Neuro-Oncology

XX(XX), 1–11, 2022 | https://doi.org/10.1093/neuonc/noac249 | Advance Access date 11 November 2022

Incidence proportion and prognosis of leptomeningeal disease among patients with breast vs. non-breast primaries

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Abstract

Background. Leptomeningeal disease (LMD) is a relatively uncommon manifestation of advanced cancer. Patients with LMD carry a poor prognosis and often decline rapidly, complicating inclusion in clinical trials. Identification of LMD subsets of greater incidence and more favorable prognosis might facilitate dedicated clinical trials in the future. We hypothesized that patients with breast cancer may represent such a population and sought to assess the relative incidence and prognosis of LMD secondary to breast vs. non-breast primaries.

Methods. We identified 2411 patients with intracranial metastases secondary to breast (N = 501) and non-breast (N = 1910) primaries at Brigham and Women's Hospital/Dana-Farber Cancer Institute between 1996 and 2020, of whom 112 presented with and an additional 161 subsequently developed LMD. A log-rank test and Cox modeling were used to compare outcomes in patients with breast vs. non-breast primaries.

Results. Among patients with newly diagnosed intracranial disease, the incidence proportion of concurrent LMD was 11.4% vs. 2.9% among patients with breast vs. non-breast primaries (P < .001). Development of LMD among initially LMD-naïve patients was also more common among patients with breast vs. non-breast primaries (HR = 1.49 [1.05–2.11], P = .03). Patients with LMD secondary to breast vs. non-breast primaries displayed lower all-cause mortality (HR 0.70 [0.52–0.93], P = .01; median survival: 5.2 vs. 2.4 months, respectively), with a greater numerical difference observed in patients with LMD at intracranial involvement (7.4 vs. 2.6 months, respectively).

Conclusions. Patients with breast cancer and LMD may represent an ideal population for clinical trials given the higher incidence and potentially more favorable prognosis seen in this population.

Key Points

- Leptomeningeal disease (LMD) is more common among patients with breast cancer.
- Prognosis for patients with breast cancer-associated LMD appears more favorable.
- Future clinical trials should be dedicated to this patient population in need.

Importance of the Study

Prognosis for patients with leptomeningeal disease (LMD) remains poor and has compromised clinical trial development focused on this population. In this 2411-cohort of patients managed at a tertiary cancer center for intracranial disease, the incidence of LMD at presentation of intracranial disease and risk of subsequent LMD development (among those LMD-naïve at diagnosis of intracranial disease) was significantly higher among patients with breast vs. non-breast primaries. Moreover, among all patients with LMD, an underlying breast primary was associated with lower all-cause mortality upon multivariable modeling compared to non-breast primaries; this difference in survival was notably higher among patients presenting with LMD at initial intracranial involvement. This work demonstrates that LMD appears to be more common and may be associated with a more favorable prognosis among patients with breast primaries compared to other primary tumor types and may set the stage for clinical trials focused on this patient population with breast cancer-associated LMD.

Oncologic leptomeningeal disease (LMD) occurs when tumor cells contaminate the cerebrospinal fluid and infiltrate the arachnoid and pia mater of the brain and spinal cord.[1] Affected patients often display contrast enhancement of the cranial nerves, cerebellar folia, supratentorial sulci, spinal nerve roots, and other subarachnoid surfaces; ventricular enlargement, transependymal flow, and hydrocephalus may also occur. Among cancer patients with newly diagnosed brain metastases, approximately 2–12% will display leptomeningeal involvement; in addition, based on prospective studies, another 1–37% develop LMD later in their clinical course.[2–8] The incidence of LMD has been challenging to characterize given heterogeneity in the definition of this entity (ie, necessity of radiographic findings, cytologic hallmarks, or both) as well as common mimickers of leptomeningeal disease which may not be consistently excluded from incidence estimates, such as post-surgical pachymeningeal seeding, which has a more favorable prognosis than LMD.[9,10] In addition the guarded sensitivity of cytology compounds the difficulties with ascribing incidence.[11,12] Typically, once a diagnosis of LMD is made, the prognosis for patients is poor, with median overall survival ranging from 1 to 4 months for most subsets.[13–17] The poor prognosis and rapid clinical decline associated with LMD complicates enrollment of such patients on clinical trials given the relative impracticality of completing study procedures and obtaining follow-up assessments in many subsets; as a result, to date, very few trials have ever been completed on patients with LMD.[18]

Although LMD is a relatively rare sequela of metastatic disease, prior studies have demonstrated that it may be increasingly more common among patients with metastatic breast cancer, affecting approximately 5% of all patients with metastatic breast cancer and up to 10–20% of those with breast cancer and brain metastases.[19–22] The rising incidence of LMD in metastatic breast cancer is thought to be secondary to improving survival with novel systemic therapies, which have yielded improved extracranial but lagging intracranial disease control.[23] With respect to prognosis, some older, smaller retrospective studies have suggested that patients with breast cancer-associated LMD may have better survival outcomes than those with LMD secondary to other primary disease sites, although data are conflicting and few contemporary studies exist.[24–27]

The historically poor prognosis of patients with LMD has resulted in the exclusion of affected patients from clinical trials. Given the potentially increasing prevalence of LMD among patients with breast cancer as well as our clinical experience, we hypothesized that patients with breast cancer would have a greater incidence of LMD than patients with other primaries and also carry a more favorable prognosis. If verified, such a finding may promote the viability of dedicated clinical trials for this population in need.

Methods

We retrospectively identified 2411 patients with intracranial metastases secondary to a solid tumor that was primarily managed within the Department of Radiation Oncology at Brigham and Women's Hospital/Dana-Farber Cancer Institute (BWH/DFCI, Boston MA) between 1995 and 2020. Of these, 273 patients manifested cranial LMD either at (N = 112) or after (N = 161) initial diagnosis of intracranial disease. All patients underwent magnetic resonance imaging (MRI) of the brain and all images, as well as imaging reports, were centrally reviewed by an attending radiation oncologist specializing in patients with intracranial metastases who assessed for the presence vs. absence of leptomeningeal disease at and any time after diagnosis of intracranial disease, with the date of development of leptomeningeal disease recorded. Diagnosis of LMD was defined as (1) MRI-based oncologic disease in the leptomeninges, which generally manifested as subarachnoid enhancement in the cranial nerves, folia of the cerebellum, supratentorial sulci, or ependyma or (2) positive CSF cytology. Mimickers of leptomeningeal disease, such as post-surgical pachymeningeal seeding (sometimes referred to in the literature as nodular leptomeningeal disease), calvarial disease with isolated, secondary pachymeningeal or leptomeningeal extension, and focal leptomeningeal extension of an intact brain metastasis without features suggesting global leptomeningeal involvement of the central nervous system were not counted as LMD.[9,10]

Statistical Methodology

Statistical analyses were performed for the entire cohort of patients with LMD as well as for subsets of patients diagnosed with LMD at vs. after identification of

intracranial, parenchymal disease. Among all cohorts, categorical baseline characteristics among patients with breast vs. non-breast primary tumors were compared using Fisher's exact test. Normally and non-normally distributed continuous covariates were compared between groups using the unpaired *t*-test and Wilcoxon rank sum test, respectively. Associations between the presence of LMD at diagnosis of intracranial disease and primary tumor type (breast vs. non-breast) were assessed via Fisher's exact test. To quantify and compare the development of LMD subsequent to intracranial disease diagnosis among patients who lacked LMD at diagnosis of intracranial involvement, cumulative incidence curves were constructed and compared with Gray's test; in addition, univariable and multivariable Fine and Gray's competing risks regression was used to identify predictors of LMD development with death from any cause as the competing risk. Median survival for each group was calculated with the Kaplan-Meier method; comparisons were made with the log-rank test. Predictors of all-cause mortality were assessed with univariable and multivariable Cox regression models adjusted for age at diagnosis of intracranial disease, primary tumor type (breast vs. non-breast), race, Charlson comorbidity index (CCI), Karnofsky performance status (KPS), and initial intracranial disease management strategy. The assumption of proportional hazards for these models was tested and verified. A 2-sided *P*-value <.05 was considered statistically significant. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board; written informed consent was waived. Analyses were performed using SAS version 9.4.

Results

Baseline Characteristics

Baseline characteristics for the 2411 patients with intracranial disease managed at BWH/DFCI from 1996 to 2020 are displayed in Supplementary Table 1. Of these, 501 (21%) had brain metastases secondary to a breast primary, while 1910 (79%) harbored a non-breast primary. Overall, patients with breast primaries were younger in age (mean 54 vs. 63 years, $P < .001$), more likely to be female (97% vs. 52%, $P < .001$), have a lower CCI (92% vs. 80% with CCI of 0–1), and harbor a greater number of brain metastases at the time of diagnosis of intracranial disease (median 3 vs. 2, $P < .001$) compared to those with a non-breast primary; in addition, there were significant differences between the two groups with respect to initial brain-directed treatment strategy ($P < .001$). Whole brain radiation therapy (without SRS/SRT or resection) was utilized as the initial intracranial management strategy for 47% of patients with breast cancer vs. 28% of patients with non-breast primaries, while stereotactic radiation therapy (without resection) was utilized for 29% vs. 38% of breast vs. non-breast patients, respectively; any neurosurgical resection was performed in 20% of patients with breast cancer vs. 29% of patients with non-breast primaries (**Supplementary Table 1**).

Incidence of LMD

Among the original 2411-patient cohort, there were 58 patients without LMD at intracranial disease diagnosis for whom the subsequent development of LMD could not be assessed; among the remaining 2353 patients, the incidence proportion of any LMD (ie, at diagnosis of or subsequent to intracranial disease development) was 20.3% (99/488) among patients with breast vs. 9.3% (174/1865) among patients with non-breast primaries ($P < .001$; Figure 1).

In total, 112 patients were noted to have LMD at the initial diagnosis of intracranial involvement. The incidence proportion of LMD at the initial oncologic intracranial involvement was 11.4% ($N = 57$) among patients with breast cancer vs. 2.9% ($N = 55$) among patients with other primaries ($P < .001$). Among 2299 patients without LMD initially, assessment regarding the subsequent development of LMD could be made in 2241 patients; of these, 9.7% (42/431) vs. 6.6% (119/1810) of patients with breast vs. non-breast primaries developed LMD. The risk of subsequent LMD development was significantly higher among patients with breast vs. non-breast primaries (hazard ratio (HR) 1.49 [1.05–2.11], $P = 0.03$; Supplementary Figure 1).

Among the 112 patients who presented with LMD at diagnosis of intracranial involvement, 42% (24/57) of breast cancer and 29% (16/55) of non-breast cancer patients had a lumbar puncture with positive cytology. Among the 162 patients who presented with LMD subsequent to initial intracranial disease diagnosis, 24% (10/42) of breast and 13% (15/119) of non-breast cancer patients had a lumbar puncture with positive cytology. To assess whether differences in the utilization of lumbar puncture among patients with breast vs. non-breast cancer affected LMD incidence in these groups, we compared the proportion of patients with cytologic evidence of LMD who also had radiographic LMD: 96% (23/24) of breast cancer vs. 88% (14/16) of non-breast cancer patients harbored radiographic evidence of LMD ($P = .55$) in addition to positive cytology; similarly, among patients with CSF-confirmed LMD subsequent to initial intracranial disease diagnosis, 90% (9/10) of breast cancer and 80% (12/15) of non-breast cancer patients also had radiographic evidence of LMD ($P = .63$). To assess whether the slight increase in cytologic sampling among patients with breast cancer accounted for the higher incidence proportion of LMD among patients with breast cancer, we performed a sensitivity analysis in which we removed patients with a diagnosis of LMD based on cytology alone (ie, patients without definitive radiographic changes consistent with leptomeningeal disease). In this sensitivity analysis, patients with breast cancer continued to demonstrate a higher incidence proportion of any LMD compared to non-breast patients (20.0%, 97/486 vs. 9.1%, 169/1860, respectively, $P < .001$). This also held true when examining just those patients with LMD at diagnosis of intracranial disease; among this group, the incidence proportion of LMD was 11.5% (56/486) in breast vs. 2.9% (53/1860) in non-breast patients ($P < .001$). Similarly, following removal of patients with a diagnosis of LMD based on cytology alone, the cumulative incidence and risk of subsequent LMD among those without LMD at initial diagnosis remained higher among patients with breast compared to those with

non-breast primaries (9.5%, 41/430 vs. 6.4%, 116/1807, respectively; hazard ratio [HR] 1.49 [1.05–2.12], $P = .03$).

Characteristics of patients with LMD diagnosed at or after diagnosis of intracranial involvement, as stratified by primary tumor site, are presented in Tables 1 and 2, respectively. Among patients who presented with LMD at diagnosis of intracranial disease, those with breast vs. non-breast primaries were more likely to be younger (mean age 54 vs. 60 years, $P = .02$), have a different year of diagnosis (mean 2013 vs. 2015, $P = .04$), and be of female sex (98% vs. 38%, $P < .001$; Table 1). There were no significant differences with respect to race, KPS, CCI, number of brain metastases, size of largest brain metastasis at diagnosis of intracranial involvement, or initial brain-directed treatment strategy among patients with breast vs. non-breast primaries. Among patients who developed LMD after initial diagnosis of intracranial disease (Table 2), patients with breast vs. non-breast primaries were more likely to be younger (mean age 50 vs. 59 years, $P < .001$), be of female sex (100% vs. 57%, $P < .001$), harbor smaller brain metastases at initial diagnosis (largest metastasis: 19 mm vs. 25 mm, $P = .02$), and differ in initial intracranial management strategy ($P = .01$); there were no significant differences among patients with respect to year of LMD diagnosis, time from intracranial disease diagnosis to LMD development, race, KPS, CCI, or number of brain metastases at time of initial intracranial disease diagnosis.

Prognosis of LMD

Median survival from time of LMD diagnosis was 5.2 (interquartile range [IQR] 1.8–11.0) vs. 2.4 (IQR 1.1–5.7) months for those with breast vs. non-breast primaries ($P = .02$); for patients with breast cancer, median survival times for hormone-receptor positive/HER2-negative ($N = 47$), HER2+ ($N = 28$), and triple-negative ($N = 23$) patients were: 7.1 (IQR 2.0–14.1) months, 5.7 (IQR 2.5–10.9) months, and 2.4 (IQR 1.3–7.4) months, respectively; receptor status was unknown for one patient. Among the subset with LMD present at diagnosis of intracranial disease, the median survival time was 7.4 (IQR 2.4–14.6) vs. 2.6 (IQR 1.2–5.8) months for those with breast vs. non-breast primaries, respectively ($P = .16$). Median survival for the subset of patients diagnosed with LMD later in their clinical course was 2.8 (IQR 1.5–8.0) vs. 2.2 (IQR 1.0–5.3) months for patients with breast vs. non-breast primaries ($P = .50$). Survival estimates of patients with LMD by primary cancer site are presented in Figure 2.

Cox regression analyses for all-cause mortality among all patients with LMD regardless of timing of LMD development are displayed in Supplementary Table 2. In the adjusted model, harboring a breast vs. non-breast primary (HR 0.70 [0.52–0.93], $P = .01$) and KPS 90–100 vs. <90 (HR 0.75 [0.57–0.99], $P = .04$) were associated with reduced all-cause mortality. Cox regression analyses for all-cause mortality among patients with LMD at and after diagnosis of intracranial disease are presented in Tables 3 and 4, respectively. In the adjusted model for patients with LMD at diagnosis of intracranial disease, breast vs. non-breast primary (HR 0.61 [0.39–0.95], $P = .03$) and KPS 90–100 vs. <90 (HR 0.44 [0.26–0.74], $P = .002$) were associated with reduced all-cause mortality; there were no other significant predictors of survival among this cohort (Table 3). Among patients with LMD after initial intracranial disease development, there were no significant predictors of survival noted, including breast vs. non-breast primary (HR 0.95 [0.62–1.45], $P = .80$; Table 4).

When limiting the cohort to only those patients diagnosed with LMD between 2008 and 2020 ($N = 248$), similar trends described above were observed; namely, breast primary was associated with reduced all-cause mortality following LMD diagnosis at any time point (HR 0.68 [0.50–0.93], $P = .01$); among the subset of patients with LMD at diagnosis of intracranial disease, both breast primary and KPS 90–100 vs. KPS <90 were associated with reduced all-cause mortality (HR 0.62 [0.40–0.96], $P = .03$, and HR 0.47 [0.27–0.80], $P = .006$, respectively); there were no predictors of reduced mortality among patients who developed LMD subsequent to initial intracranial disease diagnosis.

Discussion

In this study of over 200 patients with leptomeningeal disease managed at a large tertiary cancer center in the

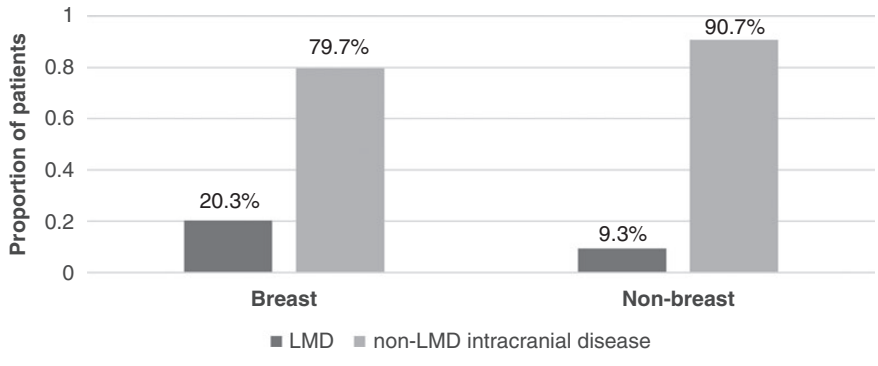

Figure 1. Incidence proportion of leptomeningeal disease among patients with breast vs. non-breast primaries and newly diagnosed intracranial disease. LMD = leptomeningeal disease.

Table 1. Characteristics of Patients With Concurrent Leptomeningeal Disease at Diagnosis of Intracranial Involvement by Primary Tumor Type

	Breast primary (*N* = 57)	Non-breast primary (*N* = 55)	*P*
Year of LMD diagnosis, mean (SD)	2013 (4)	2015 (4)	.04
Age at diagnosis of BrM, years, mean (SD)	54 (12)	60 (14)	.02
Sex, *N* (%)			<.001
Male	1 (2)	34 (62)	
Female	56 (98)	21 (38)	
Race, *N* (%)			.75
White	46 (81)	39 (71)	
African American	4 (7)	5 (9)	
Hispanic	2 (4)	2 (4)	
Asian/Pacific Islander	3 (5)	4 (7)	
Other/Unknown	2 (4)	5 (9)	
Karnofsky performance status, *N* (%)			.38
<90	41 (72)	44 (80)	
90–100	16 (28)	11 (20)	
Charlson comorbidity index, *N* (%)			.20
0–1	54 (95)	48 (87)	
>1	3 (5)	7 (13)	
Number of BrM at diagnosis of intracranial involvement, median (IQR)[a]	2 (1–12)	3 (1–11)	.70
Largest BrM in mm at diagnosis of intracranial involvement, median (IQR)[a]	11 (5–20)	11 (7–17)	.70
Initial brain-directed treatment strategy, *N* (%)			.51
WBRT, without SRS/SRT or resection	49 (86)	42 (76)	
SRS/SRT, without resection	3 (5)	4 (7)	
Any resection with or without radiation	3 (5)	7 (13)	
No local therapy	2 (4)	2 (4)	

[a]Excludes 8 patients with unknown values for this variable.
BrM = brain metastasis; IQR = interquartile range; LMD = leptomeningeal disease; mm = millimeters; N = number; SD = standard deviation; SRS/SRT = stereotactic radiosurgery/stereotactic radiotherapy; WBRT = whole brain radiation therapy.

contemporary era, we found that patients with intracranial disease secondary to breast cancer vs. other primaries displayed a greater incidence of LMD. Moreover, the risk of LMD in breast cancer was greater both at the time of initial intracranial involvement and thereafter as well. In addition, we found an association between breast cancer, particularly hormone receptor positive/HER2-negative or HER2+ subtypes, and improved survival after diagnosis of LMD among all patients with LMD and also in the subset of patients with LMD at but not after diagnosis of intracranial oncologic disease.

The exact incidence of leptomeningeal disease has been challenging to characterize due to non-standardized definitions and diagnostic modalities.[28,29] Here the use of a single, central reviewer as well as a clear and consistent definition of LMD, with exclusion of classic mimickers, likely improved the reliability of our conclusions. Our study also benefitted from a relatively contemporary cohort, with a median LMD diagnosis year of 2014 and inclusion of patients through the year 2020, reflecting utilization of contemporary MRI sequences, typically with 1.0–1.5 mm isotropic voxels on T1 post-contrast imaging of the brain, improving the sensitivity of the imaging studies used for diagnosis of LMD.[30] Although prior studies have reported on predictors of development of LMD, these studies were largely performed in an earlier era and often lacked a central review of imaging, or featured reliance on reports and not centralized, directed review of MRI images. Our results build on previous work by demonstrating a relatively higher incidence of LMD among breast cancer patients with intracranial disease compared to other primary tumor sites.

The prognosis for patients with LMD is generally very poor, with median survival times of 4–6 weeks for untreated patients and 2–4 months for treated patients.[1,31] Some studies have demonstrated better survival outcomes for patients with breast cancer-associated LMD compared to other primary tumor types; for example, in a series of 90 patients with LMD who received partial brain irradiation to sites of major clinical involvement and intraventricular methotrexate between 1975 and 1980, patients with breast cancer displayed a median survival 7.2 months compared to median survival times of 4.0 and 3.6 months for patients with lung cancer and melanoma,

Table 2. Characteristics of Patients With Sequential Leptomeningeal Disease After Initial Diagnosis of Intracranial Involvement by Primary Tumor Type[a]

	Breast primary (*N* = 42)	Non-breast primary (*N* = 119)	*P*
Year of LMD diagnosis, mean (SD)	2013 (5)	2014 (4)	.26
Time from intracranial disease involvement to LMD diagnosis, median (IQR)	14 (7–22)	9 (4–17)	.72
Age, years, mean (SD)	50 (10)	59 (11)	<.001
Sex, *N* (%)			<.001
Male	0 (0)	51 (43)	
Female	42 (100)	68 (57)	
Race, *N* (%)			.68
White	38 (90)	98 (82)	
African American	3 (7)	7 (6)	
Hispanic	0 (0)	4 (3)	
Asian/Pacific Islander	1 (2)	6 (5)	
Other/Unknown	0 (0)	4 (3)	
Karnofsky performance status, *N* (%)			.10
<90	19 (45)	73 (61)	
90–100	23 (55)	46 (39)	
Charlson comorbidity index, *N* (%)			.09
0–1	39 (93)	97 (82)	
>1	3 (7)	22 (18)	
Number of BrM, median (IQR)[b]	2 (1–6)	2 (1–6)	.62
Largest BrM in mm, mean (SD)[c]	19 (13)	25 (14)	.02
Initial brain-directed treatment strategy, *N* (%)			.01
WBRT, without SRS/SRT or resection	17 (40)	34 (29)	
SRS/SRT, without resection	14 (33)	23 (19)	
Any resection with or without radiation	8 (19)	54 (45)	
No local therapy	3 (7)	8 (7)	

[a]All co-variates pertain to patient status at time of initial intracranial disease diagnosis with the exception of year of leptomeningeal disease diagnosis.
[b]Excludes 1 patient with an unknown value for this variable.
[c]Excludes 2 patients with unknown values for this variable.
BrM = brain metastasis; IQR = interquartile range; LMD = leptomeningeal disease; mm = millimeters; N = number; SD = standard deviation; SRS/SRT = stereotactic radiosurgery/stereotactic radiotherapy; WBRT = whole brain radiation therapy.

respectively.[24] Similarly, in a study of 155 patients with LMD treated between 1980 and 2002, median survival among breast cancer patients was 11.3 months compared to 4.8 months for all other patients.[25] In another study of 135 patients diagnosed with LMD between 1989 and 2005, although patients with breast cancer-associated LMD displayed overall better survival than those with lung cancer or melanoma, median survival across all groups remained very poor (3.1 months vs. 0.8 and 0.9 months, respectively).[26] In contrast, in a relatively more recent study of 187 patients diagnosed with LMD at a large tertiary cancer center between 2002 and 2004, median overall survival for patients with breast cancer was 2.8 months, similar to the median overall survival of 2.4 months for the entire cohort.[27] In a recent study of 312 patients with breast cancer-associated LMD who received intrathecal chemotherapy, median overall survival for the entire cohort was 4.5 months, although receipt of concomitant systemic therapy was associated with a significantly improved median survival of 6.9 months compared to 2.3 months without systemic therapy; in addition, 25% of patients in this study survived for >1 year.[32] Collectively, these studies suggest that prognosis of patients with LMD is poor overall, although a subset of patients may carry a better prognosis. Moreover, while older studies suggest that breast cancer patients may do better, more recent data appears to challenge this assertion.

While most of the aforementioned studies spanned an older time period, our study included patients diagnosed with LMD through 2020, and, to the best of our knowledge, represents one of the largest contemporary series describing outcomes among patients with breast cancer-associated LMD. In addition, while prior work has not specifically separated patients by whether LMD was present

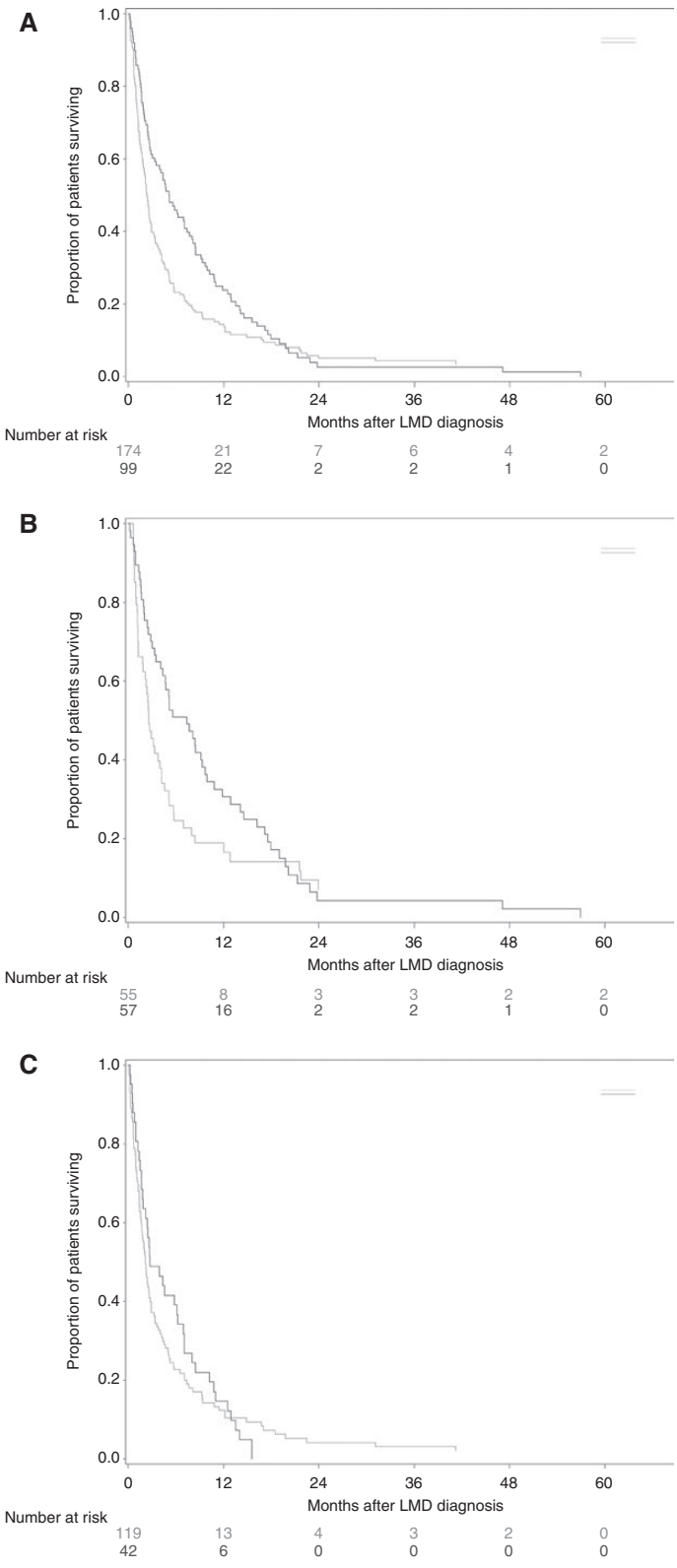

Figure 2. Overall survival by underlying primary in the entire cohort of patients with leptomeningeal disease (A) as well as in subsets diagnosed at (B) or subsequent to (C) the time of initial intracranial disease involvement. LMD = leptomeningeal disease.

Table 3. Univariable and Multivariable Cox Regression for All-Cause Mortality Among Patients With Leptomeningeal Disease at Diagnosis of Intracranial Disease

	Univariable HR (95% CI)	Univariable *P*	Multivariable HR (95% CI)	Multivariable *P*
Year of LMD diagnosis, per year increase	1.02 (0.97–1.07)	.39	1.04 (0.97–1.10)	.26
Age at diagnosis of intracranial disease, per year increase	1.01 (0.99–1.02)	.29	1.00 (0.98–1.02)	.97
Primary tumor type				
Non-breast	Ref		Ref	
Breast	0.76 (0.51–1.12)	.16	0.61 (0.39–0.95)	.03
Race				
White	Ref		Ref	
African American	0.82 (0.37–1.78)	.61	0.77 (0.33–1.78)	.54
Hispanic	1.07 (0.39–2.93)	.89	1.34 (0.46–3.94)	.59
Asian/Pacific Islander	1.00 (0.40–2.47)	1.00	0.67 (0.26–1.73)	.41
Other/Unknown	1.00 (0.43–2.29)	.99	0.87 (0.36–2.08)	.75
Charlson comorbidity index				
0–1	Ref		Ref	
>1	1.07 (0.52–2.21)	.86	0.71 (0.32–1.58)	.40
Karnofsky performance status				
<90	Ref		Ref	
90–100	0.58 (0.36–0.93)	.02	0.44 (0.26-0.74)	.002
Initial brain-directed treatment strategy				
Any resection with or without radiation	Ref		Ref	
SRS/SRT, without resection	0.50 (0.18–1.44)	.20	0.41 (0.13–1.25)	.12
WBRT, without SRS/SRT or resection	1.14 (0.57–2.27)	.72	1.77 (0.80–3.92)	.16
No local therapy	1.01 (0.31–3.29)	.99	1.10 (0.32–3.77)	.88

BrM = brain metastasis; CI = confidence interval; HR = hazard ratio; LMD = leptomeningeal disease.

at versus after initial intracranial disease diagnosis, we hypothesized that these two patient populations may be distinct with respect to the biology of their disease and therefore characterized survival for these two groups independently. Interestingly, we found that for patients who presented with LMD at the time of diagnosis of intracranial involvement, the subset with breast cancer appeared to display better survival than those with non-breast primaries (median 7.4 vs. 2.6 months, respectively); moreover, on multivariable modeling, breast as the primary tumor site was predictive of improved survival compared to non-breast primaries. However, we did not observe such a trend for patients who developed LMD later in their clinical course, with both breast and non-breast patients displaying poor median survival times of 2.8 and 2.2 months, respectively. Our data are novel in demonstrating an association in which breast cancer patients who present with LMD at the time of intracranial disease development not only have a better prognosis than patients with non-breast primary tumors, but also compared to breast cancer patients who develop leptomeningeal disease later in their disease course. Whether this reflects a unique biology of breast cancer-associated LMD or the relatively increased viability of particular treatment options at earlier time points warrants further study.

Historically, given the challenges in the diagnosis and response assessment of patients with LMD, as well as their poor prognosis even in the setting of multimodality treatment, patients with LMD have been largely excluded from clinical trials.[29,33] The relative scarcity of LMD also represents another reason for the lack of clinical studies in this population. Our study suggests that breast cancer-associated LMD is relatively more common compared to other primaries and the survival analysis suggests that breast cancer patients with LMD may carry a more favorable prognosis. For such patients, further selection using performance status and potentially biomarkers such as cerebrospinal fluid or circulating tumor cell DNA, which have previously shown promise when selecting suitable candidates with LMD for aggressive treatments,[34,35] may allow for the development of clinical trials with potential to further improve prognosis for this population; if carefully selected, such patients may live long enough to benefit from novel, more aggressive central nervous system-directed therapies, and may be more able to reach time points where response is consistently assessed.

Our work should be considered in the context of its limitations. First, given that we did not require both CSF cytology and radiographic evidence as confirmation for LMD, it is plausible that certain cases of LMD would not be considered

Table 4. Univariable and Multivariable Cox Regression for All-Cause Mortality Among Patients With Leptomeningeal Disease After Diagnosis of Intracranial Disease[a]

	Univariable HR (95% CI)	Univariable *P*	Multivariable HR (95% CI)	Multivariable *P*
Year of LMD diagnosis, per year increase	0.99 (0.96–1.03)	.62	0.99 (0.95–1.03)	.58
Age at diagnosis of intracranial disease, per year increase	1.02 (1.01–1.04)	.01	1.02 (1.00–1.03)	.10
Primary tumor type				
Non-breast	Ref		Ref	
Breast	0.88 (0.61–1.27)	.50	0.95 (0.62–1.45)	.80
Race				
White	Ref		Ref	
African American	1.17 (0.61–2.24)	.63	0.99 (0.50–1.95)	.98
Hispanic	1.82 (0.67–4.98)	.24	1.60 (0.55–4.61)	.39
Asian/Pacific Islander	0.73 (0.32–1.66)	.46	0.79 (0.34–1.84)	.59
Other/Unknown	2.07 (0.76–5.65)	.16	1.91 (0.68–5.40)	.22
Charlson comorbidity index				
0–1	Ref		Ref	
>1	1.80 (1.17–2.77)	.008	1.32 (0.79–2.20)	.29
Karnofsky performance status				
<90	Ref		Ref	
90–100	0.63 (0.45–0.87)	.006	0.74 (0.51–1.07)	.11
Initial brain-directed treatment strategy				
Any resection with or without radiation	Ref		Ref	
SRS/SRT, without resection	1.28 (0.83–1.97)	.26	1.42 (0.88–2.31)	.15
WBRT, without SRS/SRT or resection	1.35 (0.91–2.02)	.14	1.52 (0.99–2.33)	.06
No local therapy	1.15 (0.58–2.25)	.69	0.99 (0.47–2.05)	.97

[a]All co-variates pertain to patient status at time of initial intracranial disease diagnosis with the exception of year of leptomeningeal disease diagnosis.
BrM = brain metastasis; CI = confidence interval; HR = hazard ratio; LMD = leptomeningeal disease.

LMD based on standards utilized by other institutions. However, each case in our study was reviewed independently by a single attending radiation oncologist specializing in the management of metastatic central nervous system tumors. Although more patients with breast as opposed to non-breast primaries harbored positive cytology, the significant majority of patients with positive cytology also harbored radiographic changes consistent with LMD and removal of patients who only had positive cytology, without radiographic evidence of LMD, did not meaningfully impact the results. An additional limitation of our work is that all 273 patients described here were identified via a central nervous system database that is maintained for patients evaluated by radiation oncology at BWH/DFCI; therefore, the database does not include patients with LMD who were never seen by a radiation oncologist, which could bias the results described here. However, because of the central role of radiation oncology in the management of patients with LMD at our institution, we would expect that relatively few patients were missed. In addition, we would expect that patients with breast vs. non-breast primaries would be similarly evaluated by radiation oncology at our institution, minimizing the likelihood of bias. Of note, this study did not specifically assess for the presence/absence of spinal LMD at diagnosis of intracranial LMD, which should be evaluated in dedicated future studies. Finally, although this work represents one of the largest cohort studies of breast cancer-related LMD in the modern era, the overall number of patients may have still limited our power to detect a significant survival difference between breast and non-breast patients after initial diagnosis of oncologic intracranial disease. In addition, this study was not powered to explore differences among distinct molecular/biological subgroups of breast cancer patients, including HER2+, hormone receptor-positive, and/or triple-negative groups, which are known to have distinct propensities for intracranial spread.[36,37] Future validation studies consisting of a larger number of patients are needed to evaluate and verify the trends in survival observed here, as well as to explore differences among subgroups.

Conclusions

Patients with breast cancer may be more at risk of LMD than patients with other underlying primaries and may

also harbor a more favorable prognosis, particularly if of hormone receptor positive/HER2-negative or HER2+ subtypes. Future work should include validation of the results described here in larger patient populations across multiple institutions; if these results are confirmed, clinical trial development for patients with metastatic breast cancer who present with LMD should be a priority.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

Keywords

brain metastases | breast cancer | leptomeningeal disease

Funding

Kiki Fund for Breast Cancer Leptomeningeal Metastases Research.

Conflict of interest statement. Dr. Aizer reports research funding from Varian Medical Systems and NH TherAguix as well as consulting fees from Novartis and Seagen. Dr. Lin reports institutional research support from Genentech, Pfizer, Merck, Seattle Genetics, Zion Pharmaceuticals, Olema Pharmaceuticals, and AstraZeneca; consulting honoraria from Puma, Seattle Genetics, Daichii-Sankyo, AstraZeneca, Denali Therapeutics, Prelude Therapeutics, Olema Pharmaceuticals, Aleta BioPharma, Affinia Therapeutics, Voyager Therapeutics, Janssen, Blueprint Medicines, and GE Healthcare; and royalties from Up to date. The remaining authors declare no conflicts of interest.

Authorship statement. Study Conception/Design: NL, AAA, ST; Data Collection/Analysis/Interpretation: All authors; Statistical Analysis: NL, PJC, AAA; Drafting of the Manuscript: NL, AAA, ST; Manuscript Editing/Critical Revision of the Manuscript: All Authors; Supervision: AAA, ST.

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