR +/HER2- (n=29; 30%)	HR +/HER2+ (n=21; 21%)	Fisher Exact Test *P*	Non-AA N=80	AA N=39	<40 N=37	≥40 N=82
Any systemic therapy	60/99	9/21	13/16	15/27	14/19	.066	42/68	18/31	18/30	42/69
	61%	43%	81%	56%	74%		62%	58%	60%	61%
Chemotherapy	50/107	8/26	13/17	12/27	10/19	.03	36/71	14/36	17/33	33/74
	47%	31%	76%	44%	53%		51%	39%	52%	45%
Trastuzumab	16/99	0/21	5/16	2/27	8/19	.0005	13/68	3/31	6/30	10/69
	16%	0%	31%	7%	42%		19%	10%	20%	14%
Endocrine therapy	15/99	1/21	0/16	7/27	4/19	.04	12/68	3/31	2/30	13/69
	15%	5%	0%	26%	21%		18%	10%	7%	19%
Neurosurgical resection	32/118	11/30	2/18	7/28	11/21	.037	18/79	14/39	12/36	20/82
	27%	37%	11%	25%	52%		23%	36%	33%	24%
Cranial radiation	89/119	18/30	15/18	20/29	15/21	.4	63/80	26/39	29/37	60/82
	75%	60%	83%	69%	71%		79%	67%	78%	73%

CNS indicates central nervous system; ER, estrogen receptor; -, negative; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; +, positive; AA, African American.

[a] All other *P* values >.14.

>3 lines of chemotherapy at any time during the metastatic disease course (19% [7 of 36] of AA patients vs 47% [33 of 70] of non-AA patients; $P = .02$). Approximately 34% (34 of 99 patients) of patients received trastuzumab in the metastatic setting, whereas 38% (38 of 99 patients) received endocrine therapy.

Focusing specifically on treatment after CNS recurrence, 61% (60 of 99 patients) of patients received systemic therapy after CNS recurrence, among whom subtype-specific differences were not present ($P = .07$) (Table 3). As expected, a higher percentage of patients with HER2+ (both HR- and HR+) tumors received trastuzumab ($P = .0005$), whereas a higher percentage of patients with HR+ (both HER2- and HER2+) tumors received endocrine therapy ($P = .04$). Although a numerically higher percentage of patients with TNBC presented with both intracranial and extracranial disease (Table 2), a lower percentage of patients with TNBC received chemotherapy after brain metastases compared with other subtypes ($P = .03$). There were no race-related or age-related differences noted with regard to treatment after CNS recurrence (all, $P > .14$).

OS and Natural History of CNS Disease Recurrence

At a median follow-up of 6.2 years, 93 of 119 (78%) patients had died. Across all ages, races, and breast cancer subtypes, the median OS was 4.03 years (95% confidence interval [95% CI], 3.09 years-5.05 years). The median OS differed significantly by breast cancer subtype ($P = .017$). Patients with TNBC were found to have a shorter median OS (2.12 years; 95% CI, 1.14 years-3.45 years) when compared with patients with other subtypes (HR-/HER2+: 3.52 years [95% CI, 1.61 years-7.5 years]; HR+/HER2-: 5.09 years [95% CI, 3.22 years-7.24 years]; and HR+/HER2+: 5.19 years [95% CI, 2.1 years-10.05 years]). Although there was no difference noted in OS by age (<40 years or ≥40 years; $P = .51$), AA patients experienced shorter median OS when compared with non-AA patients (3.45 years [95% CI, 1.92 years-4.98 years] vs 4.78 years [95% CI, 3.52 years-6.04 years]; $P = .04$).

The median TTCNS across subtype, race, and age was 2.62 years (95% CI, 1.85 years-3.23 years). TTCNS approached a significant association by breast cancer subtype ($P = .08$). TTCNS was found to be shorter for patients with TNBC and HR-/HER2+ breast tumors (1.51 years [95% CI, 1.08 years-2.31 years] and 1.65 years [95% CI, 1.13 years-3.02 years], respectively). In

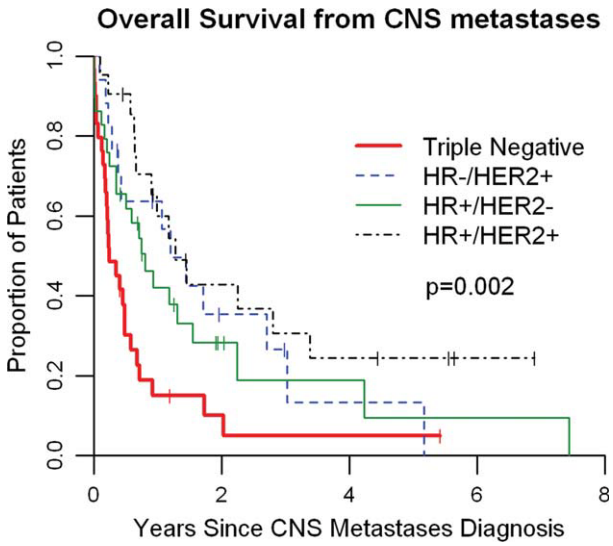

Figure 1. Survival from the time of central nervous system (CNS) metastases is shown by clinical breast cancer subtype. HR indicates hormone receptor; -, negative; HER2, human epidermal growth factor receptor 2; +, positive.

contrast, TTCNS was 3.35 years (95% CI, 1.75 years-4.98 years) for patients with the HR+/HER2- and 4.15 years (95% CI, 0.85 years-4.54 years) for patients with the HR+/HER2+ subtypes. Although TTCNS did not appear to differ by age ($P = .43$), TTCNS was shorter for AA patients when compared with non-AA patients (2.08 years [95% CI, 1.30 years-3.21 years] vs 3.06 years [95% CI, 1.85 years-3.82 years] respectively; $P = .02$).

CNS-Specific Survival by Subtype, Race, and Age

Across subtype, race, and age, the median time to death after CNS metastases (CNS survival) was 0.65 years (range, 0.48 years-0.98 years). CNS survival differed significantly by subtype ($P = .002$) (Fig. 1). CNS survival was 0.24 years (95% CI, 0.17 years-0.48 years), 1.19 years (95% CI, 0.27 years-3.02 years), 0.8 years (95% CI, 0.35 years-1.54 years), and 1.27 years (95% CI, 0.65 years-3.37 years) for the TNBC, HR-/HER2+, HR+/HER2-, and HR+/HER2+ subtypes, respectively. There was no difference in CNS survival noted by race ($P = .09$) or age ($P = .84$). Moreover, stratification by breast cancer subtype revealed no difference in CNS survival by race and age (all, $P > .1$).

Impact of Subtype, Age, Race, and Treatment on CNS-Specific Survival

The triple-negative phenotype, the presence of >3 brain lesions, a lack of neurosurgical resection, nonreceipt of systemic or radiotherapy after CNS recurrence, and lymph node-positive status at the time of diagnosis of primary breast cancer was found to predict worse survival after brain metastases in univariable analysis (Table 4). TNBC (controlled for age, race, and >3 brain metastases) was associated with worse survival after CNS recurrence (hazard ratio [HR], 2.3; 95% CI, 1.33-3.96 [$P = .003$]) when compared with non-TNBC in multivariable analysis.

Table 4. Univariable and Multivariable Analysis of Risk Factors Predictive of OS After Brain Metastases

	Univariable Analysis		Multivariable Analysis	
Clinicopathologic Variables	*P*	HR (95% CI)	*P*	HR (95% CI)
Triple negative (vs non-triple negative)	.0004	2.44 (1.50-3.98)	.003	2.30 (1.33-3.96)
Age ≥40 y	.8	0.96 (0.61-1.49)	.8	1.06 (0.63-1.78)
Race (African American)	.09	1.46 (0.94-2.28)	.9	1.01 (0.59-1.73)
>3 CNS lesions	.001	2.01 (1.31-3.09)	.0003	2.52 (1.54-4.15)
Brain resection (vs none)	.001	0.42 (0.25-0.71)		
Brain XRT (vs none)	.04	0.60 (0.37-0.97)		
Systemic after CNS (vs none)	.0005	0.44 (0.27-0.70)		
Lymph node positive	.03	1.85 (1.08-3.19)		
Pretreatment AJCC stage III-IV (vs stage I-II)	.3	1.29 (0.76-2.16)		
Tumor ≥2 cm	.2	1.79 (0.78-4.15)		
Brain as initial site of recurrence	.16	0.74 (0.48-1.12)		
Leptomeningeal disease	.14	1.60 (0.85-3.03)		
Presence of extracranial metastases	.5	1.2 (0.68-2.13)		

OS indicates overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; CNS, central nervous system; XRT, radiotherapy; AJCC, American Joint Committee on Cancer.

Taking into account the significant univariable association between treatment for brain metastases and improved CNS-specific survival, multivariable modeling revealed the following. After controlling for age, race, and >3 brain metastases, receipt of any systemic treatment after brain metastases was found to be the most important predictor of CNS-specific survival (HR, 0.4; $P = 0.02$), even above that of triple-negative status (HR, 1.4; $P = .3$). However, triple-negative status retained its significant association with CNS-specific survival after controlling for age, race, >3 brain metastases, resection (triple-negative [HR, 2.8; $P = .0005$] and neurosurgical resection [HR, 0.4; $P = .005$]), and radiation (triple-negative [HR, 2.1; $P = .0009$] and radiation [HR, 0.5; $P = .028$]).

DISCUSSION

Results from this single-institution, retrospective cohort study demonstrated that TNBC portends a worse survival after a diagnosis of CNS metastases when compared with non-triple-negative subtypes independent of AA race or young age. Moreover, within an inherently young, racially diverse patient population treated in the United States, 33% of whom were AA and 31% of whom were aged <40 years, the prognostic contribution of clinical breast cancer subtype persisted among patients diagnosed with breast cancer brain metastases. It is interesting to note that receipt of systemic therapy after CNS recurrence was an important predictor of survival after brain metastases. In contrast with observations in non-triple-negative subtypes, a recent series indicated that the administration of chemotherapy after WBRT in the setting of TNBC brain metastases does not improve survival.[10] The data from the current study continue to highlight the dire need for novel systemic approaches capable of improving outcomes for patients diagnosed with TNBC brain metastases across all racial and age groups.

In the current series of patients treated at UNC Chapel Hill between 1988 and 2008, survival after brain metastases arising from TNBC was 0.24 years compared with 1.19 years, 0.8 years, and 1.27 years for patients with the HR-/HER2+, HR+/HER2-, and HR+/HER2+ subtypes, respectively. The results of the current study are consistent with several reports evaluating the prognostic implication of tumor subtype among patients with breast cancer brain metastases.[9,10,12] Among 222 patients treated at the Cancer Center in Warsaw, Poland from 2003 to 2006, Niwinska et al reported the median survivals after brain metastases in patients with the triple-negative, HER2+, and luminal (endocrine-sensitive) subtypes of breast cancer were 3.7 months, 9 months, and 15 months, respectively.[11] A similar series by Nam et al retrospectively evaluated 126 patients with breast cancer brain metastases who were treated at the National Cancer Center Hospital in Goyang, Korea from 2001 through 2006. Survival was shortest from the diagnosis of brain metastases to death among patients with triple-negative and luminal A (HR+/HER2-) breast cancer (3.4 months and 4.0 months, respectively) compared with patients with the HER2 (HR-/HER2+) and luminal B (HR+/HER2+) subtypes (9.0 months and 5.0 months, respectively; $P = .0113$).[12] Our analysis also indicated a poor prognosis after a diagnosis of brain metastases arising from HR+/HER2- breast tumors, an observation likely attributable to the finding that CNS recurrence is a late occurrence in the natural history of HR+/HER2- breast cancer.

Recognizing that younger women of AA descent are at a higher risk for the development of TNBC and that both racial and age differences are known to affect breast cancer survival,[13-15,19] one of the goals central to our analysis was to examine the prognostic influence of race and age after CNS recurrence. Examining race as a single prognostic factor, survival after CNS recurrence was not found to be influenced by ethnicity across subtypes. However, AA patients experienced a shorter OS and developed disease recurrence within the CNS more rapidly than non-AA patients. Careful review of race-specific treatments indicated a lower percentage of AA women received >3 lines of chemotherapy in the metastatic setting compared with non-AA patients. Although this study was not designed to identify causality for this observation, the receipt of fewer lines of chemotherapy may partially explain both the inferior OS and earlier recurrence in the CNS noted among AA patients. Similar to race, age as a single prognostic factor did not appear to influence survival after CNS recurrence across subtypes. It is interesting to note that within this cohort of patients, all of whom developed brain metastases from breast cancer, the median age at breast cancer diagnosis was young (44 years). Moreover, approximately 31% of patients were aged <40years at the time of their initial diagnosis. A per the US Surveillance, Epidemiology, and End Results (SEER) database, the median age at breast cancer diagnosis is 61 years (2002-2006) and 7% of women in the US who are diagnosed with breast cancer are aged <40 years.[19,20] Although determining risk factors for the development of CNS recurrence was not the purpose of the current study,

prior reports indicate young age to be a risk factor for the development of breast cancer brain metastases and our data are supportive of this finding.[2]

Several limitations inherent to this study should be addressed. First, patients included in this analysis all developed CNS metastases from breast cancer and were treated at a single-center, academic institution largely on clinical protocols. As such, practice patterns (ie, the routine use of neoadjuvant chemotherapy, strong referral base for neurosurgical resection, etc) may have introduced bias. Moreover, results from this self-contained dataset may not be generalizable across the entire breast cancer population, but add to the existing literature surrounding the high-risk population of patients who develop disease recurrence within the CNS. In addition, the database spans a long period (1998-2008), during which time newer therapies have been introduced into clinical practice. Thus, the results of the current study may not be entirely applicable to the modern-day breast cancer patient population and should be interpreted within the confines of the study period. Second, an IHC surrogate was used to assign breast cancer subtype from archival, paraffin-embedded tissues. Because subtype assignment via gene expression is available only in research settings, this approach is generally accepted when fresh, frozen tissues samples are not available for analysis.[13] Breast cancer subtype assignment was based primarily on receptor status acquired from primary breast tumors. Although discordance between primary breast tumor and the ER, PR, and HER2 status of brain metastases may occur,[21] the routine biopsy of the CNS is not feasible (or necessary) in all cases. Moreover, receptor concordance between the clinical database and repeat IHC on available tissues was $<100\%$. As such, rare cases of subtype misclassification may have occurred. Finally, although the sample size of this retrospective analysis was comparable to works within the field, the detection of small to moderate interactions between race, subtype, and survival may have been limited by the evaluation of subsets of the larger patient population.

In summary, this informative study is, to our knowledge, the first to examine the prognostic interplay of breast cancer subtype, race, and age among patients with brain metastases in a racially diverse US patient population. The results presented herein indicate that clinical breast cancer subtype maintains prognostic significance, independent of race and age, among patients with breast cancer brain metastases. Moreover, TNBC, regardless of patient race or age, confers the worst prognosis, a finding that is consistent with those of prior series and continues to highlight the need for the development of novel, targeted agents capable of controlling both intracranial and extracranial TNBC.

CONFLICT OF INTEREST DISCLOSURES

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