Clinical characteristics and prognosis of patients with glioblastoma with infratentorial leptomeningeal dissemination

Daisuke Kawauchi
National Cancer Center Hospital
Makoto Ohno
National Cancer Center Hospital
Mai Honda-Kitahara
National Cancer Center Hospital
Yasuji Miyakita
National Cancer Center Hospital
Masamichi Takahashi
National Cancer Center Hospital
Shunsuke Yanagisawa
National Cancer Center Hospital
Yukie Tamura
National Cancer Center Hospital
Miyu Kikuchi
National Cancer Center Hospital
Koichi Ichimura
Juntendo University Faculty of Medicine
Yoshitaka Narita (yonarita@ncc.go.jp)
National Cancer Center Hospital

Research Article

Keywords: infratentorial, glioblastoma, leptomeningeal dissemination, leptomeningeal metastases

Posted Date: April 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1462235/v2

Abstract

Objective

Leptomeningeal dissemination (LMD) is a severe complication of glioblastoma (GBM) and has become a more common and indispensable clinical proposition with improved patient prognosis. Although infratentorial leptomeningeal dissemination (ITD) of GBM is rare, it is clinically significant as it may largely influence patient prognosis. Here, we investigated the clinical characteristics and prognosis of patients with ITD.

Methods

Data of patients with newly diagnosed isocitrate dehydrogenase (IDH)-wildtype GBM treated at our institution between October 2008 and December 2018 were reviewed. ITD was defined as the dissemination of GBM, which first emerged as a supratentorial tumor, and later disseminated in the infratentorial region as the first recurrent site.

Results

Of 160 patients with newly diagnosed IDH-wildtype GBM, seven (4.4%) were classified as having ITD. ITD lesions were in the fourth ventricle in two patients, extra-cerebellum or extra-brainstem in two, and intra-cerebellum in three. The primary symptoms of ITD were gait disturbance (85.7%, n = 6), nausea and vomiting (28.6%, n = 2), cerebellar mutism (14.3%, n = 1), and none (14.3%, n = 1). In four cases (57.1%), symptoms were confirmed before ITD discovery. The median progression-free survival (PFS) and overall survival of the patients were 12.2 and 19.7 months, respectively. Radiotherapy was performed in five patients, and all the patients received chemotherapy. The PFS and overall survival rates from ITD diagnosis were 2.9 and 7.1 months, respectively. Patients with favorable prognoses were younger and had higher Karnofsky performance status (KPS) scores.

Conclusions

Radiotherapy or molecular-targeted therapy may be effective in some cases of ITD and may contribute to extending survival. Carefully checking the infratentorial region of patients with GBM during follow-up and rapidly treating ITD before their KPS score starts declining are crucial.

Introduction

Glioblastoma (GBM) is the most life-threatening malignant brain tumor and is categorized as a grade 4 tumor by the World Health Organization (WHO). Even with the best treatment of maximal safe surgical resection following chemoradiotherapy with temozolomide (TMZ), recurrence is inevitable in most cases.

However, with advances in surgical techniques, including a generalization of awake surgery or assistance of fluorescence-guidance using 5-aminolevulinic acid, the introduction of an antiangiogenic drug, bevacizumab, and development of novel therapeutic modalities such as tumor-treating fields [1], the prognosis of GBM patients has steadily improved in the last decade [2].

Leptomeningeal dissemination (LMD), also called leptomeningeal metastasis, is a severe complication of GBM and is considered an end-stage disease [3]. The median overall survival (OS) of patients with GBM with LMD is 2.1–5.7 months [4–8] with various types of chemotherapy or radiation. Since long survival [9] is suspected as one of the risk factors for LMD in patients with GBM, the improvement of prognosis leads LMD to be a more common and indispensable clinical proposition [10].

The incidence of LMD in GBM is reported to be 4–25%, including autopsy cases [3]. However, infratentorial leptomeningeal dissemination (ITD) of supratentorial GBMs is rare, and its clinical features remain unclear. ITD is a clinically significant complication because it is suspected to largely influence patient prognosis, as reported for brain metastases [11]. LMD occurs through subependymal spread, subarachnoid seeding, direct infiltration along white matter tracts, and hematogenous spread. Previous studies have reported that supratentorial GBM cells metastasize into the fourth ventricle or cerebellum via the cerebrospinal fluid (CSF) through an aqueduct from the third or lateral ventricle [12, 13], or invade the brainstem through the white matter tracts of myelinated axons extending from the cortex through the midbrain [14]. Drumm et al. have reported that extensive GBM infiltration of the brainstem was present in 67% of autopsied patients [14]. Considering that refinement of GBM treatment will improve patient prognosis and consequently increase the number of patients with ITD, understanding ITD would be clinically meaningful to further improve the prognosis in patients with GBM. This study aimed to determine the clinical characteristics of ITD and examine their impact on patients' lives.

Methods

Patient characteristics

This was a single-center retrospective analysis of a consecutive series of patients with isocitrate dehydrogenase (IDH)-wild-type GBM. First, adult patients with supratentorial GBM (≥ 18 years) who were newly diagnosed and treated at our institution between October 2008 and December 2018 were identified. They had at least six months of postoperative follow-up, with MRI performed at least every two months. Patient data, including age, sex, clinical history, presurgical physical assessment, radiological images, surgical reports, and postsurgical clinical courses, were reviewed. Second, patients who developed an ITD were selected from the GBM population. ITD was defined as the dissemination of GBM, which first emerged as a supratentorial tumor and later appeared in the infratentorial region as the first site of recurrence. The ITD was radiologically diagnosed as gadolinium-enhanced on T1-weighted images or high signal intensity lesions on FLAIR images; CSF cytology was not considered imperative analysis because of its low sensitivity (25–45%) [5, 8]. Histological diagnosis of GBM was certified based on the

WHO classification 2007/2016 of tumors of the central nervous system. In this study, we conformed to WHO classification 2021 and included only GBM and IDH-wildtype cases [15].

Molecular profiles of the tumors, including IDH, telomerase reverse transcriptase (*TERT*), serine/threonine kinase B-RAF (BRAF), H3 histone, family 3A (*H3F3A*) mutation status, and O6-methylguanine-DNA-methyltransferase (*MGMT*) promoter methylation status, were extracted from medical records. The extent of resection was determined based on the surgeon's operative notes and on postoperative imaging studies, classified as either total if 100% of the enhanced lesion was resected, subtotal if 95–99% was resected, partial if < 94% was resected, or a biopsy. Consecutive Karnofsky performance status (KPS) scores were obtained from 0 to 6 months after ITD treatment.

Molecular Analysis

DNA was extracted from frozen tumor tissues for all cases using a DNeasy Blood & Tissue Kit (Qiagen, Tokyo, Japan). The presence of hotspot mutations in *IDH1* (R132) and *IDH2* (R172) was assessed by pyrosequencing as previously described [16]. Pyrosequencing assays were designed to detect all known mutations in these codons [16]. The two mutation hotspots in the *TERT* promoter were analyzed in all tumors using Sanger sequencing and/or pyrosequencing, as previously reported [17]. Mutation hotspots at codons 27 and 34 of *H3F3A* and codon 600 of BRAF were analyzed by Sanger sequencing and/or pyrosequencing [18]. The methylation status of the *MGMT* promoter was analyzed using bisulfite modification of tumor genomic DNA, followed by pyrosequencing, as previously described [17]. Methylation was considered positive when its mean level at the examined 16 CpG sites was > 16% [17, 19].

Statistical Analysis

OS was defined as the interval between the initial surgery and death. Progression-free survival (PFS) was defined as the interval between the initial surgery date and the detection of any progression. Therefore, PFS is equivalent to the interval between initial surgery and ITD development. PFS from ITD diagnosis was defined as the interval between the date of ITD treatment and any (supratentorial or infratentorial) progression, death, or last follow-up. Survival from ITD diagnosis was defined as the interval between the date of ITD treatment and death or last follow-up. Patients with unknown survival were censored at the last follow-up date. These times were calculated using the Kaplan–Meier method and compared using the log-rank test. Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, Inc., La Jolla, CA, USA). Statistical significance was defined as $P < 0.05$.

Ethics Approval

This retrospective study used data obtained for clinical purposes. This study was approved by the internal review board of the National Cancer Center (approval number: 2004-066).

Result

Patient Demographics

Altogether, 160 newly diagnosed IDH-wild-type GBM patients were treated at our institution between October 2008 and December 2018. Seven (4.4%) were classified as having ITD. Table 1 lists the clinical characteristics of the seven patients with ITD, of whom five were men, and two were women with a median age of 66 years (39–75 years). The median KPS score at ITD development was 70 (40–90).

Table 1
Clinical characteristics of the seven patients with infratentorial leptomeningeal dissemination (ITD)

Characteristics	No. (%) of patients
Age, years	
Median (range)	66 (39–75)
Sex	
Male	5 (71.4)
Female	2 (28.6)
Karnofsky performance status at the time of ITD treatment	
Median (range)	70 (40–90)
Lesion/ Time from initial surgery to ITD treatment	
All (Median (range))	12.4 (8.2–25.1) months
Fourth ventricle (n = 2)	12.2 (9.8–14.5) months
Extra-cerebellum (n = 2)	12.9 (8.2–17.6) months
Intra-cerebellum (n = 3)	12.4 (12.2–25.1) months
Symptoms	
Gait disturbance	6 (85.7)
Nausea	2 (28.6)
None	1 (14.3)
ITD treatments	
Surgery, radiation, and chemotherapy	1 (14.3)
Radiation and chemotherapy	4 (57.1)
Chemotherapy alone	2 (28.6)
Chemotherapy	
Bevacizumab	3 (42.9)
Temozolomide	3 (42.9)

ITD, infratentorial leptomeningeal dissemination; LBRT, local brain radiotherapy

Characteristics	No. (%) of patients
Procarbazine	1 (14.3)
Dabrafenib, Trametinib	1 (14.3)
Radiation	
LBRT 25Gy/5Fr	2 (28.6)
LBRT 60Gy/30Fr	2 (28.6)
Brain and whole spine 36Gy/20Fr	1 (7.1)

ITD, infratentorial leptomeningeal dissemination; LBRT, local brain radiotherapy

Characteristics and Surgical Results of the Initial Tumors

Representative images of primary tumors are summarized in Fig. 1A. All the initial GBMs exhibited ring-enhanced lesions, which were located in the temporal lobe (42.9%, n = 3), frontal lobe (28.6%, n = 2), parietal lobe (14.3%, n = 1), and thalamus (14.3%, n = 1). The tumors in patients 1, 2, 3, 4, 6, and 7 were located in the periventricular zone. The mean volume of seven preoperative enhanced tumor lesions was 26.5 cm^3 (9.2–42.7 cm^3).

Six patients underwent tumor resection by craniotomy at the initial presentation under general anesthesia, and one underwent biopsy for a thalamic lesion. The total resection was achieved in two cases (28.6%), subtotal resection in three patients (42.9%), partial resection in one case (14.3%), and limited in biopsy in one case (14.3%). The ventricle was opened as a part of the surgical procedure in six patients (85.7%), except for one with a thalamic lesion.

The molecular genetic examination was performed in all cases of initial tumors; three tumors (42.9%) had *TERT* promoter mutation, one tumor (14.3%) had *BRAF* mutation, no tumor had *H3F3A* mutation, two tumors (28.6%) had high *MGMT* promoter methylation status (cut-off value: 16.0%).

The radiological images of the ITD and postoperative tumor cavity during ITD development are summarized in Fig. 1B and C. The ITDs were classified into four groups according to CSF flow: fourth ventricle (patients 1 and 2), extra-cerebellum or extra-brainstem (patients 3 and 4), intra-cerebellum (patients 5–7), and intra-brainstem (no patient in this study). CSF cytology was performed in patients 2 and 7, and malignant cells were not observed.

Characteristics and Outcomes of ITDs

The interval from the initial GBM surgery to the diagnosis of ITD (PFS) was 12 months (range, 6–21 months). The symptoms observed when ITD developed were gait disturbance (85.7%, n = 6), nausea and vomiting (28.6%, n = 2, patients 1 and 2), cerebellar mutism (14.3%, n = 1, patient 1), and none (14.3%, n = 1, patient 6). Four patients (57.1%) presented with new symptoms before radiological diagnosis of ITD. Additionally, light FLAIR high lesions were observed in three cases (42.9%, patients 1, 3, and 7) before ITD development. The ITD treatments included surgery following chemoradiation (14.3%, n = 1, patient 5), radiation and chemotherapy (57.1%, n = 4, patients 1, 2, 4, and 7), and chemotherapy alone (28.6%, n = 2, patients 3 and 6). TMZ and procarbazine were used for ITD treatment in patient 3. Dabrafenib plus trametinib chemotherapy was administered to patient 4, who had the BRAF-V600E mutation. It demonstrated a good clinical response and prolonged patient survival. The most used therapeutic agents were bevacizumab (BEV; 57.1%, n = 4) and TMZ (42.9%, n = 3). The most applied radiation dose was 25 Gy in 5 fractions (28.6%, n = 2) or 60 Gy in 30 fractions (28.6%, n = 2). No severe adverse effects due to chemoradiotherapy were documented. Two (28.6%) patients with fourth ventricular ITD (patients 1 and 2) presented nausea and intractable vomiting during ITD treatment. Serotonin 5-HT3 receptor antagonists did not affect these symptoms, and these symptoms were relieved one or two weeks after chemotherapy or radiotherapy. Gait disturbance was also observed in six (85.7%) patients and did not improve with any treatment. Patient 1 did not recover from cerebellar mutism. These symptoms largely contributed to worse patient performance status.

The median PFS and OS of patients were 12.2 and 19.7 months, respectively (Fig. 2A and B). The prognosis of patients with ITD was poor as the median PFS and survival from ITD diagnosis were 2.9 and 7.1 months, respectively (Fig. 3A and B). We observed that PFS from ITD diagnosis of the younger ITD patient group (age $\leq$ 49 years) was better than the older group (age $\geq$ 50 years) (7.1 vs. 2.8 months, P = 0.15, Fig. 3C). The survival from ITD diagnosis was significantly better in the younger group than in the older group (11.2 vs. 4.1 months, P = 0.041, Fig. 3D). Moreover, patients with KPS $\geq$ 70 at ITD treatment demonstrated a significantly better PFS (4.1 vs. 2.2 months, P = 0.048, Fig. 3E) and OS (7.4 vs. 3.4 months, P = 0.010, Fig. 3F) than those with KPS $\leq$ 60.

The sequential KPS changes in patients with ITD are summarized in Fig. 4. No improvement in the KPS was observed after ITD treatment. Even in the good prognosis group (age $\leq$ 40 years and KPS $\geq$ 70), the KPS score was maintained > 50 only for three months.

Discussion

ITD is a rare complication with an incidence of 4.4% in our study. Due to additional radiotherapy, the prognosis of ITD is better than that of the generally reported LMD [4–8]. Furthermore, young age and good KPS are good prognostic factors for ITD.

The pathogenesis of LMD in patients with GBM remains unclear. Tumor cells reach and invade leptomeninges in various ways, such as through hematogenous spread, perineural and perivascular lymphatic spread, and direct seeding from the brain parenchyma.[20, 21] Direct spread to the CSF space

is particularly relevant to primary brain tumors,[22] as tumor contact with the subventricular zone is a known risk factor for LMD.[23] Moreover, tumor cells may disseminate through the CSF with a predilection to regions with slow CSF flow or gravity-dependent sites, such as the basal cisterns or posterior fossa.[24] In this study, the majority (85.7%) of initial tumors were located in the periventricular zone, and no basal cistern opening was observed during the surgical procedures in our series. Therefore, we hypothesized that ITD also develops due to the direct spread of tumor cells to the CSF spaces. The timing of tumor cell spreading is unknown; it may constantly occur during tumor growth or occur at the ventricle opening by surgical intervention. The tumor cells drift from the supratentorial region to the posterior fossa via the lateral and third ventricles, the aqueduct, and the fourth ventricle. They depart from the fourth ventricle through the median and lateral apertures, reach the extra-cerebellar space, and eventually infiltrate the cerebellum and brainstem. Thus, the brainstem infiltration reported by Drumm et al. is considered a terminal stage of GBM.

Previous studies have identified that other than a tumor located in the periventricular zone, the risk factors for LMD are long survival [9], young age [7, 9], larger initial tumor size [7], and *MGMT* promoter methylation [6]. Patients with ITD have a longer OS (19.7 months) than the general GBM population (10.1–15.2 months) [25–29]. By contrast, the median age of the patients (66.0 years) is consistent with that of the patients with GBM (63–65 years) [27, 30–32]. Moreover, the *MGMT* promoter's low methylation status (21.4%) in the patients was lower than that in the general GBM population (45%) [33]. and the extent of resection (total resection 28.6%) did not exceed previous reports (20–43%) [30, 34]. The initial tumor size of ITD (mean volume, 26.5 cm^3) is comparably smaller than that in a previous study (33.2 cm^3) [35]. Hence, ITD may be an atypical subtype of LMD with a unique biological nature.

The median patient survival after ITD was 7.1 months, which is better than that of the patients with LMD (2.1–5.7 months) [4–8]. One clinical advantage of ITD is that radiotherapy would be a good therapeutic strategy. In the case of supratentorial GBM recurrence, including dissemination, radiotherapy is not a widely approved therapeutic option since a total of 40–60 Gy of maximal dose radiotherapy has already been performed in the supratentorial area as an initial treatment. Therefore, therapeutic options for LMD are generally limited to chemotherapy such as bevacizumab and lomustine therapy [36]. By contrast, in the case of ITD, the infratentorial region is generally a radio-intact area, and additional radiotherapy is a good therapeutic strategy. No optimal radiation dose regimen has been established for ITDs. Here, three different doses (25, 36, and 60 Gy) of radiotherapy were administered, and no significant difference was observed in their prognoses. A previous study also used various doses ranging from 21 Gy to 45 Gy for radiotherapy [13]. The optimal radiation dose regimen for ITD should be established in future studies. At the same time, choosing the optimal radiation dose regimen for ITD patients based on their age and physical status is equally important.

One finding was the efficacy of dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) for ITD in a patient with the BRAF-V600E mutation. The incidence of BRAF-V600E mutation in adult GBM is approximately 1–3% [37, 38]. Due to its rarity, the effectiveness of BRAF inhibitors in GBM is unclear [39]. Burger et al. have reported one case of ITD of BRAF-V600E mutation and IDH-wildtype GBM [40]. In their

study, one month of dabrafenib treatment resulted in a nearly complete response to ITD. In this study, dabrafenib plus trametinib was administered as a second-line chemotherapeutic agent to patient 4, whose tumor harbored the BRAF-V600E mutation. This patient experienced a favorable therapeutic response and extended survival after ITD diagnosis (15 months). Thus, dabrafenib plus trametinib may be a promising therapeutic strategy for the BRAF-V600E mutation and IDH-wildtype in patients with GBM, even after ITD development.

The expected survival improves for patients who develop ITD earlier at the age of 50 years or those with a high KPS (> 70). The age of 50 years and KPS of 70 are essential thresholds for patients with GBM. Li et al. have reported that age (< 50 vs. ≥ 50 years) and KPS 70 produces a significant split and set as the bifurcation of the recursive partitioning analysis model of GBM [41]. In the general population with GBM, younger age and good performance status may be beneficial for patients with ITD.

The symptoms observed in ITD were often systemic, such as gait disturbance and nausea, rather than neurologically focused symptoms such as hemiparesis or language deficits. These symptoms can easily be misdiagnosed as side effects of chemotherapy and can be observed on the left side. In fact, four cases (57.1%) exhibited new symptoms several weeks before MRI examination. Thus, ITD must be considered when patients present with unusual and neurologically nonfocused symptoms.

Moreover, patients with ITD often experience persistent nausea and intractable vomiting, leading to appetite loss. Cohen et al. have reported three cases of uncontrollable vomiting from a GBM that disseminated to the fourth ventricle [13]. In these cases, additional irradiation to the infratentorial region achieved complete remission of symptoms. Here, patients 1 and 2, who developed ITD in the fourth ventricle, experienced persistent nausea. Although the serotonin 5-HT_3 receptor antagonist did not affect the symptoms, chemotherapy and radiotherapy relieved intractable vomiting within one week, as previously reported.

By contrast, no improvement was observed in gait disturbance, which makes it challenging for patients to independently perform activities of daily living. Consequently, the patients became weaker, and their performance status declined. Even young patients hardly maintained their KPS score after treatment. Their clinical course suggests that once the physical performance of ITD drops, there is no optimal treatment to improve it. Early detection and intervention are the best efforts to improve the performance status and prognoses of patients with ITD.

The main limitation of this study was the small sample size due to the rarity of ITD; therefore, our results need to be carefully interpreted. Another significant limitation is that the therapeutic strategies employed may be biased based on patient performance status. Since this was a retrospective study, patients with a good performance status might have received more intensive treatment, and those with a poor performance status might have undergone more palliative treatment. These therapeutic differences reflect realistic clinical decisions, although they hinder the objective assessment of outcomes in patients with ITD.

Conclusion

Radiotherapy or molecular-targeted therapy may be effective in some cases and may contribute to extending survival. An ITD significantly impacts a patient's performance status because once it declines, the performance status is not completely recovered. Moreover, the symptoms of ITD are neurologically unfocused and are easily misdiagnosed as side effects of chemotherapy. Therefore, carefully checking the infratentorial region of supratentorial GBM located in the periventricular zone during patient follow-up and rapidly treating ITD before the KPS score starts declining are crucial.

Declarations

Ethical Approval and Consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and the 1964 Helsinki declaration and its later amendments. This study was approved by the internal review board of the National Cancer Center (2004–066). Written informed consent was obtained from all individual participants.

Consent for publication

Not applicable.

Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All the authors have nothing to disclose except Dr. Ichimura and Dr. Narita. Dr. Ichimura reports grants from Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Daiichi Sankyo Co.Ltd., outside the submitted work. Dr. Narita reports grants from Japan Agency for Medical Research and Development, Chugai Pharmaceutical co., MSD, Eisai, Toshiba, SBI pharma, Glaxo, Abbive, Ono, Stella-pharma, Ohtuka, Meiji-seika, and Daiichi-Sankyo, outside the submitted work.

Funding

None to report.

Authors' contributions

DK and YN designed the study. DK, MO, YM, MT, SY, YT, MK, and YN contributed to patients’ treatment and management. MHK and KI identified IDH1/2 mutations and MGMT status. DK and YN interpreted the

data and performed the biostatistical analysis. DK and MO wrote the manuscript. All the authors reviewed and approved this manuscript.

Acknowledgements

Not applicable

References

1. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, Toms S, Idbaih A, Ahluwalia MS, Fink K, Di Meco F, Lieberman F, Zhu JJ, Stragliotto G, Tran D, Brem S, Hottinger A, Kirson ED, Lavy-Shahaf G, Weinberg U, Kim CY, Paek SH, Nicholas G, Bruna J, Hirte H, Weller M, Palti Y, Hegi ME, Ram Z (2017) Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA 318: 2306–2316 doi:10.1001/jama.2017.18718
2. Lakomy R, Kazda T, Selingerova I, Poprach A, Pospisil P, Belanova R, Fadrus P, Vybihal V, Smrcka M, Jancalek R, Hynkova L, Muckova K, Hendrych M, Sana J, Slaby O, Slampa P (2020) Real-World Evidence in Glioblastoma: Stupp's Regimen After a Decade. Front Oncol 10: 840 doi:10.3389/fonc.2020.00840
3. Birzu C, Tran S, Bielle F, Touat M, Mokhtari K, Younan N, Psimaras D, Hoang-Xuan K, Sanson M, Delattre JY, Idbaih A (2020) Leptomeningeal Spread in Glioblastoma: Diagnostic and Therapeutic Challenges. Oncologist 25: e1763-e1776 doi:10.1634/theoncologist.2020-0258
4. Bae JS, Yang SH, Yoon WS, Kang SG, Hong YK, Jeun SS (2011) The clinical features of spinal leptomeningeal dissemination from malignant gliomas. J Korean Neurosurg Soc 49: 334–338 doi:10.3340/jkns.2011.49.6.334
5. Mandel JJ, Yust-Katz S, Cachia D, Wu J, Liu D, de Groot JF, Yung AW, Gilbert MR (2014) Leptomeningeal dissemination in glioblastoma; an inspection of risk factors, treatment, and outcomes at a single institution. J Neurooncol 120: 597–605 doi:10.1007/s11060-014-1592-1
6. Chan DT, Hsieh SY, Kam MK, Cheung TC, Ng SC, Poon WS (2016) Pattern of recurrence and factors associated with cerebrospinal fluid dissemination of glioblastoma in Chinese patients. Surg Neurol Int 7: 92 doi:10.4103/2152-7806.192723
7. Noh JH, Lee MH, Kim WS, Lim DH, Kim ST, Kong DS, Nam DH, Lee JI, Seol HJ (2015) Optimal treatment of leptomeningeal spread in glioblastoma: analysis of risk factors and outcome. Acta Neurochir (Wien) 157: 569–576 doi:10.1007/s00701-015-2344-5
8. Andersen BM, Miranda C, Hatzoglou V, DeAngelis LM, Miller AM (2019) Leptomeningeal metastases in glioma: The Memorial Sloan Kettering Cancer Center experience. Neurology 92: e2483-e2491 doi:10.1212/WNL.0000000000007529
9. Vertosick FT, Jr., Selker RG (1990) Brain stem and spinal metastases of supratentorial glioblastoma multiforme: a clinical series. Neurosurgery 27: 516–521; discussion 521 – 512

doi:10.1097/00006123-199010000-00002

10. Akmal S, Ginalis EE, Patel NV, Aiken R, Dicpinigaitis AJ, Hanft SJ (2021) Leptomeningeal disease in glioblastoma: endgame or opportunity? Journal of Neuro-Oncology 155: 107–115 doi:10.1007/s11060-021-03864-x
11. Dou Z, Wu J, Wu H, Yu Q, Yan F, Jiang B, Li B, Xu J, Xie Q, Li C, Sun C, Chen G (2021) The Infratentorial Localization of Brain Metastases May Correlate with Specific Clinical Characteristics and Portend Worse Outcomes Based on Voxel-Wise Mapping. Cancers (Basel) 13 doi:10.3390/cancers13020324
12. Khan MN, Poulin A, Essig M (2017) Fourth Ventricular Lesions in Metastatic Gliomas: A Rare Predilection? Brain Tumor Res Treat 5: 24–29 doi:10.14791/btrt.2017.5.1.24
13. Cohen ZR, Hassenbusch SJ, Maor MH, Pfeffer RM, Ram Z (2002) Intractable vomiting from glioblastoma metastatic to the fourth ventricle: three case studies. Neuro Oncol 4: 129–133 doi:10.1093/neuonc/4.2.129
14. Drumm MR, Dixit KS, Grimm S, Kumthekar P, Lukas RV, Raizer JJ, Stupp R, Chheda MG, Kam KL, McCord M, Sachdev S, Kruser T, Steffens A, Javier R, McCortney K, Horbinski C (2020) Extensive brainstem infiltration, not mass effect, is a common feature of end-stage cerebral glioblastomas. Neuro Oncol 22: 470–479 doi:10.1093/neuonc/noz216
15. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW (2021) The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 23: 1231–1251 doi:10.1093/neuonc/noab106
16. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, Miyakita Y, Ohno M, Shibui S, Ichimura K (2015) Development of a robust and sensitive pyrosequencing assay for the detection of IDH1/2 mutations in gliomas. Brain Tumor Pathol 32: 22–30 doi:10.1007/s10014-014-0186-0
17. Arita H, Narita Y, Fukushima S, Tateishi K, Matsushita Y, Yoshida A, Miyakita Y, Ohno M, Collins VP, Kawahara N, Shibui S, Ichimura K (2013) Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol 126: 267–276 doi:10.1007/s00401-013-1141-6
18. Arita H, Yamasaki K, Matsushita Y, Nakamura T, Shimokawa A, Takami H, Tanaka S, Mukasa A, Shirahata M, Shimizu S, Suzuki K, Saito K, Kobayashi K, Higuchi F, Uzuka T, Otani R, Tamura K, Sumita K, Ohno M, Miyakita Y, Kagawa N, Hashimoto N, Hatae R, Yoshimoto K, Shinojima N, Nakamura H, Kanemura Y, Okita Y, Kinoshita M, Ishibashi K, Shofuda T, Kodama Y, Mori K, Tomogane Y, Fukai J, Fujita K, Terakawa Y, Tsuyuguchi N, Moriuchi S, Nonaka M, Suzuki H, Shibuya M, Maehara T, Saito N, Nagane M, Kawahara N, Ueki K, Yoshimine T, Miyaoka E, Nishikawa R, Komori T, Narita Y, Ichimura K (2016) A combination of TERT promoter mutation and MGMT methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas. Acta Neuropathol Commun 4: 79 doi:10.1186/s40478-016-0351-2

19. Ohno M, Miyakita Y, Takahashi M, Igaki H, Matsushita Y, Ichimura K, Narita Y (2019) Survival benefits of hypofractionated radiotherapy combined with temozolomide or temozolomide plus bevacizumab in elderly patients with glioblastoma aged >/= 75 years. Radiat Oncol 14: 200 doi:10.1186/s13014-019-1389-7
20. Le Rhun E, Taillibert S, Chamberlain MC (2013) Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. Surg Neurol Int 4: S265-288 doi:10.4103/2152-7806.111304
21. Pellerino A, Internò V, Muscolino E, Mo F, Bruno F, Pronello E, Franchino F, Soffietti R, Rudà R (2020) Leptomeningeal metastases from non-small cell lung cancer: state of the art and recent advances. Journal of Cancer Metastasis and Treatment 2020 doi:10.20517/2394-4722.2020.80
22. Boyle R, Thomas M, Adams JH (1980) Diffuse involvement of the leptomeninges by tumour–a clinical and pathological study of 63 cases. Postgrad Med J 56: 149–158 doi:10.1136/pgmj.56.653.149
23. Mistry AM, Kelly PD, Gallant JN, Mummareddy N, Mobley BC, Thompson RC, Chambless LB (2019) Comparative Analysis of Subventricular Zone Glioblastoma Contact and Ventricular Entry During Resection in Predicting Dissemination, Hydrocephalus, and Survival. Neurosurgery 85: E924-E932 doi:10.1093/neuros/nyz144
24. Pellerino A, Bertero L, Ruda R, Soffietti R (2018) Neoplastic meningitis in solid tumors: from diagnosis to personalized treatments. Ther Adv Neurol Disord 11: 1756286418759618 doi:10.1177/1756286418759618
25. Weller M, Felsberg J, Hartmann C, Berger H, Steinbach JP, Schramm J, Westphal M, Schackert G, Simon M, Tonn JC, Heese O, Krex D, Nikkhah G, Pietsch T, Wiestler O, Reifenberger G, von Deimling A, Loeffler M (2009) Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. J Clin Oncol 27: 5743–5750 doi:10.1200/JCO.2009.23.0805
26. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS (2011) An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 115: 3–8 doi:10.3171/2011.2.JNS10998
27. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, Villano JL (2014) Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev 23: 1985–1996 doi:10.1158/1055-9965.EPI-14-0275
28. Li YM, Suki D, Hess K, Sawaya R (2016) The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? J Neurosurg 124: 977–988 doi:10.3171/2015.5.JNS142087
29. Vand Rajabpour M, Yahyazadeh H, Beheshti M (2017) Prognostic Factors and Survival of Glioblastoma Multiform (GBM) in Iranian Patients. International Journal of Cancer Management 10 doi:10.5812/ijcm.6260
30. (2017) Brain Tumor Registry of Japan (2005–2008). Neurol Med Chir (Tokyo) 57: 9–102 doi:10.2176/nmc.sup.2017-0001

31. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C, Barnholtz-Sloan JS (2013) CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. Neuro Oncol 15 Suppl 2: ii1-56 doi:10.1093/neuonc/not151
32. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS (2020) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013–2017. Neuro Oncol 22: iv1-iv96 doi:10.1093/neuonc/noaa200
33. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352: 997–1003 doi:10.1056/NEJMoa043331
34. Chang SM, Parney IF, Huang W, Anderson FA, Jr., Asher AL, Bernstein M, Lillehei KO, Brem H, Berger MS, Laws ER, Glioma Outcomes Project I (2005) Patterns of care for adults with newly diagnosed malignant glioma. JAMA 293: 557–564 doi:10.1001/jama.293.5.557
35. Awad AW, Karsy M, Sanai N, Spetzler R, Zhang Y, Xu Y, Mahan MA (2017) Impact of removed tumor volume and location on patient outcome in glioblastoma. J Neurooncol 135: 161–171 doi:10.1007/s11060-017-2562-1
36. Chen W, Wang Y, Zhao B, Liu P, Liu L, Wang Y, Ma W (2021) Optimal Therapies for Recurrent Glioblastoma: A Bayesian Network Meta-Analysis. Front Oncol 11: 641878 doi:10.3389/fonc.2021.641878
37. Behling F, Barrantes-Freer A, Skardelly M, Nieser M, Christians A, Stockhammer F, Rohde V, Tatagiba M, Hartmann C, Stadelmann C, Schittenhelm J (2016) Frequency of BRAF V600E mutations in 969 central nervous system neoplasms. Diagn Pathol 11: 55 doi:10.1186/s13000-016-0506-2
38. Ballester LY, Fuller GN, Powell SZ, Sulman EP, Patel KP, Luthra R, Routbort MJ (2017) Retrospective Analysis of Molecular and Immunohistochemical Characterization of 381 Primary Brain Tumors. J Neuropathol Exp Neurol 76: 179–188 doi:10.1093/jnen/nlw119
39. Schreck KC, Grossman SA, Pratilas CA (2019) BRAF Mutations and the Utility of RAF and MEK Inhibitors in Primary Brain Tumors. Cancers (Basel) 11 doi:10.3390/cancers11091262
40. Burger MC, Ronellenfitsch MW, Lorenz NI, Wagner M, Voss M, Capper D, Tzaridis T, Herrlinger U, Steinbach JP, Stoffels G, Langen KJ, Brandts C, Senft C, Harter PN, Bahr O (2017) Dabrafenib in patients with recurrent, BRAF V600E mutated malignant glioma and leptomeningeal disease. Oncol Rep 38: 3291–3296 doi:10.3892/or.2017.6013
41. Li J, Wang M, Won M, Shaw EG, Coughlin C, Curran WJ, Jr., Mehta MP (2011) Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. Int J Radiat Oncol Biol Phys 81: 623–630 doi:10.1016/j.ijrobp.2010.06.012

Figures

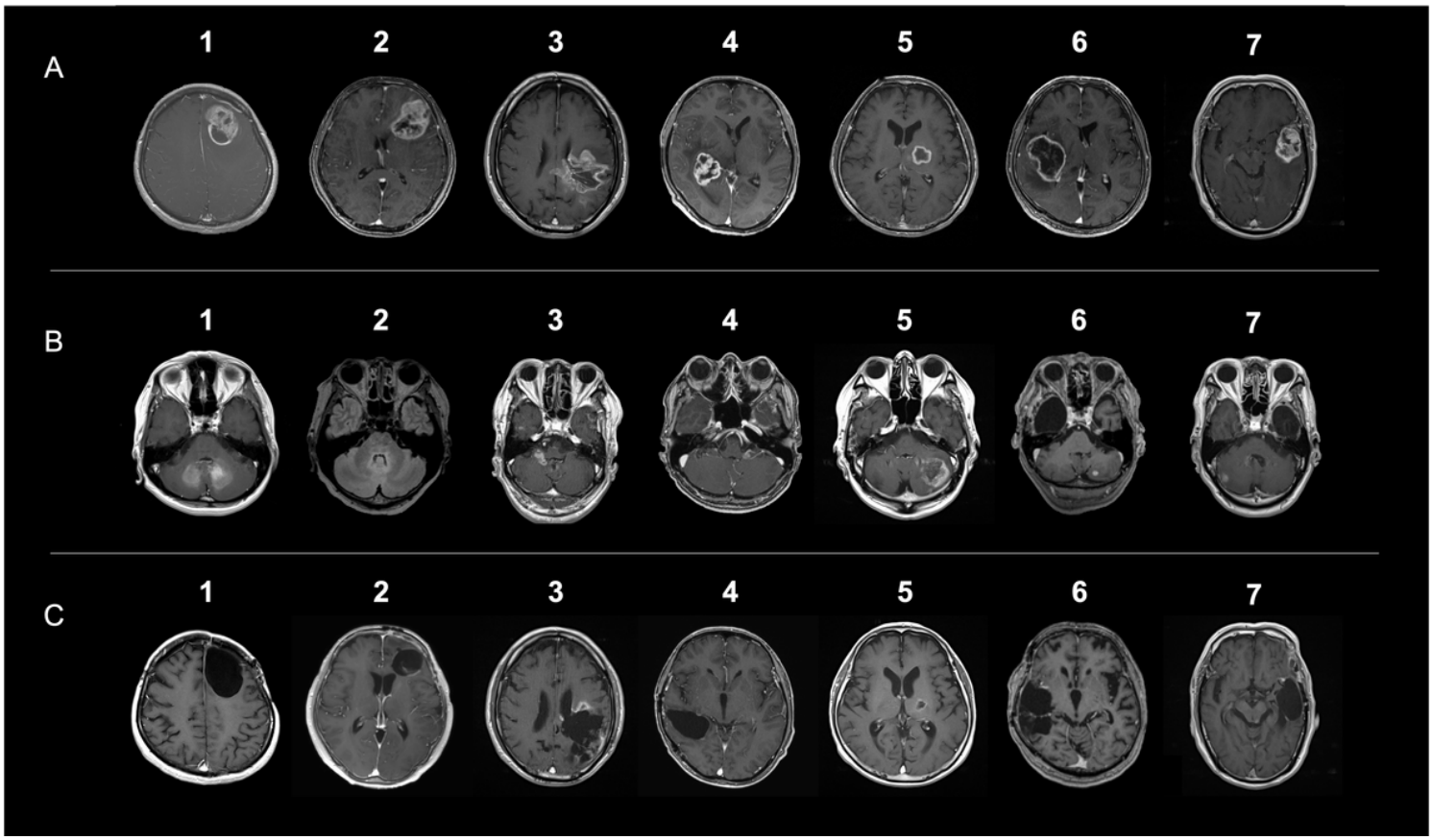

Figure 1

Axial gadolinium-enhanced T1-weighted images of patients with infratentorial leptomeningeal dissemination (ITD). (A) Representative images of the initial tumors. (B) Representative images of the ITD l patient 2 who had a FLAIR image. (C) Images of the cavities of the initial tumors when ITD developed.

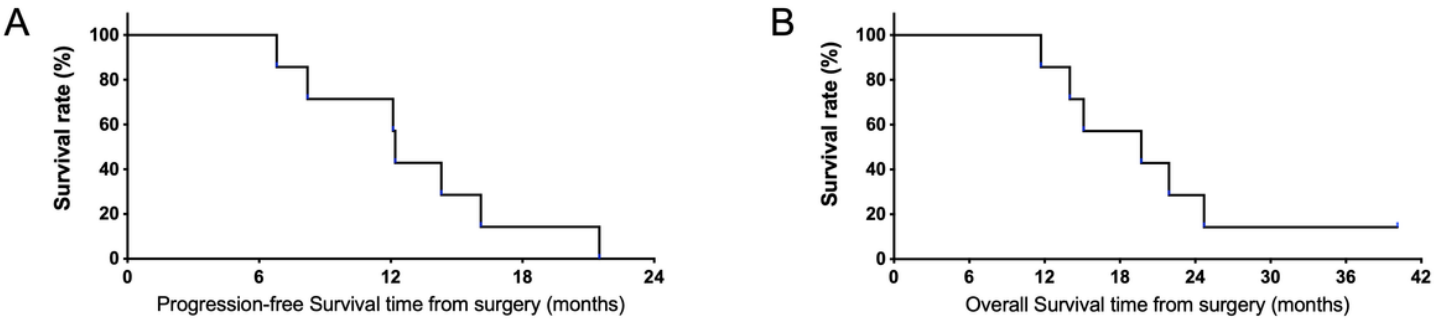

Figure 2

Kaplan–Meier curves of progression-free survival (PFS) (A) and overall survival (OS) (B). The median PFS and OFS were 12.2 months and 19.7 months, respectively.

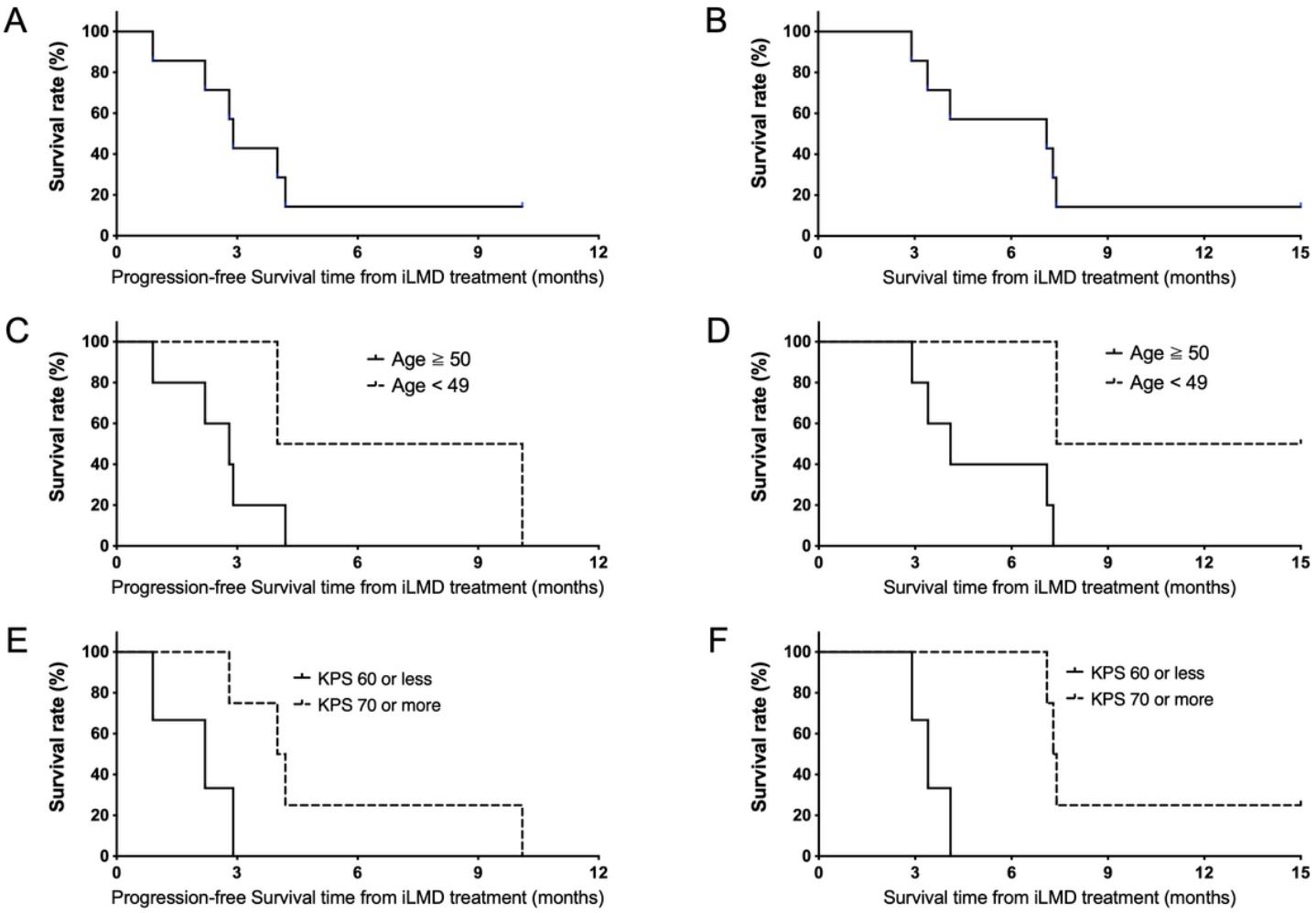

Figure 3

Kaplan–Meier curves of progression-free survival (PFS) from the infratentorial leptomeningeal dissemination (ITD) diagnosis (A, C, E) and survival from ITD diagnosis (B, D, F). (A) The median PFS from ITD diagnosis was 2.9 months. (B) The median survival from ITD diagnosis time was 7.1 months. (C) The median PFS from ITD diagnosis of the younger patient group (age ≤ 49 years, N = 2) and older patient group (age ≥ 50 years, N = 5) were 7.1 and 2.8 months, respectively (P = 0.15). (D) The median survival from ITD diagnosis of the younger and older patient groups was 11.2 and 4.1 months, respectively (P = 0.041). (E) The median PFS from ITD diagnosis of patients with Karnofsky performance tatus (KPS) ≥ 70 at ITD development was 4.1 months (N = 5), and those with KPS ≤ 60 was 2.2 months (N = 2) (P = 0.048). (F) The median survival of patients with KPS ≥ 70 at ITD development was 7.4 months, and those with KPS ≤ 60 was 3.4 months (P = 0.010).

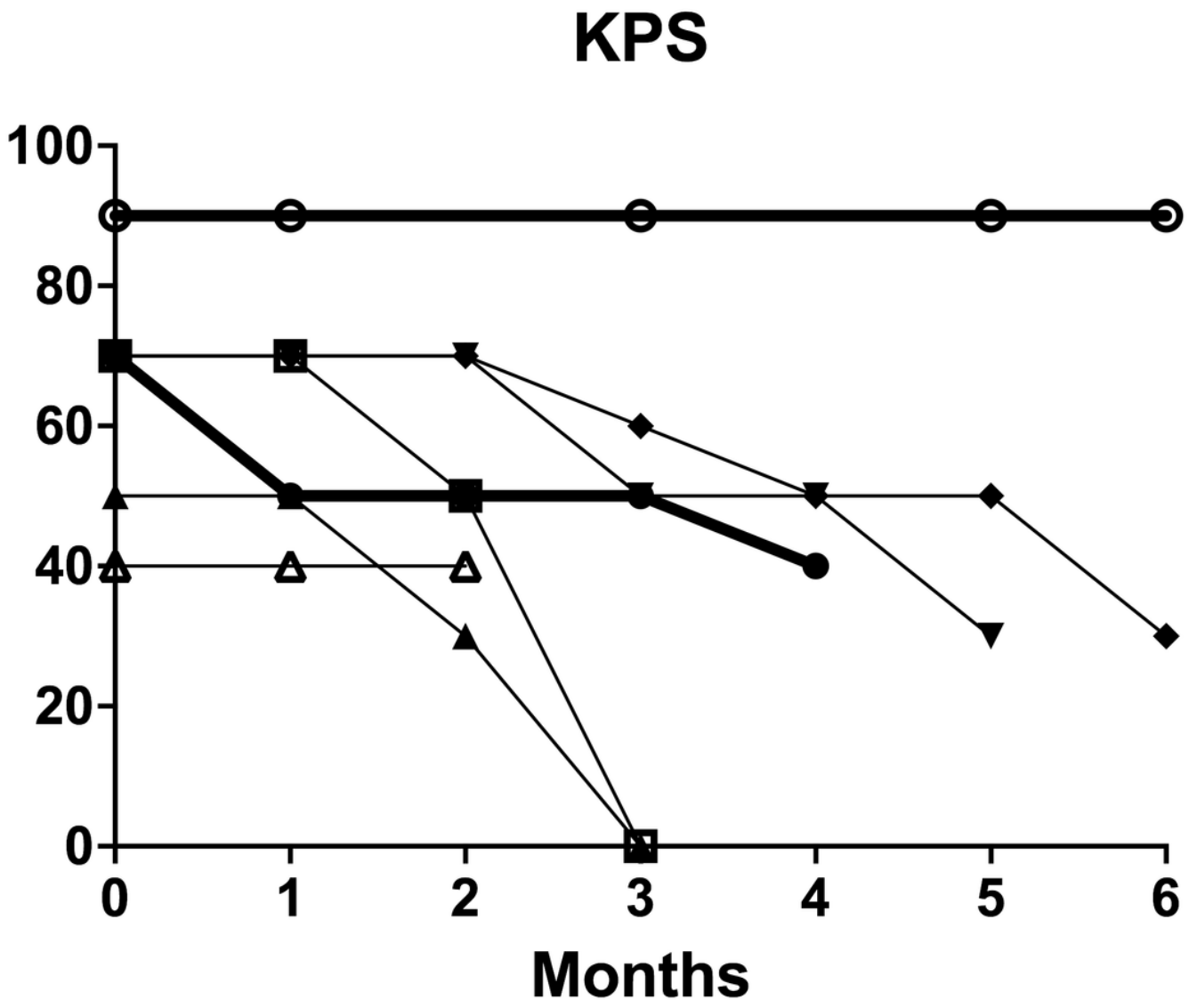

Figure 4

A spider plot shows Karnofsky performance status (KPS) score changes from the beginning to six months after infratentorial leptomeningeal dissemination (ITD) treatment. The x-axis indicates months, and zero indicates the time of ITD treatment. The y-axis indicates the KPS. Even in patients with good prognosis factors (age ≤ 40 years and KPS ≥ 70, indicated by bold lines), the KPS score was maintained >50 only for three months.