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ORIGINAL ARTICLE

Impact of initial midline shift in glioblastoma on survival

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Abstract

The impact of midline shift (MLS) on long-term survival and progression in glioblastoma (GBM) is unknown. The objective of this study was to analyze the influence of mass effect on survival and progression with consideration of the patient demographics, tumor morphology, operative techniques, molecular pathology, and postoperative treatment. One hundred ninety-eight patients with GBM were analyzed retrospectively. Both MLS groups (< or ≥ 10 mm) were compared with regard to survival, progression-free survival (PFS), and postoperative course of Karnofsky Performance Status (KPS). A two-sided Fisher exact test showed no statistically significant differences in the confounders between the low- and high-MLS groups. The median survival was 18.0 months (95% confidence interval (CI) = 15.3–20.7) in the low-MLS group ($n = 173$) and 9.0 months (95% CI = 4.8–13.2) in the high-MLS group ($n = 25$) ($p = 0.045$). In the high-MLS group, 59.1% (13/22) with an initially high MLS had a KPS of less than 70% after 3 months, whereas 20.5% of the low-MLS group had a KPS of less than 70% ($p < 0.001$). Binary logistic regression analysis including the O-6-methylguanine-DNA methyltransferase (MGMT) status, extent of resection, baseline KPS, and MIB-I index showed low MLS as the only predictor for survival at 12 months ($p = 0.046$, odds ratio (OR) = 2.70, 95% CI = 1.0–7.2). Median PFS was 6.0 months in the high-MLS group and 9.0 months in the low-MLS group (log-rank test; $p = 0.08$). An initial midline shift of 10 mm or greater seems to be an imaging characteristic that independently predicts the survival in glioblastoma.

Keywords Glioblastoma · Mass effect · Midline shift · Survival

Introduction

Glioblastoma (GBM) is still a fatal diagnosis with poor survival. Female sex, age less than 70 years, and Karnofsky Performance Status (KPS) of 80 or higher are some general predictors for long-term survival in GBM [1–3]. The extent of resection greater than 98% with functional preservation is also a known predictor for prolonged survival and progression-free survival (PFS) [4, 5]. Mutations in biological markers are also essential characteristics used to predict survival in patients with GBM. Hypermethylation of the O-6-methylguanine-DNA methyltransferase (MGMT) promoter [6, 7], codeletion of 1p19q in patients harboring tumors with oligodendroglial components [8], and mutations in isocitrate dehydrogenase (IDH)-1 codon 132 are factors that positively influence the overall survival (OS) [9]. Furthermore, mutations of the promotor TERT gene are also independently associated with lower survival [10].

The prognostic benefits of a concomitant chemoradiotherapy regimen including temozolomide (TMZ) or lomustine-TMZ are also evident [7, 11]. Median OS in patients with a hypermethylated MGMT promoter and treated with standard TMZ-based radiochemotherapy were living 23.4 to 31.4 months in reported phase III trials with prospective randomized data [7, 11]. However, with new and promising experimental treatment regimens, there is also a need for prognostic imaging biomarkers to construct personalized treatments.

Midline shift (MLS) is caused by growing tumor mass and the adjacent edema pushing and displacing surrounding brain structures [12]. Therefore, even in this chronic disease, patients can present with a decreased level of consciousness, attention, and awareness.

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There is only exiguous data reporting on MLS in GBM and the possible prognostic value of mass effect in the context of the known predictors such as MGMT [6, 7], KPS [3], and extent of resection [4, 5]. MLS is a common finding and was seen in 74% of patients with GBM [12]. In the period before GBM resections via 5-aminolevulinic acid (5-ALA) or intraoperative magnetic resonance imaging (MRI) [13, 14], concomitant chemoradiotherapy [7, 11], and molecular biomarkers [6–10], it was proclaimed that a MLS in patients with a KPS of 70 or greater is an independent prognostic factor [12]. Furthermore, Kreth et al. described a doubling in the short-term risk of death after biopsy alone in GBMs when a midline shift was present [15]. Recent data confirmed those earlier findings with regard to poorer survival when mass effect is present [16]. However, known predictors such as IDH-1 or MGMT were not evaluated in this investigation.

The objective of this study is to analyze the influence of MLS during the initial presentation in the context of the known predictors on survival, PFS, and KPS in GBMs treated by 5-ALA and neuronavigation-guided resections.

Material and methods

Study design and patient characteristics

From January 2015 to December 2018, a total of 270 patients with GBM were treated surgically and analyzed retrospectively. The criteria for inclusion in this study were histopathologically confirmed GBM, age greater than 18 years, availability of survival information and KPS, single intracranial tumor lesion, and patients treated by neurosurgical resections via craniotomy. Seventy-two patients were excluded because only conventional stereotactic or VarioGuide (BrainLAB AG, Feldkirchen, Bavaria, Germany) biopsy without additional cytoreductive surgery was performed, and multiple intracranial lesions or no clinical follow-up (≥ 1 month) was given. Biopsy was performed if lesions were detected within the thalamus, internal capsule, splenium of the corpus callosum, brainstem, MRI revealed multiple or bilateral disease, and functional status was graded as a KPS < 60%.

Surgical procedure

Initially, a white-light resection under neuronavigation guidance (Brainlab Curve, BrainLAB AG, Feldkirchen, Germany) was performed. When the surgeon assumed that gross total resection (GTR) of the tumor was achieved, hemostasis was performed. Afterward, the resection cavity was examined using 5-aminolevulinic acid (5-ALA) (20 mg/kg, Gliolan; medac GmbH, Wedel, Germany), and areas that were suspicious for remaining tumor tissue were demarcated and resected. Postoperative MRI was obtained within 72 h after surgery by a senior neuroradiologist to determine the extent of resection.

Immunohistochemistry

Histological evaluation was conducted according to the World Health Organization 2016 diagnostic consensus criteria [17]. For this purpose, paraffin sections were stained with hematoxylin and eosin (H&E). Sections were examined immunohistochemically with Molecular Immunology Borstel-I (MIB-I) antibody, glial fibrillary acidic protein (GFAP), and IDH1. MGMT status was determined by methylation-specific polymerase chain reaction (PCR) and reported according to Hegi et al. [6].

Tumor morphology

Midline shift measurement

MLS was measured independently by two reviewers (M.S. and J.W.) in millimeters, as the perpendicular distance between the septum pellucidum and the ideal midline. Ideal midline was defined as the line being coplanar with the falx cerebri [18, 19].

Measurements were done using T2-weighted MR images that were obtained within 5 days before surgery. Midline shifts were dichotomized in low (< 10 mm) and high ($\geq$ 10 mm) deviations of the septum pellucidum.

Tumor area

Tumor area was calculated in mm^2 based on the two largest tumor diameters perpendicular to each other on the axial T1-weighted postcontrast images in the preoperative MRI, which was obtained within 5 days before surgery [20].

Peritumoral edema

Peritumoral edema was measured as the maximum extent of the increased T2 signal intensity on the tumor margin in the preoperative MRI, which was obtained within 5 days before surgery [21].

Definitions

Gross total resection (GTR) is the complete resection without any residual nodular enhancement. Subtotal resection (STR) was defined as resection of a gross tumor by 90 to 99%. Partial resection (PR) was defined as resection of a gross tumor by 10 to 90%. Eloquence of the lesion was assessed by the system of Sawaya et al. in grade I (noneloquent brain: frontal or temporal pole, right parieto-occipital lesions, cerebellar hemisphere lesions), grade II (near-eloquent brain: near the motor or sensory cortex, near calcarine fissure, near speech center, corpus

callosum, near the dentate nucleus, near brain stem), and grade III (eloquent brain: motor/sensory cortex, visual center, speech center, internal capsule, basal ganglia, hypothalamus/thalamus, brain stem, dentate nucleus) [22].

Post-surgery treatment protocols were evaluated at the local tumor board review. Follow-up MRI was routinely performed every 3 months. Decision-making and definitions of progression were based on the Response Assessment in Neuro-Oncology (RANO) criteria as actualized in 2017 [23]. OS was defined as survival after the date of primary diagnosis in months.

Statistics

We used the Fisher exact test (two-sided) for nominal variables and the Student *t* test for metric variables to compare the low- versus the high-midline shift groups. Only two-sided *p* values were reported. Kaplan-Meier charts of OS and PFS were calculated. Differences between the high- and low-MLS groups were analyzed using the log-rank test. A p value < 0.05 was defined as statistically significant. Furthermore, a binary logistic regression analysis was performed to analyze independent predictors of PFS or survival in patients with GBM with high- or low-MLS at a fixed time point (12 months).

Data were organized and analyzed using SPSS© for windows version 24.0 (IBM Corp, Armonk, NY, USA).

Results

Patient characteristics

One hundred ninety-eight patients were included in this analysis. Mean age (± SD) was 63.12 ± 13.75 years and there was a male predominance among the patients (female:male = 1:1.475). The mean midline shift was 3.9 mm (standard deviation (SD), ± 4.5 mm). One hundred seventy-three (87.4%) patients had a low MLS, and 25 patients (12.6%) had a high MLS. Age, preoperative KPS, tumor area, maximum diameter of peritumoral edema, relative cerebral blood volume (rCBV) values, MIB-I index values, rate of tumors located in the eloquent area, and MGMT promoter hypermethylation status were homogenously distributed between both MLS arms. IDH-1 mutations were more common in the high-MLS group but not statistically significantly distributed (4/25 (16.0%) vs. 9/173 (5.4%); $p = 0.07$). The baseline patient characteristics and analyses by two-sided Fisher exact test are summarized in Table 1.

Survival outcomes in low- and high-midline shift groups

The median clinical follow-up time was 12.0 months (25th–75th percentile, 9.0–21.0 months), with a median MRI surveillance period of 9.0 months (25th–75th percentile, 6.0–18.0 months). The median OS in the entire population was 18.00 months (95% CI = 15.61–20.39, $n = 198$).

Twenty-five (12.6%) patients were in the high-MLS and 173 (87.4%) were in the low-MLS group. Median OS in the low-MLS group was 18 months (95% CI = 15.34–20.66, $n = 173$). The median OS in the high-MLS group was 9 months (95% CI = 4.80–13.21, $n = 25$).

Log-rank showed a statistically significant superiority of the low-MLS group to achieve longer OS ($p = 0.045$). The Kaplan-Meier analysis of low- and high-midline shift groups with regard to OS is shown in detail in Fig. 1.

Multivariate logistic regression analysis of survival at a fixed time point (12 months) was performed considering baseline KPS at admission, MLS, extent of resection, MGMT methylation status, and the MIB-I labeling index. The survival rate after diagnosis was 46.0% (91/198) at 1 year. Ten (10/25; 40.0%) patients of the high-MLS group and 81 (81/173; 46.8%) of the low-MLS group reached this fixed time point, respectively ($p = 0.67$).

Binary logistic regression analysis revealed low-MLS as the only statistically significant predictor for prolonged OS ($p = 0.046$, OR = 2.7, 95% CI = 1.02–7.18) (Table 2).

Progression-free survival in low- and high-midline shift groups

The median PFS in the entire study population was 9.0 months (95% CI = 8.0–10.0). Patients with a GBM with high MLS had a median PFS of 6.0 months (95% CI = 3.7–8.3), whereas a median PFS of 9.0 months (95% CI = 7.9–10.1) was observed in the low-MLS group (log-rank test, $p = 0.08$) (Fig. 2).

Multivariate logistic regression analysis of variables associated with PFS was performed. High MLS was not significantly associated with shortened PFS ($p = 0.09$, OR = 3.1, 95% CI = 0.8–11.8). MGMT methylation status was the only statistically significant predictor for prolonged PFS ($p = 0.049$, OR = 2.1. 95% CI = 1.0–4.4) (Table 3).

Clinical outcome

Baseline KPSs were homogenously distributed among both MLS groups (Table 1 and Fig. 3).

At discharge, 28% (7/25) of patients in the high-MLS group and 18.7% (32/171) of patients in the low-MLS group had a KPS of less than 70% ($p = 0.29$).

Table 1 Comparison of low- versus high-midline shift group (using Pearson's chi-squared test (two-sided and paired independent *t* test)

Characteristics	Low-midline shift (< 10 mm ($n = 173$))	High-midline shift (≥ 10 mm ($n = 25$))	*p* value
Age			
≤ 65	91 (52.6%)	9 (36.0%)	0.14
> 65	82 (47.4%)	16 (64.0%)	
Gender (man:woman)	100:73	18:7	0.2
Preoperative KPS			
≥ 70	162 (93.6%)	23 (92.0%)	0.67
< 70	11 (6.4%)	2 (8.0%)	
ASA			
≤ 2	118 (68.6%)	16 (64.0%)	0.65
≥ 3	54 (31.4%)	9 (36.0%)	
Secondary malignant neoplasms	13 (7.5%)	1 (4.5%)	0.99
Tumor area (mean ± SD), mm^2	1460.0 ± 1062.7	1475.3 ± 879.2	0.94
Peritumoral edema (mean ± SD), mm	22.9 ± 11.0	24.9 ± 8.7	0.32
Laterality			
Right	99 (57.2%)	12 (48.0%)	0.398
Left	74 (42.8%)	13 (52.0%)	
Sawaya			
1	27 (15.7%)	3 (12.0%)	0.77
≥ 2	145 (84.3%)	22 (88.0%)	
Extent of resection			
≥ 90%	163 (94.2%)	23 (92.0%)	0.65
< 90%	10 (5.8%)	2 (8.0%)	
rCBV elevation	90/129 (69.8%)	12/17 (70.6%)	0.99
IDH-1 mutation	9 (5.4%)	4 (16.0%)	0.07
MGMT promoter hypermethylation	73 (44.5%)	9 (42.9%)	0.99
MIB-I index (mean ± SD)	17.1 ± 7.93	17.7 ± 7.2	0.71
Concomitant chemoradiotherapy	133 (76.8%)	20 (80.0%)	0.79
Chemotherapy only	7 (4.0%)	0 (0.0%)	0.6
Radiotherapy only	11 (6.4%)	4 (16.0%)	0.10
No post-surgery therapy	21 (12.1%)	1 (4.0%)	0.32
Tumor treating fields	1 (0.6%)	0 (0.0%)	0.99

ASA American Society of Anesthesiologists (ASA); *GTR* gross total resection; *IDH-1* isocitrate dehydrogenase-1; *KPS* Karnofsky Performance Status; *MGMT* O6-methylguanine methyltransferase; *MIB-I* Molecular Immunology Borstel-I index; *PR* partial resection; *rCBV* relative cerebral blood volume; *STR* subtotal resection

Moreover, 59.1% (13/22) of the patients with an initial high MLS had a KPS of less than 70% after 3 months, whereas 20.5% (33/161) of the patients in the low-MLS group had a KPS of less than 70% ($p < 0.001$).

After 6 months, 42.9% (6/14) of patients in the high-MLS group had a KPS of less than 70% compared with 20.4% (28/137) in the low-MLS group ($p = 0.09$). The clinical course, which demonstrates the KPS before surgery, at discharge, and at 3- and 6-month follow-up, is shown in Fig. 3. The poorer clinical course of the patients with a high-MLS did not significantly influence the completion of the postoperative treatment protocols. Forty-three (43/151; 28.5%) patients of the low-MLS group and 10 (10/24; 41.66%) of the high-MLS group had a preterm termination of the postoperative adjuvant therapy, respectively (Fisher's exact test (two-sided), $p = 0.23$).

Discussion

This study investigated the potential role of initial midline shift as a predictor of survival and progression-free survival. We found that a midline shift ≥10 mm is significantly associated with survival in glioblastoma patients and a worse postoperative clinical course.

Mass effect is a known predictor of poor prognosis in traumatic brain injury [24, 25], stroke [26, 27], and tumor [12, 16]. Associations between molecular subtypes of GBM and increased MDS are unknown.

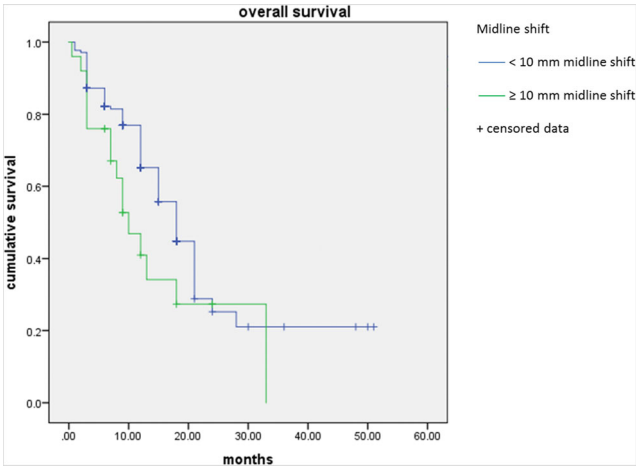

Fig. 1 Kaplan-Meier analysis of cumulative survival stratified by the parameters "high-midline shift" (≥ 10 mm) and "low-midline shift" (< 10 mm). Censored patients (alive at last follow-up) are indicated on the curves. The time axis is right-censored at 60 months. $p = 0.045$ (log-rank test)

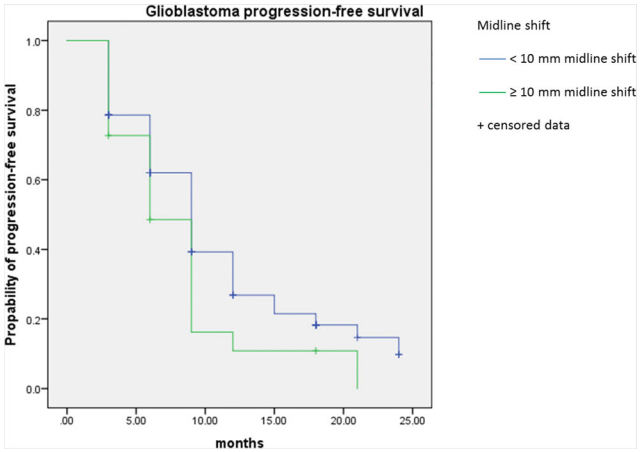

Fig. 2 Kaplan-Meier analysis of progression-free survival stratified by the parameters "high-midline shift" (≥ 10 mm) and "low-midline shift" (< 10 mm).Censored patients (without progression at last follow-up) are indicated on the curves. The time axis is right-censored at 25 months. $p = 0.08$ (log-rank test)

General demographics such as age of approximately 64 years and predominantly male gender among patients with GBM did not differ between high- and low-MLS groups [28, 29]. Consequently, there seems to be no relevant association.

And preoperative KPS score was not statistically different between MLS groups.

Known confounders in the survival analysis such as high rates of additional malignant neoplasms and high ASA classifications, which reflect the patients' physical status and systemic diseases, were not given among the patient groups. Elevated MIB-I index values (≥ 20%) as an immunohistochemical proliferation marker did not differ between low- and high-MLS groups ($p = 0.67$). Furthermore, rates of elevated rCBV were also homogeneously distributed between the groups. Consequently, elevated angiogenesis in the high-MLS group seems to be not present. Otherwise, higher expression of gene signatures associated with cell growth, mitochondrial metabolism, cellular component biogenesis, and oxidative phosphorylation were observed [16].

The extent of resection [5], MGMT promoter hypermethylation [6, 30], IDH-1 mutation [9], and concomitant chemoradiotherapy are also known variables associated with a statistically significant longer OS and were homogenously distributed in both arms of the MLS groups [7, 11]. Rates of tumors resected with an extent of resection of 90% and greater (low-MLS group, 94.2%; high-MLS group, 92.0%) are high in both MLS arms despite high rates of tumors located near or in eloquent areas (tumors categorized according to Sawaya grading [20] ≥ 2 in low-MLS group, 84.3%; high-MLS group, 88.0%). Univariate analyses excluded heterogeneity among low- and high-MLS patients in our single-center series.

MGMT hypermethylation is known to be a positive predictor of prolonged survival [1, 6, 30]. The extent of resection is also associated with longer OS [5, 31]. These predictors were also given in our analyses, and patients had a survival benefit from those established variables despite the fact that statistical significance was barely passed when the p value threshold is < 0.05.

The median survival time was 18.0 months in the low-MLS group compared with 9.0 months in the high-MLS group ($p = 0.045$). Multivariate analysis showed that low-MLS was statistically significantly associated with prolonged OS. This finding is in accordance with another study evaluating the mass effect of GBMs by measuring the lateral ventricle displacement. They

Table 2 Binary logistic regression analysis of predictors for Survival in patients with glioblastoma

Predictor	Adjusted odds ratio	95% CI	p value
Baseline KPS (</≥ 70%)	1.99	0.53–7.45	0.31
Midline shift (</≥ 10 mm)	2.70	1.02–7.18	0.046
Extent of resection (< 90/ ≥ 90%)	3.6	0.9–14.68	0.07
MGMT methylation status (non/hypermethylated)	1.73	0.92–3.26	0.09
MIB-I index (≤/> 20%)	0.92	0.49–1.74	0.80

KPS Karnofsky Performance Status; *MGMT* O6-methylguanine methyltransferase; *MIB-I* Molecular Immunology Borstel-I index

Table 3 Binary logistic regression analysis of predictors for PFS in patients with glioblastoma

Predictor	Adjusted odds ratio	95% CI	*p* value
Baseline KPS (</≥ 70%)	0.91	0.17–4.90	0.91
Midline shift (</≥ 10 mm)	3.10	0.81–11.84	0.09
Extent of resection (< 90/≥ 90%)	2.56	0.61–10.77	0.20
MGMT methylation status	2.1	1.00–4.41	0.049
MIB-I index (≤/> 20%)	0.90	0.43–1.87	0.77

KPS Karnofsky Performance Status; *MGMT* O6-methylguanine methyltransferase; *MIB-I* Molecular Immunology Borstel-I index

found a strong association between higher lateral ventricle displacements and GBM survival in a Cox model [16].

Regarding our uni- and multivariate analyses, a midline shift of 10 mm or greater seems to be an independent imaging feature for poor survival rates in GBM.

However, an MLS of 10 mm or greater in the high-MLS group was not statistically significantly associated with shortened PFS ($p = 0.08$). MGMT hypermethylation was the only independent predictor for prolonged PFS in the multivariate analysis. One reason explaining this result could be that the number of patients in the low-MLS group was much higher. The poorer clinical course OS of the high-MLS group is also reflected in the decrease of the KPS in our data and was statistically significant at the 3-month clinical follow-up between the low- and the high-MLS groups. It is unclear if patients with a high preoperative MLS could benefit from a more aggressive resection in order to relieve the mass effect. Additionally, it has to be discussed if postoperative radiotherapy should be reduced in this patient cohort with a high baseline midline shift in order to spare the patient intensive weeks with many hospital visits due to their reduced physical state, which is reflected in the worse course of the KPS at the follow-up examinations compared with the low-MLS group.

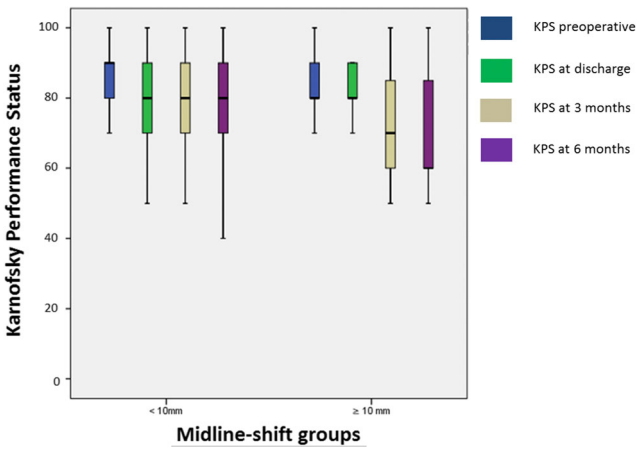

Fig. 3 Boxplots of KPS stratified by the parameters "high-midline shift" (≥ 10 mm) and "low-midline shift" (< 10 mm). The median is displayed as the line within the box, the length of the boxplot represents the interquartile range and the boxplot whiskers are 1.5 times the interquartile range

The shorter OS despite no statistically significant association with PFS in the high-MLS group could be explained by the poorer general state that is reflected in the course of the KPS of this GBM group. Furthermore, patients with a decreased and non-ambulatory general state often do not pass the follow-up brain MRIs as frequently as ambulatory patients with an excellent KPS. This bias might also influence the analysis of PFS and is a common limitation of retrospective oncological studies.

Steed et al. also observed that the extent of mass effect is independent of the contrast-enhancing volume of the tumor [16]. In our study, we also observed no differences concerning tumor area and extent of peritumoral edema between the high- and the low-MLS group. Steed et al. observed also a wide range of lateral ventricle displacement in 214 glioblastomas with high or low tumor volumes in the T1 Gd-enhanced sequences and FLAIR sequences. An explanation for this "arbitrary" extent of mass effect seems to be their results of the genomic expression profile which contribute to the mass effect. Their findings suggest that mass effect is represented by the proliferation potential or the invasive potential of the tumor. The mRNA analysis of the genomic expression profile in their study revealed that tumor tissues with a high lateral ventricle displacement or mass effect showed more gene expressions associated with cell growth, such as genes required for translation, mitochondrial metabolism, cellular component biogenesis, and oxidative phosphorylation. In contrast, the analysis of tumors with a low lateral ventricle displacement or mass effect revealed more expression of genes associated with invasion/migration, including those required for cell adhesion, cadherin accumulation, cell-cell adherens junctions, motility (lamellipodium), and angiogenesis [16]. Our findings and the results by Steed et al. with regard to the role of mass effect and tumor size in GBM survival are in conflict with other studies reporting a correlation between contrast-enhancing lesion volume, intensity in T2-weighted imaging or FLAIR volume, and survival [32, 33]. Consequently, due to the heterogeneity in the results in the literature, tumor size and mass effect should be always evaluated as a prognostic variable in combination with the MLS and the capability of the brain to compensate for mass effect. However, the value of noninvasive methods to monitor the compliance of the human brain such as transcranial Doppler

sonography with pulse sequencing technology [34], evoked tympanic membrane displacement measurement [35], ultrasound measurement of optic nerve sheath diameter [36], and assessment via calculation of intracranial volume changes and elastance of the brain using MRI is unknown and seems to be a potential basis on which to proceed further [37].

A study evaluating the impact of mass effect on survival in 41 right hemispheric GBMs suggested poorer OS compared with a control group of 48 left-sided tumors. Decreased survival time was assumed to be caused by the increased mass effect of right-sided tumors on the contralateral functionally eloquent areas such as language area, social cognition, visual perception, emotion, somatosensory area, and cognitive and motor control functions, particularly in the memory areas in the left hemisphere [38]. In our data, there were no statistically significantly higher amounts of right-sided tumors that could confirm this interesting hypothesis and potential mass effect's influence on functional areas in the left hemisphere. Hence, the biological behavior that explains the sometimes "arbitrary" extent of mass effect in many GBMs and the pathophysiological pathway of a poorer OS are still unknown.

All in all, poorer OS in GBMs with initial high MLS is evident. This can be a result of the reduced general state that is reflected in the course of KPS among these patients. PFS between the MLS groups differed, but not statistically significantly. This could be explained by the fact that patients with reduced KPS often do not undergo diagnostic follow-up imaging via MRI and some "possible" disease progressions in those patients are overlooked.

Future investigations analyzing the molecular pathological background of the elevated mass effects in a selected few patients with GBMs are needed.

Limitations

The present investigation has several limitations. Data were acquired retrospectively. The number of patients included in the high-midline shift arm is low because of the short analyzed time period. However, this time period was chosen in order to rule out lacking data of prognostic markers such as IDH mutations and MGMT promoter status in one of the two midline shift groups. Furthermore, the present data represent a single-center experience only.

Conclusions

Initial MLS of the septum pellucidum of 10 mm or greater seems to be an independent prognostic imaging biomarker for poorer OS and postoperative clinical course in GBM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The present study was approved by the local ethics committee at the University of Bonn.

Informed consent Informed consent was not sought as a retrospective design was used.

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