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Leptomeningeal carcinomatosis as the primary presentation of relapse in breast cancer (Review)

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Abstract. Leptomeningeal metastasis (LM) is an uncommon presentation of relapse in breast cancer, which is associated with poor clinical outcomes and poor prognosis. Notably, LM most commonly occurs in breast cancer. The aim of the present review was to investigate the occurrence of LM as the primary presentation of relapse following remission in breast cancer patients and to determine whether specific histological subtypes are predisposed to meningeal metastases. In addition, the present review evaluated whether patients presenting with LM as the primary site of relapse exhibit differences in survival when compared with patients exhibiting metastasis to other sites. Cross-sectional studies have demonstrated that LM is commonly associated with other sites of distant metastasis including lung, liver and bone metastases. The histological breast cancer subtype most commonly associated with LM was invasive lobular carcinoma, while triple-negative breast cancer patients appear to be predisposed to the development of LM when considering the overall prevalence of histological breast cancer subtypes. At present, data regarding LM as the primary site of relapse are limited due to its rarity as the first site of metastasis in breast cancer. Case-controlled studies are required to investigate the incidence of LM as the primary site of recurrence in breast cancer patients as this would enable treatment standardization and identification of prognostic factors for improved survival.

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1. Introduction

Leptomeningeal metastasis (LM) occurs when solid tumour cells diffusely metastasize to the meninges within the central nervous system (CNS) (1). It is a manifestation of metastatic disease whereby tumour cells spread through the subarachnoid space (1). LM occurs in 4-7% of patients with solid tumours and is common in breast cancer, lung cancer and malignant melanoma (1). The highest rates of LM are observed in melanoma and small lung cancer, with incidence rates of 23 and 11%, respectively (2,3). LM occurs in ≤5% of patients diagnosed with breast cancer (4). Previous studies have reported that the frequency of triple-negative (TN) breast cancer among LM patients ranges between 21 and 40.5% (5-7). The annual age-standardized incidence rates of LM are 78 and 90 cases per 100,000 women in Western Europe and North America, respectively (8). Considering this high incidence, breast cancer patients constitute the majority of cases diagnosed with LM (9). Furthermore, LM usually occurs after diagnosis of distant metastasis to other sites. Concurrent lung and liver metastases have been reported at a frequency of 27% in each organ in breast cancer patients with LM. Brain and bone metastases have also been reported to occur in 49 and 51% of breast cancer patients with LM, respectively (10). Survival in patients diagnosed with LM is poor with an estimated median survival time of 4.9 months (11). Current treatment recommendations for LM patients with modest tumor burden include intrathecal chemotherapy, radiation therapy to disease obstructing cerebrospinal fluid flow and strategies to decrease intracranial pressure (12).

Table I. Summary of previous literature regarding median age at diagnosis of leptomeningeal metastases and median survival time from diagnosis in breast cancer patients.

First author, year	Total LM patient cohort, n	Median age at diagnosis, years	Median survival time (months)	(Ref.)
Gauthier H *et al*, 2010	91	53.0	4.5	(5)
Yust-Katz S *et al*, 2013	103	49.2	4.2	(6)
Niwińska A *et al*, 2013	118	49.0	4.2	(7)
Lara-Medina F *et al*, 2012	49	42.4	1.6	(10)
Meattini I *et al*, 2012	33	46.7	4.9	(11)
Torrejón D *et al*, 2013	38	54.8	2.6	(13)
de Azevedo CR *et al*, 2011	60	46.0	3.3	(14)

LM, leptomeningeal metastasis.

The primary aim of the present review was to investigate the frequency of LM as the primary presentation of distant metastasis in breast cancer patients, as reported in the current literature, and to determine whether such patients exhibit different survival outcomes when compared with LM patients that exhibit metastasis to other sites. The secondary aim was to investigate the association between LM incidence and specific histological and biological subtypes of breast cancer and their prognostic significance.

2. Methodology

Medical databases including Medline (http://www.medline.com/), Embase (https://www.embase.com) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed) were searched to retrieve articles published between 2004 and 2015 for the present literature review. The keywords used included 'breast cancer', 'leptomeningeal carcinomatosis', 'leptomeninges', 'metastasis', 'clinical outcomes' and 'relapse'. Keywords were entered using appropriate database selection headings in MeSH or Emtree. Prospective and retrospective studies that included patients with LM as a presentation of relapse in breast cancer were selected. Case reports and case series were excluded. Only studies published in English were reviewed.

3. Frequency of LM as the first presentation of distant metastasis

The majority of studies conducted on LM in breast cancer included patients diagnosed clinically and pathologically with LM as a complication of breast cancer (Table I). Such patients were followed up prospectively following diagnosis with the aim to identify prognostic markers of survival (7,11). No prospective studies that determined the absolute rate of LM as the only presentation of distant metastasis in breast cancer were identified.

A study by Niwińska *et al* (7) evaluated a cohort of 118 consecutive breast cancer patients treated for LM between 1999 and 2009. At presentation, 25% (29/118) of patients presented with metastasis of the leptomeninges as the first presentation of metastatic disease (7). However, this study was limited as the authors did not mention whether the 29 patients were previously treated for metastasis. In a study by Torrejón *et al* (13), 13.2% (5/38) of breast cancer patients exhibited LM as the first presentation of metastatic disease (13). Although this was not the primary outcome of the study and despite the small cohort size, it identified patients with LM indicating that this was the primary presentation of metastasis.

Lara-Medina *et al* (10) reported patient characteristics at the time of diagnosis of LM: At diagnosis of LM, 8/61 (13.1%) exhibited no systemic disease, while 8/49 (16.3%) of patients exhibited controlled systemic disease and 33/49 (67.3%) exhibited systemic disease (10). Although the study did not report whether patients were in remission prior to presenting with LM, the incidence rate was similar to that reported by Niwińska *et al* (7). Niwińska *et al* (7) also reported the concurrent occurrence of distant metastases in breast cancer patients: 48% of patients exhibited bone metastases, 38% exhibited metastases of the brain parenchyma, 36% exhibited lung metastases and 25% exhibited liver metastases (7). These results are consistent with the hypothesis that the majority of breast cancer patients who exhibit LM present with systemic disease at diagnosis, with 25% of patients exhibiting LM as the only site of distant metastasis. Previous studies have reported that in 9-15% of breast cancer patients, LM is the first presentation of metastasis (11,14). However, data that demonstrates the frequency of LM as the first presentation of relapse following breast cancer treatment is limited and thus, only a comparative assessment of such studies was performed.

4. Predilection of histological and biological breast cancer subtypes for meningeal metastases

Metastasis to the leptomeninges is most common in patients diagnosed with the invasive lobular carcinoma histological subtype of breast cancer (5,15). While the rate of lobular carcinoma varies between 17 and 28% among patients initially diagnosed with breast cancer, studies have revealed that ≤35% of patients with LM exhibit lobular carcinoma (Table II). This indicates that metastasis to the meninges is most common in this histological subtype of breast cancer (7). However, only 7% of breast patients with brain parenchymal metastasis

Table II. Summary of previous literature regarding the histological and molecular subtypes of breast cancer patients with LM.

	Histological subtype (%)		Molecular subtype (%)					
First author, year	IDC	ILC	ER+	PR+	ER+ and/ or PR+	HER2+	TN	(Ref.)
Gauthier H *et al*, 2010	63	28	70	44	74	10	21	(5)
Yust-Katz S *et al*, 2013	78.2	21.8	ND	ND	55.3	47.4	22.8	(6)
Niwińska A *et al*, 2013	59	35	42	ND	ND	19	40.5	(7)
Lara-Medina F *et al*, 2012	76	14	20	27	ND	20	39	(10)
Meattini I *et al*, 2012	63.6	36.4	ND	ND	60.6	ND	ND	(11)
Torrejón D *et al*, 2013	ND	ND	34.2	26.3	ND	26.3	23.7	(13)
de Azevedo CR *et al*, 2011	78.3	21.6	51.7	43.3	ND	15	30	(14)

ND, no data available; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER+, estrogen receptor positive; PR+, progesterone receptor positive; HER2+, human epidermal growth factor receptor 2 positive; TN, triple-negative.

exhibit lobular carcinoma (16). This specific predisposition exhibited by lobular cancer to metastasize to the meninges has been attributed to changes in cell adhesion molecules (17). Autopsy data from metastatic breast cancer patients has demonstrated that the estimated incidence of LM in infiltrating lobular breast carcinoma is 14% compared with 1% in cases of infiltrating ductal breast carcinoma (18).

Breast cancer subtypes are considered to exhibit particular patterns of metastasis, which leads to distinct survival rates following relapse (5). Previous studies have analysed the incidence and prognostic implications of LM in the following four molecular subtypes: Luminal A [estrogen receptor (ER)/progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative]; luminal B (ER/PR positive, HER2 positive); HER2 positive (ER/PR negative, HER2 positive); and TN (ER/PR negative, HER2 negative) (7,10,13). In a cohort of 99 patients with LM, 40.5% patients were classified as TN, 37.5% as luminal A, 14% as HER2 positive and 8% luminal B, which indicates that metastasis to the meninges is most common in patients exhibiting TN breast cancer (7). When comparing the frequency of molecular subtypes in LM with that in the whole breast cancer population, the results indicate that TN patients exhibit a higher predisposition for LM than the luminal A subtype. Two previous studies reported TN breast cancer frequencies of 39 and 21% in cohorts of 61 and 91 breast cancer patients, respectively (5,10).

Patients exhibiting HER2 positive subtypes generally exhibit metastasis to the brain parenchyma; however, metastasis to the leptomeninges is less common (5,16). The most common molecular subtype of lobular carcinoma with dissemination to the leptomeninges was luminal A, as observed in >50% of the lobular carcinoma patients. Notably, in ductal carcinoma patients with LM, at initial diagnosis the four main biological subtypes were equally represented (7). Although studies have classified patients with LM into histological and molecular subtypes, few studies have investigated the molecular subtypes in patients exhibiting LM as the first presentation of distant metastasis.

5. Survival and prognosis

Various prognostic markers, including age at diagnosis, tumor histology, histologic grade and biomarker receptor status (ER, PR and HER2), have been evaluated, however, their value in guiding the management of cancer remains controversial. The most important prognostic factor for breast cancer patients diagnosed with LM. remains the performance status at the time of diagnosis (19). In a previous study, multivariate analysis revealed that a Karnofsky performance status of ≥70 vs. <70 was significantly associated with increased survival (7,20). Systemic therapy is also a critical factor that influences survival. It is hypothesized that thick LM (lesions >3 mm) is well-penetrated by systemic therapy as opposed to intrathecal therapy due to the abundant vasculature. Intrathecal chemotherapy only achieves 2-3 mm penetration into meningeal metastases (7). Additional factors associated with poor outcome during treatment include multiple-fixed neurological deficits (21), bulky CNS disease (22), abnormalities in cerebrospinal fluid flow (23) and diffusely disseminated cancer that is unresponsive to systemic chemotherapy (21).

In a previous study, multivariate analysis revealed no significant differences in survival between histological and biological breast cancer subtypes (7). Notably, the absence of PR expression in primary breast cancer has been reported as a poor prognostic factor (10). However, this study had a number of limitations: The study was retrospective and certain results regarding prognostic factors were not consistent with previously published literature. To date, no studies have investigated the association between patients presenting with LM as the primary site of recurrence and improved survival and prognostic outcomes.

The significance of such prognostic factors remains unclear, as the previous studies discussed were retrospective and included non-randomised participants. Furthermore, marked variability in the median age at diagnosis of patients was evident between studies. Thus, the context of such results must be considered. Therefore, future longitudinal and prospective studies, which include multivariate analysis, are required to investigate the associations between prognostic factors and clinical outcomes.

6. Conclusion

Of all solid tumour types, LM most commonly occurs in breast cancer (1). LM most commonly occurs at an advanced stage of disease and occurs as the primary presentation of metastatic disease in 9-25% of patients diagnosed with breast cancer. LM most commonly occurs in patients histologically diagnosed with lobular carcinoma, and patients exhibiting TN breast cancer appear to exhibit a predisposition for LM. Although few studies have investigated LM as the primary site of relapse in breast cancer, anecdotal evidence and case reports suggest that such patients exhibit improved overall survival compared with patients that exhibit distant metastasis at other sites (24). The main factors that appear to affect prognosis and treatment outcomes include the location of distant metastasis, response to treatment and performance status (7). Previous studies have suggested that histological subtypes and receptor expression may have less prognostic significance than the aforementioned factors (7,10). To further evaluate this hypothesis, case-controlled studies are required that investigate breast cancer patients presenting with LM as the primary site of recurrence. Patients with the same histological subtype of breast cancer and performance status should be treated uniformly to establish a standard care. At present, multimodal chemotherapy and radiotherapy treatment for breast cancer should be individualized according to the patient's performance status and response to treatment.

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