

Clinicopathological Features, Treatment Modalities, and Prognostic Factors of Leptomeningeal Carcinomatosis in Patients with Breast Cancer: A Single-Center Retrospective Analysis

 Mehmet Mutlu Kızı^{1*},  Ömer Kaya²,  Sedat Biter³,  Tolga Köşeci⁴,  Hatice Asoğlu⁴,
 Yasemin Aydıralp Camadan⁵,  Oguz Kara⁴,  Berksoy Şahin⁴,  Ertuğrul Bayram⁴

¹ Department of Medical Oncology, Seyhan State Hospital, Adana, Türkiye

² Department of Radiology, Faculty of Medicine, Çukurova University, Adana, Türkiye

³ Department of Medical Oncology, Necip Fazıl City Hospital, Kahramanmaraş, Türkiye

⁴ Department of Medical Oncology, Faculty of Medicine, Çukurova University, Adana, Türkiye

⁵ Department of Medical Oncology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Türkiye

*Correspondence: Mehmet Mutlu Kızı; mehmetmutlu_01@hotmail.com

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Abstract

Aim: Leptomeningeal metastasis (LM) from breast cancer carries a poor prognosis. We aimed to describe the clinicopathological features, diagnostic classification, and treatment patterns of breast cancer-related LM and to explore factors associated with overall survival (OS). **Methods:** We retrospectively reviewed consecutive women with breast cancer-related LM treated at a single tertiary center between February 2018 and December 2023. LM was classified by the EANO–ESMO criteria as cytologically or histologically confirmed (type I) or as probable or possible (type II). OS was measured from the LM diagnosis (Kaplan–Meier). Candidate variables were examined by Cox regression; all prognostic analyses were exploratory. Landmark analyses at 4 weeks limited immortal time bias. **Results:** Among 38 women, median age was 57.0 years. The diagnosis was cytologically or histologically confirmed (type I) in 12 patients (31.6%). After the LM diagnosis, 32 patients (84.2%) received systemic therapy, 22 (57.9%) radiotherapy, and 5 (13.2%) intrathecal methotrexate; these categories were not mutually exclusive. Thirty-five patients (92.1%) had died. Median OS was 2.8 months (95% confidence interval [CI], 1.4–8.8); 6- and 24-month survival were 39.5% and 12.3%. No variable reached $P < 0.10$ in univariable analysis; radiotherapy had the lowest P value (hazard ratio 0.57; 95% CI, 0.28–1.15; $P = 0.11$). **Conclusions:** Median survival was 2.8 months; no candidate variable showed a statistically significant association with OS, and these exploratory estimates were imprecise and do not exclude clinically relevant effects. Fewer than one third of diagnoses were cytologically or histologically confirmed, which limits comparison with series reporting higher confirmation rates.

Keywords: Breast Neoplasms; Meningeal Carcinomatosis; Methotrexate; Prognosis; Survival Analysis

1. Introduction

Leptomeningeal carcinomatosis, also termed leptomeningeal metastasis (LM), is the dissemination of tumor cells within the leptomeninges and the cerebrospinal fluid (CSF) compartment, and is among the most disabling complications of advanced solid malignancy.¹ The latter term is used throughout this article for consistency with the terminology of current guidelines. Breast cancer is one of the solid tumors most commonly complicated by LM, which affects an estimated 5%–8% of patients.² Its recognized frequency has risen over the past two decades,³ attributed to wider use of contrast-enhanced magnetic resonance imaging (MRI) and better control of extracranial disease.⁴ Prognosis has changed far less: median overall survival (OS) after an LM diagnosis is generally reported between 2 and 6 months,⁵ and remains 3–4 months even with multimodal treatment.⁶

The disease is not uniform. Invasive lobular carcinoma and triple-negative breast cancer (TNBC) show a disproportionate propensity for leptomeningeal spread,^{4,7} whereas survival after an LM diagnosis is shortest in TNBC and longest in human epidermal growth factor receptor 2 (HER2)-positive disease.^{2,6} Performance status, receipt of systemic therapy, and the level of diagnostic evidence supporting the LM diagnosis have each been associated with survival in retrospective series^{5,7} and have been combined into prognostic scores.⁸ Reported effect sizes vary considerably between cohorts, however, which limits their application to individual patients.

No standard of care has been established. Management combines radiotherapy, intrathecal pharmacotherapy, systemic treatment, and supportive care, and is driven largely by performance status and goals of care.^{1,6} Randomized evidence is scarce and inconsistent: intraventricular methotrexate added to systemic therapy and involved-field radiotherapy improved neither neurologic response nor survival,⁹ intrathecal liposomal cytarabine prolonged LM-related progression-free survival without a significant effect on OS in the phase III DEPOSEIN trial,¹⁰ and a large retrospective cohort showed no survival advantage for intrathecal chemotherapy.¹¹ Newer strategies — proton craniospinal irradiation,³ tucatinib-based therapy,¹² and trastuzumab deruxtecan¹³ — are promising but were evaluated in selected, predominantly HER2-positive populations. Response assessment remains a further obstacle, although the European Association of Neuro-Oncology–European Society for Medical Oncology (EANO–ESMO) classification⁵ and the Response Assessment in Neuro-Oncology (RANO)-LM criteria^{14,15} have improved standardization.

Diagnostic pathways and treatment practices for LM differ appreciably between centers and health systems, and real-world data on breast cancer-related LM from Türkiye are limited. We reviewed consecutive women treated for breast cancer-related LM at a single tertiary center to describe their clinicopathologic spectrum, diagnostic classification, and treatment patterns, and to explore factors associated with OS. Given the size of the cohort, the analyses of prognostic factors and treatment associations were planned as exploratory.

2. Materials and Methods

2.1. Study design and setting

This retrospective, single-center cohort study was conducted at the Division of Medical Oncology, Faculty of Medicine, Çukurova University (Adana, Türkiye), a tertiary referral center. The protocol was approved by the Çukurova University Faculty of Medicine Research Ethics Committee (meeting no. 166, decision no. 76; 8 May 2026), and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived because the analysis was retrospective and used anonymized records. Reporting follows the STROBE statement for observational studies.¹⁶

2.2. Patients

Patients with histologically confirmed breast cancer in whom LM was diagnosed between February 2018 and December 2023 were identified consecutively from institutional electronic medical records and departmental follow-up files. Ninety patients were screened. Fifty-two were excluded because follow-up after the LM diagnosis was absent or too irregular to determine treatment and survival, or because LM was attributable to a concurrent non-breast primary malignancy. Thirty-eight patients formed the analysis cohort.

The diagnosis of LM followed the EANO–ESMO framework.^{1,5} It was regarded as confirmed (type I) when malignant cells were identified in the CSF or by leptomeningeal biopsy, and as type II in the absence of cytological or histological confirmation, with type II classified further as probable or possible according to the combination of clinical and MRI findings. Within type II, the diagnosis is regarded as probable when typical clinical findings and typical MRI findings are both present, and as possible when only one of the two is present, that is, typical MRI findings without typical clinical signs, or typical clinical signs with a normal MRI or hydrocephalus only. Because the presenting neurological findings and the MRI findings had not been recorded systematically for the whole cohort (see Variables), this distinction could not be applied retrospectively with sufficient reliability, and type II patients are reported as a single group.

Patients who received at least one intrathecal administration of any agent after the LM diagnosis constituted the intrathecal group. Treatment was given at the discretion of the treating physician and was neither protocol-based nor randomized; no formal survival comparison was planned for this subgroup.

2.3. Variables

The following were abstracted from institutional records: age at breast cancer and at LM diagnosis, histologic type, modified Bloom–Richardson grade, Ki-67 index, estrogen (ER) and progesterone receptor (PR) expression, HER2 status, molecular subtype, primary tumor size, stage (AJCC/UICC 8th edition), de novo versus recurrent presentation, number of systemic treatment lines before LM, Eastern Cooperative Oncology Group (ECOG) performance status at LM diagnosis, method of LM diagnosis, and LM-directed treatment (intrathecal therapy, cranial or focal radiotherapy, systemic therapy). Hormone receptor positivity was defined as ER or PR staining in at least 1% of tumor cells and HER2 positivity as an immunohistochemistry score of 3+, or 2+ with gene amplification on in situ hybridization; tumors negative for all three markers were classified as triple-negative.

Six further variables, including the pattern of leptomeningeal enhancement on MRI, presenting neurologic symptoms, and concurrent parenchymal brain metastases, were documented for only 15 of the 38 patients and could not be recovered from the source records; they were therefore not analyzed.

2.4. Endpoints

The primary endpoint was OS. Secondary descriptive outcomes were the interval from breast cancer diagnosis to LM and the investigator-recorded clinical and radiological course. Clinical status and imaging were reassessed at approximately 3-month intervals as part of routine follow-up, and each patient was assigned a single category — improvement, stable disease, or deterioration — reflecting the overall course documented by the treating team during follow-up rather than the status at a protocol-defined assessment timepoint; conversion of CSF cytology to negative was recorded separately. They were not reassessed centrally against the RANO-LM scorecard^{14,15} and are therefore reported as the investigator-recorded course rather than as formal treatment-response endpoints.

2.5. Statistical analysis

Continuous variables are summarized as median with interquartile range (IQR) and categorical variables as counts and percentages; groups were compared with the Mann–Whitney *U* test and the chi-square or Fisher exact test.

OS was calculated from the date of LM diagnosis to death from any cause, with censoring at last contact and a data cutoff of 1 April 2025; it was estimated by the Kaplan–Meier method with 95% confidence intervals (CI) and compared using the log-rank test. Median follow-up was estimated by the reverse Kaplan–Meier method.

Because LM-directed treatment can only begin after the LM diagnosis, comparisons anchored at that date are subject to immortal time bias; landmark analyses for systemic therapy and for radiotherapy were therefore performed at 4 weeks, excluding patients who died or were censored earlier and resetting the time origin to the landmark. Four weeks was chosen as the shortest interval within which treatment could realistically be initiated and documented, while still retaining most of the cohort given a median OS of under 3 months.

Ten candidate variables, selected a priori on clinical grounds, were examined in univariable Cox models. None reached the prespecified threshold of $P < 0.10$, so no variable-selection-based model was constructed; an exploratory model specified before fitting and containing ECOG performance status, systemic therapy, and radiotherapy was used instead, because performance status is the prognostic factor most consistently reported in LM cohorts,^{5,7} these were the only modalities delivered to more than a small minority of patients, and the number of events limited the model to three covariates. Hazard ratios (HR) are reported with 95% CI (reference categories in Table 2); the interval from breast cancer diagnosis to LM was modeled per 12-month increment, and model diagnostics are given in the footnote to Table 2.

Because the survival curves of the two EANO–ESMO types crossed, a single hazard ratio may be uninformative; the difference between these groups was therefore also quantified as the difference in restricted mean survival time (RMST) at 6, 12, and 24 months, with 95% CI and *P* values obtained by bootstrapping.

All prognostic and treatment-related analyses were exploratory and hypothesis-generating. Tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed using R version 4.6.0 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patients

Of the 90 patients screened, 38 women with breast cancer–related LM formed the analysis cohort. Median age at LM diagnosis was 57.0 years (IQR, 44.5–65.4), and 17 patients (44.7%) had ECOG performance status 2–3. Invasive ductal carcinoma predominated (31 patients, 81.6%), 7 patients (18.4%) had a lobular component, and 21 tumors (55.3%) were grade 3. Ten tumors (26.3%) were HER2-positive and 3 (7.9%) were triple-negative; 15 patients (39.5%) had de novo metastatic disease. Patient and tumor characteristics are summarized in Table 1.

3.2. LM diagnosis and treatment

The median interval from breast cancer diagnosis to LM was 46.3 months (IQR, 23.0–82.2). Half of the patients had received two or more systemic treatment lines before LM. The diagnosis was cytologically or histologically confirmed (EANO–ESMO type I) in 12 patients (31.6%) and was based on clinical and imaging findings (type II) in 26 (68.4%). After the LM diagnosis, 32 patients (84.2%) received systemic therapy, 22 (57.9%) cranial or focal radiotherapy, and 5 (13.2%) intrathecal therapy.

Table 1. Patient, tumor, and leptomeningeal metastasis characteristics of the whole cohort (n = 38).

Characteristic	Whole cohort (n = 38)
Age at LM diagnosis, years, median (IQR)	57.0 (44.5–65.4)
ECOG performance status, n (%)	
1	21 (55.3)
2–3	17 (44.7)
Histology, n (%)	
Invasive ductal carcinoma	31 (81.6)
Invasive lobular carcinoma	5 (13.2)
Mixed ductal-lobular carcinoma	2 (5.3)
Histologic grade, n (%)	
1	1 (2.6)
2	16 (42.1)
3	21 (55.3)
Ki-67 index, %, median (IQR)	25.0 (20.0–40.0)
Molecular subtype, n (%)	
HR+/HER2–	25 (65.8)
HR+/HER2+	8 (21.1)
HR–/HER2+	2 (5.3)
Triple-negative	3 (7.9)
HER2-positive overall, n (%)	10 (26.3)
De novo metastatic disease (stage IV at initial diagnosis), n (%)	15 (39.5)
Primary tumor size, cm, median (IQR)	2.8 (2.5–3.6)
Interval from breast cancer diagnosis to LM, months, median (IQR)	46.3 (23.0–82.2)
Systemic treatment lines before LM, n (%)	
1	19 (50.0)
≥2	19 (50.0)
EANO–ESMO diagnostic type, n (%)	
Type I (confirmed)	12 (31.6)
Type II (probable or possible)	26 (68.4)
LM-directed treatment, n (%)	
Systemic therapy	32 (84.2)
Cranial or focal radiotherapy	22 (57.9)
Intrathecal therapy	5 (13.2)
Best supportive care only	5 (13.2)

There were no missing data for any variable listed. ECOG performance status 2 and 3 are shown combined; the individual counts were 16 and 1. Systemic therapy, radiotherapy, and intrathecal therapy were not mutually exclusive; patients could receive more than one of these modalities. Best supportive care only was mutually exclusive of LM-directed treatment. Type II includes probable and possible disease; these two categories could not be distinguished retrospectively (see Methods). ECOG, Eastern Cooperative Oncology Group; EANO–ESMO, European Association of Neuro-Oncology–European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IQR, interquartile range; LM, leptomeningeal metastasis.

These categories are not mutually exclusive, since systemic therapy, radiotherapy, and intrathecal therapy could be combined in the same patient. Thirty-three patients

(86.8%) received at least one LM-directed treatment; the remaining 5 (13.2%) received best supportive care only. Investigator-recorded clinical status improved in 8 patients (21.1%), was stable in 7 (18.4%), and deteriorated in 23 (60.5%); imaging improved in 9 (23.7%), was stable in 9 (23.7%), and deteriorated in 20 (52.6%).

3.3. Overall survival

Thirty-five patients (92.1%) had died. Median follow-up was 43.0 months, an estimate resting on the three patients alive at cutoff (16.1, 28.1, and 43.0 months). Median OS from LM diagnosis was 2.8 months (95% CI, 1.4–8.8). Estimated survival was 39.5% (95% CI, 24.2–54.4) at 6 months, 26.3% (95% CI, 13.7–40.8) at 12 months, and 12.3% (95% CI, 4.1–25.1) at 24 months (Figure 1).

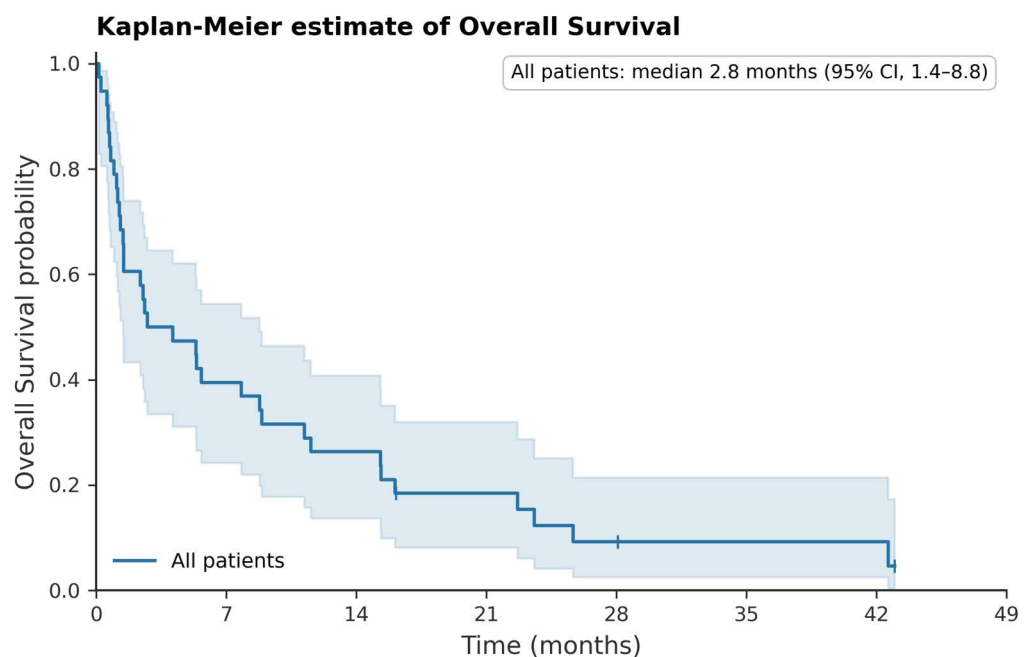


Figure 1. Kaplan–Meier estimate of overall survival from the diagnosis of leptomeningeal metastasis in the whole cohort ($n = 38$). Shading indicates the 95% confidence interval; vertical ticks indicate censored observations.

3.4. Treatment modalities and survival

Median OS was 5.4 months (95% CI, 1.5–11.2) in patients who received systemic therapy after LM and 1.2 months (95% CI, 0.3–not reached) in those who did not (HR 0.56; 95% CI, 0.22–1.48; $P = 0.25$). In the 4-week landmark analysis (31 of 38 patients; 7 died or were censored before the landmark), median OS from the landmark was 6.9 months with systemic therapy ($n = 27$) and 0.3 months without it ($n = 4$) (HR 0.66; 95% CI, 0.19–2.21; $P = 0.50$). Radiotherapy was associated with a hazard ratio of 0.57 (95% CI, 0.28–1.15; $P = 0.11$) in univariable analysis; in the corresponding landmark analysis, median OS from the landmark was 7.9 months in irradiated patients ($n = 19$) and 1.7 months in those not irradiated ($n = 12$) (HR 0.59; 95% CI, 0.26–1.29; $P = 0.19$). Neither modality showed a statistically significant association with OS in the primary or the landmark analysis, and these estimates are exploratory.

3.5. EANO–ESMO diagnostic type

Median OS was 7.8 months (95% CI, 0.7–16.1) in type I and 2.5 months (95% CI, 1.2–5.7) in type II (HR for type II versus type I 1.07; 95% CI, 0.53–2.17; log-rank $P = 0.86$). The

survival curves crossed between 12 and 24 months (Figure 2). The scaled Schoenfeld residual test did not reject proportional hazards ($P = 0.13$), but the crossing curves make a single hazard ratio difficult to interpret. The difference in RMST favored type I at every truncation point but included the null: +1.02 months (95% CI, -0.57 to 2.55) at 6 months, +2.19 months (-1.09 to 5.22) at 12 months, and +2.40 months (-2.98 to 8.21) at 24 months (all $P \geq 0.20$).

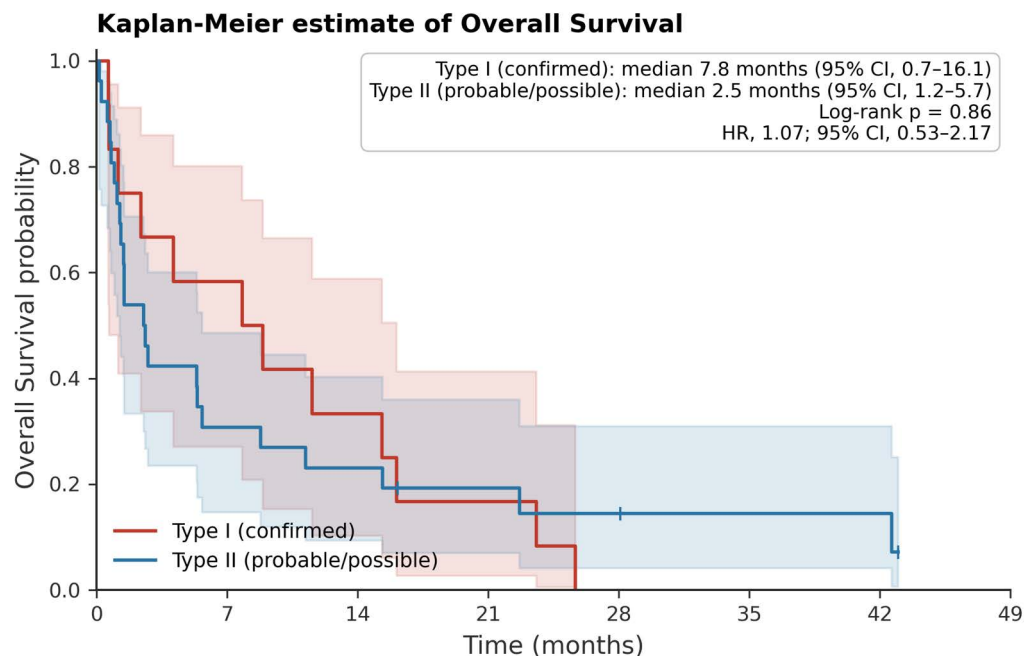


Figure 2. Kaplan–Meier estimates of overall survival according to the EANO–ESMO diagnostic type. The hazard ratio shown is for type II versus type I. The curves cross between 12 and 24 months; the difference in restricted mean survival time is reported in the text.

3.6. Prognostic factors

None of the ten candidate variables reached the prespecified threshold of $P < 0.10$ in univariable Cox analysis (Table 2); the lowest P value was for receipt of radiotherapy (HR 0.57; 95% CI, 0.28–1.15; $P = 0.11$). In the exploratory multivariable model, none of ECOG performance status, receipt of systemic therapy, or receipt of radiotherapy was independently associated with OS (HR 1.35, 0.72, and 0.61, respectively; all $P \geq 0.21$; Table 2).

3.7. Intrathecal therapy

Five patients (13.2%) received intrathecal therapy, all with methotrexate. The number of administrations was one in three patients, two in one, and nine in one. CSF cytology converted to negative in four patients, after the first administration in three and after the third or a later administration in one. Four also received radiotherapy and all five received systemic therapy; all had died by the data cutoff, with individual OS ranging from 8.9 to 25.7 months. Patients who received intrathecal therapy differed from those who did not at baseline: they were younger (median age 42.5 years [IQR, 41.0–43.5] versus 58.3 years [IQR, 48.4–66.2]; $P = 0.016$) and more often had confirmed type I disease (4 of 5, 80.0%, versus 8 of 33, 24.2%; $P = 0.027$). These observations are descriptive; no survival comparison was performed, and the cytological conversions should not be interpreted as evidence of treatment efficacy.

Table 2. Univariable and exploratory multivariable Cox proportional hazards analysis of overall survival from leptomeningeal metastasis diagnosis (n = 38; 35 events).

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
Age at LM diagnosis, per year	1.01 (0.99–1.04)	0.30	—	—
ECOG 2–3 vs 1	1.24 (0.63–2.42)	0.53	1.35 (0.68–2.69)	0.39
HER2-positive vs HER2-negative	0.75 (0.34–1.66)	0.47	—	—
EANO–ESMO type II vs type I	1.07 (0.53–2.17)	0.86	—	—
≥2 vs 1 prior systemic line	1.31 (0.67–2.59)	0.43	—	—
Systemic therapy vs none	0.56 (0.22–1.48)	0.25	0.72 (0.24–2.15)	0.55
Radiotherapy vs none	0.57 (0.28–1.15)	0.11	0.61 (0.28–1.33)	0.21
Lobular component vs no lobular component	0.87 (0.38–2.01)	0.75	—	—
De novo metastatic vs recurrent	0.84 (0.42–1.66)	0.61	—	—
Interval from breast cancer diagnosis to LM, per 12 months	0.98 (0.91–1.06)	0.64	—	—

The multivariable model was exploratory and was specified before fitting: no variable reached $P < 0.10$ in univariable analysis, so no variable-selection-based model was constructed. Type I disease is the reference category for EANO–ESMO type. Events per variable 11.7; all variance inflation factors < 5 ; no statistically significant violation of the proportional hazards assumption was detected for any covariate (scaled Schoenfeld residuals, $P = 0.11$ – 0.64). HR denotes hazard ratio throughout this table; HR+ in Table 1 denotes hormone receptor positivity. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EANO–ESMO, European Association of Neuro-Oncology–European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; LM, leptomeningeal metastasis.

4. Discussion

In this single-center cohort of 38 women with breast cancer–related LM, median OS from the LM diagnosis was 2.8 months, and no clinicopathologic or treatment-related variable was independently associated with survival in exploratory analyses. Two features qualify comparison with other series: fewer than one third of diagnoses were confirmed cytologically or histologically, and intrathecal therapy consisted of methotrexate in every case.

Only 12 patients (31.6%) met the EANO–ESMO criteria for confirmed (type I) disease, compared with 74% in the multicenter cohort that validated the classification.⁵ Our proportion is closer to the Memorial Sloan Kettering series, in which only 44% underwent cytological examination,¹⁷ and to a Canadian series in which CSF cytology was not routinely performed.¹⁸ A cohort dominated by type II disease is therefore not interchangeable with one dominated by type I. The prognostic direction of the classification also differed from the validation cohort, in which type I disease carried the shorter survival:⁵ our medians favored type I (7.8 versus 2.5 months), but the curves crossed and the difference in RMST included the null at every truncation point, so we regard this as a numerical pattern in a small cohort rather than a contradictory finding.

Systemic therapy was given to 84.2% of patients after the LM diagnosis, exceeding the 60% reported by Morikawa et al., and radiotherapy to 57.9%, comparable with the 64% in that series.¹⁷ Intrathecal therapy was used in 13.2%, close to the 14% in the same series¹⁷ but well below the 37.8% and 45.9% reported elsewhere.^{6,11} Every treated patient received methotrexate; liposomal cytarabine has not been commercially available for several years,⁶ and thiotepea and intrathecal trastuzumab were not used. Our median OS of 2.8 months lies within the range reported by comparable retrospective series, which extends from 2.5 months or less¹¹ to 3.5–4.2 months.^{6,17,19} Features consistent with an estimate at the lower end of that range include the absence of any patient with ECOG 0, the half who

had already received two or more systemic lines, and the 13.2% who received no LM-directed treatment.

No variable reached the prespecified threshold and the exploratory model showed no independent association, in contrast to series in which performance status and receptor subtype were prognostic.^{7,17,18,19} The most plausible explanation is statistical rather than biological: with 38 patients and 35 events, the confidence intervals were wide enough to accommodate clinically important effects in either direction, and the narrow performance status distribution further limited the available contrast. These results should be read as uninformative rather than as evidence that such effects are absent.

Intrathecal therapy is reported descriptively because only five patients received it and they differed systematically from the remainder. The wider evidence supports this caution: intraventricular methotrexate showed no survival or neurological benefit and more neurotoxicity in a randomized study,⁹ a propensity-adjusted cohort found no survival gain,¹¹ and DEPOSEIN improved LM-related progression-free survival without a significant effect on OS.¹⁰ CSF cytology converted to negative in four of the five treated patients; with so few patients and no comparison group, this observation remains descriptive and cannot support any causal inference.

4.1. Limitations

This study has several limitations. The sample size of 38 patients is the principal one: it left the analysis unable to detect moderate prognostic effects, restricted the exploratory multivariable model to three covariates, and made subgroup comparison unreliable. Fifty-two of the 90 screened patients were excluded, mainly because follow-up after the LM diagnosis was insufficient, so the analysis cohort may be selected towards patients who remained under regular institutional care. Six variables, including concurrent parenchymal brain metastases and the pattern of leptomeningeal enhancement on MRI, were recorded for only 15 patients; the models are therefore unadjusted for intracranial disease burden, and probable and possible type II disease could not be distinguished. Treatment was not allocated by protocol, so the associations reported for systemic therapy and radiotherapy remain vulnerable to confounding by indication even after landmark analysis. Clinical, radiological, and cytological outcomes were recorded by the treating team rather than reassessed centrally against the RANO-LM scorecard^{14,15} and are not comparable with response rates from trials using that instrument. No patient received trastuzumab deruxtecan or tucatinib-based therapy, both of which have shown activity in HER2-positive leptomeningeal disease,^{12,13} so the outcomes of the 10 patients with HER2-positive disease here do not reflect what may be achievable with these agents. Finally, the findings derive from a single tertiary center, and intrathecal treatment was confined to methotrexate by institutional preference.

5. Conclusion

In this single-center cohort of 38 women with breast cancer-related LM, median overall survival from the LM diagnosis was 2.8 months (95% CI, 1.4–8.8). Fewer than one third of diagnoses were cytologically or histologically confirmed and probable and possible disease could not be distinguished, so the cohort is diagnostically heterogeneous. No candidate variable showed a statistically significant association with survival, but with 38 patients and 35 events these exploratory estimates were imprecise and do not exclude clinically relevant effects. Prospective cohorts with complete diagnostic work-up and standardized response assessment are needed.

Statement of ethics: The study was approved by the Çukurova University Faculty of Medicine Research Ethics Committee (meeting no. 166, decision no. 76; 8 May 2026) and was conducted in

accordance with the Declaration of Helsinki. Given the retrospective design and the use of anonymized records, the committee waived the requirement for written informed consent.

Use of generative artificial intelligence: During the preparation of this manuscript, the authors used a generative artificial intelligence tool solely for English-language editing and to improve clarity and readability. All AI-assisted revisions were reviewed and approved by the authors, who take full responsibility for the final content of the manuscript.

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Availability of data and materials: The datasets used and/or analyzed during the current study are not publicly available because they contain information that could compromise patient privacy, but are available from the corresponding author upon reasonable request.

Author contributions: M.M.K.: Conceptualization, Methodology, Formal analysis, Data curation, Visualization, Investigation, Writing – original draft, Project administration. Ö.Kaya: Investigation, Radiological assessment of leptomeningeal involvement, Writing – review & editing. S.B.: Investigation, Writing – review & editing. T.K.: Investigation, Writing – review & editing. H.A.: Investigation, Writing – review & editing. Y.A.C.: Investigation, Writing – review & editing. O.Kara: Investigation, Supervision, Writing – review & editing. B.Ş.: Investigation, Supervision, Writing – review & editing. E.B.: Investigation, Supervision, Writing – review & editing. All authors read and approved the final manuscript and meet the ICMJE criteria for authorship.

References

1. Le Rhun E, Weller M, van den Bent M, Brandsma D, Furtner J, Rudà R, et al. Leptomeningeal metastasis from solid tumours: EANO–ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *ESMO Open*. 2023;8(5):101624. doi:10.1016/j.esmoop.2023.101624
2. Wallace G, Kundalia R, Vallebuona E, Cao B, Kim Y, Forsyth P, et al. Factors associated with overall survival in breast cancer patients with leptomeningeal disease (LMD): a single institutional retrospective review. *Breast Cancer Res*. 2024;26:55. doi:10.1186/s13058-024-01789-7
3. Yang JT, Wijetunga NA, Pentsova E, Wolden S, Young RJ, Correa D, et al. Randomized phase II trial of proton craniospinal irradiation versus photon involved-field radiotherapy for patients with solid tumor leptomeningeal metastasis. *J Clin Oncol*. 2022;40:3858–67. doi:10.1200/JCO.22.01148
4. Laakmann E, Schmidt M, Lübke K, Agostinetti E, van Ramshorst M, Decker T, et al. Clinical characteristics and prognostic factors in patients with breast cancer and leptomeningeal metastases from a large registry of BMBC. *Breast*. 2025;81:104433. doi:10.1016/j.breast.2025.104433
5. Le Rhun E, Devos P, Weller J, Seystahl K, Mo F, Compter A, et al. Prognostic validation and clinical implications of the EANO ESMO classification of leptomeningeal metastasis from solid tumors. *Neuro Oncol*. 2021;23(7):1100–12. doi:10.1093/neuro-onc/noaa298
6. Huppert LA, Fisch S, Tsopurashvili E, Somepalle SS, Salans M, Vasudevan HN, et al. Demographic and clinical characteristics of patients with metastatic breast cancer and leptomeningeal disease: a single center retrospective cohort study. *Breast Cancer Res Treat*. 2024;206:625–36. doi:10.1007/s10549-024-07339-1
7. Niwińska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: propensity of breast cancer subtypes for leptomeninges and the analysis of factors influencing survival. *Med Oncol*. 2013;30(1):408. doi:10.1007/s12032-012-0408-4
8. Narjoux G, Mainguéné J, Guilhaume MN, Brenet O, Borcoman E, Escalup L, et al. Development of a prognostic score in patients with advanced breast cancer treated for meningeal carcinomatosis. *Breast J*. 2025;2025:5438600. doi:10.1155/tbj/5438600
9. Boogerd W, van den Bent MJ, Koehler PJ, Heimans JJ, van der Sande JJ, Aaronson NK, et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. *Eur J Cancer*. 2004;40(18):2726–33. doi:10.1016/j.ejca.2004.08.012

10. Le Rhun E, Wallet J, Mailliez A, Le Deley MC, Rodrigues I, Boulanger T, et al. Intrathecal liposomal cytarabine plus systemic therapy versus systemic chemotherapy alone for newly diagnosed leptomeningeal metastasis from breast cancer. *Neuro Oncol.* 2020;22(4):524-38. doi:10.1093/neuonc/noz201
11. Meneguetti RT, Cruz FJ, del Giglio A. Role of intrathecal chemotherapy in the management of meningeal carcinomatosis in patients with breast cancer. *einstein (São Paulo).* 2023;21:eAO0481. doi:10.31744/einstein_journal/2023AO0481
12. Murthy RK, O'Brien BJ, Berry DA, Singareeka-Raghavendra A, Monroe MG, Johnson J, et al. Tucatinib–trastuzumab–capecitabine for treatment of leptomeningeal metastasis in women with HER2+ breast cancer: TBCRC049 phase 2 study results. *Nat Cancer.* 2026;7(3):424-34. doi:10.1038/s43018-026-01120-7
13. Vaz Batista M, Pérez-García JM, Garrigós L, García-Sáenz JÁ, Cortez P, Racca F, et al. The DEBBRAH trial: trastuzumab deruxtecan in HER2-positive and HER2-low breast cancer patients with leptomeningeal carcinomatosis. *Med.* 2025;6:100502. doi:10.1016/j.medj.2024.08.001
14. Chamberlain M, Junck L, Brandsma D, Soffiatti R, Rudà R, Raizer J, et al. Leptomeningeal metastases: a RANO proposal for response criteria. *Neuro Oncol.* 2017;19(4):484-92. doi:10.1093/neuonc/now183
15. Griguolo G, Aldegheri V, Bottosso M, Pittaro A, Caumo F, Guarascio MC, et al. Radiological response of leptomeningeal metastases according to revised RANO criteria is associated with overall survival in breast cancer patients. *Int J Cancer.* 2023;153(6):1217-26. doi:10.1002/ijc.34571
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;61:344-9. doi:10.1016/j.jclinepi.2007.11.008
17. Morikawa A, Jordan L, Rozner R, Patil S, Boire A, Pentsova E, et al. Characteristics and outcomes of patients with breast cancer with leptomeningeal metastasis. *Clin Breast Cancer.* 2017;17(1):23-8. doi:10.1016/j.clbc.2016.07.002
18. Id Said B, Jerzak KJ, Chen H, Moravan V, Warner E, Myrehaug S, et al. Survival outcomes among patients with breast cancer and leptomeningeal disease. *Sci Rep.* 2025;15:24170. doi:10.1038/s41598-025-07191-3
19. Niwińska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: the results of combined treatment and the comparison of methotrexate and liposomal cytarabine as intra-cerebrospinal fluid chemotherapy. *Clin Breast Cancer.* 2015;15(1):66-72. doi:10.1016/j.clbc.2014.07.004