Leptomeningeal Metastases in Glioma Revisited: Incidence and Molecular Predictors Based on Post-contrast FLAIR Imaging

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Abstract

Background: Leptomeningeal metastases (LM) in glioma have been underestimated due to low incidence and lack of reliable imaging. This study aimed to investigate a real-world incidence of LM using a CSF-sensitive imaging, namely post-contrast FLAIR, and analyze molecular predictors for LM in the molecular era.

Patients and Methods: Total 1,405 adult glioma patients underwent post-contrast FLAIR imaging at initial diagnosis and during treatment monitoring between 2001 and 2021. Molecular data included isocitrate dehydrogenase (IDH) mutation, 1p/19q co-deletion, H3 K27M alteration, and O6-methylguanine-methyltransferase (MGMT) promoter methylation status. LM diagnosis was performed with MRI including post-contrast FLAIR. Logistic regression analysis for LM development was performed with molecular, clinical, and imaging data. Overall survival (OS) was compared between patients with and without LM.

Results: LM was identified in 228 patients (16.2%), with 110 patients (7.8%) at initial diagnosis, and 118 patients (8.4%) at recurrence. Among molecular diagnostics, IDH-wildtype (odds ratio [OR] 3.14, P = .001) and MGMT promoter unmethylation (OR=1.43, P=.034) were independent predictors of LM. WHO grade 4 (OR=10.52, P <.001) and nonlobar location (OR=1.54, P=.048) were associated with LM at initial diagnosis, whereas IDH-wildtype (OR=5.04, P<.001) and H3 K27M alteration (OR=3.39, P=.003) were associated with LM at recurrence. Patients with LM had a worse median OS than those without LM (16.7 vs. 32.0 months, log-rank test; P<.001).

Conclusions: CSF-sensitive imaging aid diagnosis of LM demonstrating a high incidence of LM in adult gliomas. Furthermore, molecular markers are associated with LM development in glioma, and patients with aggressive molecular markers warrant imaging surveillance of LM.

Highlights

- With CSF-sensitive MRI, 16.2% of glioma patients were diagnosed with leptomeningeal metastases either at initial diagnosis or at recurrence.
- Aggressive molecular markers such as IDH wildtype and MGMT promoter unmethylation were associated with LM.
- Glioma patients with aggressive molecular markers warrant imaging surveillance with CSF-sensitive MRI.

Introduction

In glioma, the reported incidence of tumor cell invasion into leptomeninges either through direct invasion or cerebrospinal fluid (CSF), known as leptomeningeal metastases (LM), is gradually increasing\(^1\) as the prognosis of glioma improves over time. LM is one of the most
severe complications of glioma, with 75% of patients dying within 18 months of diagnosis.\(^1\) The reported incidence of LM ranges from 3.8–6.9% based on clinical studies\(^2\)\(^-\)\(^4\) and be as high as 20–25% on autopsy,\(^5\)\(^,\)\(^6\) suggesting the LM is an under-recognized downstream result of glioma. The markedly lower incidence of LM reported on clinical studies compared to autopsy results is due to the lack of imaging dedicated for LM diagnosis.\(^7\) Post-contrast fluid attenuated inversion recovery (FLAIR), namely CSF-sensitive, imaging has shown superior performance of LM detection in brain metastases patients,\(^7\)\(^,\)\(^8\) and the EANO-ESMO guideline recommends routine inclusion of post-contrast FLAIR to diagnose LM in patients with solid tumors.\(^9\) However, post-contrast FLAIR is not a routinely recommend sequence in glioma MRI protocol,\(^10\) and the efficacy of post-contrast FLAIR in LM detection has not been studied in a large cohort of glioma patients.

The recently published 2021 World Health Organization (WHO) classification of central nervous system tumors, as well as the previous 2016 WHO classification, emphasizes the role of molecular markers in the classification of adult-type diffuse gliomas, of which isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion status are of utmost importance.\(^11\)\(^,\)\(^12\) On the other hand, \(\text{O}^6\)-methylguanine-methyltransferase (MGMT) methylation is a strong prognostic marker and is predictive of response to temozolomide chemotherapy.\(^13\)\(^-\)\(^15\) Although classified as a pediatric-type diffuse high-grade glioma, diffuse midline glioma, H3 K27-altered, is also frequently encountered in adults.\(^16\) The expression of these molecular markers has been reported to have distinct prognostic differences and different chemosensitivity in gliomas.\(^17\)\(^-\)\(^19\)

However, molecular alterations in gliomas that precipitate LM is currently limited; previous studies have reported associations of H3 K27M alteration with LM, but the sample size was limited.\(^20\)\(^,\)\(^21\)

A comprehensive analysis of clinical and imaging predictors for LM in glioma patients has not yet been performed, as previous studies only had small datasets. Earlier studies have reported that young age and tumor location may be associated with a high risk of LM,\(^22\)\(^,\)\(^23\) whereas other studies have failed to identify this association.\(^2\)\(^-\)\(^4\) Owing to the relative paucity of data examining these factors in the entire glioma dataset, further investigations are needed to inform clinicians. We hypothesized that CSF-sensitive MRI of post-contrast FLAIR would aid to diagnose LM. Also, risk analysis of recent molecular diagnostics in a large cohort will enable to find predictors for LM.

Therefore, this study aimed to investigate a real-world incidence of LM using a CSF-sensitive MRI technique and analyze molecular predictors for LM in adult glioma patients.

**Materials And Methods**

**Standard Protocol Approvals, Registrations, and Patient Consents**
The requirement for patient consent was waived owing to the retrospective study design. This study was approved by the institutional review board of the Severance Hospital (approval number 4-2021-1638). The study was conducted in accordance with the Declaration of Helsinki.

Patient Enrollment

Between March 2001 and October 2021, 1,502 adult patients with glioma from our institution were recruited in this study. The inclusion criteria were as follows: 1) gliomas confirmed by histopathology, 2) known IDH mutation, 1p/19q codeletion status, 3) aged > 18 years, and 4) underwent MRI including post-contrast FLAIR. The exclusion criteria were as follows: 1) follow-up loss within 3 months (n = 92), and 2) tissue insufficiency (n = 5). A total of 1,405 patients were analyzed in this study. Figure 1 shows the flow chart for patient inclusion.

MRI Protocol

Brain MRI scans, including T1-weighted (T1), T2-weighed, T2-weighted, pre-contrast fluid-attenuated inversion recovery (FLAIR), and post-contrast 3D T1 images, were acquired with a 3T unit (Achieva or Ingenia; Philips Healthcare). Post-contrast FLAIR (repetition time, 10,000-11,000 ms; echo time, 110-125 ms; inversion time, 2500 ms; field of view, 230-240 mm; section thickness, 5 mm; matrix, 256 × 256) was acquired 10 minutes and 30 seconds after injection of gadolinium-based contrast (0.1 mL/kg of gadobutrol, Gadovist; Bayer Schering Pharma, Berlin, Germany).

Spine MRI scans, including axial and sagittal T1, T2-weighted images, and post-contrast axial and sagittal T1 images, were acquired using a 1.5T unit (Achieva dStream; Philips Healthcare). The detailed brain and spine MRI protocol is found in Supplementary Material S1.

Molecular Classification
All surgical tissues from the institutional dataset were diagnosed according to the WHO classification. Both immunohistochemical analysis and peptide nucleic acid-mediated clamping polymerase chain reaction were performed to detect IDH1 R132H mutation. In IDH1-negative patients on immunohistochemical analysis, IDH1/2 status was confirmed by peptide nucleic acid-mediated clamping polymerase chain reaction. Fluorescent in situ hybridization analysis was performed to detect 1p/19q codeletion. The presence of histone H3 K27M mutant protein was evaluated by immunohistochemistry analysis using polyclonal antibodies to detect the histone H3.3 tail. MGMT promoter methylation was evaluated by methylation-specific polymerase chain reaction. MGMT promoter methylation status was available in a subset of 1,372 (97.7%) patients.

Targeted next-generation sequencing was performed in a subset of patients using the Illumina TruSight Tumor 170 panel. For copy number analysis, epidermal growth factor receptor (EGFR) genes with ≥ 2 fold-change relative to the average level were considered to have undergone amplification. EGFR amplification status was available in a subset of 587 (41.8%) patients. Telomerase reverse transcriptase promoter (TERTp) mutation was determined using a pyrosequencing assay, and C228T and C250T mutations were analyzed. TERTp mutation status was available in a subset of 877 (62.4%) patients.

Clinical data and Imaging Features

Data on patient age, sex, date of initial glioma diagnosis, MRI results, CSF results, and date of death or last follow-up, were collected. In the case of patients with LM, the date of LM diagnosis, KPS at LM diagnosis, and data on initial and subsequent treatments before and after LM were additionally collected.

The location (frontal, temporal, insular, parietal, occipital, brainstem, corpus callosum, and cerebellum) of glioma was recorded. Bidimensional perpendicular measurement of CE and NE tumor was performed in baseline and immediate postoperative imaging taken within 48 hours. Resection extent was categorized as total (gross tumor removal, 100%), subtotal (gross tumor removal, ≥ 75% but < 100%), and partial (gross tumor removal, < 75%) or biopsy. Tumor location and extent of resection were established by independent review of two neuroradiologists (with 11 and 18 years of experience, respectively). In the rare case of ambiguity, a senior neuroradiologist (with 30 years of experience) was consulted for the final decision.
Overall survival (OS) was defined as the time from glioma diagnosis until death.

Patients who were alive at the time of the data cutoff for the final analysis were censored at their last follow-up date. Patients were censored at the date of medical record abstraction or at the date of the last imaging report, whichever came last.

Diagnosis of LM

Cases detected by the initial database inquiry and MRI review were manually confirmed by a chart review, including clinical notes and pathology reports. For confirmation of presence or absence of LM, all MRI data from patients were reviewed independently from the MRI report. LM was diagnosed in patients whose brain or spine MRI reviews showed LM or with positive CSF cytology based on the pathology report.

On MRI, brain LM was defined as linear or nodular leptomeningeal enhancement or linear ependymal enhancement, cranial nerve root enhancement; spine LM was defined as linear or nodular leptomeningeal enhancement or spinal nerve root enhancement. True leptomeningeal enhancement on post-contrast FLAIR could be confirmed by using the pre-contrast FLAIR as the reference image; abnormalities on pre-contrast FLAIR without additional enhancement on post-contrast FLAIR were not diagnosed as LM, according to the Response Assessment in Neuro-Oncology (RANO) recommendation. For confirmatory diagnosis of equivocal cases, only patients with follow-up MRIs demonstrating consistent leptomeningeal enhancement were diagnosed as LM. Disseminated LM and subependymal LM were separately recorded according to the previous criteria. Disseminated LM was defined as leptomeningeal or nerve root enhancement, whereas subependymal LM was defined as a subependymal or ependymal enhancement on MRI, which is radiographically indistinguishable (Supplementary Figure 1). Imaging diagnosis was established with a two-week washout period after imaging feature evaluation by independent review of two neuroradiologists (with 11 and 18 years of experience, respectively). In the rare case of ambiguity, a senior neuroradiologist (with 30 years of experience) was consulted for the final decision.

Statistical Analysis
The clinical and imaging characteristics of patients were compared according to LM status using the Chi-square for categorical variables and the independent samples t-test or Mann–Whitney U test for continuous variables according to normality.

Logistic regression analyses were performed in patients without missing information. Significant variables for LM development were selected using univariable logistic regression. Variables of interest in the univariable analysis (P < 0.05) were included in the multivariable models using backward elimination according to the likelihood ratio with a variable selection criterion of P < 0.05. The variance inflation factor was used to detect multicollinearity between variables; all variables showed a variance inflation factor < 10.

Survival rates were determined using the Kaplan–Meier method, and curves were compared using the log-rank test. Comparison of disseminated and subependymal LM patients were performed to confirm whether the clinical outcomes were comparable between these groups. Statistical analysis was performed in SPSS version 25 for Windows (SPSS, Inc). Statistical significance was set at P < 0.05. Owing to the exploratory nature of this study, adjustment for multiple testing was not performed. A biostatistician (with 11 years of experience) was consulted for statistical analysis.

Data availability

Our anonymized data can be obtained by any qualified investigators for the purposes of replicating procedures and results, after ethics clearance and approval by all authors.

Results

Patient characteristics

This study included 1,405 glioma patients (mean age: 53.6 ± 15.2 years) comprising 539 females and 866 males, with a median follow-up period of 18.9 months (interquartile range [IQR]: 10.5–39.7). The characteristics of the entire study cohort and the patients stratified by the presence of LM are summarized in Table 1. There were 184 (13.1%, 85 grade 2 and 99 grade 3 patients) patients with oligodendroglioma; 212, IDH-mutant astrocytoma (15.1%, 126 grade 2, 54 grade 3, and 32 grade 4 patients); 973, IDH-wildtype astrocytoma, including
glioblastomas (69.3%, 55 grade 2, 137 grade 3, and 781 grade 4 patients); 36 (2.6%), H3 K27M-altered diffuse midline glioma. Among each subgroup of patients with available information, 671 (48.9%) had MGMT promoter methylation, 130 (22.1%) had EGFR amplification, and 314 (35.8%) had TERTp mutation. The median OS was 18.0 months (IQR: 10.3–38.6), and 763 patients (54.3%) expired. There were 228 patients (16.2%) with LM. According to the date of LM diagnosis, 110 patients (7.8%) had LM at diagnosis, and 118 (8.4%) had LM at recurrence (The patient characteristics of the initial and recurrent LM patients are summarized in Supplementary Table 1). According to the MRI criteria, 184 patients (13.1%) had disseminated LM, and 44 (3.1%) had subependymal LM.

A total of 19 LM cases (8.3% of LM cases; 18 initial and one recurrent LM) were missed on the initial MRI scan when a retrospective review was performed, suggesting an underdiagnosis of LM on MRI. Among recurrent LM cases, early LM was missed in 28 cases (23.7%) on the MRI report, which progressed and was detected in the follow-up MRI, leading to a delayed diagnosis of LM. Supplementary Figure 2 shows a representative case of an early LM diagnosis missed on the initial MRI report.

Predictors for the development of LM

In a subset of 1,372 patients without missing MGMT promoter methylation information, subsequent analysis was performed to evaluate the predictors of LM. Univariable analysis showed that older age (odds ratio [OR]: 1.01, P = 0.005), male sex (OR: 1.39, P = 0.029), WHO grade 4 (OR: 4.53, P < 0.001), IDH-wildtype (OR: 7.51, P < 0.001), no 1p/19q codeletion (OR: 4.65, P < 0.001), H3 K27M alteration (OR: 3.16, P = 0.002), MGMT promoter unmethylation (OR: 2.44, P < 0.001), and nonlobar location (OR = 1.88, P < 0.001) are predictors of LM. On multivariable analysis, WHO grade 4 (OR: 2.30, P < 0.001), IDH-wildtype (OR: 3.14, P = 0.001), MGMT promoter unmethylation (OR: 1.43, P = 0.034), and nonlobar location (OR: 1.43, P = 0.035) were identified as independent predictors of LM. The results of univariable and multivariable analyses are shown in Table 2.

Predictors for the development of LM at initial diagnosis

In a subset of 1,372 patients without missing MGMT promoter methylation information, subsequent analysis was performed to identify the predictors of LM at initial diagnosis. On
univariable analysis, age at initial glioma diagnosis (OR: 1.03, P < 0.001), male sex (OR: 1.62, P = 0.023), WHO grade 4 (OR: 12.60, P < 0.001), IDH-wildtype (OR: 11.60, P < 0.001), no 1p/19q codeletion (OR: 5.69, P = 0.001), MGMT promoter unmethylation (OR: 2.53, P < 0.001), and nonlobar location (OR: 1.89, P = 0.003) were identified as predictors of LM at initial diagnosis. Multivariable analysis showed that WHO grade 4 (OR: 10.52, P < 0.001) and nonlobar location (OR: 1.54, P = 0.048) are independent predictors of LM at initial diagnosis. The results of univariable and multivariable analyses of LM at initial diagnosis is shown in Supplementary Table 2.

Predictors for the development of LM at recurrence

To evaluate the predictors of LM at recurrence, subgroup analysis was performed after excluding patients with initial LM, resulting in 1,264 patients without missing molecular information. The age at LM diagnosis and resection extent were also included in the analysis. Univariable analysis identified WHO grade 4 (OR: 2.58, P < 0.001), IDH-wildtype (OR: 5.36, P < 0.001), no 1p/19q codeletion (OR: 3.77, P = 0.001), H3 K27M alteration (OR: 4.65, P < 0.001), MGMT unmethylation (OR: 2.22, P < 0.001), and nonlobar location (OR: 1.77, P = 0.008) as predictors of LM at recurrence. On multivariable analysis, IDH-wildtype (OR: 5.04, P < 0.001) and H3 K27M alteration (OR = 3.39, P = 0.003) were revealed as independent predictors of LM at recurrence. The results of univariable and multivariable analyses of LM at recurrence is shown in Table 3. Figure 2 shows representative cases of patients with aggressive molecular markers who developed LM at recurrence.

OS of patients without and with LM

Figure 3 shows the Kaplan–Meier curves of patients with and without LM in each subgroup. Patients with LM had a worse median OS than those without LM (16.7 vs 32.0 months, log rank test; P < 0.001). A similar trend was observed in grade 4 glioma patients (14.3 vs 18.5 months, log rank test; P < 0.001) and IDH-wildtype astrocytoma patients (16.1 vs 19.4 months, log rank test; P < 0.001).
Comparison of disseminated and subependymal LM patients

Among the 228 patients with LM, 184 had disseminated LM, and 44 had subependymal LM. The distribution of WHO grades were significantly different between disseminated and subependymal LM patients (P = 0.022). All other characteristics, including the OS and OS after LM diagnosis, showed no significant difference. The patient characteristics of the disseminated and subependymal LM patients are summarized in Supplementary Table 3.

Discussion

Our results provide insights into the LM in gliomas by utilizing post-contrast FLAIR imaging and molecular diagnostics, which has previously been underestimated. In a large cohort study of 1,405 glioma patients, CSF-sensitive imaging using post-contrast FLAIR revealed a high incidence of 16.2% in adult glioma patients. Among molecular diagnostics, IDH-wildtype and MGMT promoter unmethylation were independent predictors of development of LM. Aggressive molecular markers such as IDH wildtype and H3 K27M alteration were associated with LM at recurrence. Thus, patients with IDH wildtype or H3 K27M alteration warrant imaging surveillance with CSF-sensitive MRI.

Our study reports the real-world incidence of LM using CSF-sensitive post-contrast FLAIR as 16.2% in glioma patients, compared with previous clinical studies reporting a substantially lower LM incidence ranging from 3.8–6.9%. This higher incidence may be attributed to the routine inclusion of post-contrast FLAIR in glioma imaging protocol. Post-contrast FLAIR is known to have superior performance than post-contrast T1 gradient echo images in the detection of LM. FLAIR effectively suppresses the normal vasculature of the leptomeninges, which can be confused with abnormal leptomeningeal enhancement in post-contrast T1 gradient echo imaging. Currently, post-contrast FLAIR is not a routinely recommended sequence in glioma MRI protocol and the efficacy of post-contrast FLAIR in LM detection has not been studied in glioma patients. Furthermore, there is discrepancy between the suggested imaging protocol for LM in solid tumors between EANO-ESMO and the RANO working group; recommendation from EANO-ESMO includes both post-contrast 3D T1 and post-contrast FLAIR images, while the RANO working group only includes post-contrast 3D T1 images. Our results suggest that inclusion of CSF-sensitive post-contrast FLAIR in glioma imaging protocol may aid diagnosis of LM.

Molecular markers have not been comprehensively reviewed in previous studies
owing to limited molecular data; thus, to date, no molecular signature has been validated as a risk factor of LM in gliomas. Innate-specific molecular characteristics have been suggested to make some gliomas more successful to develop LM.\textsuperscript{2,4} Our study results showed that IDH wildtype in gliomas confer a higher risk of LM development. This finding can be easily understood considering the more invasive phenotype of IDH-wildtype gliomas compared with its IDH-mutant gliomas.\textsuperscript{31} MGMT promoter unmethylation status was also a risk factor for LM development, suggesting underlying biological differences according to MGMT unmethylation status beyond mere treatment resistance.\textsuperscript{15} Because the exact pathogenesis on how these molecular markers influence the migration of tumor cells into leptomeninges is currently unknown,\textsuperscript{32} future studies are warranted.

IDH wildtype and H3 K27M alteration were associated with LM at recurrence, highlighting the importance of aggressive molecular markers for development of LM at recurrence. Specifically, 10.2\% of patients with IDH-wildtype gliomas and 25\% of patients with diffuse midline glioma, H3 K27M-altered developed LM at recurrence in our cohort. There has been lack of previous studies demonstrating IDH-wildtype for LM at recurrence, whereas several studies in the pre-molecular era showed high incidence of LM in diffuse intrinsic pontine glioma.\textsuperscript{33,34} Several studies with molecular markers have reported associations of H3 K27M alteration with LM in small case reports.\textsuperscript{20,21} Our results suggest that glioma patients with IDH wildtype or H3 K27M alteration should undergo CSF-sensitive MRI with post-contrast FLAIR for imaging surveillance.

There have been limited studies evaluating the clinical and imaging risk factors of LM in gliomas, and conflicting results have been reported.\textsuperscript{1} WHO grade 4 gliomas confer a higher risk of LM development, which may be due to the invasiveness according to histological grade.\textsuperscript{31} Nonlobar location was also identified as a predictor of LM, which may be due to the anatomical proximity to the CSF route, leading to a faster invasion of the CSF.\textsuperscript{3}

Of note, female sex had a lower risk of LM development, although it failed to remain significant in the multivariable results. In glioblastoma, female survival advantage has been suggested,\textsuperscript{35,36} explained by sexually dimorphic molecular mechanisms.\textsuperscript{36,37} Our study shows the possibility that sex may also involve in different incidences of LM development.

Our results corroborate the poor prognosis of glioma patients with LM.\textsuperscript{2} Although glioma itself has a poor prognosis,\textsuperscript{24} patients with LM showed an even poorer prognosis than those without LM. Previously, conflicting results have been reported on whether patients with LM have a significantly poorer prognosis than those without LM.\textsuperscript{2,22} To date, this is the first study to analyze a large cohort of glioma patients and confirm the poor prognosis of glioma patients with LM, even within WHO grade 4 glioma or IDH-wildtype astrocytoma patients with a higher risk of developing LM.
Our study had some limitations. First, our study analyzed a single-center, retrospectively collected dataset; thus, there is inevitable heterogeneity in diagnosis and treatment over the long study period. Second, CSF cytology or flow cytometry was performed in a small proportion of patients diagnosed with LM, which is the gold standard for LM diagnosis.\textsuperscript{38,39} However, owing to its invasiveness and low diagnostic value, CSF cytology is not routinely performed in clinics; a recent multi-institutional survey revealed that only a few glioma patients with suspected LM undergo CSF cytology, which reflects its low practicality.\textsuperscript{39} Despite these limitations, this study comprehensively identified the risk factors for LM development and demonstrated the poor prognosis of glioma patients with LM.

**Conclusions**

CSF-sensitive imaging aid diagnosis of LM demonstrating a high incidence of LM in adult gliomas. Furthermore, molecular markers are associated with LM development in glioma, and patients with aggressive molecular markers warrant imaging surveillance of LM.

**Declarations**

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**Competing Interests**

The authors declare that there are no competing interests.

**Author Contribution**
Yae Won Park: Design and conceptualized study; analyzed the data; interpreted the data; drafted the manuscript for intellectual content; final approval of the manuscript
Kyunghwa Han: Statistical analysis; final approval of the manuscript
Ji Eun Park: revised the manuscript for intellectual content; final approval of the manuscript Sung Soo Ahn: Design and conceptualized study; revised the manuscript for intellectual content; final approval of the manuscript
Eui Hyun Kim: Major role in the acquisition of data; final approval of the manuscript Jinna Kim: Major role in the acquisition of data; final approval of the manuscript Seok-Gu Kang: Major role in the acquisition of data; final approval of the manuscript Jong Hee Chang: Major role in the acquisition of data; final approval of the manuscript Se Hoon Kim: Major role in the acquisition of data; final approval of the manuscript Seung-Koo Lee: Major role in the acquisition of data; final approval of the manuscript

References


Tables

Tables 1-3 are in the supplementary files section.

Supplementary Material

Supplementary materials not available with this version.

Figures
Figure 1

Flowchart for patient selection.
Figure 2

Representative cases of patients with aggressive molecular markers who developed LM at recurrence. (a) A 63-year-old male with glioblastoma, IDH-wildtype, who underwent gross total removal of tumor. On follow-up imaging after 12 months, disseminated LM developed. (b) A 55-year-old female with diffuse midline glioma, H3 K27M-altered, who underwent subtotal removal of tumor. On follow-up imaging after 12 months, disseminated LM developed.
Figure 3

Kaplan–Meier curves of the OS of patients with and without LM in (a) the entire study cohort, (b) with WHO grade 4 gliomas, and (c) with IDH-wildtype glioma. IDH, isocitrate dehydrogenase; LM, leptomeningeal metastases; OS, overall survival; WHO, World Health Organization.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx