# Leptomeningeal Metastasis in ER+HER2- Advanced Breast Cancer Patients: A Review of the Cases in a Single Institute Over a 14-year Period

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# Abstract

**Purpose:** While leptomeningeal metastases (LM) from estrogen receptor-positive, HER2-negative advanced breast cancer (ER+HER2-ABC) has a poor prognosis, the details of LM ER+HER2- are unclear. We therefore retrospectively investigated patients with LM from ER+HER2-ABC.

**Methods:** ER+HER2-ABC patients who received any therapy at Shizuoka Cancer Center between October 2002 and December 2017 were retrospectively analyzed. Patients with central nervous system (CNS) metastases were divided into three groups: brain metastasis (BM) only (B group); BM with LM (BL group); and LM only (L group).

**Results:** Among 369 patients, 102 developed CNS metastases: 70 (68.6%), 13 (12.8%), and 19 (18.6%) in the B, BL, and L groups, respectively. The L group showed a later onset, poorer performance status, more symptoms, and more skull metastasis than the other groups. Radiotherapy as the initial treatment was introduced to 13/13 (100%) and 15/19 (78.9%) in the BL and L groups, respectively. Subsequent systemic therapy excluding best supportive care was introduced to 5/13 (38.5%) and 5/19 (26.3%) in the BL and L groups, respectively. The median overall survival (OS) from the diagnosis of CNS lesions was 295.0, 146.0, and 99.0 days in the B, BL, and L groups, respectively, and worsening of CNS lesions was the major cause of death in the BL and L groups. Multivariate analyses showed that concurrent soft tissue metastasis (hazard ratio, 4.620) and subsequent systemic therapy (hazard ratio, 0.063) were prognostic for the L group.

**Conclusion:** Management of LM from ER+HER2-ABC remains challenging, so a multimodal approach with novel systemic therapy is warranted.


# Introduction

Metastases to the central nervous system (CNS) is commonly seen in up to 25% of advanced breast cancer (ABC) patients [1]; however, the pattern of development of CNS metastases and the prognosis after the diagnosis of CNS metastases differ among ABC subtypes [2]. In patients with human epidermal growth factor receptor-2-positive (HER2+) ABC, CNS metastases develop not only in the late phase of the disease but also in its early phase. In contrast, HER2-negative (HER2-) ABC patients develop CNS metastases mostly in the late phase of the illness (i.e. when patients become refractory to systemic therapies) [2, 3]. Furthermore, in HER2 + ABC, novel systemic therapies (e.g. tyrosine kinase inhibitor [TKI] [4] and antibody drug conjugate [ADC] [5]) are expected to improve the patient survival, regardless of concomitant CNS metastases.

However, the outcomes of patients with CNS metastases may differ not only by the primary disease subtype but also by the metastasis pattern. Leptomeningeal carcinomatosis, or leptomeningeal metastasis (LM), is a pattern of CNS metastases relatively infrequently observed in ABC patients compared with brain metastasis (BM) [6], and some reports have shown that it occurs more frequently in ABC patients with triple-negative subtype than in those with the estrogen receptor-positive (ER+) and

HER2 + subtypes; the epidemiology and outcome of patients with LM from ER + HER2-ABC thus remain unclear because of the notably poor outcome compared with BM [6–9].Therefore, in the present study, we retrospectively investigated the actual situation of ER + HER2-ABC patients with LM in a single institute.

## Patients And Methods

We reviewed the medical records of ER + HER2-ABC patients who were treated at our hospital from October 2002 to December 2017 to assess the incidence, background, and outcomes of ER + HER2-ABC patients with CNS metastases, including LM.

CNS metastases was diagnosed by gadolinium-enhanced magnetic resonance imaging (Gd-MRI) with or without confirmation by cerebrospinal fluid (CSF) cytology. Patients with CNS lesions were subclassified into three groups based on the patterns on Gd-MRI images (Fig. 1a-c) at the diagnosis of CNS lesions: BM without obvious LM (B group, **Fig. 1a**), BM with LM (BL group, **Fig. 1b**), and LM without obvious BM (L group, **Fig. 1c**).

The overall survival (OS) was defined as the period from the diagnosis of CNS metastases to death by any cause otherwise specified. The classification and definition of “cause of death” based on clinical judgement are shown in **Table 1**.

Statistical analyses were performed using the chi-squared test, Kaplan-Meyer method, log-rank test, and a multivariate Cox regression analysis. These statistical analyses were performed using the JMP 13.2.0 software program, Japanese version (SAS Institute Inc., Cary, NC, USA).

All procedures performed in studies that involved human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This retrospective study was approved by the institutional review board of Shizuoka Cancer Center (approval number: J2020-129-2020-1).
Informed consent was obtained in the form of an opt-out option on the hospital website from all individual participants included in the study.

## Results

# Findings from whole dataset

We identified 369 ER + HER2- unresectable/recurrent breast cancer patients (i.e. ER + HER2-ABC patients) from the database. The median observational period from the diagnosis of ABC was 1259.5 (range, 61-6827) days. Of the 369 ER + HER2-ABC patients, 102 (27.6%) developed CNS metastases within the observational period, and all of them showed positive findings on Gd-MRI. the median time to the diagnosis of CNS metastases from the diagnosis of ABC was 649.0 (95% confidence interval [CI], 538.0-

885.0) days, and the median observational period from the diagnosis of CNS lesions was 199.0 (range, 10.0-1702.0) days.

# Epidemiologic background of patients with CNS lesions

The majority of patients with CNS lesions were classified into the B group (n = 70, 68.6%), followed by the L group (n = 19, 18.6%) and BL group (n = 13, 12.8%). The breakdown of patients' background characteristics is shown in **Table 2**. The median time to the diagnosis of CNS lesions from the diagnosis of ABC was significantly longer in the L group than in the other groups (P = 0.0403, log-rank; 1408.0 [95% CI, 501.0-2059.0] days in the L group; 616.5 [95% CI, 461.0-862.0] days in the B group; 622.0 [95% CI, 486.0-876.0] days in the BL group; **Supplemental Fig. 1**).

Multivariate analyses revealed that the existence of lung metastasis at the initial diagnosis of ABC was an independent risk factor for the development of BM (e.g. patients in the B and BL groups) (hazard ratio [HR], 1.983; 95% CI, 1.253–3.096; P = 0.0038), while metastasis to the liver (HR, 1.696; 95% CI, 0.963–2.850; P = 0.0663), soft tissue (HR, 1.248; 95% CI, 0.798–1.988; P = 0.3351), or bone (HR, 1.008; 95% CI, 0.647–1.572; P = 0.9731) did not increase the risk of subsequent CNS metastases. In contrast, in the L group, bone metastasis at the initial diagnosis of ABC showed a strong trend toward increasing the risk of subsequent LM (HR, 2.344; 95% CI, 0.847–7.495; P = 0.1025) on a multivariate analysis, although no independent risk factors were identified.

Patients in the BL and L groups showed a poorer performance status (PS) and more symptoms at the diagnosis of CNS lesions than those in the B group. Bone involvement at the diagnosis of ABC and/or CNS lesions were commonly documented in this study, as previously reported [10], and all L group patients showed bone involvement at the diagnosis of CNS lesions. Furthermore, a significantly higher incidence of skull involvement was documented in the BL and L groups than in the B group (31.4%, 61.5%, and 84.2%, respectively; P < 0.01; chi-squared test). No other significant differences in patients' background characteristics were found.

# Treatments after the diagnosis of CNS lesions

The breakdown of the initial treatment after the diagnosis of CNS lesions is shown in **Table 3**. Radiotherapy (RT) to CNS lesions was typically introduced to patients as an initial therapy, but 4 of 19 (21.1%) patients in the L group and 18 of 70 (25.7%) patients in the B group underwent best supportive care (BSC) without any RT because of a poor PS, comorbidity, old age, or poor control of extracranial lesions. Craniospinal irradiation (CSI) was introduced to 4 patients with LM (2 each in the BL and L groups), and the survival after the diagnosis from LM was 10 and 355 days in the BL group and 30 and 1185 days in the L group. While none of the patients in the BL or L group received systemic therapy prior to RT, 9 of 70 (12.9%) patients in the B group with asymptomatic BM received systemic therapy (7 chemotherapy, 2 endocrine therapy) prior to RT to control their extracranial lesions.

# Outcomes

At the time of the data cut-off, 99 of 102 (97.1%) patients with CNS had died (**Table 3**). The median OS from the diagnosis of CNS lesions was 295.0 (95% CI, 181.0-365.0) days in the B group, 146.0 (95% CI 36.0-206.0) days in the BL group, and 99.0 (95% CI 725.0-220.0) days in the L group (Fig. 2). Furthermore, both the B (803.0, 95% CI, 553.0-989.0 days) and BL (1198.0, 95% CI, 843.0-1461.0 days) groups showed a significantly ($P < 0.001$) poorer median OS from the diagnosis of ABC than the L group (1723.0, 95% CI, 620.0-2507.0 days) and patients without CSN lesions (1830.0, 95% CI 1501.0-2167.0 days) (**Table 3** and **Supplemental Fig. 2**).

Because of aggressive and therapy-resistant nature of LM, patients in the L and BL groups were more likely to die from worsening of CNS lesions than those in the B group ($P < 0.01$ by chi-squared test) as shown in **Table 3**.

We performed further analyses to investigate the risk factors for the OS (**Table 4**) in all patients with CNS lesions and in the L group. In all patients with CNS lesions (N = 102), multivariate analyses showed that age ≥ 65 years old at the diagnosis of CNS metastases increased the risk of death (HR, 1.918; $P = 0.0446$), but local RT (HR, 0.583; $P = 0.0433$) and subsequent systemic therapy (HR, 0.128; $P < 0.0001$) decreased the mortality risk. When limited to patients in the L group (N = 17), documented soft tissue metastasis, mainly pleural carcinomatosis and/or pulmonary lymphangitis, at the diagnosis of LM increased the mortality risk (HR, 4.620; $P = 0.0206$), but subsequent systemic therapy decreased the mortality risk (HR, 0.063; $P = 0.0002$).

# Discussion

Our current study showed that ER + HER2-ABC patients with LM (L and BL groups) were distinctively different from those with BM only (B group) in their real-life (e.g., epidemiology, responses to therapies, and cause of death).

Compared with patients in the B group, even those in the BL group, the L group patients had a longer history of preceding bone metastasis with more frequent skull involvement and required a longer time to CNS metastases. Cancer cells in bone lesions may infiltrate into the leptomeninges by direct extension or via the system of intraosseous venous anastomoses [11], and Johnson et al. [12] revealed that the presence of bone metastasis, especially vertebral or paravertebral lesions, increased the risk of LM. It was recently reported that stereotactic radiosurgery (SRS) for BM from ABC increases the risk of postoperative LM [13]; however, the mechanisms or risk factors for LM after SRS have not been clarified. In the present study, the BL group showed the worst OS after the diagnosis of ABC, and no patients had received prior SRS. Regarding the features of their clinical course, such as a relatively early onset of CNS lesions and relatively poor response to RT, these patients may be considered to have “LM secondary to BM”. Taken together, these findings suggest that BM that developed on the surface of the brain, as in **Fig. 1-b**, may have seeded cancer cells to the region, and those cells may have then spread along the leptomeninges rather than by direct infiltration from the bone lesion, as previously described [12]. Invasive lobular carcinoma (ILC) of the breast, tumor cells show decreased expression of the E-cadherin, often shows

distinct pattern of metastases (e.g., metastases to the gastrointestinal tract, the genitourinary system, the peritoneum, and the leptomeninges) compared with invasive ductal carcinoma [14]. In the present study, we found that patients in BL and L groups were more likely to be diagnosed as having ILC with a significant degree ($P < 0.05$, Fisher's exact test) (**Table 2**) compared with patients in B group, however, there was a limitation that specimen itself or pathological report of the primary site was missing in around 10% of the cases in each group.

Under the current guideline for ABC [15], routine screening of CNS metastases in patients with ABC is not recommend; however, in ABC patients, symptoms that suggest CNS, such as headache, nausea or anorexia, are often seen in daily clinical practice. When ABC patients with any risk factors for CNS lesions, such as HER2-positive, triple-negative, or late-phase ER + HER2- disease, complain of such neurologic symptoms or show obvious neurologic disorder (neuralgia, paresis, or seizures), regardless of the subtype, Gd-MRI of the CNS should be performed to detect CNS lesions and plan the radiation field [16, 17]. Positive CSF cytology may be strong evidence for the existence of LM; however, the sensitivity of CSF cytology is not very high [16, 17]. Therefore, in daily practice, the combination of Gd-MRI findings and neurologic symptoms are acceptable and useful for diagnosing LM in ABC patients [17–19].

Once a patient has been diagnosed with LM, regardless of the presence of BM, radiation therapy (RT) should be introduced as the primary therapy for LM in order to control symptoms from LM, unless the patient is in a poor condition [15, 20]. According to the report based on a web-based survey of European oncologists [21], a majority of respondents routinely consider focal RT or radiation to symptomatic lesions for patients with LM from solid tumors. Such RT for the responsible lesion is routinely introduced for patients with LM from ABC to relieve symptoms; however, to our knowledge, there is no strong evidence that this improves the survival.

CSI is one of the standards of care for primary CNS tumors that often accompany LM, such as medulloblastoma, [22]; however, to our knowledge, the clinical utility and indication of CSI for metastatic LM from breast cancer or other solid tumors has not been established due to a lack of evidence from prospective controlled studies. Recently, Devecka et al. [23] reported the clinical utility of CSI for metastatic LM from various cancers, including five ABC cases, based on real-world experiences. In that report, the survival of ABC patients who underwent CSI was 3.3 to 13.0 (median 4.7) months in cases with moderate to severe hematologic toxicities; however, the receptor statuses, PS, and presence of concurrent illness were not mentioned. Our 2 "long-term" survivors who received CSI and had an OS of 355 and 1185 days had CNS symptoms at the diagnosis of LM but maintained a fair PS. In both of those patients, the overall toxicities from CSI were durable, and severe lymphopenia was considered to be related to corticosteroid administration (**Supplemental Table 1**). Two out of four patients were unable to complete CSI because of worsening of CNS or pleural lesions, so the indication of CSI for patients with LM from ABC should be considered.

The efficacy and indication of intrathecal injection of anticancer agents, such as methotrexate, for LM from ABC remains controversial [6, 20]; however, such intrathecal therapy (IT) for LM from ABC has been

accepted and introduced in clinical practice [18–21]. The majority of reports regarding IT are retrospective, and furthermore, there has been no prospective, randomized clinical trial demonstrating an improvement in the OS of patients with LM from ABC [6, 20, 24], even in HER2-positive subtypes [20, 25]. Taken together, these findings suggest that IT for LM from ABC, especially with the HER2-negative subtype, is still controversial in terms the balance between benefits and harm; for this reason, in the present study, IT using methotrexate and corticosteroid was attempted in only one patient in the L group prior to CSI.

Novel molecular-targeted agents are awaited to overcome the issues encountered when managing both systemic and local illness simultaneously. In HER2-positive ABC patients with CNS metastases, some molecular-targeted agents have been reported as useful. Neratinib, a pan-HER family tyrosine kinase inhibitor (TKI), combined with capecitabine revealed a 49% volumetric overall response in a single-arm phase 2 study (TBCRC 022) for HER2-positive ABC patients with known CNS lesions [26], and in a pivotal phase 3 study (NALA trial), neratinib plus capecitabine significantly prolonged the time to intervention for CNS metastases [27] compared with lapatinib plus capecitabine. Likewise, tucatinib, a highly HER2-selective EGFR/HER2-TKI, clearly demonstrated intracranial efficacy when combined with trastuzumab and capecitabine in a randomized phase 2 study (HER2CLIMB) [4]. Furthermore, novel ADCs, such as trastuzumab emtansine and trastuzumab deruxtecan, for HER2-positive ABC have been introduced into daily practice, and their substantial efficacy for HER2 + ABC patients with CNS lesions has been reported [5, 28]. However, the efficacy in cases with LM was not well described in those reports and thus remains unclear. Preventing or controlling CNS lesions in patients with ER + HER2-ABC by systemic therapy remains challenging because of the existence of the blood-brain-barrier (BBB) [29]. Abemaciclib, a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor is a potent agent for managing ER + HER2-ABC as first- or second-line systemic therapies and it can penetrate the BBB [30]. Tolaney et al. [30] reported the results of a phase 2 study of abemaciclib monotherapy in ER + ABC patients with CNS lesions, including an LM cohort. Seven ER + HER2-patients with LM (N = 10) maintained stable disease for ≥ 4 weeks following local RT with 200 mg of abemaciclib twice daily, showing a median progression-free survival of 5.9 months and median OS of 8.4 months; however, the study included no RT-naïve LM patients in whom disruption of the BBB by preceding RT would have been expected, which facilitated the drug penetration. Recently, Trousseier et al. [31] reported a case of LM from ER + HER2-ABC wherein a radiological complete response was achieved and maintained for over one year by abemaciclib plus letrozole subsequent to RT. In an early-phase clinical trial, ANG1005 (paclitaxel trevatide), an investigational peptide-drug conjugate designed to cross the BBB, demonstrated efficacy in ER + HER2-LM patients (N = 8), most of whom had completed RT prior to enrollment, with an OS rate at 6 months of 67% [32].

Immune checkpoint inhibitors (ICIs), such as nivolumab, ipilimumab, and pembrolizumab, have been reported to be somewhat effective for patients with CNS metastases from melanoma [33] and from lung cancer with or without LM [34, 35] Recently, Brastianos et al. [36] reported the results of a single-arm phase 2 trial including 17 ABC patients among 20 advanced solid tumor patients with LM using pembrolizumab; however, the therapeutic value of pembrolizumab remains unclear, as the background of the patients thus far has been too heterogenous, and the observational period has been relatively short.

In summary, to our knowledge, there is currently no systemic therapy for ER + HER2-LM that should precede local RT.

This study has several limitations, such as its retrospective nature, relatively small number of patients, and lack of a control arm inside the study; however, this study is strengthened by its single-institutional setting, as patients were followed diligently; in this study, no patient was untraceable, all deceased patients died in our hospital, their causes of death were identified, and the treatment strategies were consistent.

# Conclusions

Our retrospective analysis at a single institute revealed that the prognosis of LM in patients with ER + HER2-ABC was still extremely poor and was almost same as that in previous reports. The data suggest that LM with or without BM is distinct from BM in terms of its pathogenesis and response to therapy (i.e. more direct, more aggressive, more symptomatic, and more resistant to therapy). Novel systemic therapies are being developed; however, there is no standard of care for ER + HER2-LM aside from local RT at present. Thus, oncologists should pay attention to symptoms from the CNS, especially in patients at risk of LM (e.g. skull and/or vertebral metastasis from the early phase of illness, lobular histologic feature), and should start treatment promptly before a patient's PS deteriorates. To improve the actual situation of LM patients, multimodal approaches with novel systemic therapy, especially those using molecular-targeted agents, are warranted.

# Declarations


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### Conflict of Interest Disclosures

JW reports having received personal fees from AstraZeneca, Chugai Pharmaceuticals, Daiichi-Sankyo, Eisai Co., Ltd., Eli-Lilly, Novartis Pharma, Pfizer, and Taiho Pharmaceuticals outside the submitted work. HH reports having received; personal fees from AstraZeneca, Brain Lab, Chugai Pharmaceuticals, Daiichi-Sankyo, Eli-Lilly, Novartis Pharma and Pfizer; grants from Japan Agency for Medical Research and Development, The National Cancer Center Research and Development fund, Health, Labor and Welfare Science Research Grant; outside the submitted work. The other authors report no conflicts of interest.

### Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection and data analyses were performed by JW and SN. The first draft of the manuscript was written by JW, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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# Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.

# Figures

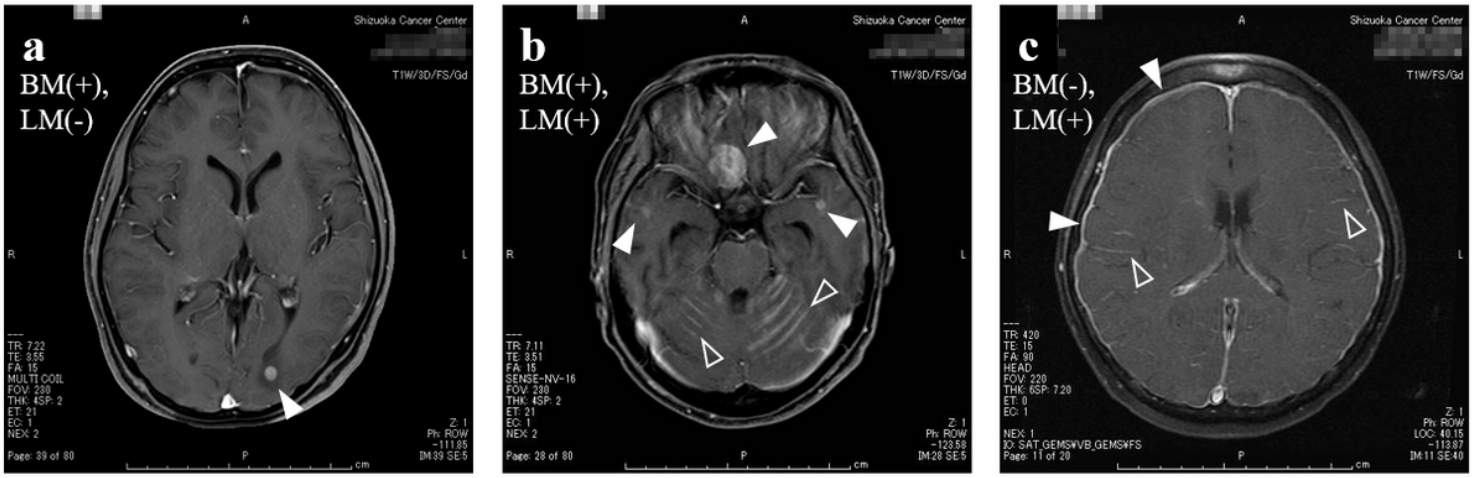


**Figure 1**

Classifications of the type of CNS metastases according to Gd-MRI. (a, left): B group, brain metastasis (BM) with peripheral edema (arrow) in the left occipital lobe without obvious leptomeningeal metastasis (LM); (b, center): BL group, BMs in the right frontal lobe, bilateral temporal lobes (arrows) and LM along cerebellar sulci (outlined arrows); (c, right): L group, Gd enhancement along the dura and sulci (outlined arrows) without obvious BM. CNS, central nervous system; Gd, gadolinium; MRI, magnetic resonance imaging

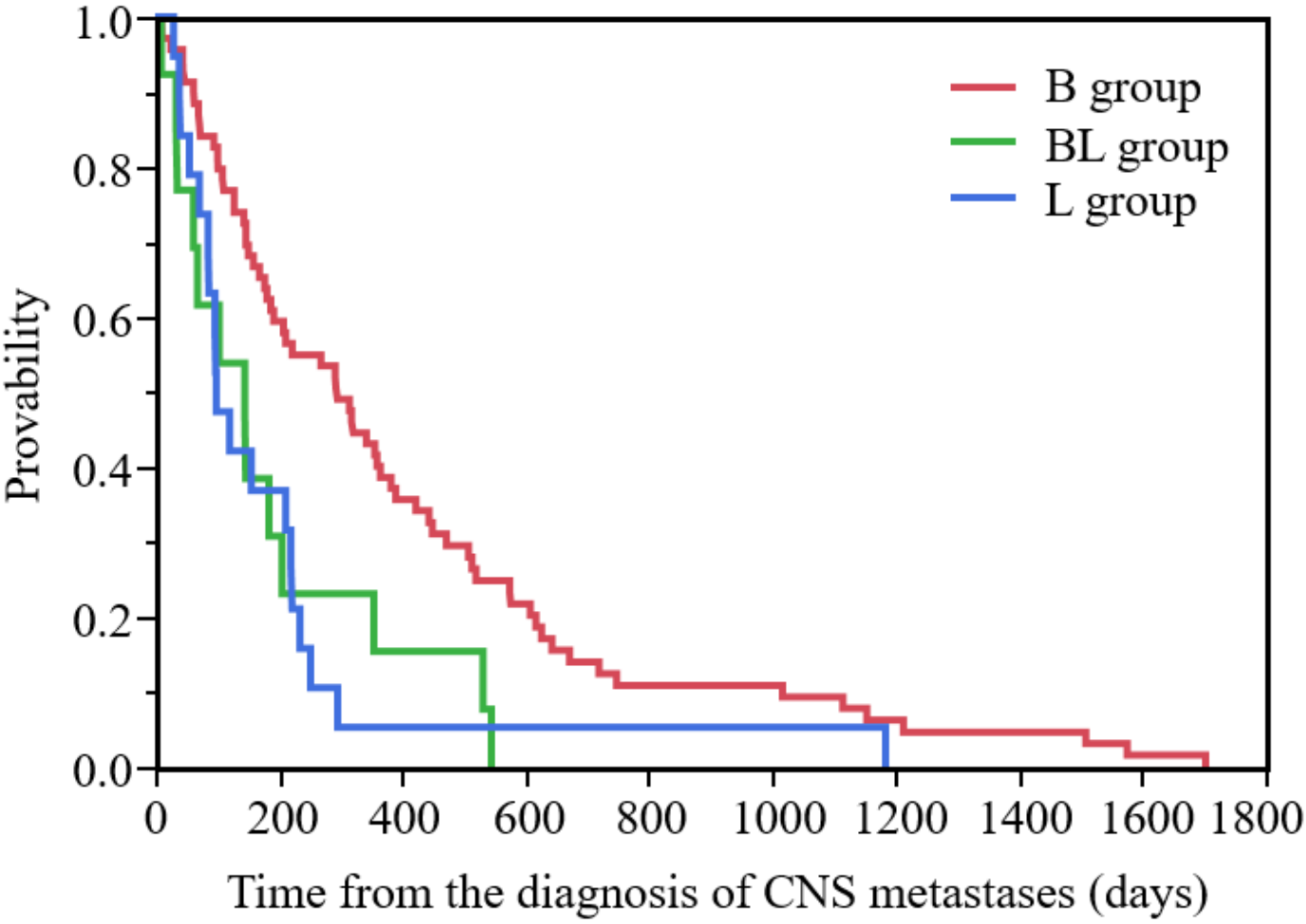


**Figure 2**

Kaplan-Meyer plots of the overall survival from the diagnosis of CNS metastases. CNS, central nervous system

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