Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-024-04933-7

RESEARCH

# Leptomeningeal dissemination in H3 K27M- mutant diffuse midline gliomas: clinical characteristics, risk factors, and prognostic insights

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Received: 23 November 2024 / Accepted: 27 December 2024


## Abstract

**Purpose** This study aimed to describe the incidence, clinical and pathological features, and outcomes of H3 K27M- mutant Diffuse Midline Glioma (DMG) patients with leptomeningeal dissemination (LMD) and systematically investigate the predictive and prognostic factors to clarify the response to treatment after the onset of LMD.

**Methods** A total of 304 patients diagnosed with DMG from October 17, 2017, to October 17, 2023, were enrolled in this study, of which 32 patients were diagnosed with LMD. Logistic regression analyses were conducted to identify the predictors of LMD, including clinical, molecular, and imaging data. Univariable and multivariable cox regression analyses were used for overall survival (OS) and post-LMD survival (PLS) analysis.

**Results** The median OS and PLS were 12.5 and 8.0 months respectively. Tumor with contrast-enhanced lesions reaching ependyma (Ventricular contact type I) was the only independent risk factor for LMD. Male sex and ventricular contact type I were independent risk factors for primary LMD. In all LMD patients, Karnofsky Performance Status (KPS) of ≥90 and radiotherapy were statistically significantly associated with longer OS, and primary LMD was significantly associated with shorter OS. Supratentorial location and chemotherapy after LMD diagnosis were independent favorable prognostic factors on PLS. In primary LMD subgroup analysis, radiotherapy was the only independent favorable prognostic factor on OS.

**Conclusions** The association between contrast-enhanced lesions and ventricular involvement is an independent predictive factor for LMD in DMG patients. Radiotherapy and preoperative KPS may contribute to improved overall survival in these patients. Chemotherapy is a potential treatment option following an LMD diagnosis.

**Keywords** Leptomeningeal dissemination · Diffuse midline glioma · Risk factors · Prognostic factors · Outcome

## Introduction

Diffuse midline glioma (DMG), H3 K27M-mutant, is one of the most malignant diffuse brain tumors in the central nervous system (CNS). It was first classified as a separate tumor entity in the 2016 WHO classification of tumors of the CNS, characterized by diffuse infiltrative brain tumors in the midline location harboring H3K27M mutation [1]. With the deepening of understanding, this entity was redefined in the 2021 WHO classification as "diffuse midline glioma, H3 K27-altered," now encompassing cases with H3F3A wild-type and overexpression of Enhancer of Zest Homologs Inhibitory Protein (EZHIP) and EGFR-altered [2]. Unfortunately, due to their deep midline locations, gross-total resection is often impossible for DMGs [3, 4]. Radiotherapy remains a standard treatment to improve the prognosis of DMG [3, 4]. However, the prognosis of these tumors remains poor with a dismal median overall survival (OS) of 10.0–14.0 months, due to its aggressive clinical behavior and limited treatment methods [5–7].

Leptomeningeal dissemination (LMD) results from the spread of tumor cells from brain parenchyma to leptomeninges and cerebrospinal fluid (CSF) [8]. It represents a challenging, often terminal complication in gliomas, with a median OS of 2–5 months after LMD diagnosis [8]. There is no standardized treatment method for LMD patients. Radiotherapy combined with chemotherapy, Chemotherapy, and intrathecal methotrexate (MTX) treatment are potential therapeutic options in LMD patients [9–11]. LMD can also develop hydrocephalus due to impaired CSF resorption and

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Published online: 15 January 2025

ventriculoperitoneal (VP) shunt has been shown to improve survival and symptoms [12]. Previous studies have reported that some molecular factors such as IDH-wildtype, MGMT promoter unmethylation, H3 K27 alteration, or tumor contact with the subventricular zone (SVZ) might be associated with leptomeningeal dissemination [13, 14].

However, previous studies predominantly focused on high-grade gliomas, particularly glioblastoma. LMD in H3K27M-mutant DMG was rarely reported. Research indicates that approximately one-third of diffuse intrinsic pontine glioma (DIPG) patients experience LMD [15]. Meanwhile, LMD in DMG patients has a variable incidence ranging from 4.1 to 42.0% [4, 16–18]. LMD is a negative prognostic indicator in DMG, with a worse median OS of 11.4 months, compared to 18.5 months for those without LMD [16]. However, a comprehensive analysis of H3K27M-mutated DMG patients with LMD is lacking.

Therefore, we retrospectively collected data from 32 H3 K27M-mutated DMG patients with LMD, making this the largest systemic study on the topic to date. The present study aimed to describe the incidence, clinicopathological features, and outcomes of DMG patients with LMD and systematically investigate predictive and prognostic factors of LMD in DMG to enhance the awareness of this rare subset of tumors.

## Materials and methods

### Patients cohort

We retrospectively collected data of patients with DMG at Sanbo Brain Hospital, Capital Medical University, from October 17, 2017, to October 17, 2023. The inclusion criteria were DMG confirmed by histopathology harboring H3 K27M mutation. The exclusion criteria were spinal cord DMG, incomplete preoperative magnetic resonance imaging data, and loss to follow-up. All diagnoses were confirmed by experienced neuropathologists according to the 2021 WHO classification when necessary. A total of 304 patients were included in this study for logistic regression analysis and 31 patients for Cox analysis. Among the 31 LMD patients, 17 were classified into the primary LMD subgroup, defined as those with LMD at the initial DMG diagnosis, while 14 patients were assigned to the secondary LMD subgroup, which includes those who developed LMD later in the course of their disease. Figure 1 shows the flow chart for patient inclusion and exclusion. The Medical Ethics Committee of Capital Medical University approved this study.

### Imaging data

Patients were routinely followed up with brain MR scans at an interval of three months, or one month if there was evidence suggesting LMD. Spinal cord MRI scans were not part of routine follow-up but were performed when LMD was suspected. The LMD was defined as linear or nodular contrast enhancement of the subarachnoid spaces or the cerebral subependymal zone, described in detail in a previous study [19]. The evaluation criteria of the extent of tumor resection based on postoperative imaging were as follows: gross total resection (GTR) was defined as the removal of more than 98% of the tumor mass; non-GTR, referring to the removal of less than 98%, included subtotal resection and partial resection of craniotomy and biopsy. We initially

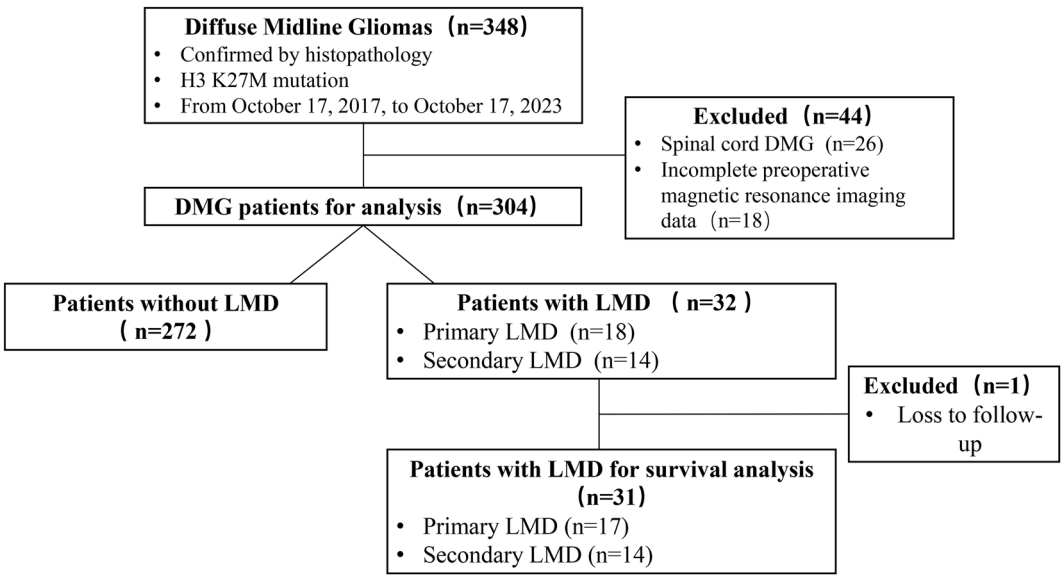


**Fig. 1** Patient selection flow chart

aimed to evaluate the relationship between SVZ and LMD. Previous studies suggested that SVZ is confined to the lining of the lateral ventricle [20, 21], which complicates the effective assessment of the relationship between SVZ and LMD in infratentorial DMGs. Therefore, we propose a new classification system based on the anatomical relationships between contrast-enhanced lesions (CEL) or non-CEL and the ventricle as follows: Type I: CEL contacting the ependyma (Supplementary Fig. 1a); Type II: Non-CEL contacting the ependyma (Supplementary Fig. 1b and 1c); Type III: Both CEL and non-CEL not contacting ependyma (Supplementary Fig. 1d). The MRI type of LMD was classified as our previous study [9]: Type Ia: CEL contacted subependymal zone (Supplementary Fig. 2a); Type Ib: enhancement in subarachnoid space (Supplementary Fig. 2b); Type II: enhancement in both subarachnoid space and subependymal zone (Supplementary Fig. 2c and 2d). Two well-experienced radiologists independently confirmed LMD on imaging.

### Statistical analysis

Categorical data are presented as counts (frequencies), and continuous variables are expressed as medians (ranges). The Chi-square test tested differences between groups for categorical variables and the Mann–Whitney *U* test for continuous variables. Logistic regression analyses were conducted on all patients with variables showing p-values less than 0.05 included in the multivariate analyses to identify the predictors of LMD. OS was defined as the time from glioma diagnosis to the time of death or last follow-up. Post-LMD survival (PLS) was defined as the time from LMD diagnosis to death. Univariable Cox regression analysis was performed for the entire LMD patients and a primary LMD subgroup. Variables that reached a significance level of $p < 0.05$ in univariable analyses were included in a multivariate Cox model. Survival analyses were illustrated using Kaplan–Meier curves, with differences between curves compared using the log-rank test. OS data were censored during the last follow-up if the patient was still living. Statistical Package for the Social Sciences version 25.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Probability values were obtained using two-sided tests with statistical significance defined as p-values less than 0.05.

## Results

### Patient characteristics

A total of 32 patients out of the 304 H3 K27M-mutated DMG patients were identified to have developed LMD, resulting in an incidence rate of 10.5%. The cohort included 175(57.6%) males and 129 (42.4%) females with a median age of 24.0 years, ranging from 2 to 71. The clinical, radiological, and molecular data of our cohort and the patients with and without LMD are summarized in Supplementary Table 1. No significant differences were observed in gender or age distribution between the two groups. Tumors in supratentorial locations were more common in the LMD group compared to those without LMD (71.9% vs. 50.0%, $p=0.019$). There was a significant difference in the extent of resection between the groups ($p=0.001$). Patients with LMD have a higher incidence of VE than those without LMD (68.8% vs. 39.0%, $p=0.001$). Additionally, patients with LMD were more likely to develop hydrocephalus than those without LMD (62.5% vs. 34.2%, $p=0.002$). A significant difference was also noted in the percentage of ventricular contact type ($p=0.000$). A total of 113 patients were diagnosed with hydrocephalus, and 41 of them underwent ventriculoperitoneal shunt surgery.

The clinical, radiological, and pathological characteristics of LMD patients are illustrated in Table 1. And the detailed treatments of 31 patients with LMD are illustrated in Supplementary Table 2. The cohort comprised 21(67.7%) males and 10 (25.8%) females with a median age of 20.0 years (range: 6–53 years). The baseline characteristics of the primary and secondary LMD groups were similar. No significant differences were observed between the groups regarding age, gender, tumor location, Karnofsky Performance Status (KPS), presence of hydrocephalus, extent of resection, or ventricular contact. Patients with secondary LMD have a higher incidence of receiving radiotherapy compared to those with primary LMD (100.0% vs. 70.6%, $p=0.048$). Patients with primary LMD had a worse median OS than those with secondary LMD (8.0 vs. 13.5 months, $p=0.002$, log-rank test). The PLS showed no difference between the two groups.

### Risk factors of LMD

Univariable analysis identified supratentorial location (OR: 2.556, 95% CI: 1.141–5.724, $p=0.023$), hydrocephalus (OR: 3.208, 95% CI: 1.503–6.847, $p=0.003$), ventricular contact type I (OR: 5.952, 95% CI: 2.485–14.255, $p=0.000$) as risk factors for LMD. Multivariate analysis showed that Ventricular contact type I (OR: 3.912, 95% CI: 1.363–11.222, $p=0.011$) was the only independent risk factor for LMD (Table 2).

### Prognostic factors of OS in all LMD patients

Out of 32 patients with LMD, 30 were recorded as deceased, and 1 was lost to follow-up. Consequently, 31 patients were

**Table 1** Clinical, radiological and pathological characteristics of LMD patients

| Variable | | Total ($n=31$)(%) | Primary LMD ($n=17$)(%) | Secondary LMD ($n=14$)(%) | *P*-value |
|---|---|---|---|---|---|
| **Age at DMG diagnosis** | 20.0(6–53) | | 23.0(7–53) | 12.5(6–39) | 0.357 |
| **Age at LMD diagnosis** | | 21.0(7–53) | 23.0(7–53) | 13.5(7–44) | 0.297 |
| **Gender** | | | | | 0.121 |
| male | | 21(67.7) | 14(82.4) | 7(50.0) | |
| female | | 10(25.8) | 3(17.6) | 7(50.0) | |
| **Tumor location**[a] | | | | | 0.233 |
| Supratentorial | | 22(71.0) | 14(82.4) | 8(57.1) | |
| Infratentorial | | 9(29.0) | 3(17.6) | 6(42.9) | |
| **KPS≥90**[a] | | 19(61.3) | 10(58.8) | 9(64.3) | 1.000 |
| **KPS≥90 at LMD diagnosis** | | 14(45.2) | 10(58.8) | 4(28.5) | 0.149 |
| **Hydrocephalus**[a] | | 19(61.3) | 10(58.8) | 9(64.3) | 1.000 |
| **Ventricular contact**[a] | | | | | **0.044** |
| Type I | 24 (77.4) | | 16(94.1) | 8(57.1) | |
| Type II | | 5(16.1) | 1(5.9) | 4(28.5) | |
| Type III | | 2(6.5) | 0(0) | 2(14.3) | |
| **Extent of resection**[a] | | | | | 0.933 |
| Biopsy | | 7(22.6) | 4(23.5) | 3(21.4) | |
| Subtotal | | 14(45.2) | 8(47.1) | 6(42.9) | |
| Gross total resection | | 10(32.3) | 5(29.4) | 5(35.7) | |
| **Treatment after DMG diagnosis** | | | | | |
| **Chemotherapy** | | 25(80.6) | 12(70.6) | 13(92.9) | 0.185 |
| **Radiotherapy** | | 26(83.9) | 12(70.6) | 14(100.0) | **0.048** |
| **Antiangiogenic therapy** | | 11(35.5) | 4(23.5) | 7(50.0) | 0.153 |
| **Clinical trials** | | 4(12.9) | 2(11.8) | 2(14.3) | 1.000 |
| **MRI of LMD** | | | | | 0.699 |
| Type Ia | | 8(25.8) | 4(23.5) | 4(28.6) | |
| Type Ib | | 9(29.0) | 6(35.3) | 3(21.4) | |
| Type II | | 14(45.2) | 7(41.2) | 7(50.0) | |
| **Treatment after LMD diagnosis** | | | | | |
| **Chemotherapy** | | 19(64.5) | 12(70.6) | 7(50.0) | 0.288 |
| **Radiotherapy** | | 12(38.7) | 12(70.6) | 0(0) | **0.000** |
| **Antiangiogenic therapy** | | 10(32.3) | 4(23.5) | 6(42.9) | 0.441 |
| **Clinical trials** | | 4(12.9) | 2(11.8) | 2 (14.3) | 1.000 |
| **OS, Median (Min-Max), y** | | 12.5(2–60) | 8.0(2–19) | 13.5(5–60) | **0.002** |
| **PLS, Median (Min-Max), y** | | 8(1–19) | 8.0(2–19) | 6(1–14) | 0.191 |
| **ATRX loss** | | 8(25.8) | 5(29.4) | 3(21.4) | 0.698 |
| **MGMT promoter methylation** | | 1/17[b](5.9) | 1/8(12.5) | 0/9(0) | 1.000 |

LMD leptomeningeal dissemination, KPS Karnofsky Performance Scale, OS overall survival, PLS post-LMD survival, DMG diffuse midline glioma, ATRX alpha-thalassemia/mental retardation syndrome X-linked, MGMT O6-methylguanine-methyltransferase

[a] at glioma diagnosis

[b] The MGMT methylation status was available in 17 patients

included in the Cox regression analysis. The median OS was 12.5 months. Univariate analysis revealed that KPS of ≥90 (HR: 0.258, 95% CI: 0.103–0.645, $p=0.004$), GTR (HR: 0.409, 95% CI: 0.169–0.990, $p=0.047$), radiotherapy (HR: 0.051, 95% CI: 0.012–0.226, $p=0.000$), chemotherapy (HR: 0.142, 95% CI: 0.048–0.419, $p=0.000$) were associated with longer OS. Primary LMD (HR: 3.416, 95% CI: 1.483–7.871, $p=0.004$) was associated with shorter OS. Multivariable analysis identified KPS of ≥90 (HR: 0.187, 95% CI: 0.063–0.549, $p=0.002$), radiotherapy (HR: 0.134, 95% CI: 0.030–0.597, $p=0.008$) and primary LMD (HR: 4.349, 95% CI: 1.628–11.618, $p=0.003$) as independent prognostic factors on OS (Table 3). The median OS was significantly longer in patients with KPS of ≥90 and radiotherapy compared to those with KPS<90, non-radiotherapy (15.0 vs. 8.0 months, $p=0.001$; 13.0 vs. 4.0 months, $p=0.000$, respectively; log-rank test; Fig. 2). Additionally, patients with primary LMD had a shorter median OS compared to those with secondary LMD (8.0 vs. 13.5 months, $p=0.002$, log-rank test; Fig. 2).

**Table 2** Predictors of LMD by univariable and multivariable logistic regression analyses

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| Age (≥18) | 0.962 | 0.456–2.030 | 0.920 | | | |
| Gender (Male) | 1.711 | 0.781–3.751 | 0.180 | | | |
| Supratentorial location | 2.556 | 1.141–5.724 | **0.023** | | | |
| Hydrocephalus | 3.208 | 1.503–6.847 | **0.003** | | | |
| Ventricular contact | | | | | | |
| Type I | 5.952 | 2.485–14.255 | **0.000** | 3.912 | 1.363–11.222 | **0.011** |
| Type II | 0.407 | 0.152–1.094 | 0.075 | | | |
| Type III | 0.147 | 0.034–0.628 | **0.010** | | | |
| Ki-67>20% | 2.215 | 0.880–5.572 | 0.091 | | | |
| ATRX loss | 1.274 | 0.522–3.113 | 0.595 | | | |
| MGMT promoter methylation | 0.484 | 0.059–3.987 | 0.500 | | | |

ATRX alpha-thalassemia/mental retardation syndrome X-linked, MGMT O6-methylguanine-methyltransferase

**Table 3** Overall survival of all LMD patients by univariable and multivariable Cox analyses

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Age (≥18) | 0.696 | 0.318–1.523 | 0.364 | | | |
| Gender (Male) | 1.101 | 0.494–2.452 | 0.815 | | | |
| Supratentorial location | 0.488 | 0.204–1.169 | 0.107 | | | |
| KPS≥90 | 0.258 | 0.103–0.645 | **0.004** | 0.187 | 0.063–0.549 | **0.002** |
| Hydrocephalus | 1.058 | 0.486–2.303 | 0.887 | | | |
| Ventricular contact | | | | | | |
| Type I | 0.760 | 0.314–1.842 | 0.544 | | | |
| Type II | 1.413 | 0.528–3.780 | 0.492 | | | |
| Type III | 1.019 | 0.236–4.395 | 0.980 | | | |
| Gross total resection | 0.409 | 0.169–0.990 | **0.047** | | | |
| Chemotherapy | 0.142 | 0.048–0.419 | **0.000** | | | |
| Radiotherapy | 0.051 | 0.012–0.226 | **0.000** | 0.134 | 0.030–0.597 | **0.008** |
| Antiangiogenic therapy | 0.854 | 0.400-1.822 | 0.638 | | | |
| Clinical trials | 1.044 | 0.359–3.036 | 0.937 | | | |
| Primary LMD | 3.416 | 1.483–7.871 | **0.004** | 4.349 | 1.628–11.618 | **0.003** |
| ATRX loss | 1.917 | 0.803–4.573 | 0.143 | | | |
| MGMT promoter methylation | 3.531 | 0.394–31.630 | 0.259 | | | |

KPS Karnofsky Performance Scale, LMD leptomeningeal dissemination, ATRX alpha-thalassemia/mental retardation syndrome X-linked, MGMT O6-methylguanine-methyltransferase

## Prognostic factors of PLS in all LMD patients

The median PLS was 8.0 months. Univariate analysis demonstrated supratentorial location (HR: 0.244, 95% CI: 0.096–0.621, $p=0.003$), KPS of ≥90 at LMD diagnosis (HR: 0.355, 95% CI: 0.156–0.804, $p=0.013$), radiotherapy after LMD diagnosis (HR: 0.363, 95% CI: 0.156–0.846, $p=0.019$), chemotherapy after LMD diagnosis (HR: 0.277, 95% CI: 0.122–0.628, $p=0.002$) were associated with longer PLS. Multivariable analysis revealed supratentorial location (HR: 0.312, 95% CI: 0.120–0.812, $p=0.017$) and chemotherapy after LMD diagnosis (HR: 0.333, 95% CI: 0.143–0.776, $p=0.011$) were independent prognostic factors on PLS (Table 4). The median PLS was significantly longer in patients with supratentorial location and chemotherapy after LMD diagnosis compared to those with infratentorial location and non-chemotherapy (9.0 vs. 2.5 months, $p=0.001$; 9.0 vs. 2.5 months, $p=0.001$, respectively; log-rank test; Fig. 2).

## Risk factors of primary LMD

In univariable analysis, male sex (OR: 3.937, 95% CI: 1.115–13.901, $p=0.033$), supratentorial location (OR: 4.931, 95% CI: 1.397–17.401, $p=0.013$), hydrocephalus (OR: 2.835, 95% CI: 1.066–7.538, $p=0.037$), ventricular contact type I (OR: 27.200, 95% CI: 3.569–207.270, $p=0.001$) are risk factors for LMD. In multivariable analysis, male sex (OR: 4.169, 95% CI: 1.143–15.210, $p=0.031$) and ventricular contact type I (OR: 23.309, 95% CI: 2.759-196.925, $p=0.004$) were independent risk factors (Supplementary Table 3).

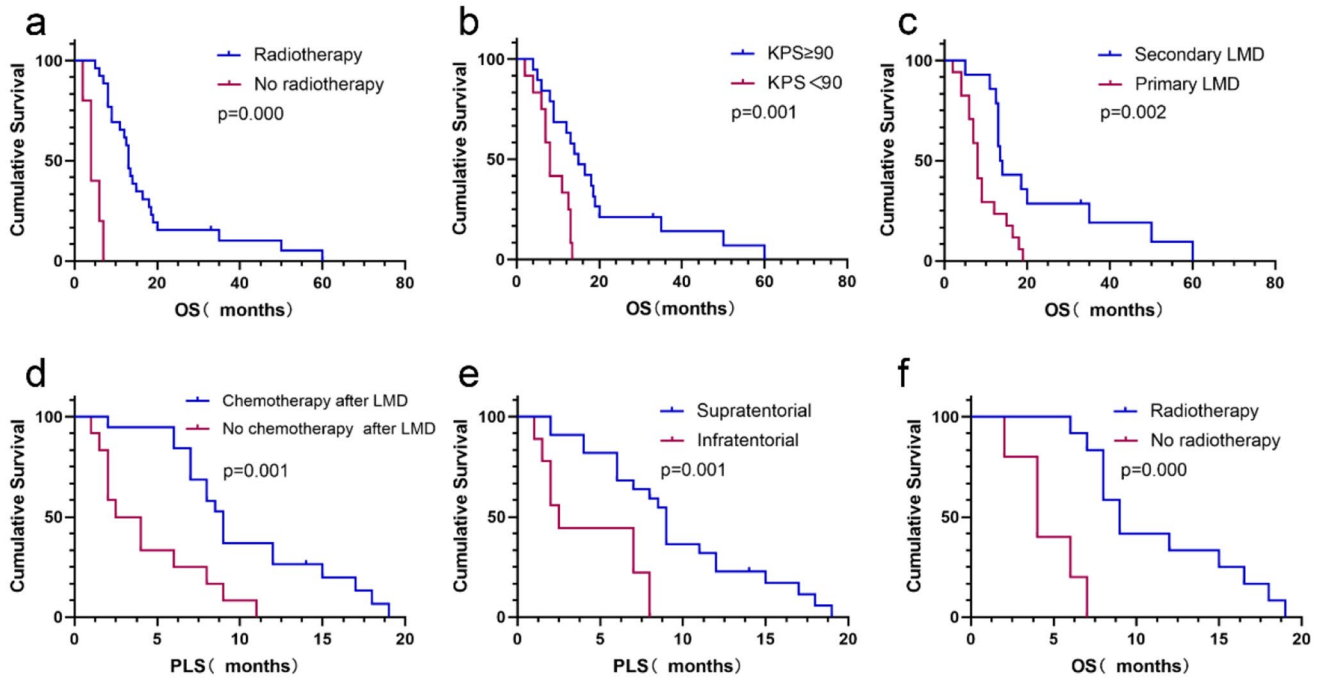


**Fig. 2** Comparison of OS and PLS by Kaplan–Meier curves. (**a**) Patients who received radiotherapy have longer OS. (**b**) Patients with KPS of ≥90 have longer median OS. (**c**) Primary LMD was associated with a poorer prognosis. (**d**) Patients undergoing chemotherapy after LMD diagnosis have longer PLS. (**e**) Patients with tumors located in the supratentorial region have longer PLS. (**f**) In the primary LMD subgroup, patients undergoing radiotherapy have a better prognosis

**Table 4** Post-LMD survival by univariable and multivariable Cox analyses in all LMD patients

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Age (≥18)[a] | 0.525 | 0.248–1.111 | 0.092 | | | |
| Gender (Male) | 0.676 | 0.299–1.527 | 0.346 | | | |
| Supratentorial location | 0.244 | 0.096–0.621 | **0.003** | 0.312 | 0.120–0.812 | **0.017** |
| KPS≥90[a] | 0.355 | 0.156–0.804 | **0.013** | | | |
| MRI of LMD | | | | | | |
| Type Ia | 0.874 | 0.378–2.018 | 0.752 | | | |
| Type Ib | 1.191 | 0.535–2.651 | 0.669 | | | |
| Type II | 0.960 | 0.439–2.099 | 0.919 | | | |
| Gross total resection[a] | 0.703 | 0.265–1.865 | 0.480 | | | |
| Chemotherapy[a] | 0.277 | 0.122–0.628 | **0.002** | 0.333 | 0.143–0.776 | **0.011** |
| Radiotherapy[a] | 0.363 | 0.156–0.846 | **0.019** | | | |
| Antiangiogenic therapy[a] | 0.998 | 0.451–2.207 | 0.996 | | | |
| Clinical trials[a] | 1.593 | 0.543–4.674 | 0.396 | | | |
| Primary LMD | 0.619 | 0.286–1.339 | 0.223 | | | |
| ATRX loss | 1.516 | 0.633–3.635 | 0.351 | | | |
| MGMT promoter methylation | 1.101 | 0.140–8.658 | 0.927 | | | |

KPS Karnofsky Performance Scale, LMD leptomeningeal dissemination, ATRX alpha-thalassemia/mental retardation syndrome X-linked, MGMT O6-methylguanine-methyltransferase

[a] after LMD diagnosis

### Prognostic factors of OS in primary LMD patients

Univariate analysis revealed KPS of ≥90 (HR: 0.185, 95% CI: 0.047–0.734, $p=0.016$), radiotherapy (HR: 0.073, 95% CI: 0.013–0.395, $p=0.002$), chemotherapy (HR: 0.163, 95% CI: 0.045–0.591, $p=0.006$) were associated with longer OS. Multivariable analysis revealed radiotherapy (HR: 0.073, 95% CI: 0.013–0.395, $p=0.002$) was the only independent prognostic factor on OS (Supplementary Table 4). The median OS was significantly longer in patients who received radiotherapy than those who did not (9.0 vs. 4.0 months, $p=0.000$, log-rank test; Fig. 2).

## Discussion

LMD is considered to be a late-stage manifestation of glioma, associated with a particularly poor prognosis [12]. However, prior research on LMD has primarily focused on DIPG, with limited studies addressing supratentorial DMGs [4, 15–18, 22]. The present study analyzed the clinicopathological characteristics of H3 K27M-mutant DMGs with LMD, representing the largest series of cases to date. Our study confirmed a high incidence (10.5%) of LMD among H3 K27M-mutated DMG patients and identified several novel and interesting findings. Notably, we observed that LMD is more prevalent in supratentorial DMG patients, contrasting with the previously held belief of the high incidence of LMD in DIPG [22]. Additionally, we also found a strong correlation between LMD and the occurrence of hydrocephalus.

Previous studies have shown that contact with SVZ is associated with the development of LMD and decreased survival [14, 21]. Our original objective was to investigate the relationship between SVZ contact and tumor dissemination in DMG. However, previous SVZ classification methods were only applicable to supratentorial tumors [20, 21], making them unsuitable for all DMG patients, including DIPG. Therefore, we proposed a new classification method to assess the relationship between tumors and ventricles in DMG. Surprisingly, we found that contrast-enhanced lesions (CEL) rupture into the ventricles is an independent risk factor for LMD, indicating that contrast-enhanced lesions are more likely to disseminate once they invade the ventricles. Jiang et al. reported that male gender was correlated with a higher risk for distant progression and LMD [23]. Similarly, our subgroup analysis revealed that male gender is an independent risk factor for primary LMD, suggesting a potential sex-related influence on LMD development. Lee et al. reported that male mice experienced a worse outcome and exhibited accelerated tumor growth than female mice. T cells are a critical component driving these sex differences in glioblastoma progression [24]. Generally, females exhibit stronger immune responses than males, and the differences are attributed to sex hormones and/or sex chromosomes [24]. Thus, we hypothesize that certain immunologic mechanisms underlying sex differences may help explain the higher male risk for primary LMD.

Our results indicated that the baseline characteristics of primary and secondary LMD were similar. However, the median OS of patients with primary LMD was shorter than that of those with secondary LMD, consistent with our previous findings in high-grade gliomas [9]. It could be speculated that the earlier the onset of LMD, the poorer the prognosis. Previous studies have reported that higher KPS was associated with longer OS in H3 K27M-mutated DMGs [3, 25]. Similarly, our study observed that higher KPS in DMG patients with LMD also demonstrated this survival benefit, potentially due to their improved ability to adhere to more effective adjuvant treatments, such as radiation and chemotherapy.

Currently, radiation therapy is the standard of care for DMG patients, while chemotherapy has been considered largely ineffective [6]. Our findings also reveal that radiotherapy is an independent prognostic factor for OS in both the total LMD patients and the primary LMD subgroup. However, we do not deny the role of radiotherapy in prolonging survival, as 24 patients in this cohort received both radiotherapy and chemotherapy. Additionally, we also found that chemotherapy after LMD diagnosis is an independent risk factor for PLS. This indicates that chemotherapy plays a more active role in patients with LMD than radiotherapy. Chemotherapy can eliminate the tumor cells in the CSF and reduce the incidence of non-local progression [23]. Thus, we hypothesize that this may be due to chemotherapy's systemic effects, which can target the entire central nervous system, in contrast to the localized nature of radiotherapy. While tumor resection is generally thought to have a limited impact on OS [3, 4, 25, 26] Our results demonstrated that GTR has the potential to improve OS in LMD patients in univariable analysis. However, GTR is not an independent prognostic factor, leading us to conclude that it does not significantly enhance the prognosis of DMG patients with LMD.

Previous studies have demonstrated significant differences in median OS between pediatric and adult populations [4, 18]. However, this trend has not been observed in DMG patients with LMD. The loss of ATRX had been confirmed to be associated with a longer OS [3, 27]. Our study identified a trend toward longer OS in DMG patients with primary LMD, though it did not reach statistical significance. Wang et al. reported that DMG patients with brainstem tumors had a poorer prognosis compared to those with tumors in other anatomical locations [28]. In this study, we

found no significant difference in OS between supratentorial and infratentorial locations. However, we did observe that patients with tumors in supratentorial DMGs have longer PLS.

This single-center retrospective study has several limitations. First, the retrospective study design and small sample size of patients make it impossible to detect more meaningful results and might influence generalizability. Second, this study is unable to obtain additional molecular indicators for a more comprehensive analysis. Third, insufficient spinal cord MRI scans and CSF cytological data may lead to an underestimation of the incidence of secondary LMD.

## Conclusion

This retrospective study provides a comprehensive analysis of the clinical, radiographic, and pathological features of H3 K27M-mutant DMG patients with LMD, representing the largest systematic study on this subject to date. The association between contrast-enhanced lesions and ventricular involvement serves as an independent predictive factor for LMD in DMG patients. Thus, patients with contrast-enhanced lesions reaching ependyma should be more closely monitored for LMD during follow-up. DMG patients with primary LMD typically have a poor prognosis. Radiotherapy and preoperative KPS may contribute to improved overall survival in these patients. Moreover, the treatment of DMG patients after an LMD diagnosis remains highly challenging and is limited in effectiveness. Chemotherapy is a potential treatment option following an LMD diagnosis. However, more basic research is helpful to understand the underlying molecular mechanism of LMD and the mechanism of effectiveness of chemotherapy.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11060-024-04933-7 .

**Author contributions** Shuai Zhong conceptualized the idea, collected data, and wrote the manuscript; Jinyi Zuo performed the data analysis; Xiaojun Fu and Chenxing Wu performed the formal analysis; Rui Liu and Zheng Huang prepared figures and tables. Shouwei Li performed the validation; All authors reviewed the manuscript.

**Funding** None.

**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethical approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board/Ethics Committee of Sanbo Brain Hospital of Capital Medical University.

**Consent to participate** Informed consent was obtained from all the patients included in the study.

**Consent for publication** All patients or legal guardians provided written informed consent to publish their data.

**Competing interests** The authors declare no competing interests.



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