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REVIEW

Leptomeningeal disease and breast cancer: the importance of tumor subtype

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Abstract Breast cancer (BC) is one of the most common tumors to involve the leptomeninges. We aimed to characterize clinical features and outcomes of patients with LMD based on BC subtypes. We retrospectively reviewed records of 233 patients diagnosed with LMD from BC between 1997 and 2012. Survival was estimated by the Kaplan–Meier method and significant differences in survival were determined by Cox proportional hazards or log-rank tests. Of 190 patients with BC subtype available, 67 (35 %) had hormone receptor positive (HR+)/human epidermal growth factor receptor 2 (HER2)-negative BC, 56 (29 %) had HER2+BC, and 67 (35 %) had triple-negative BC (TNBC). Median age at LMD diagnosis was 50 years. Median overall survival (OS) from LMD diagnosis was 4.4 months for HER2+BC (95 % CI 2.8, 6.9), 3.7 months (95 % CI 2.4, 6.0) for HR+/HER2−BC, and 2.2 months (95 % CI 1.5, 3.0) for TNBC ($p = 0.0002$). Older age was associated with worse outcome ($p < 0.0001$). Patients with HER2+BC and LMD were more likely to receive systemic therapy (ST) ($p = 0.001$). Use of intrathecal therapy (IT) (52 %) was similar ($p = 0.35$). Both IT ($p < 0.0001$) and ST ($p < 0.0001$) administration were associated with improved OS. After adjusting for age, IT, extracranial disease, and ST, patients with HER2+BC had better OS compared with HR+/HER2−BC (HR 1.72; 95 %CI 1.07–2.76) and TNBC (HR 3.30; 95 %CI 1.98–5.52). LMD carries a dismal prognosis. Modest survival differences by tumor subtype were seen. Patients with HER2+BC had the best outcome. There is an urgent need to develop effective treatment strategies.

Keywords Breast cancer · Leptomeningeal disease · Tumor subtype · Outcome

Introduction

Breast cancer (BC) is one of the most common solid tumors to involve the leptomeninges, with reported incidences close to 5 % [1, 2]. Leptomeningeal disease (LMD) is diagnosed with increasing frequency as progresses in the

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locoregional and systemic treatments have resulted in more patients living long enough to develop it. Furthermore, advancements in diagnostic imaging techniques have led to improved detection. The diagnosis is most commonly made by clinical signs and symptoms, positive cerebrospinal spinal fluid analysis (CSF), and/or supporting radiographic findings [1, 3]. In spite of earlier detection and recognition of LMD, treatment algorithms are not well established, as no standard approach is yet available.

Across all solid tumors, the median survival of untreated patients with LMD is 1 month [4]. Death commonly occurs from progressive neurologic dysfunction. Intrathecal (IT) chemotherapy is associated with an increased median survival of 3–6 months [1, 3, 5]. Long-term survival is occasionally observed in patients with LMD from breast cancer; however, the exact benefit afforded by IT chemotherapy alone is questionable, and no single modality has been shown to be conclusively beneficial [6, 7]. To date, no randomized controlled trials of IT and or systemic chemotherapy have been completed for LMD, and patients with LMD have been traditionally excluded from clinical trials due to poor performance status and limited survival [6]. It is important to note that available therapies for LMD do not take into account tumor subtype [8]. Until recently, most information about LMD in BC had been extrapolated from data in solid tumors in general, and were not BC specific [9]. With more targeted therapies available, looking at subgroups has become critical. A few studies have attempted to address the effects of BC subtype on LMD presentation and clinical outcomes. These have, in general, faced challenges due to small patient numbers ultimately affecting the power of those observations [10–12]. Data on patients with triple-negative BC (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive BC are limited [10]. In studies of BC patients with CNS parenchymal metastasis reported outcomes based on BC subtype have become more readily available and are leading to subtype specific clinical trial development [13, 14]

In this new era of multiple targeted agents, in addition to the more common use of IT chemotherapy and other readily available diagnostic tests, reporting outcomes of LMD and BC by subtype is imperative in order to improve the outcome of these patients and to design prospective studies.

We aimed in this single institution study to determine if the clinical outcomes of patients with LMD differ by BC subtype and treatment modalities, including targeted therapies.

Patients and methods

Patients

The BC management system database at The University of Texas MD Anderson Cancer Center was retrospectively searched, and 343 patients with invasive BC who were diagnosed with LMD between 1997 and 2012 were identified. The institutional review board approved the retrospective review of the medical records for the purposes of this study. Patients were included if they had BC, with confirmed LMD diagnosis. Diagnosis of LMD was based on positive CSF cytology and/or imaging findings. All patients included in this analysis had CSF examined for malignant cells. For patients with negative cytology after repeated lumbar punctures, they were included in the analysis if the diagnosis of LMD was confirmed by the treating oncologist in conjunction with the neuro-oncologist, and with supportive MRI findings. Patients were excluded if they had incomplete records, unconfirmed LMD, and/or no follow-up information available. After exclusion, 233 patient records were available for review. The histology, stage, analysis of the estrogen receptor (ER), progesterone receptor (PR), and HER2 status were retrieved from patient's pathology reports. When available, tumor receptor status from a metastatic site was included. Patients were followed and treated according to general practice guidelines at the time and as indicated. Staging was performed according to AJCC updated 7th edition. Treatment decisions with systemic chemotherapy, radiation therapy (RT), and/or IT chemotherapy at the time of LMD were reached through a multidisciplinary approach. As this is a retrospective study, there were no specified time points for follow-up. The status of the patients is updated yearly in the database and information on progression and death is obtained from their medical record.

Pathology

Tumors were classified as ER, and/or PR positive if they had at least 10 % positive staining by immunohistochemistry (IHC). HER2 status of primary tumors was determined using either IHC method and/or a gene amplification method using fluorescent in situ hybridization (FISH) technique. Tumors were classified as HER2-positive if the protein was overexpressed by IHC (score 3+) or amplified by FISH (HER2/CEP17 ratio $\geq$2). CSF cytology results were retrieved from the patient's records and were considered positive for LMD if malignant cells were identified.

Treatment

Treatment at the time of LMD was subdivided into systemic therapy (ST), IT, and RT. Most common ST administered after the diagnosis of LMD were capecitabine, vinorelbine, platinum salts (cisplatin/carboplatin), taxanes (paclitaxel, nab-paclitaxel, and docetaxel), temozolamide, and targeted therapies (trastuzumab, lapatinib, and bevacizumab), and endocrine therapies. Therapies used

intrathecally included methotrexate, thiotepa, cytarabine, topotecan, and investigational agents for three patients (I-131 sodium iodide, mafosfamide, and trastuzumab). RT was delivered to the brain and/or spine depending on the localization of LMD and clinical symptoms. Patients who were referred to hospice and or did not receive any of the above treatment modalities at the time of LMD diagnosis had their therapies classified as "supportive only".

Statistical analysis

Overall survival (OS) distributions were estimated using the Kaplan–Meier method and confidence intervals for median survival were based on the method of Brookmeyer and Crowley. Univariate differences in survival for categorical variables were evaluated by the log-rank test. Age-adjusted survival, hazard ratios, and multivariate survival differences were evaluated using a Cox proportional hazards model. Bivariate comparisons of categorical factors were based on Chi square or Fisher's exact tests as appropriate. Descriptive statistics were used to summarize continuous variables. The Kruskal–Wallis test was used to evaluate continuous variable differences among levels of categorical factors. Nettleton's method was used to evaluate the supremacy of a category. All statistical analyses were performed using SAS 9.3 [SAS Institute Inc., Cary, NC, USA)], and statistical significance was defined as $p < 0.05$.

Results

Patient demographics and clinical characteristics

A total of 233 patients with BC and LMD were evaluated. All but one patient have died at the time of this analysis. The median follow-up from time of LMD diagnosis among the deceased patients was 3.15 months. The follow-up time for the patient still alive at last follow-up is 20 months. 190 patients had known tumor subtype. An equal proportion of patients with LMD had hormone receptor positive (HR+)/HER2−BC (35 %), HER2+BC (29 %), and TNBC (35 %) ($p = 0.5$). Median age at LMD diagnosis was 50 years and was not different across BC subtypes ($p = 0.49$). Median age at initial BC diagnosis was 45 years. Patient characteristics are summarized in Table 1. Analysis of CSF cytology yielded malignant cells in the majority of patients (87 %); the remainder had an LMD diagnosis based on MRI imaging and clinical findings.

Most patients (80 %) had evidence of extracranial metastasis before or at the time of LMD. A diagnosis of parenchymal brain metastasis preceded LMD diagnosis in 62 % of patients. Patients with HER2+BC were more likely to have parenchymal brain metastasis (87.5 %) compared with others ($p < 0.0001$).

After the diagnosis of LMD, most patients (75 %) received RT to the brain or spine. This was not different across BC subtypes ($p = 0.07$). Over half the patients across all subtypes received IT chemotherapy ($p = 0.35$). The most common intrathecally prescribed therapies were topotecan, cytarabine, and methotrexate. One third of patients received more than one type of IT therapy for progression. One patient received trastuzumab intrathecally and remains on treatment. Patients with HER2+BC were more likely to receive ST after LMD diagnosis (69 %) ($p = 0.001$). The most commonly prescribed ST was capecitabine. HER2-targeted ST (trastuzumab and/or lapatinib) was administered to 51 % of patients after LMD diagnosis. Supportive therapy alone was given to 10 % of patients, this was not different across subtypes ($p = 0.28$).

Survival estimates

In patients with metastatic BC (MBC) prior to LMD, the median time to LMD diagnosis was 9.8 months. More than 75 % of the LMD occurred within 2 years of initial MBC diagnosis (range 0–164 months). The median time to LMD after MBC was longest for patients with HR+/HER2−BC (13.5 months) ($p = 0.0001$). After LMD diagnoses, there was a 12.0 % chance patients would survive 1 year and 1.3 % chance they would survive at least 3 years. OS from the time of LMD diagnosis was 3.1 month. This was significantly different by BC subtype ($p = 0.0002$), median OS among patients with HER2+BC was longest at 4.4 months. Survival for HR+/HER2−BC, and TNBC was 3.7 and 2.2 months, respectively (Fig. 1a). At 6 months, twice as many patients with HER2+BC were alive compared with TNBC. This survival difference is even more apparent at 1 year where 12 patients (21 %) with HER2+BC were still alive compared with three patients (4 %) with TNBC. From the time of first distant metastasis, median OS was 15 months. This also differed by subtype ($p < 0.0001$), patients with TNBC having the shortest survival time from first distant metastasis (11 months) (Fig. 1b). The univariate survival outcomes are listed in Table 2. Older age was associated with worse survival ($p < 0.0001$). The presence of extracranial disease did not significantly associate with survival after LMD ($p = 0.08$) (Fig. 1c), except for patients with HR+/HER2−BC, where it was significantly associated with worse outcome (HR 2.33; 95 % CI 1.17–4.64) (Fig. 1d). The presence of parenchymal brain metastasis did not significantly associate with survival after LMD ($p = 0.15$).

Survival and therapies

Median OS from time of LMD diagnosis was statistically different among patients who received IT (5.0 months)

Table 1 Patient Characteristics

	Total* % (N)	HER2+ % (N)	HR+/HER2− % (N)	TNBC %(N)	*P*
	(233)	29(56)	35.5(67)	35.5(67)	0.50
Median age LMD (years)	50	49.5	51	49	0.49
Race					
White/Other	86(201/233)	84(47/56)	85(57/67)	87(58/67)	0.97
Black	14(32/233)	16(9/56)	15(10/67)	13(9/67)	
Stage at BC presentation[a]					
I	5(8/144)	0(0/42)	12(6/51)	4(2/51)	0.29
II	26(37/144)	29(12/42)	24(12/51)	25(13/51)	
III	39(56/144)	43(18/42)	31(16/51)	43(22/51)	
IV	30(43/144)	29(12/42)	33(17/51)	27(14/51)	
Extracranial metastasis	80(186/233)	73(41/56)	84(56/67)	79(53/67)	0.37
Visceral metastasis	–	25(14/56)	42(28/67)	40(27/67)	0.11
Brain metastasis	62(144/233)	88(49/56)	58(39/67)	52(35/67)	<0.0001
Intrathecal therapy[b]	52(115/220)	51(28/56)	47(32/67)	59(40/67)	0.35
Systemic therapy after LMD[c]	55 (119/217)	69(39/56)	41 (28/67)	41(28/67)	0.002*
Endocrine		11(6/56)	28 (19/67)	–	
Capecitabine	31(68/217)	39(22/56)	24(16/67)	24(16/67)	0.22
Platinum salts		5(3/56)	4 (3/67)	6(4/67)	
Taxanes		9(5/56)	6(4/67)	4(3/67)	
Vinorelbine		12(7/56)	6(4/67)	6(4/67)	
Temozolamide		11(6/56)	3(2/67)	7(5/67)	
HER2 therapy after LMD		51(29/56)	–	–	–
RT after LMD[d]	75(165/218)	88(49/56)	70(47/67)	76(51/67)	0.07
Supportive care only[e]	10(22/217)	5(3/56)	11(7/67)	14(9/67)	0.28

Abbreviations: *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *HR+* hormone receptor positive, *LMD* leptomeningeal disease, *BC* breast cancer, *RT* radiation therapy

* Total of all patients with LMD including patients with unknown breast cancer subtype

[a] Stage at presentation available for 144 of the total 233 patients

[b] IT therapy information available for 220 of the total 233 patients

[c] Systemic therapy information available for 217 of the total 233 patients

[d] RT information available for 218 of the total 233 patients

[e] Supportive therapy information available for 217 of the total 233 patients

compared with patients who did not (2.2 months) ($p < 0.0001$) (Fig 2a). As shown in Table 2, administration of IT was associated with longer survival (HR 0.50; 95 % CI 0.38–0.65). This association remained across each BC subtype, HER2 + ($p = 0.005$), TNBC ($p = 0.001$), and HR+/HER2−BC ($p = 0.03$). Administration of ST was associated with improved OS (HR 0.31; 95 % CI $p < 0.0001$) (Fig. 2b). Median survival among patients who did not receive ST was 1.7 months compared with 6.4 months for those who did. Upon subgroup analysis, this association remained favorable across all subtypes (Table 2). In regards to the different systemic therapies used, capecitabine intake was associated with longer OS (HR 0.50; 95 % CI 0.37–0.66). It is important to note that this was also the most commonly prescribed treatment. While both IT and ST after LMD were associated with significant improvement in OS, RT was not ($p = 0.79$) (Fig. 2c). Except for patients with TNBC, where RT was associated with longer OS ($p = 0.002$) (Table 2).

Patients who received supportive care only (10 %) and no further treatment had shorter OS compared to those who received additional treatments ($p = 0.004$) (Fig. 2d).

After adjustment for age at LMD diagnosis, ethnicity, presence of parenchymal brain metastasis, presence of extracranial disease, IT therapy, ST, stage at BC diagnosis, HER2-directed therapy, capecitabine, visceral site as first metastasis, RT, and supportive care, HER2+BC subtype remained associated with longer OS when compared with HR+/HER2−BC (HR 1.72; 95 % CI 1.07–2.76) and TNBC (HR 3.30; 95 % CI 1.98–5.52) (Table 3).

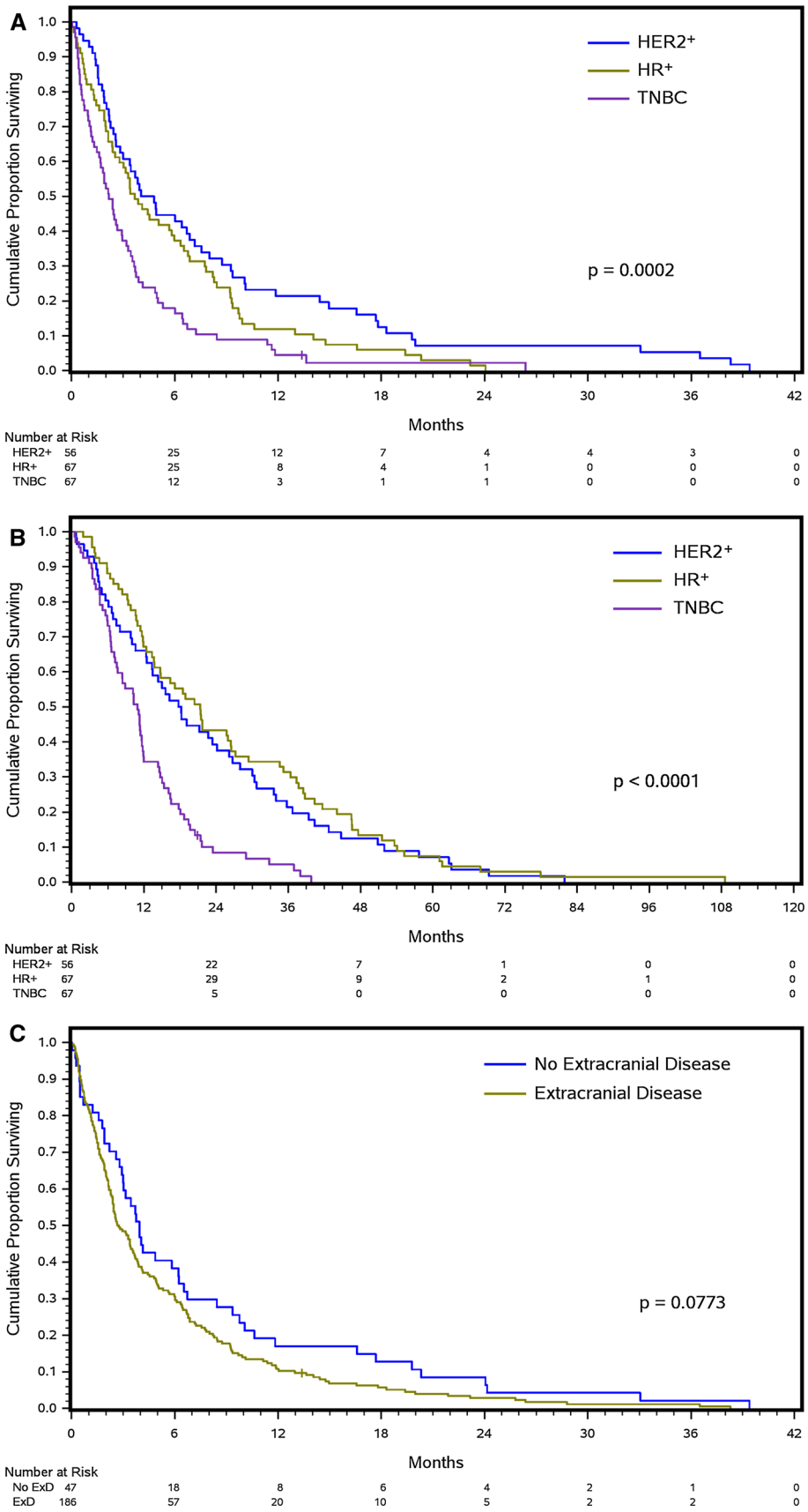

Fig. 1 Overall Survival **A** overall survival from leptomeningeal disease diagnosis by subtype **B** overall survival from date of first distant metastasis by subtype **C** overall survival by presence of extracranial disease **D** overall survival from leptomeningeal disease diagnosis by presence of extracranial disease for hormone receptor positive breast cancer subtype

Fig. 1 continued

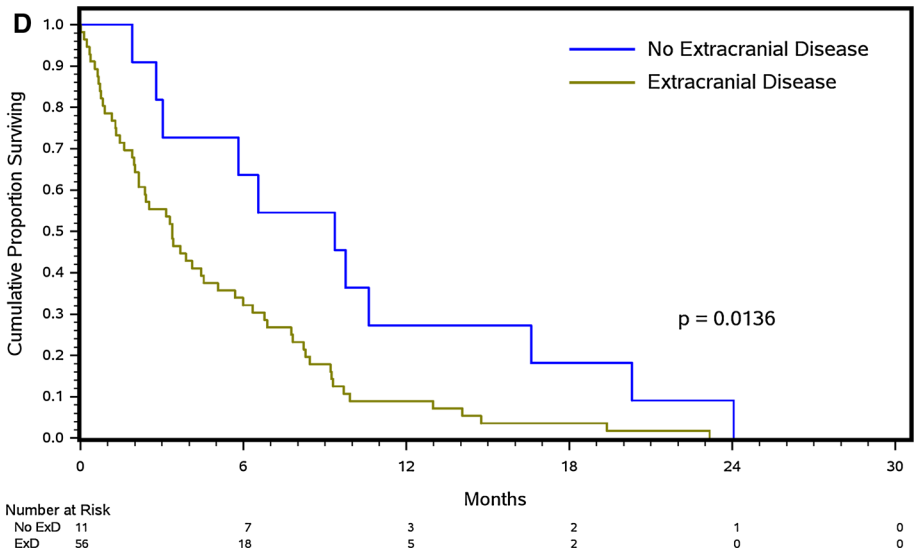

Table 2 Overall survival estimates (univariate) patient and clinical characteristics

	All patients			HER2+			TNBC			HR+		
	HR	95 % CI	*P*	HR	95 %CI	*P*	HR	95 %CI	*P*	HR	95 %CI	*P*
Age LMD diagnosis	1.03	1.01, 1.04	<0.0001	1.03	1.00, 1.06	0.053	1.03	1.01, 1.06	0.016	1.03	1.01, 1.06	0.005
Race (Black vs. Other)	1.37	0.94, 2.00	0.101	2.12	0.99, 4.53	0.052	2.68	1.26, 5.68	0.010	1.12	0.56, 2.21	0.752
Stage												
I versus III	0.61	0.30, 1.23	0.163				0.23	0.03, 1.79	0.161	0.48	0.17, 1.34	0.160
II versus III	0.86	0.58, 1.27	0.435	0.60	0.28, 1.28	0.186	0.68	0.34, 1.36	0.271	1.10	0.52, 2.35	0.800
IV versus III	0.93	0.64, 1.34	0.680	0.70	0.33, 1.47	0.346	0.81	0.41, 1.60	0.544	1.38	0.68, 2.78	0.371
Extracranial metastasis	1.34	0.97, 1.85	0.079	1.13	0.61, 2.10	0.690	1.14	0.63, 2.07	0.659	2.33	1.17, 4.64	0.016
Visceral metastasis	1.21	0.93, 1.58	0.161	1.37	0.74, 2.53	0.318	1.01	0.61, 1.67	0.974	0.99	0.60, 1.62	0.961
Brain	0.82	0.63, 1.07	0.148	1.02	0.46, 2.28	0.963	0.66	0.40, 1.10	0.110	0.78	0.47, 1.28	0.323
IT	0.50	0.38, 0.65	<0.0001	0.46	0.26, 0.79	0.005	0.39	0.23, 0.67	0.001	0.58	0.35, 0.95	0.032
Systemic therapy	0.31	0.24, 0.42	<0.0001	0.25	0.13, 0.48	<0.0001	0.07	0.03, 0.17	<0.0001	0.41	0.24, 0.69	0.001
Capecitabine	0.50	0.37, 0.66	<0.0001	0.69	0.39, 1.22	0.206	0.35	0.19, 0.63	0.001	0.31	0.16, 0.59	0.0004
HER2 therapy				0.74	0.43, 1.28	0.286						
RT	0.96	0.70, 1.31	0.788	0.75	0.34, 1.68	0.485	0.38	0.21, 0.71	0.002	1.17	0.67, 2.04	0.579
Supportive care alone	1.91	1.23, 2.98	0.004	2.00	0.62, 6.51	0.249	6.36	2.92, 13.87	<0.0001	1.06	0.44, 2.53	0.896

Abbreviations: *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *HR* + hormone receptor positive, *LMD* leptomeningeal disease, *IT* intrathecal, *RT* radiation therapy

Discussion

In this large retrospective study of patients with BC and LMD, we found differences in outcomes based on tumor subtypes and treatments rendered. Specifically having HER2+BC and LMD is associated with longer OS when compared with other tumor subtypes. We also found that administration of IT and ST, were both associated with longer survival. This is the first study to report on these findings.

The majority of patients in the current study received multimodality treatment with RT, IT therapy, and ST after the diagnosis of LMD. In fact only 10 % of patients proceeded on to hospice immediately after diagnosis and this was not different across subtypes. This pattern may be reflective of a tertiary care setting. It is important to point out that a direct comparison between the active treatment patients and the supportive care only patients cannot be made due to small sample size and treatment selection bias. Specifically, patients who received no active therapies likely had worse PS, more advanced disease and more co-morbidities. After adjustment for treatments rendered, patients with HER2+BC continued to have the longest survival compared with their counterparts with HR+/

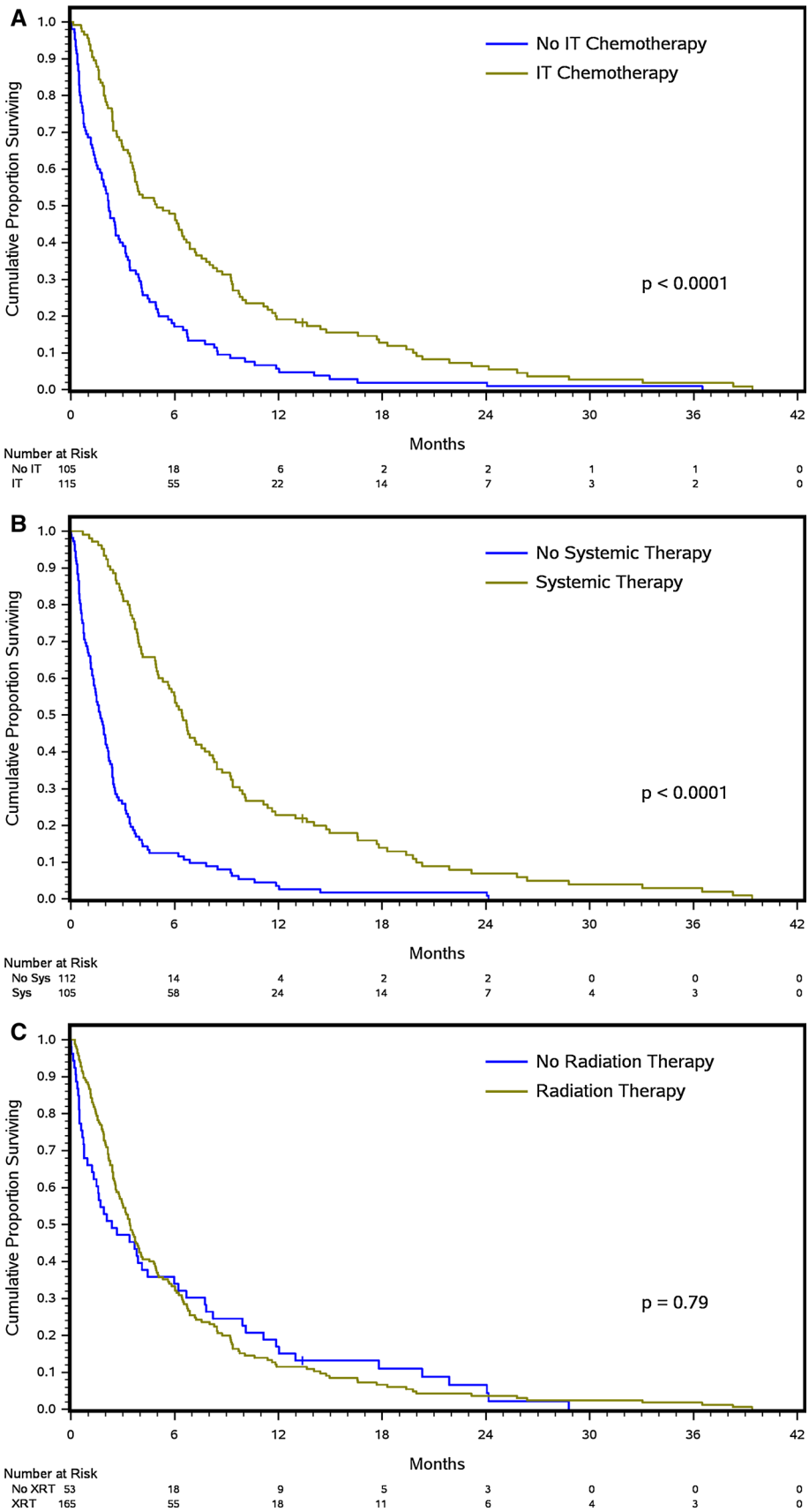

Fig. 2 Overall survival by treatment **A** overall survival from leptomeningeal disease diagnosis by intrathecal therapy (IT) Chemotherapy **B** overall survival from leptomeningeal disease diagnosis by systemic therapy **C** overall survival from leptomeningeal disease diagnosis by radiation therapy **D** overall survival from leptomeningeal disease diagnosis by supportive care alone (no radiation treatment, no systemic treatment, and no intrathecal treatment)

Fig. 2 continued

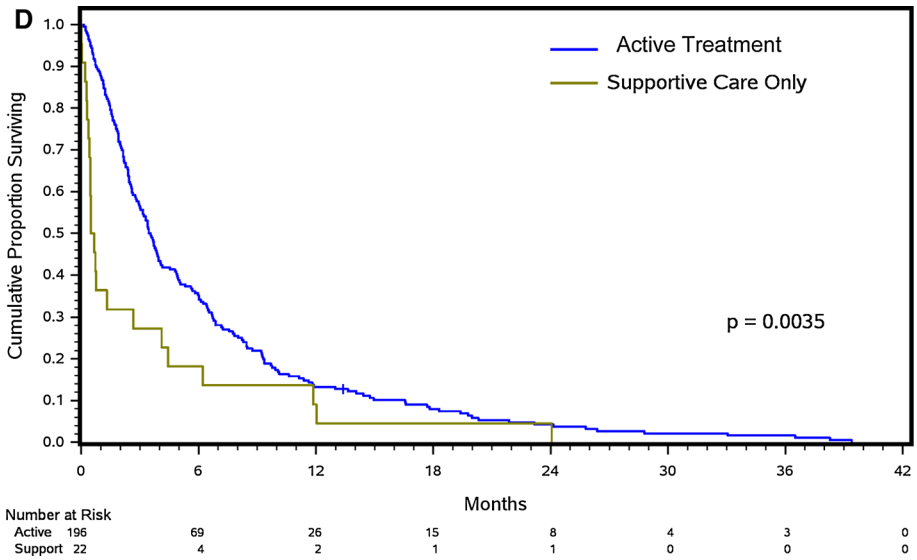

Table 3 Multivariate analysis for overall survival

	HR	95 %CI	*P*
Subtype			
HR+ versus HER2+	1.72	1.07–2.76	0.026
TNBC versus HER2+	3.05	1.84–5.08	<0.0001
Age at LMD diagnosis	1.04	1.02–1.06	0.0005
Stage			
I versus III	0.32	0.14–0.73	0.007
II versus III	0.92	0.59–1.45	0.720
IV versus III	1.13	0.72–1.79	0.599
Intrathecal therapy	0.44	0.31, 0.64	<0.0001
Systemic therapy			
Non-Capecitabine versus none	0.45	0.27–0.73	0.001
Capecitabine versus none	0.33	0.22–0.51	<.0001

Abbreviations: *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *HR* + hormone receptor positive, *LMD* leptomeningeal disease

HER2−BC and TNBC. This finding echoes previous reports in patients with parenchymal brain metastasis, whereby the HER2+BC subtype conferred a better prognosis [15]. The reasons behind the longer survival for patients with HER2+BC are not immediately clear. The majority of patients with HER2+ disease either began or continued to receive ST after the diagnosis of LMD, however, only half of it was in combination with HER2-directed therapy. Interestingly, as seen in Fig. 1a, there was a clear separation of the survival curves at 6 months that persisted beyond 1 year. In fact, almost twice as many patients with HER2+BC were still alive at 6 months compared with TNBC. It is important to point out that the only surviving patient in this study has HER2+BC and is currently receiving treatment with IT trastuzumab with no evidence of active disease by imaging or cytology. These data support the premise that survival after a diagnosis of LMD in patients with BC may be improving with modern therapies especially in the subset with HER2+ disease. Thus providing support for future clinical trials targeting LMD.

We also noted that patients with HER2+BC have longest median OS from time of LMD diagnosis, although those with HR+/HER2-disease with LMD had longest OS from time of initial distant metastasis. This is possibly due to patients with HR+/HER2−BC receiving multiple therapies for their metastatic disease and having a longer "pre" LMD OS, as many more treatment options are available for HR+/HER2−BC, including hormonal therapies. In fact, the presence of extracranial disease was associated with a significantly worse outcome only in the subset of patients with HR+/HER2−BC, again pointing toward a more treatment resistant patient subset with more extensive prior therapies when compared to other subsets. The beneficial association between RT and TNBC subtype only is also not entirely clear. One potential explanation is that most patients with TNBC have more rapid disease progression and thus RT was an effective measure for disease control. It is, however, hard to draw conclusions in regards to the association of RT with prolonged OS in this dataset, as the majority of patients did receive RT. The apparent lack of survival benefit with RT across other subtypes may be due to LMD being a systemic disease throughout the CNS, and as a result may not particularly benefit from RT, but also perhaps masked by this being retrospective data. Overall, it is disappointing to note how little progress has been made in this subset of BC patients in greater than 30 years, as OS remains about the same [16].

The proportion of patients with HER2+, HR+/HER2−, and TNBC was similar in our patient population. This suggests overrepresentation of the TNBC and HER2+ histology in the LMD population compared with newly diagnosed BC patients, in whom the prevalence of HR+/HER2- disease is estimated to be higher. It does, however, mirror the findings in the brain metastasis population [13, 15]. This finding is not unexpected as the majority of the patients had concomitant parenchymal brain lesions.

There are several potential limitations in the current study. First, this is retrospective data, and patients who received therapy may have had better performance status (PS) and less advanced disease causing bias in survival. We were unable to adjust for PS in the current analysis because the data were not collected prospectively and could not be reliably determined from a retrospective chart review of medical records. However, it is important to note, that most patients with LMD have a poor PS at baseline. They present with severe neurological symptoms and in general, the diagnosis is made quite late. Furthermore, there are no screening modalities in place that would detect LMD before symptoms occur. As such, we do not expect significant variability across our patient population. We also do not expect PS to be different across patients with different BC subtypes. Most patients received therapy in our study and this was not significantly different across subtypes. As would be expected, all the patients were evaluated because of neurologic manifestations, and thus had very advanced disease, controlling for poor PS in such a patient population with LMD would be very difficult as all patients would be affected. Secondly, it is important to note that a minority of our patients were offered Hospice immediately (10 %), reflective of a tertiary care setting. As such, the selection bias of a tertiary care center may remain and may have inflated the median survival data. In addition, we could not draw conclusions regarding the superiority of various treatment modalities because of a limited sample size and concern that residual confounders by indication would remain despite adjustment for known prognostic factors particularly as it relates to RT. This study was underpowered to determine whether the delivery of HER2 targeted therapies after a diagnosis of LMD impacted survival in HER2+ patients because of the limited sample size, although we suspect it may have played a role. Furthermore, information regarding orally administered therapies such as capecitabine and lapatanib was obtained by chart review and compliance could not be assessed.

To our knowledge, our study provides evidence that there may be differences in survival based on BC subtypes in the LMD population. This finding may be related to tumor biology and/or treatments rendered and cannot be ascertained retrospectively. However, it stresses the importance of studying LMD prospectively in a subtype specific approach as differences may exist. This strategy is currently being implemented for parenchymal brain metastasis [14, 15]. Despite the dismal prognosis noted in our study, it is quite possible that some progress is being made with more novel agents for HER2+ disease, along with other treatment modalities. The noted median OS of 4.4 months for patients with HER2+BC, along with the encouraging outcome of the only surviving patient with LMD treated with IT trastuzumab offer an impetus to conduct clinical trials in this subset of patients. More targeted therapies aimed at HER2+BC have now received federal drug agency approval for use in BC; this offers a potential opportunity to assess their use in clinical trials for LMD. At the same time, an improved understanding of the potential risk–benefit ratio of various therapies currently being offered to patients with LMD is urgently needed to provide appropriate recommendations. This information can only be obtained through prospective evaluation.

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