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Original Article

Incidence, characteristics, and management of central nervous system metastases in patients with inflammatory breast cancer

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BACKGROUND: Patients with inflammatory breast cancer (IBC) have a high risk of central nervous system metastasis (mCNS). The purpose of this study was to quantify the incidence of and identify risk factors for mCNS in patients with IBC. **METHODS:** The authors ret-rospectively reviewed patients diagnosed with IBC between 1997 and 2019. mCNS-free survival time was defined as the date from the diagnosis of IBC to the date of diagnosis of mCNS or the date of death, whichever occurred first. A competing risks hazard model was used to evaluate risk factors for mCNS. **RESULTS:** A total of 531 patients were identified; 372 patients with stage III and 159 patients with de novo stage IV disease. During the study, there were a total of 124 patients who had mCNS. The 1-, 2-, and 5- year incidence of mCNS was 5%, 9%, and 18% in stage III patients (median follow-up: 5.6 years) and 17%, 30%, and 42% in stage IV patients (1.8 years). Multivariate analysis identified triple- negative tumor subtype as a significant risk factor for mCNS for stage III patients. For patients diagnosed with metastatic disease, visceral metastasis as first metastatic site, triple- negative subtype, and younger age at diagnosis of metastases were risk factors for mCNS. **CONCLUSIONS:** Patients with IBC, particularly those with triple-negative IBC, visceral metastasis, and those at a younger age at di-agnosis of metastatic disease, are at significant risk of developing mCNS. Further investigation into prevention of mCNS and whether early detection of mCNS is associated with improved IBC patient outcomes is warranted. ***Cancer* 2022;128:4085-4094.** *© 2022 American Cancer Society.*

KEYWORDS: brain metastases, incidence, inflammatory breast cancer, outcomes, risk factors.

INTRODUCTION

Previous studies have demonstrated a relatively high incidence of central nervous system metastasis (mCNS) in patients with breast cancer, in particular in patients with inflammatory breast cancer (IBC).[1–5] These studies have been limited by the rarity of the diagnosis and resultant limited numbers of eligible patients. Younger age and tumor subtype, specifically triple-negative and human epidermal growth factor receptor 2 (HER2)-positive tumors, have been identified as risk factors for the development of mCNS. Disease metastatic to the central nervous system (CNS) can markedly impact quality of life,[6] and although a recent study suggested an improvement in median survival in contemporary cohorts, the prognosis remains limited for women with breast cancer after a diagnosis of mCNS.[7]

The management of brain metastases is typically guided by a number of factors including the number and size of intracranial metastases, patient performance status and prognosis, and whether the intracranial disease is symptomatic.[8–10] Because many systemic therapies do not penetrate the blood–brain barrier effectively,[11] often radiotherapy and/or surgical resection is recommended. Despite the propensity toward mCNS in certain subgroups of patients with breast cancer, particularly those with HER2$^+$ or triple-negative breast cancer (TNBC),[12–16] consensus guidelines published by the National Comprehensive Cancer Network do not recommend routine screening magnetic resonance imaging (MRI) of the brain to evaluate for mCNS in women with breast cancer.[17]

The purpose of this study was to quantify the incidence of and risk factors for mCNS in a population of patients with IBC and to estimate survival after a diagnosis of mCNS. Additionally, given improvements during the study period in surgical and radiosurgical techniques and the development of systemic therapies with increased CNS penetrance, we investigated trends in the utilization of surveillance brain MRI. Last, we described the patterns of the treatment of intracranial disease,

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specifically the utilization of whole brain radiotherapy (WBRT) over time.

MATERIALS AND METHODS

Study design and patient selection

This study was a retrospective review of patients with IBC diagnosed between January 1, 1997, and December 31, 2019, who were seen at the IBC Program at Dana-Farber Cancer Institute and were enrolled in an institutional review board–approved IBC registry. Patients with both stage III and stage IV IBC were included. The methods of an earlier analysis have been previously described.[1] Eligible patients presented with signs and symptoms consistent with a clinical diagnosis of IBC, as defined by the American Joint Committee on Cancer and International Expert Consensus diagnosis criteria for IBC.[18,19] Patients with both stage III and stage IV disease at diagnosis were included. Patients had a minimum of 2 weeks of follow-up. All patients in the IBC registry were included in this study.

Statistical analysis

The primary end point of the study was the cumulative incidence of mCNS with death as a competing risk. CNS-metastasis-free survival time was defined as the date from the diagnosis of IBC to the date of diagnosis of mCNS or the date of death, whichever occurred first, or censoring at the date of the most recent follow-up. For the subgroup analysis of patients who completed trimodality therapy (TMT), consisting of preoperative chemotherapy, surgery, and radiotherapy, the completion date of TMT was the starting time for estimating cumulative incidence of mCNS.

Using the Fine and Gray method,[20] a competing risks hazard model for patients with Stage III disease at diagnosis was used to assess if specific patient, pathologic, or treatment variables were associated with mCNS; subdistribution hazard ratios (sHR) with 95% confidence intervals (CI) were reported. To reduce the utilization of time-varying covariates, only patients who underwent surgery were included in the group of patients with stage III IBC and the starting point for the time to mCNS was the date of surgery. Variables included in this model were age at diagnosis, menopausal status, tumor grade, tumor subtype, involved lymph node (LN) location (no LN involvement, axillary lymph nodes [ALN] alone, ALN plus additional LN sites), dermal lymphatic invasion, preoperative receipt of HER2-directed therapy (for $HER2^+$ disease), and pathologic complete response at the time of surgery.

All patients with metastatic disease were included in a separate model. Variables included in this model were age at diagnosis of metastatic disease, tumor grade, tumor subtype, first site of metastatic disease (bone, serosa, soft tissue, and viscera), and metastatic disease at diagnosis or subsequent development of metastatic disease after presentation with stage III disease at diagnosis. The classification of first site of metastatic disease was done hierarchically for patients who reported multiple first sites of metastasis based on the site with the worst prognosis where metastatic disease was identified. The hierarchy was defined as: bone < soft tissue < visceral (internal organs) < serosa < CNS, with mCNS deemed the poorest prognostic location. Excluded from the analysis of patients with metastatic disease were five patients with mCNS at the time of IBC diagnosis and 22 patients with stage III disease at diagnosis who developed mCNS as the first site of metastatic disease. However, these stage III patients were included in the stage III model if they underwent surgery. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 531 patients met eligibility criteria for inclusion. Patient, tumor, and treatment characteristics are shown in Table 1. The median age at diagnosis was 51 years (range, 24–91 years). The majority of patients (n = 372, 70%) presented with stage III disease. A total of 159 patients (30%) had metastatic disease at diagnosis; of these, five (3%) had mCNS at diagnosis in addition to distant metastatic disease. The distribution of tumor subtypes included 157 (30%) estrogen receptor (ER)-positive or progesterone receptor (PR)-positive (also called hormone receptor [HR]-positive) and $HER2^-$; 114 (21%) HR^- $HER2^+$; 113 (21%) HR^+ $HER2^+$; 125 (24%) HR^- $HER2^-$ or triple-negative (TN); and 22 (4%) with unknown subtype due to missing receptor data.

During the study, there were a total of 124 patients who had mCNS (23% of all patients), including the previously mentioned five patients with mCNS at diagnosis and 49 patients (9% of all 531 patients) for whom the CNS was their first site of disease recurrence or progression. Of these 124 patients for whom the type of mCNS was known, 102 had parenchymal metastases and 35 had leptomeningeal disease, with 20 having both parenchymal and leptomeningeal disease. During the observed follow-up, 258 of 531 patients (49%) died, including 83% (103/124) of patients with mCNS. The median overall survival after a diagnosis of mCNS was 0.6 years (95% CI, 0.5–0.8). When stratified by date of diagnosis, patients diagnosed with IBC between 2000 and 2008 had a median survival after mCNS of 0.6 years (interquartile range [IQR], 0.2–1.2) similar to those diagnosed 2009 or later (0.6 years; IQR, 0.2–1.6).

TABLE 1. Patient and Tumor Characteristics (n = 531)

	Stage at diagnosis				Total	
	III		IV			
	No.	%	No.	%	No.	%
Total patients	372	100	159	100	531	100
Age at diagnosis (years)						
Median	50		52			
<40	63	17	33	21	96	18
40–50	131	35	38	24	169	32
>50	178	48	88	55	266	50
Menopausal status at diagnosis						
Pre/peri	195	52	74	47	269	51
Post	167	45	83	52	250	47
Unknown	10	3	2	1	12	2
Tumor grade						
I	6	2	3	2	9	2
II	99	27	33	21	132	25
III	215	58	95	60	310	58
Unknown	52	14	28	18	80	15
Tumor subtype						
$HR^+/HER2^+$	73	20	40	25	113	21
$HR^-/HER2^+$	74	20	40	25	114	21
HR^+HER2^-	114	31	43	27	157	30
$HR^-/HER2^-$	98	26	27	17	125	24
Unknown	13	3	9	6	22	4
Involved LNs						
Axillary only	213	57	46	29	259	49
Axillary + additional LN involvement	95	26	96	60	191	36
None	64	17	17	11	81	15
PCR at time of surgery						
Yes	69	19	11	7	80	15
No	272	73	53	33	325	61
Had surgery, PCR unknown	2	1	2	1	4	1
Did not have surgery	29	8	93	58	122	23
Completion of trimodality therapy						
Yes	304	82	50	31	354	67
No	68	18	109	69	177	33
Site of first metastasis[a]						
Soft tissue	49	13	61	38	110	21
Bone	20	5	27	17	47	9
Serosa	31	8	—	—	31	6
Viscera	55	15	66	42	121	23
CNS	22	6	5	3	27	5
No metastasis	195	52	—	—	195	37
Development of CNS metastases						
Yes	66	18	58	36	124	23
No	306	82	101	64	407	77
Timing of development of CNS metastases						
Stage III relapsed/progressed in CNS first	22	6	—	—	22	4
Stage IV CNS at diagnosis	—	—	5	3	5	1
Stage IV progressed in CNS first	—	—	27	17	27	5
CNS after other site of relapse/progression	44	12	26	16	70	13
Did not develop CNS metastases	306	82	101	64	407	77

Abbreviations: CNS, central nervous system; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LNs, lymph nodes; PCR, pathological complete response.

[a]Site of first metastasis is hierarchically defined based on the patient's site of metastasis associated with the worst prognosis. The hierarchy was defined as: bone < soft tissue < visceral < serosa < CNS, with CNS being considered the site with the worst prognosis.

When stratified by tumor type, patients with TN-IBC had the shortest median overall survival (OS) after being diagnosed with mCNS (0.2 years; IQR, 0.1–0.5) compared to patients with HR^+ $HER2^-$ (0.6 years; IQR, 0.2–1.2) or $HER2^+$ IBC (1.4 years; IQR, 0.6–3.7) (Fig. 1). When stratified by tumor type and excluding patients with known leptomeningeal disease, the median OS after being diagnosed was similar to the overall population: TN-IBC, 0.2 years (IQR, 0.1–0.6); HR^+ $HER2^-$, 0.6 years (IQR, 0.2–1.2); and $HER2^+$, 1.5 years (IQR, 0.8–4.5). Of the 35 patients with leptomeningeal disease, 11 (31%) were treated with WBRT alone; four (11%) were treated with WBRT and intrathecal (IT) chemotherapy; one (3%) received WBRT, IT chemotherapy, and systemic therapy; eight (23%) received WBRT and systemic therapy; one (3%) received IT chemotherapy and systemic therapy; two (6%) received systemic therapy alone; three (9%) received IT chemotherapy alone; five (14%) transitioned to hospice after the diagnosis without further cancer-directed therapies; and the treatment of one (3%) patient was unknown.

At a median follow-up of 5.6 years (range, 0.3–21.9) for the 372 patients with stage III disease at diagnosis, 66 developed mCNS, and 76 died before a diagnosis of mCNS. The 1-, 2-, and 5-year cumulative incidence of CNS metastasis after diagnosis in this population was 5% (95% CI, 3%–7%), 9% (95% CI, 6%–12%), and 18% (95% CI, 14%–23%), respectively (Fig. 2A). Of these 66 patients, 17 (26%) developed mCNS as their first and only site of distant disease. Five additional patients (8%) developed mCNS synchronously with extracranial distant disease. Of the 372 patients with stage III disease at diagnosis, 304 (82%) completed TMT. Within this subgroup, 51 patients developed mCNS and 58 patients died before developing mCNS. The 1-, 2-, and 5-year cumulative incidence of CNS metastasis after TMT in this population (n = 304) was 5% (95% CI, 3%–8%), 11% (95% CI, 8%–16%), and 19% (95% CI, 14%–24%), respectively (Fig. 3A).

Results of the multivariate competing risk modeling for patients presenting with stage III disease who underwent surgery (n = 343) are shown in Table 2. In this subgroup, 58 patients were diagnosed with mCNS and 66 patients died before developing mCNS. In this analysis, patients with TN-IBC were more likely to develop mCNS than those with HR^+ $HER2^-$ cancers (sHR, 1.98; 95% CI, 1.02–3.84). The remaining variables did not show a significant association.

Within the cohort of 154 patients with stage IV disease at diagnosis and without mCNS at a median follow-up of 1.8 years (range, 0.2–17.6), 53 developed mCNS and 36 died before a diagnosis of mCNS. The

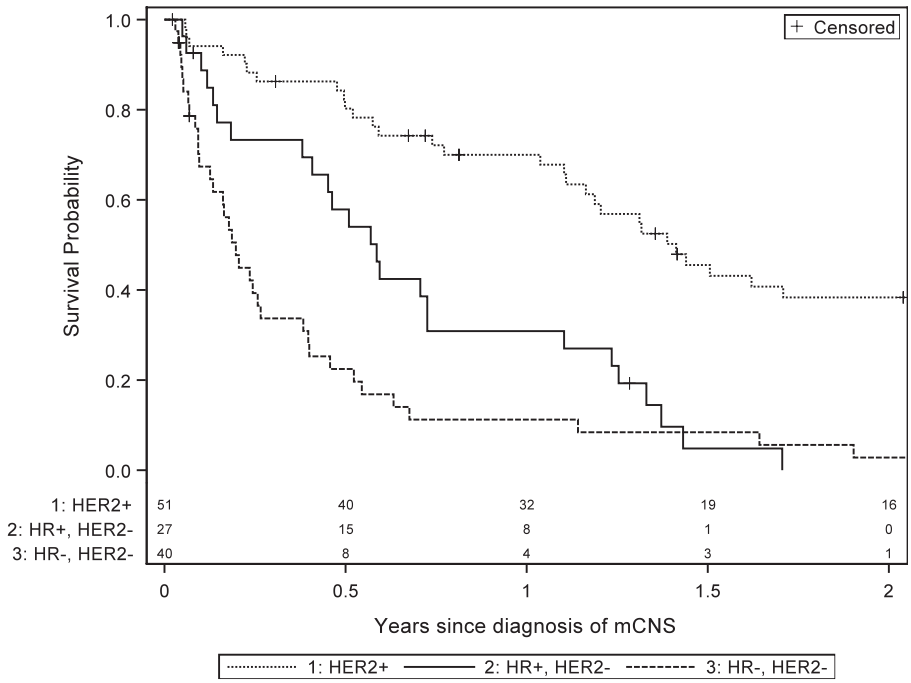

Figure 1. Survival after diagnosis of central nervous system metastases (mCNS) according to tumor subtype among 124 patients with inflammatory breast cancer who had mCNS at diagnosis or subsequently developed mCNS.

1-, 2-, and 5-year cumulative incidence of CNS metastasis after diagnosis in this population was 17% (95% CI, 12%–24%), 30% (95% CI, 22%–37%), and 42% (95% CI, 32%–51%), respectively (Fig. 2B). Fifty of these patients (32%) received TMT, of whom four developed mCNS before completing TMT. Of the remaining 46 patients, 14 developed mCNS and 10 died before developing mCNS. The 1-, 2-, and 5-year cumulative incidence of CNS metastasis after TMT in this population was 21% (95% CI, 10%–34%), 28% (95% CI, 16%–43%), and 35% (95% CI, 20%–50%), respectively (Fig. 3B).

Results of the modeling for patients diagnosed with metastatic disease either at diagnosis or as disease relapse or progression during the study period (n = 309) without CNS as the first site of metastases are shown in Table 3. In this subgroup, 97 patients were diagnosed with mCNS and 101 patients died before developing mCNS after their stage IV diagnosis. Patients with visceral metastasis as their first site of metastatic disease experienced a significantly higher risk of mCNS than those with bone as their first site (sHR, 1.96; 95% CI, 1.08–3.58). Patients with TN-IBC were also more likely to develop mCNS compared with those with HER2$^+$ disease (sHR, 2.31; 95% CI, 1.25–4.13). Patients who were older at the time of diagnosis of metastatic disease were less likely to be diagnosed with mCNS (sHR, 0.97; 95% CI, 0.96–0.99).

Neurologic symptoms prompted CNS imaging in 70% (87 of 124) of patients diagnosed with mCNS. The specific reason to obtain CNS imaging in the remaining 30% was unable to be captured in this retrospective study. The proportion of patients who were symptomatic when diagnosed with mCNS did not meaningfully change over time. The proportion of CNS imaging that was prompted by symptoms was 73%, 73%, 73%, 71%, and 67% during 1997–1999 (total number of patients diagnosed with mCNS during this period = 11), 2000–2004 (n = 15), 2005–2009 (n = 15), 2010–2014 (n = 44), and 2015–2019 (n = 39), respectively.

Eighty-one patients (65%) with mCNS received WBRT, either as monotherapy or in combination with other CNS-directed therapies (Table S1). Twenty-two (18%) patients received stereotactic radiosurgery alone. The percentage of patients receiving WBRT declined over the study period: 73% (1997–1999), 87% (2000–2004), 73% (2005–2009), 57% (2010–2014), and 46% (2015–2019).

DISCUSSION

Our study demonstrated that patients with IBC have a high incidence of mCNS, approaching 20% at 5 years for

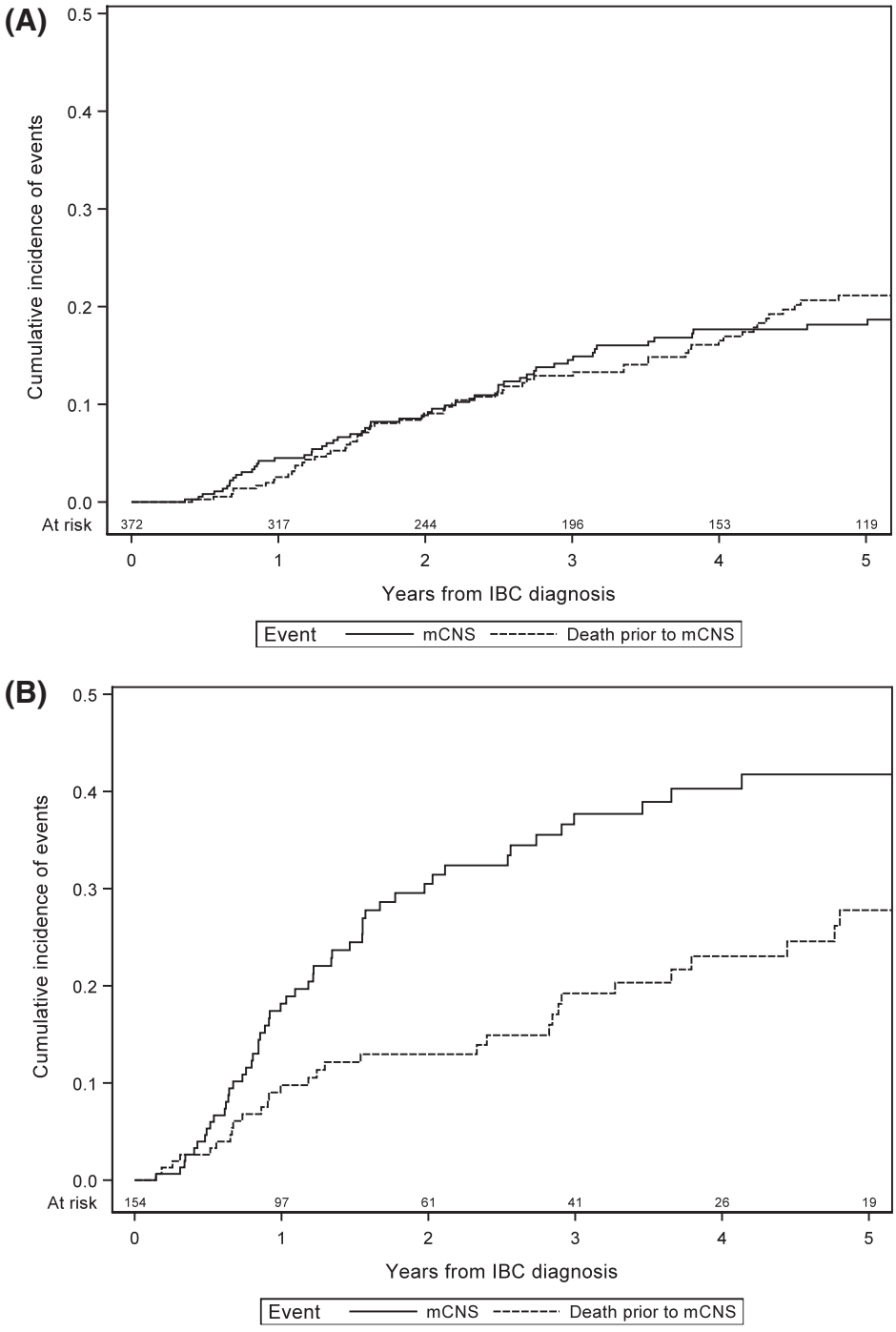

Figure 2. Cumulative incidence of central nervous system metastasis (mCNS) and of death without mCNS for (A) 372 patients presenting with stage III inflammatory breast cancer (IBC) and (B) 154 patients presenting with stage IV IBC (and without mCNS at presentation).

patients with stage III disease and 30% at 2 years for those with de novo stage IV disease. Because most patients in this study were diagnosed with mCNS in the context of neurologic symptoms, it is likely that the true incidence of mCNS in patients with IBC is even higher than reported in our study because some patients likely have undetected, asymptomatic mCNS.

Our results are consistent with previously reported data from Uemura and colleagues,[3] who found a 5-year incidence of mCNS in 589 patients presenting with

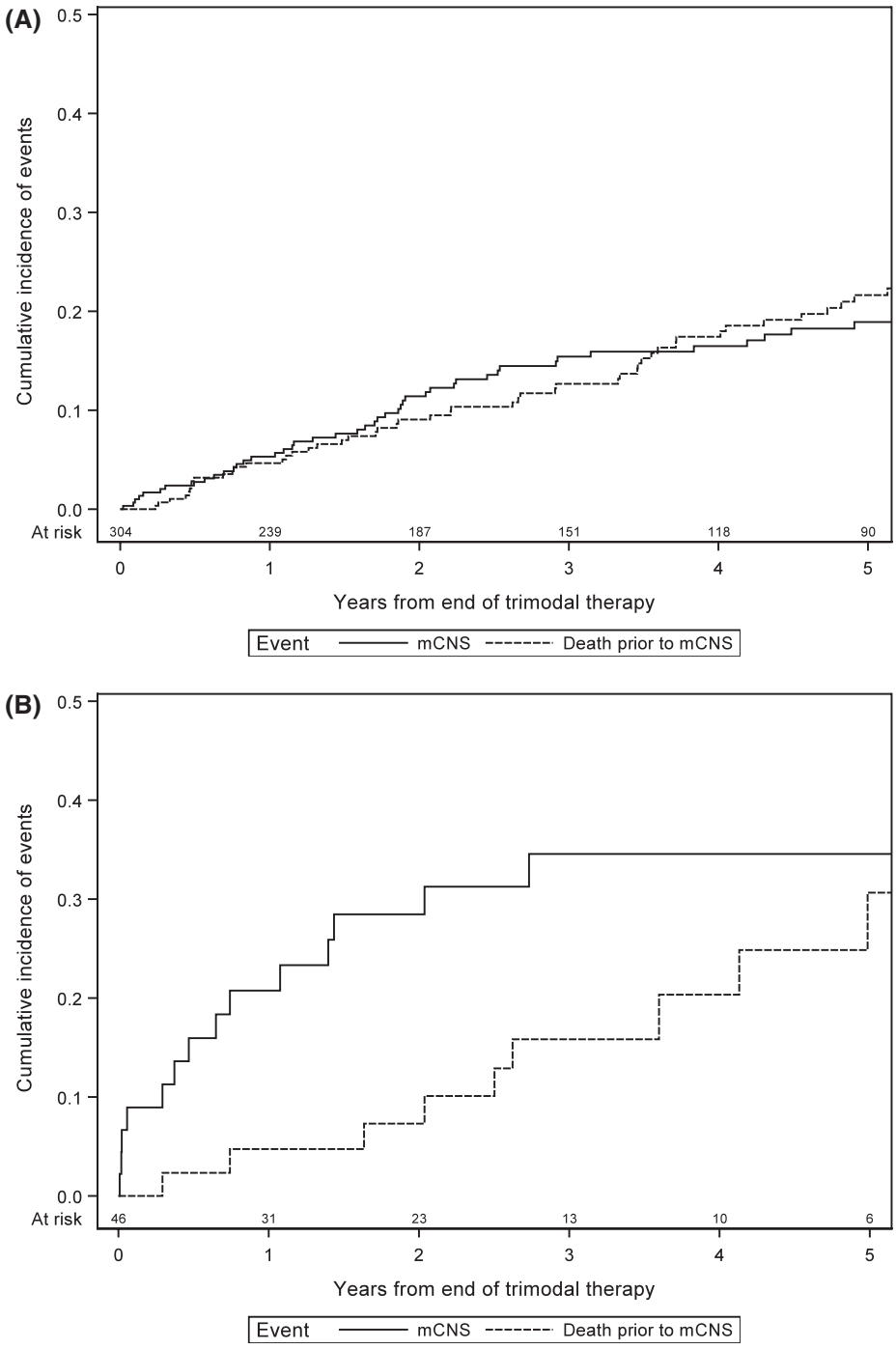

Figure 3. Cumulative incidence of central nervous system metastasis (mCNS) and of death without mCNS for (A) 304 patients presenting with stage III inflammatory breast cancer (IBC) who completed trimodality therapy and (B) 46 patients presenting with stage IV IBC who completed trimodality therapy.

stage III IBC of 15.8%. Dawood and colleagues[2] evaluated the incidence of mCNS disease and reported that patients with HR^+ $HER2^-$ IBC had a lower risk of developing brain metastases compared to women with TN-IBC (HR, 0.55; 95% CI, 0.19–1.51). Our study also identified a significantly higher risk of mCNS in patients with TN-IBC compared to those with HR^+ $HER2^-$ disease in our stage III model. This stands in comparison to the study by Uemura et al.[3] that did not identify any significant associations with ER or HER2 status in their

TABLE 2. Competing Risk Regression Model Examining Patient and Tumor Features as Risk Factors for Mcns in Patients with Stage III Inflammatory Breast Cancer at Diagnosis who Underwent Surgery (n = 343)

Risk factor	Alive, mCNS free	mCNS ever	Death without mCNS	sHR[a]	95% LCL	95% UCL
Age at diagnosis (years)				0.98	0.94	1.01
Menopausal status at diagnosis						
Pre/peri/unknown	122	36	29	—	—	—
Post	97	22	37	1.05	0.50	2.23
Tumor grade						
I/II/unknown	91	24	29	—	—	—
III	128	34	37	1.08	0.63	1.85
PCR						
Yes	58	5	6	—	—	—
Had surgery, PCR unknown	1	—	1	—	—	—
No	160	53	59	2.32	0.86	6.26
Subtype and use of neoadjuvant AHER2 treatment						
HR^+, $HER2^-$ (no AHER2)	70	17	21	—	—	—
$HER2^+$, AHER2	91	10	8	0.71	0.31	1.61
$HER2^+$, no AHER2	14	7	8	1.43	0.63	3.22
HR^-, $HER2^-$ (no AHER2)	38	22	27	1.98	1.02	3.84
Unknown	6	2	2	0.95	0.28	3.23
Involved LNs						
Axillary LN only	126	36	39	—	—	—
Axillary plus additional LN involvement	61	10	14	0.76	0.37	1.58
None	32	12	13	1.08	0.55	2.13
Dermal lymphatic invasion						
No	142	43	46	—	—	—
Yes	77	15	20	0.76	0.39	1.46

Abbreviations: AHER2, anti-HER2; HER2, human epidermal growth factor receptor 2; LCL, lower confidence limit; LNs, lymph nodes; mCNS, central nervous system metastases; PCR, pathological complete response; sHR, subdistribution hazard ratio; UCL, upper confidence limit.
[a]sHR for cumulative incidence of mCNS in the presence of competing risk of death without mCNS with 95% confidence intervals (LCL, UCL).

TABLE 3. Competing Risk Regression Model Examining Patient and Tumor Features as Risk Factors for Mcns in Patients with Stage IV Inflammatory Breast Cancer that did not Present with Cns Metastases (n = 309)

Risk factor	Alive, mCNS free	mCNS	Death without mCNS	sHR[a]	95% LCL	95% UCL
Age at diagnosis of metastases (years)				0.97	0.96	0.99
Tumor grade						
I/II/unknown	53	38	40	—	—	—
III	58	59	61	1.01	0.67	1.53
Tumor subtype						
HR^+, $HER2^-$	35	20	33	—	—	—
$HER2^+$	56	39	26	1.33	0.78	2.27
HR^-, $HER2^-$	16	32	36	2.27	1.25	4.13
Unknown	4	6	6	1.44	0.61	3.37
First site of metastatic disease[b]						
Bone	18	12	17	—	—	—
Serosa	5	8	18	1.45	0.54	3.92
Soft tissue	49	29	32	1.29	0.67	2.47
Viscera	39	48	34	1.96	1.08	3.58
Metastatic disease classification						
Subsequent progression	46	44	65	—	—	—
De novo at diagnosis	65	53	36	1.28	0.81	2.03

Abbreviations: CNS, central nervous system; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LCL, lower confidence limit; mCNS, central nervous system metastases; sHR, subdistribution hazard ratio; UCL, upper confidence limit.
[a]sHR is subdistribution hazard ratio for cumulative incidence of mCNS in the presence of competing risk of death without mCNS with 95% confidence intervals (LCL, UCL).
[b]Site of first metastasis is hierarchically defined based on the patient's site of metastasis associated with the worst prognosis. The hierarchy was defined as: bone < soft tissue < visceral < serosa < CNS, with CNS being considered the site with the worst prognosis.

multivariate model in patients with stage III IBC. In our model of patients with metastatic disease, patients with TN-IBC were also more likely to develop mCNS compared with patients having $HER2^+$ disease. Patients with TNBC, not limited to IBC, have been shown to have a higher risk of both local and distant disease

recurrence compared with other breast cancer subtypes, higher rates of developing brain metastasis after lumpectomy for early-stage breast cancer, and a higher proportional incidence of having brain metastasis at the time of breast cancer diagnosis.[21–23]

In our model of patients with metastatic IBC, the presence of visceral metastasis compared to bone metastasis was associated with a higher risk of developing mCNS. We also showed that younger patients are at a higher risk of developing mCNS, consistent with other studies of women with metastatic breast cancer (not IBC specifically).[24] Prior studies evaluating IBC patients specifically have not identified first extracranial site of metastatic disease or patient age to be risk factors for mCNS, perhaps because of small numbers of patients in these other studies.[2,3]

In this study, where the majority of patients were diagnosed with mCNS in the context of neurologic symptoms, 60% of the patients received WBRT. A stable number of patients were diagnosed with symptomatic mCNS over the study period, suggesting that there was not an increase in utilization of surveillance brain MRI over time. However, the utilization of WBRT did decline over the study period, likely reflective of the accumulating data during this time showing equivalent overall survival and decreased neurocognitive toxicity when omitting WBRT from management paradigms in the context of limited intracranial metastases.[8,9] Despite this trend away from using WBRT, we found that even in the most recent cohort (2015–2019) of patients diagnosed with CNS disease, nearly half still received WBRT, possibly reflective of a significant burden of intracranial disease seen in our IBC population. Although hippocampal-avoidance WBRT,[25] if clinically appropriate to recommend, and memantine[26] have been shown to reduce the neurocognitive side effects of WBRT, patients still experience short- and long-term sequelae of WBRT. Patterns of the treatment of intracranial disease in IBC have not been previously reported. Early detection of mCNS in IBC using surveillance brain MRI may facilitate the identification of limited intracranial disease burden, thus enabling focal local therapy with surgery and/or stereotactic radiosurgery. The high incidence of mCNS in patients with IBC and the high utilization of WBRT in our study lend support to the investigation of surveillance brain MRI in this patient population. An ongoing prospective study of screening brain MRI in patients with stage III IBC at diagnosis is currently underway as a means by which to prospectively quantify the incidence of CNS metastasis, determine the rates of utilization of WBRT, and capture patient-reported quality of life outcomes (NCT04030507).

The limitations of our study are inherent to any retrospective study and include the following: it was single-institution cohort of patients seen at the Dana-Farber Cancer Institute, and recommendations regarding the decision to obtain brain imaging for asymptomatic patients and/or treatment were made at the discretion of the treating clinical team. Additionally, we were unable to capture whether systemic therapies with potential CNS penetration were specifically recommended to address mCNS, which also may have influenced local therapy recommendations. Another limitation is inherent to all studies focused on a rare disease such as inflammatory breast cancer (i.e., small numbers of patients diagnosed with the disease) requiring our analysis to encompass a wide period of time (1997–2019), during which the treatment and diagnosis of mCNS disease was actively changing.

To our knowledge, however, this study represents the largest cohort of patients with IBC diagnosed with mCNS treated at a single institution. Our study is unique for its analysis of patients with metastatic IBC, either de novo or diagnosed at disease relapse, and for the discovery of a very high incidence of developing mCNS. It offers novel insight into the high incidence of symptomatic mCNS in our population of patients with IBC and the ongoing utilization of WBRT in the treatment of mCNS in patients with IBC. The multivariable analysis did identify several risk factors for the development of mCNS, which could have implications for surveillance and prognosis. Our findings suggest there may be a role for early detection of asymptomatic mCNS in this high-risk patient population and this strategy is currently under investigation.

In conclusion, patients with IBC, specifically those with extracranial metastatic disease, are at significant risk of developing mCNS. At particularly high risk are those patients with TN-IBC, visceral metastasis, and those diagnosed with metastatic disease at a younger age. Treatment of mCNS often includes WBRT, putting patients at risk for resultant neurocognitive toxicities. Further investigation into prevention of mCNS and whether earlier detection of mCNS results in better patient outcomes is warranted. Patients with IBC should be included in clinical trials focused on mCNS.

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AUTHOR CONTRIBUTIONS

Laura E.G. Warren: Conceptualization, procurement of patient data, data investigation and analysis, writing–original draft, and writing–review and editing. Samuel M. Niman: Conceptualization, data investigation, formal

data analysis, writing and editing of original draft, and writing–review and editing. Marie C. Remolano: Data gathering and writing–review. Jean M. Landry: Procurement of patient data and writing–review. Faina Nakhlis: Conceptualization, procurement of patient data, and writing–review. Jennifer R. Bellon: Conceptualization, procurement of patient data, and writing–review. **Ayal A. Aizer:** Conceptualization, procurement of patient data, and writing–review. **Nancy U. Lin:** Conceptualization, procurement of patient data, and writing–review. **Sara M. Tolaney:** Conceptualization, procurement of patient data, and writing–review. **Meredith M. Regan:** Conceptualization, formal data analysis, writing and editing of original draft, and writing–review. **Beth A. Overmoyer:** Conceptualization, procurement of patient data, data investigation and analysis, and writing–review. **Filipa Lynce:** Conceptualization, procurement of patient data, data investigation and analysis, writing–original draft, and writing–review and editing.

CONFLICTS OF INTEREST

Nancy U. Lin reports grants and/or research funds (paid to her institution) from Genentech, Novartis, Merck, Pfizer, SeaGen, AstraZeneca, Zion Pharmaceuticals, and Olema Pharmaceuticals; consulting honorariums from Prelude Therapeutics, Denali Therapeutics, Olema Therapeutics, Aleta BioPharma, Affinia Therapeutics, SeaGen, Voyager Therapeutics, Daiichi Sankyo, Pfizer, and Puma; steering committee honorariums from SeaGen and AstraZeneca; and stock options (<5%, <$150 k and currently unpaid) with Artera Inc. Sara M. Tolaney reports grants and/or research funds (paid to her institution) from AstraZeneca, Eli Lilly, Merck, Nektar, Novartis, Pfizer, Genentech/Roche, Gilead, Exelixis, Bristol-Myers Squibb, Eisai, Nanostring, Cyclacel, Sanofi, Odonate, and SeaGen; and honorarium payments for participation in advisory boards/consulting from AstraZeneca, Eli Lilly, Merck, Novartis, Pfizer, Genentech/Roche, Gilead, Bristol-Myers Squibb, Eisai, Sanofi, Odonate, SeaGen, Daiichi-Sankyo, Athenex, OncoPep, Kyowa Kirin Pharma, CytomX, Certara, Mersana Therapeutics, Ellipses Pharma, 4D Pharma, OncoSec, Infinity Therapeutics, BeyondSpring Pharma, OncXerna, Zymeworks, Zentalis, ARC Therapeutics, Reveal Genomins, and Blueprint Medicines. Ayal A. Aizer reporst consulting fees from Novartis and Seagen; and other financial or nonfinancial interests from Varian Research Funding and NH TherAGuIX Research Funding. Filipa Lynce reports grants and/or research funds (paid to her institution) from AstraZeneca, CytomX, Zentalis, Merck, Bristol-Myers Squibb, and Pfizer; payment or honoraria from Prime, National Association of Managed Care Physicians Conference, ION (AmeriSource Bergen), and Practicing Clinicians Exchange Breast Cancer Bootcamp Clinical Education; participation on a data safety monitoring board or advisory board from AstraZeneca, Bristol-Myers Squibb, Daiichi, and Pfizer; and committee leadership (not remunerated) from the American Society of Clinical Oncology and the Inflammatory Breast Cancer International Consortium. Meredith M. Regan reports research funding (paid to her institution) from Bayer and Bristol-Myers Squibb; research funding from Novartis, Pfizer, Ipsen, TerSera, and DebioPharm as director of International Breast Cancer Study Group Statistical & Data Management Center; consulting fees from Tolmar, Ipsen, and DebioPharm; honoraria from WebMD, Institut Hospital del Mar d'Investigacions Mèdiques, SONK (St. Gallen Oncology Conferences); participation on a data safety monitoring board or advisory board from AstraZeneca and Bristol-Myers Squibb; and a leadership or fiduciary role in ETOP-IBCSG Partners Foundation (formerly International Breast Cancer Study Group Foundation). The other authors made no disclosures.

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