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CLINICAL STUDY

Breast cancer and leptomeningeal disease (LMD): hormone receptor status influences time to development of LMD and survival from LMD diagnosis

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Abstract Leptomeningeal disease (LMD) occurs in 5 % of breast cancer patients. The aim of this study was to identify risk factors related to survival and time to development of LMD in breast cancer patients. A retrospective analysis of breast cancer patients with LMD, evaluated in MDACC between 1995 and 2011. 103 patients with diagnosis of breast cancer and LMD were identified (one male). The median age at LMD diagnosis was 49.2 years. 78.2 % had invasive ductal carcinoma. Hormone receptors (HRs) were positive in 55.3 % of patients, 47.4 % were human epidermal growth factor receptor 2-positive and 22.8 % were triple negative. 52 % of the patients were treated with WBRT, 19 % with spinal radiation, 36 % with systemic chemotherapy and 55 % with intrathecal chemotherapy. Estimated median overall survival from time of breast cancer diagnosis was 3.66 years. Median survival from time of LMD diagnosis was 4.2 months. Time from breast cancer diagnosis to LMD was 2.48 years. In multivariate analysis, HR status and stage at diagnosis were significantly associated with time to LMD diagnosis ($p < 0.05$). In triple negative patients, time to LMD was shorter. In patients who were HR positive, time to LMD was longer. Survival from LMD diagnosis was significantly associated with both treatment, as well as positive HR status (multivariate analysis $p < 0.05$). In conclusion LMD has dismal prognosis in breast cancer patients. HR status contributes to time to LMD diagnosis and survival from LMD diagnosis. The impact of treatment aimed at LMD cannot be ascertained in our retrospective study due to the inherent bias associated with the decision to treat.

Keywords Leptomeningeal disease · Breast cancer · Estrogen receptor · Progesterone receptor · HER2 · Survival

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Introduction

Breast cancer is the most common female cancer in the US and the second most common cause of cancer death in women [1]. Biologic markers, such as hormone receptor (HR) status, human epidermal growth factor receptor 2 (HER2) over expression and tumor burden, have both prognostic and predictive value in these patients [2].

Leptomeningeal disease (LMD) is a devastating complication of neoplastic diseases which is characterized by the formation of secondary tumor deposits within the thin membranes surrounding the brain [3]. LMD resulting from solid tumors usually arises from breast and lung cancers, followed by melanoma, with breast being the most common [4, 5].

The incidence of LMD in cancer patients varies with the type of primary cancer as well as the stage of the disease, but it is often broadly estimated to range between 3 and 5 % [6]. It is considered a late manifestation of cancer and is most often diagnosed at the time of cancer relapse. The prognosis of LMD is poor [7]. Without therapy, the median survival is 4–6 weeks and death is often accompanied by progressive neurological dysfunction [8]. With LMD targeted therapy, median survival is generally under 6 months [8].

The risk of central nervous system (CNS) metastases among women with stage IV breast cancer is 16 %; however autopsy series reveal twice as many cases (34 %) [9]. Of the patients with brain metastases at autopsy, 19 % are identified as having LMD [10], however the reported incidence in clinical series is 5 % [6]. HER2-positive and triple negative breast cancer subtypes are associated with an increased risk of CNS metastasis [11, 12].

Several factors, including performance status, low CSF glucose levels, CSF positive cytology and cranial nerve symptoms have been identified as possible predictors of survival in patients with LMD from various solid tumors [8], however studies evaluating prognostic factors for patients with breast cancer and LMD are scarce. Few papers regarding LMD and breast cancer are published [13–18]. Four reports found a correlation between KPS at the time of diagnosis of LMD and survival [14, 16–18]. Three studies investigated the correlation between HR and HER2 expression and LMD prognosis. de Azevedo et al. [13], Torrejon et al. [17] found no correlation between hormonal receptor status and HER2 expression and survival after LMD diagnosis. Gauthier, et al. [18] found a correlation between hormonal receptor status, but not HER2 status and survival after the diagnosis of LMD.

The aim of this study was to characterize the clinical and pathological features and outcomes of patients with breast cancer and LMD, and to identify risk factors related to time to development and survival after LMD diagnosis in breast cancer patients. We aimed to define whether hormonal and HER2 statuses have a role in the prognosis of LMD patients.

Since triple negative breast cancer is associated with higher rates of brain, liver, and lung metastases and worse prognosis [19] and patients with brain metastases secondary to triple negative breast cancer have worse survival compared to patients who are hormone positive [19], by extension, our hypothesis was that patients with positive hormonal receptors would have better prognosis once diagnosed with LMD.

We also assumed that parenchymal brain metastases and the load of systemic disease would be associated with worse prognosis once LMD was diagnosed.

Materials and methods

After securing institutional board review approval (protocol RCR 03-0331), we queried the MD Anderson cancer center database for patients diagnosed with LMD and breast cancer between 1995 and 2011.

Breast cancer staging was reported according to the American Joint Committee on Cancer (AJCC) [20]. The diagnosis of LMD was based on: (1) the detection of malignant cells in the CSF, and/or (2) the demonstration of findings consistent with LMD on neuraxis magnetic resonance imaging (MRI), such as cranial nerve enhancement, thickening of the meninges, or subarachnoid enhancing nodules.

The records and imaging studies of all patients with breast cancer and LMD were retrospectively reviewed.

We analyzed the following clinical and pathological prognostic factors: age at diagnosis of breast cancer (BC); age at diagnosis of LMD, performance status at time of diagnosis of LMD (PS); presence of systemic disease and sites of systemic metastasis at time of diagnosis of LMD; CSF features (cell count, glucose and protein); histology of breast cancer; nuclear and histological grade; biological marker status [hormone receptor status (HR), estrogen and progesterone receptors, HER2 expression]; previous systemic treatment; new systemic therapy at time of LMD diagnosis; intrathecal therapy and radiation therapy; CSF markers and MRI findings at time of LMD diagnosis. HER2 expression was assessed either by immunohistochemistry or florescent in situ hybridization (Tables 1, 2).

Statistical methods

Data was first summarized using standard descriptive statistics and frequency tabulation. Time to event endpoints included OS from LMD diagnosis, OS from BC diagnosis, and Time from BC to LMD diagnosis, and were estimated using the Kaplan–Meier method. The comparisons between or among patients' characteristics groups were assessed using log-rank test. Univariate and multivariate Cox proportional hazard models were applied to assess the effect of the covariates of interest on time to event endpoints. All computations were carried out in SAS 9.2 and S-plus 8.0.

Results

Of the 154 patients identified in the database, 39 were not included in this report due to incomplete data. One patient was male and 103 female. Analysis was conducted on these 103 female patients.

Table 1 Patient and tumor characteristics at time of diagnosis of breast cancer

	N (%)
Age (median, range) 45.4 (27.5–68.7)	
Histology	
Invasive ductal	86 (86.8)
Infiltrating lobular	10 (10.1)
Ductal in situ	1 (1.1)
Mixed ductal/lobular	2 (2)
Unknown	4
Grade	
1	13 (16.7)
2	26 (33.3)
3	39 (50)
Unknown	25
Stage	
0	1 (1)
1	16 (15.5)
2	28 (27.2)
3	32 (31.1)
4	26 (25.2)
HR	
Negative	46 (44.7)
Positive	57 (55.3)
ER	
Negative	51 (49.5)
Positive	52 (50.5)
PR	
Negative	64 (62.1)
Positive	39 (37.9)
HER2	
Negative	41 (52.6)
Positive	37 (47.4)
Unknown	25
TNBC	
TNBC	18 (20.7)
Non TNBC	69 (79.3)
Unknown	16

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple negative breast cancer

Median age at breast cancer diagnosis was 45.4 (range 27.5–68). At the time of their breast cancer diagnosis, the majority of patients had invasive ductal carcinoma (78.2 %), 50 % had high grade breast cancer (grade 3–4), and more than 50 % presented with stage III or stage IV disease.

HR (either ER or PR or both) were positive in 55 % patients. Estrogen receptor was positive in 50.5 % of

Table 2 Patient characteristics at time of LMD diagnosis and treatment

Age	49.2 (28.6–76.2)
KPS	
<80	52
≥80	46
Unknown	5
Brain metastases	
No	55 (53.9 %)
Yes	47 (46.1 %)
Unknown	1
Cytology	
Neg	8 (9.9 %)
Pos	73 (90.1 %)
Unknown	22
Imaging	
Neg	13 (13.3 %)
Pos	85 (86.7 %)
Unknown	5
Cytology negative imaging positive	8 (10.3 %)
Cytology and imaging positive	58 (75.3 %)
Cytology positive imaging negative	11 (14.3 %)
Unknown	26
CSF content	
WBC	
≤5	24 (43 %)
>5	32 (57 %)
Unknown	47
Protein	
>50	33 (56 %)
≤50	26 (44 %)
Unknown	44
Glucose	
<40	12 (25 %)
≥40	45 (75 %)
Unknown	46
Treatment—any treatment	
Therapy	80 (80.8 %)
No therapy	19 (19.2 %)
Unknown	4
WBRT	
No	47 (47.5 %)
Yes	52 (52.5 %)
Unknown	4
Spinal radiation	
No	81 (81 %)
Yes	19 (19 %)
Unknown	3
Systemic chemotherapy	
No	63 (63.6 %)
Yes	36 (36.4 %)

Table 2 continued

Unknown	4
Intrathecal chemotherapy	
No	44 (44.4 %)
Yes	55 (55.6 %)
Unknown	4
Type of Intrathecal chemotherapy	
Methotrexate	17
Topotecan	22
Cytarabine	24
Multiple	9

CSF cerebrospinal fluid, *TNBC* triple negative breast cancer, *WBRT* whole brain radiation therapy

patients, progesterone receptor was positive in 37.9 %, and HER2 was overexpressed in 47.4 %.

The patient characteristics at time of diagnosis of breast cancer are shown in Table 1.

Two patients were diagnosed with LMD at time of breast cancer diagnosis. Both of them had triple negative breast cancer. One of them had systemic disease and for the other LMD was an isolated site of metastasis. At time of LMD diagnosis median KPS was 70 (range 10–100). 24.3 % of the patients had no evidence of systemic disease outside the CNS.

Cytology was positive for malignant cells in 90 % of patients; MRI was consistent with an LMD diagnosis in 86 % of patients. All patients included in this report had either CSF or imaging evidence of disease. Seventy-five percent had both diagnostic modalities positive at diagnosis.

Eighty percent of the patients were treated for their LMD. Of those, 52 % received whole brain radiation, 19 % were treated with spinal radiation, 36.4 % received systemic chemotherapy and 55.6 % were treated with intrathecal chemotherapy. 29 patients (36 %) were treated with more than one modality of treatment.

Patient characteristics at time of LMD diagnosis and treatment are shown in Table 2.

At the time of this analysis 102 patients have died; one patient that is still alive 3.5 years after diagnosis of LMD (positive cytology and imaging at diagnosis). This patient had triple negative breast cancer and was treated with WBRT and IT chemotherapy.

Overall median survival from time of breast cancer diagnosis was 3.6 years (95 % CI 2.54, 4.66). Median time from breast cancer diagnosis to LMD diagnosis was 2.5 years (range 0.14–14.6 years) (the 2 patients that were diagnosed with LMD at time of breast cancer diagnosis were excluded from this analysis). Median survival from LMD diagnosis was 4.27 months (range for those who died 0.11–3.78 years); 24 patients (23 %) survived from time of LMD diagnosis more than a year.

Survival from time of breast cancer diagnosis was significantly associated with stage at diagnosis of breast cancer ($p < 0.0001$). The survival from time of breast cancer diagnosis of patients with positive HR was significantly longer than those with HR negative disease (<0.0001). Patients with triple negative cancer had the worst prognosis. HER2 status was not significantly associated with survival from breast cancer diagnosis. On multivariate analysis breast cancer stage and HR status was significantly associated with survival from breast cancer diagnosis ($p = 0.0003$, 0.004).

Time from the diagnosis of BC to time of LMD diagnosis was significantly associated with stage at diagnosis of BC ($p < 0.0001$) and HR status ($p \leq 0.0001$). Patients with HR positive disease had a longer period from time of BC to time of LMD diagnosis. Patients with triple negative breast cancer had significantly shorter time from BC diagnosis to LMD diagnosis (Table 3; Fig. 1).

There was a trend toward better survival from the time of LMD diagnosis for patients with better performance status; however it was not statistically significant ($p = 0.087$, Table 4). The load of systemic disease, as measured by involvement of bone only, viscera only, or both, or a history of brain metastases, was not associated with survival from time of LMD diagnosis. HR positivity was significantly associated with survival from time of LMD diagnosis ($p = 0.0357$). Any treatment (WBRT, systemic chemotherapy or IT chemotherapy) was associated with a longer survival from the time of LMD diagnosis ($p < 0.0001$). Patients who received therapy had a significantly higher KPS compared to those who did not receive therapy (mean 72 ± 19 compared to 52 ± 17, $p = 0.0002$). Treatment with more than one modality of treatment (combination of radiation, systemic chemotherapy or IT chemotherapy) was associated with better survival ($p < 0.0001$).

The 24 patients who survived more than a year from time of LMD diagnosis had a better KPS at time of LMD diagnosis (mean 73 ± 18 compared to 67 ± 21), however the difference was not statistically significant ($p = 0.23$). The receptor status was not different between the patients that survived more than a year and those who survived less than a year from time of LMD diagnosis. 15/37 (40.5 %) patients that were HER2 positive were treated with HER2 targeted therapies during the course of their illness. Treatment with those agents was not associated with better survival from LMD diagnosis or time from breast cancer to LMD diagnosis.

Discussion

LMD is a complication of breast cancer with dismal prognosis; here, about 23 % of such patients survived more than a year. We found that HR status and stage at diagnosis

Table 3 Time from breast cancer diagnosis to LMD diagnosis

Univariate Cox model			
Covariate	Level	Hazard ratio	*p* value
Age at breast cancer diagnosis		1.01 (0.99–1.03)	0.16
Breast cancer grade	1 vs 3	0.99 (0.5–1.9)	0.99
	2 vs 3	0.76 (0.45–1.26)	0.28
Breast cancer stage	0/1 vs 4	0.16 (0.08–0.32)	<0.0001
	2 vs 4	0.32 (0.8–0.57)	0.0001
	3 vs 4	0.54 (0.3–0.93)	0.0263
HR	Positive vs negative	0.42 (0.28–0.64)	<0.0001
ER	Negative vs positive	1.63 (1.1–2.4)	0.0159
PR	Negative vs positive	1.92 (1.3–2.9)	0.0024
HER2	Positive vs negative	0.85 (0.53–1.34)	0.49
TNBC	Non TNBC vs TNBC	2.04 (1.18–3.5)	0.0102

Multicovariate Cox model 1 of survival and breast cancer stage and receptor status

Parameter	Hazard ratio	*p* value
Breast cancer stage at diagnosis		
0/1 vs 4	0.089 (0.04–0.19)	<0.0001
2 vs 4	0.218 (0.12–0.4)	<0.0001
3 vs 4	0.49 (0.28–0.86)	0.0124
HR		
Positive vs negative	0.21 (0.13–0.34)	<0.0001
ER		
Positive vs negative	0.45 (0.29–0.7)	0.0004
PR		
Positive vs negative	0.48 (0.3–0.77)	0.0023
TNBC		
TNBC vs non-TNBC	0.3 (0.0001–3.13)	1.14084

HR hormone receptor, *ER* estrogen receptor, *PR* progesterone receptor, *TNBC* triple negative breast cancer, *HER2* human epidermal growth factor receptor 2

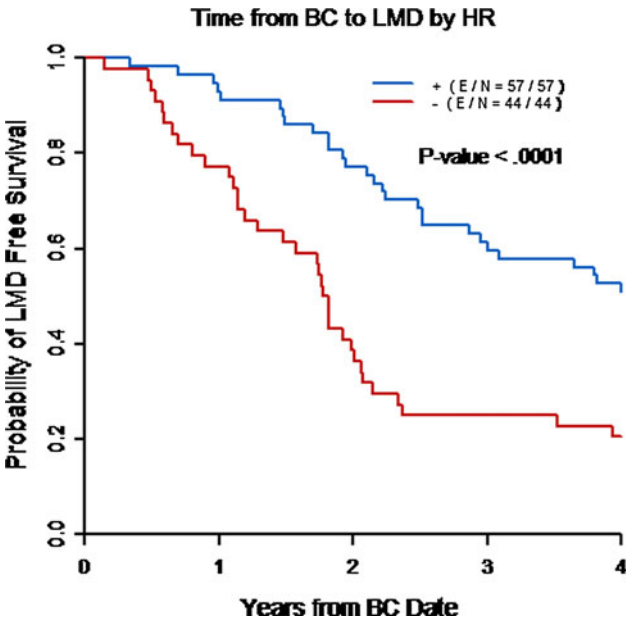

Fig. 1 Time from breast cancer diagnosis to LMD diagnosis according to hormone receptor status

are the most important factors contributing to time from breast cancer diagnosis to LMD diagnosis. Once LMD is diagnosed HR status and treatment targeting the LMD were the most important factors related to survival.

In accordance with our hypothesis, patients with HR positive disease had a longer duration from BC diagnosis to LMD diagnosis and a longer survival after LMD diagnosis. HR status is a well-known factor that correlates with survival from BC diagnosis. Furthermore in previous studies, survival in patients with brain metastases and time to development of brain metastases, were found to be related to HR status (12, 19). Thus, we expected to find correlation between HR status and those two time lines.

Limited data is available about the correlation between prognosis of LMD and hormonal receptors and HER2 expression. Jayson et al. [16], Torrejon et al. [17] found no correlation between hormonal receptor status or HER2 expression and survival after LMD diagnosis. These studies included small patient numbers (<40 patients). Gauthier et al. [18] whose series included 91 patients, had similar findings to this report. These authors found a correlation between hormonal receptor status, but not HER2 status and survival after diagnosis of LMD.

The incidence of HER2 amplification in patients with breast cancer is 25–30 % [21]. Among the patients reported here, a higher proportion of patients had HER 2/neu amplification (47.4 %) (although there was substantial missing data). Before the era of anti HER2 agents, HER2 positive breast cancer was correlated with diminished disease free and overall survival [21]. Previous reports show a higher incidence of brain metastases among patients whose tumors are HER2 positive [2]. In the era of HER2 directed therapy, several studies have reported improved survival from the time of diagnosis of CNS metastases in patients who had HER2-positive versus those with HER2-negative disease [22]. In this study HER status was not associated with time to, or survival from, LMD diagnosis. The low number of patients who received anti HER2 agents might correlate with poor prognosis of those patients and the high proportion of patients who were HER2 positive. Another reason for the high proportion of HER2 positive cases could be that trastuzumab does not cross the blood brain, or blood CSF barrier, thus not protecting this region of the body. Further, this finding suggests that targeting HER2 using intrathecal strategies, or with systemic anti-HER2 agents that penetrate the CNS, may be worth testing.

Table 4 Survival from time of LMD

Univariate Cox model			
Covariate	Level	Hazard Ratio	*p* value
Age		1.002 (0.98–1.02)	0.8466
KPS		0.70 (0.47, 1.05)	0.087
CSF white blood cells		1.0006 (0.99–1.01)	0.8282
CSF protein		1.0006 (0.99–1)	0.1595
CSF glucose		0.99 (0.98–1.01)	0.5805
Breast cancer stage at diagnosis	0/1 vs 4	0.72 (0.38–1.35)	0.2997
	2 vs 4	0.95 (0.55–1.64)	0.8650
	3 vs 4	1.11 (0.65–1.87)	0.6994
HR	Positive vs negative	0.65 (0.44–0.97)	0.0357
ER	Negative vs positive	1.46 (0.98–2.16)	0.0599
PR	Negative vs positive	1.58 (1.05–2.38)	0.0285
HER2	Positive vs negative	1.12 (0.71–1.76)	0.6299
TNBC	TNBC vs NonTNBC	1.59 (0.93–2.71)	0.0900
Systemic disease outside CNS	Positive vs negative	0.7 (0.46–1.18)	0.2060
Brain parenchymal metastases	Positive vs negative	0.89 (0.6–1.33)	0.5728
LMD at brain metastases	Positive vs negative	0.99 (0.54–1.8)	0.9754
Positive cytology	Positive vs negative	0.57 (0.27–1.2)	0.1408
Positive imaging	Positive vs negative	1.38 (0.76–2.49)	0.2870
WBRX	Yes/No	1.6 (1.07–2.4)	0.0219
Spinal radiation	Yes/No	1.27 (0.76–2.1)	0.3565
Systemic chemotherapy	Yes/No	2.84 (1.8–4.4)	<0.0001
Intrathecal chemotherapy	Yes/No	2.2 (1.4–3.35)	0.0002
No therapy	Yes/No	0.31 (0.18–0.52)	<0.0001

Multicovariate Cox model		
Parameter	*p* value	Hazard ratio
HR		
Positive vs negative	0.0453	0.66 (0.44–0.99)
WBRX		
Yes vs no	0.0081	0.57 (0.37–0.86)
Systemic chemotherapy		
Yes vs no	<0.0001	0.38 (0.23–0.61)
Intrathecal chemotherapy		
Yes vs no	0.0002	0.43 (0.28–0.68)

LMD leptomeningeal disease, *CSF* cerebrospinal fluid, *ER* estrogen receptor, *PR* progesterone receptor, *TNBC* triple negative breast cancer, *WBRR* whole brain radiation therapy, *HR* hormone receptor, *PR* progesterone receptor, *WBRT* whole brain radiation therapy

We did not identify predictive factors for the patients who survived more than a year after LMD diagnosis. The patients who survived more than one year did not have specific receptor status (compared to the patients surviving less than a year) and their KPS was not significantly higher.

There is no standard of care for LMD; few prospective studies have been published. Treatment including intrathecal chemotherapy, systemic chemotherapy and WBRT was associated with increased survival in this series. This suggests the importance of treatment; though it might represent a selection bias of patients selected for treatment, since the patients that were treated had a better KPS.

Survival from primary breast cancer diagnosis was 3.6 years which is significantly lower than expected for the general population of patients with newly diagnosed breast cancer [1]. This might represent the aggressive nature of cancer among those patients and correlates with the high proportion of patients (50 %) with high stage at diagnosis of breast cancer.

Previous studies revealed that survival from LMD diagnosis is correlated with the following factors: functional status (KPS), low CSF glucose, high protein, prior lung metastases. In our study there was a trend between KPS and better survival ($p = 0.059$). The other factors mentioned were not associated with survival from LMD diagnosis. This may be due to small sample size and missing data.

In contrast to our hypothesis, once LMD was diagnosed, parenchymal brain metastases and the load of systemic

disease were not associated with worse survival. This is in accordance with a previous study that investigated the importance of disease burden in patients with melanoma and LMD. In that study load of disease was not correlated with survival [23]. Based on this finding, it may not be necessary to exclude breast cancer patients with LMD from enrollment into clinical trials of LMD treatments, simply due to the fact that they carry a higher burden of overall disease or have parenchymal brain metastases.

Further studies are needed to explore the nature and risk factors of LMD, define the patients with better prognosis and to find better treatment for this complication of cancer.

In conclusion, LMD is a devastating complication of breast cancer with dismal prognosis. Receptor status and stage at diagnosis are the most important factors contributing to time form breast cancer to LMD diagnosis. Once LMD is diagnosed HR status impacts survival. Even though treatment aimed at LMD correlates with a better survival after diagnosis, its impact cannot be ascertained due to the inherent bias associated with the decision to treat, which is typically associated with a better performance status.

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