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RESEARCH

Ventricular entry during surgical resection is associated with intracranial leptomeningeal dissemination in glioblastoma patients

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Abstract

Purpose Glioblastoma (GBM) is associated with a poorer prognosis when leptomeningeal dissemination (LMD) occurs. Recently, the role of both ventricular entry (VE) during surgery and subventricular zone localization of tumors in promoting LMD in GBM patients has been debated. This article investigates the role of VE in causing LMD in GBM patients.

Methods We conducted a retrospective analysis of GBMs operated on at our Institution between March 2018 and December 2020. We collected pre- and post-surgical images, anamnestic information, and surgical reports.

Results Two hundred cases were collected. The GBM localization was periventricular in 69.5% of cases, and there was a VE during the surgical procedure in 51% of cases. The risk of post-surgical LMD in the case of VE was 16%. The rate of LMD was higher in the case of VE than not-VE (27.4% vs. 4%, $p < 0.0001$). The rate of LMD in periventricular GBM was 19% ($p = 0.1131$).

Conclusion According to our data, VE is an independent factor associated with a higher rate of post-surgical LMD, and the periventricular localization is not independently correlated to this negative outcome. Neurosurgeons should avoid VE when possible. The correct surgical strategy should be founded on balancing the need for maximal EOR and the risks associated with VE.

Keywords Glioblastoma · Leptomeningeal dissemination · Ventricular entry

Introduction

Glioblastoma (GBM) is the most frequent primary brain tumor in adults [1–4]. The current standard treatment, the Stupp protocol, employs post-surgical radiotherapy plus adjuvant chemotherapy and has improved median survival up to 16.7 months [5–8]. Many factors influencing the prognosis have been cleared, such as the tumor size, the spread through the corpus callosum, multifocality, and the extent of resection (EOR) [9–13]. Earlier studies have shown a shorter survival after diagnosis of leptomeningeal dissemination (LMD) (12–20 weeks [14]), with OS sinking to 6 months [5, 15]. The ventricular entry (VE) during surgical exeresis has a debated role in influencing the prognosis of GBM [16–20].

Neurosurgeons have speculated whether VE during GBM excision could favor the cerebrospinal fluid (CSF) dissemination of tumor cells [18, 19, 21, 22]. Due to the lack of clear scientific evidence, the safest surgical strategy has often been adopted, sometimes compromising the EOR. Subsequently, to the increasingly scientific solid demonstration of EOR as the main positive prognostic factor for GBMs and how greater EOR was associated with better outcomes [11, 23, 24], the problem of VE has been tackled again in the literature. At first, VE was associated with a higher rate of LMD and worst prognoses [16–19, 25]. Recent works [20, 26] aimed at distinguishing VE from primary subventricular zone (SVZ) localization of GBM, identifying the latter as the only factor linked to higher rates of LMD of GBM. The SVZ, a pluripotent stem cell niche in adults, is localized in the wall of lateral ventricles [20, 27, 28]. In the case of GBM invasion, it would be linked with disease progression

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[29]. Despite the latest reports supporting this hypothesis, the level of evidence is low [20].

Although the EOR should be as maximal as possible [11, 30–32], the effect of VE on GBM progression has to be clarified. Our work aimed to compare the post-surgery LMD associated with VE and SVZ localization to determine the risk associated with both factors and define the best surgical strategy in supratentorial GBM.

Materials and methods

The prospectively collected electronic database of our Institute was retrospectively searched for surgically treated GBM (WHO grade IV) between March 2018 and December 2020. In all cases, the histological diagnosis was GBM without any other component (as PNET). Pre- and postoperative radiological exams (brain computed tomography [CT] and magnetic resonance imaging [MRI]), surgical and clinical reports, and histological diagnoses were retrieved. Brain imaging was performed on either a 3 T (Ingenia 3 T, Philips Medical Systems, Best, The Netherlands) or a 1.5 T (Magnetom Aera, Siemens Healthcare) MRI scanner. The protocol included bi-dimensional non-contrast and contrast-enhanced T1-weighted spin-echo (SE), T2-weighted SE, T2* gradient-echo (GE), and diffusion-weighted (DWI) sequences, plus three-dimensional (3D) Fluid Attenuated Inversion Recovery (FLAIR), non-contrast and contrast-enhanced T1 Turbo Field Echo (TFE) or Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequences. Both 3D-FLAIR and T1-weighted imaging were obtained with 1 mm slice thicknesses. Postcontrast T1-weighted imaging was performed after the Dynamic Susceptibility Contrast Perfusion Weighted (DSC-PWI) sequence for perfusion imaging, acquired during intravenous administration of 0.1 mmol/Kg bolus of a gadolinium-based macrocyclic contrast agent (Gadoteridol).

Preoperative MRIs were examined in T1-weighted and gadolinium-enhanced T1-weighted sequences for identifying GBM localization (Fig. 1).

The SVZ localization was considered a contrast-enhanced area less than 1 cm from the ventricular wall without an apparent subependymal spread (Fig. 1A, B; C, D). Postoperative MRIs (at least one-month post-operatively to avoid confounding surgery-related alterations) were used to detect VE, which was considered present if a clear breach between ventricles and surgical cavities was observed(Fig. 1E, F). Surgical reports were screened if radiological images were inconclusive.

Postoperative brain MRIs (one month and six months after surgery) were examined to identify LMD, and FLAIR and gadolinium-enhanced T1-weighted sequences were analyzed by two independent observers (DG and FB), blinded to the violation of ventricular walls during surgery. We used a numerical code instead of the patients' names to identify them: this allowed us to examine the two scans independently, preventing a potential bias related to the previous knowledge of VE. The LMD was defined as leptomeningeal contrast enhancement along the contours of the gyri and sulci, as nodular enhancement in the subarachnoid space, or along the subependymal zone [15]. A six-month follow-up was considered the cut-off for the absence of LMD. Patients with consolidated disease recurrence at early postoperative imaging were excluded from the analysis since LMD could develop directly from the relapsing tumor.

To highlight the specific risk of LMD associated with VE, we analyzed the LMD rate in the subgroup of periventricular

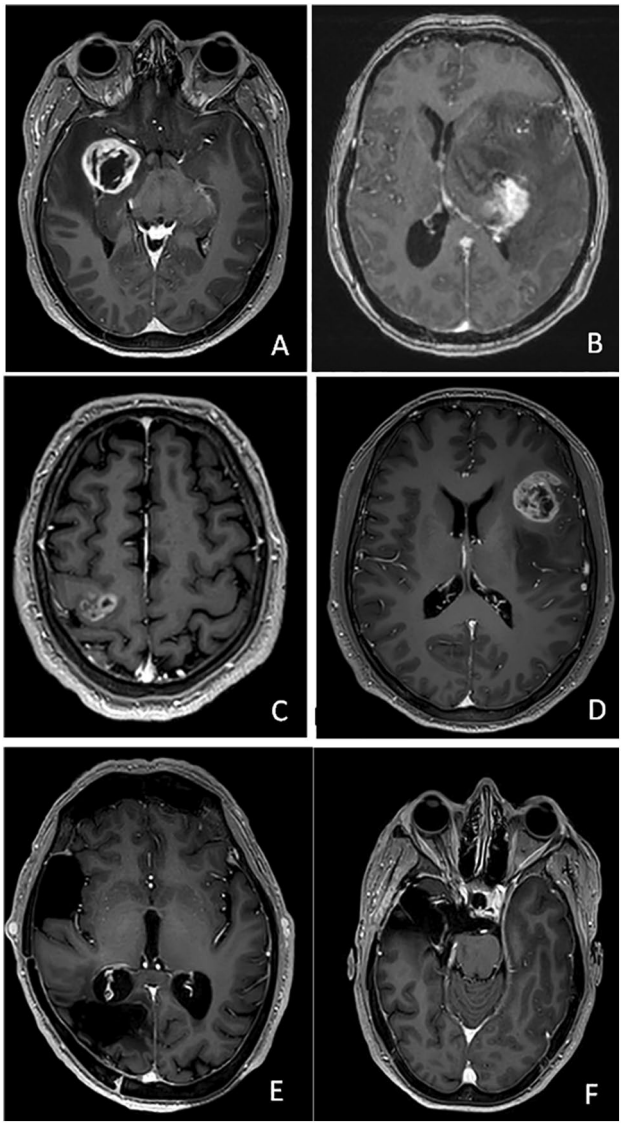

Fig. 1 periventricular GBM (**A**, **B**); not periventricular GBM (**C**, **D**); VE (**E**, **F**); *VE* ventricular entry, *GBM* glioblastoma multiforme

GBM. We subdivided this subgroup into VE and not-VE and calculated each LMD rate.

A forward and backward logistic regression analysis was performed to evaluate the association of periventricular location and VE with LMD, considering demographic data and, when available, molecular biomarkers (Isocitrate dehydrogenase [IDH]1/2 and ATRX gene mutations, O-6-Methylguanine-DNA Methyltransferase [MGMT] promoter methylation) as covariates. Variables with p values <0.2 in the univariate analysis were included in the multivariate analysis. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were thus estimated by a logistic regression model. Statistical analysis was performed with MedCalc (version 9.6.2.0; Mariakerke, Belgium). The statistical significance threshold was set at $p<0.05$.

Results

All results are summarized in Table 1.

During the study period, 200 patients (110 male and 90 female, 55% vs. 45%) with a median age of 63.28 years (± 10.32, range 21–86) underwent exeresis of intracranial GBM (191 patients [95.5%] were GBM of the first diagnosis; nine patients [4.5%] were recurrences).

The mean follow-up was 8.6 months (± 6.7). GBM localization was periventricular in 139 patients (69.5%) and far from the ventricle in 61 patients (30.5%). The VE was observed in 102 cases (51%), and MRI was inconclusive for VE in 10 of these patients. In these cases, we searched for VE in surgical reports, which was present in 6 of these 10 cases.

The IDH status was available for 50 patients (25%), and an IDH-1 or -2 mutation was detected in 11 cases (5.5%). The MGMT promotor methylation was present in 119 cases (59.5%) and not reported in 12 cases (6%). The localization was periventricular in 139 cases (69.5%), and the VE was more frequent in peri-ventricular GBM (80 patients) than in cases of GBM far from the ventricle (22 patients) (58% vs. 36%). LMD was observed in 32 cases (16%): in 13 cases among these (40.6%), LMD arose between one and six months of follow-up, and in 19 cases (59.4%) occurred 6 months after surgery. LMD was strongly associated with VE ($p<0.0001$) (see also Table 1). We did not find higher rates of post-surgical LMD in periventricular GBM: in this group, the rate of LMD was 19% (26 patients), and in non-periventricular GBM, it was 10% (6 cases) ($p=0.11$) (Fig. 2).

Concerning VE during surgical exeresis, LMD rates in periventricular GBM was 31% when VE was performed (25 cases), whereas it was 4% when VE did not occur (1 patient) ($p=0.01$).

Analyzing data in univariate logistic regression, VE was the only factor significantly associated with LMD (OR 8.89, CI 2.98–26.47, $p<0.001$). The periventricular localization was included in the multivariate analysis since it seemed to be associated with LMD, although not significantly (OR 2.1, CI 0.82–5.42, $p=0.121$). Both forward and backward multivariate logistic regression analyses gave the same results and, thus, the same OR. Only VE showed a strong significant association with LMD (OR 8.36, CI 2.78–25.11, $p<0.001$), whereas periventricular localization did not (OR 1.48, CI 0.54–4.02, p 0.436). A univariate logistic regression included the IDH status and the MGMT promotor methylation. Detailed results of logistic regression analyses are reported in Tables 2 and 3.

Table 1 Final population characteristics (*GBM* glioblastoma multiforme, *VE* ventricular entry)

Total number	200
Sex	
- Male	110 (55%)
- Female	90 (45%)
Type of resection	
- First exeresis	191 (95.5%)
- Exeresis of recurrences	9 (4.5%)
Mean age	63.28 (± 10.32)
Mean time of follow-up (months)	8.6 (± 6.7)
Relationship with ventricle	
- Periventricular GBM	139 (69.5%)
- Periventricular GBM	61 (30.5%)
Ventricular entry	102 (51%)
Genotype	
- IDH mutant	11 (5.5%)
- Wild-type	39 (19.5%)
- Reported	150 (75%)
- Methylated	119 (59.5%)
- Non MGMT-methylated	69 (34.5%)
- Reported	12 (6%)
VE	
- In periventricular GBM	80 (58%)
- In not periventricular GBM	22 (36%)
LMD	
- VE	28 (27.4%)
- Not-VE	4 (4%)

Discussion

In this work, we aimed to clarify the influence of VE during GBM exeresis on the spread of glial tumor cells through CSF. LMD related to GBM is associated with shorter OS [5, 15, 22], thereby representing an adverse prognostic factor. We observed higher rates of LMD when VE was performed than in cases where this surgical event did not occur.

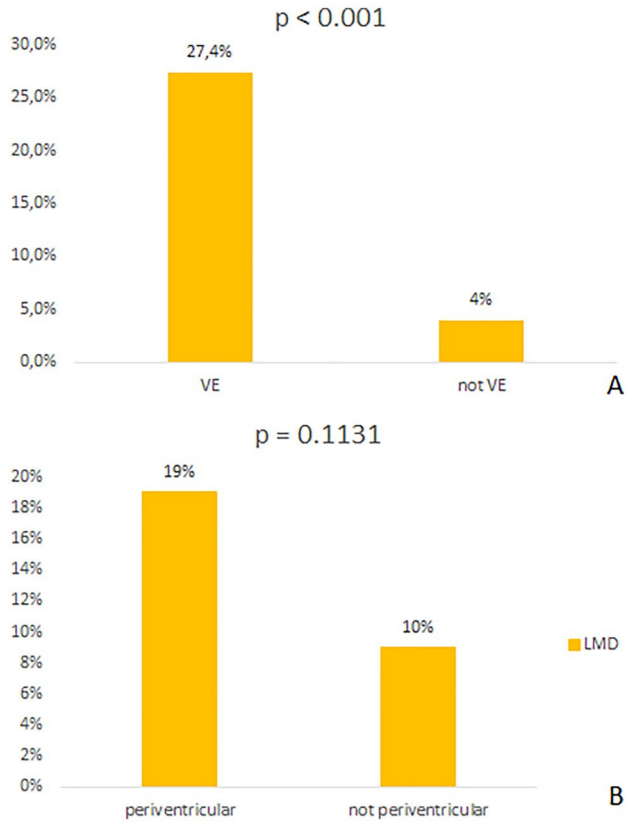

Fig. 2 LMD in VE and not VE group (**A**). LMD in the periventricular and not the periventricular group (**B**). *LMD* leptomeningeal dissemination, *VE* ventricular entry, *not VE* not ventricular entry

Table 2 Odds ratio with 95% confidence interval and p values after univariate analysis for association with LMD

Variable	P value	Odds ratio	95% CI
Ventricular entry	**< 0.001**	**8.89**	**2.98–26.47**
Periventricular location	0.121	2.1	0.82–5.42
Age	0.522	0.99	0.96–1.02
Male sex	0.315	0.67	0.31–1.44
MGMT methylation	0.613	0.81	0.37–1.78
IDH wild-type	0.417	2	0.37–10.69
ATRX mutation	0.463	0.41	0.04–4.33

Table 3 Odds ratio with 95% confidence interval and p values after multivariate logistic regression

Variable	P value	Odds ratio	95% CI
Ventricular entry	**< 0.001**	**8.36**	**2.78–25.11**
Periventricular location	0.436	1.48	0.54–4.02

Our definition of LMD is based on a review of the literature and shared guidelines such as EANO and RANO [15, 33–36]. We decided to consider LMD when lesions disseminated along the subependymal zone, a leptomeningeal contrast enhancement around the gyri and sulci appeared, or multiple contours of nodular deposit in the subarachnoid space were detected: all of these occurrences have been observed to be associated with worse outcomes. We did not use the 5-ALA-derived fluorescence to detect the ventricular wall infiltration because its usage for ventricles is poorly understood and may not always represent tumor infiltration [37].

Indeed, a theoretical risk of false negatives concerning LMD is present since the CSF cytology or ctDNA in the blood sample would be the ultimate test to exclude actual disease spread [37]. However, such exams are not routinely performed, and MRI is the gold standard for GBM follow-up in clinical practice. Moreover, ctDNA blood sampling, despite its promising results so far, is still being investigated.

Cases of SVZ localization with subependymal spread were excluded. This subgroup could arguably be defined as subventricular since an apparent intraventricular spread is already present in these patients, and the ventricular violation by the tumor growth could intuitively bear higher rates of tumor cells spread through CSF.

The risks related to VE during GBM exeresis have been debated in the literature in the last few years [25, 36], but no univocal evidence has been reported, and few works dealt with this topic [20, 26, 38–40]. Jhon et al. [25] indicated that 50% of patients with VE during tumor resection had complications, with hydrocephalus being the most common [36, 41]. We decided not to investigate the onset of hydrocephalus. In fact, given the sequelae of the post-surgical treatments (i.e., brain atrophy, disease progression, side effects), it is hard to distinguish hydrocephalus from hydrocephalus ex vacuo and link potential neurological variations to the onset of hydrocephalus.

Moreover, our work aims to investigate the possible role of VE in causing progression in GBM patients. Typically hydrocephalus is quite common in these patients, but it does not strictly represent disease progression.

The metanalysis of Mistry et al. [16] collects all previous reports about VE and its potential consequences. The Authors found higher odds of developing LMD after VE [16] and also higher rates of complications in SVZ GBM [42] as the only independent variable associated with post-surgical LMD [26]. Young et al. [20] have shown that VE was not associated with worse outcomes and LMD. Because of the insufficient evidence in the literature, neurosurgeons based their surgical strategies on their own experience.

Our results confirm the hypothesis [18, 19] of glial tumor cell dissemination through CSF. We observed higher rates of LMD after VE, with similar results in the subgroup of periventricular GBM. We also confirmed that periventricular GBMs without VE have no higher rates of post-surgical LMD. These results seem to challenge recent findings [20,

26], probably due to higher rates of VE during surgical exeresis in our series (51%) compared to the literature (Young 26.5% [20] and Mistry 36.6% [26]). Different neurosurgeons in different Institutions and the consequent different decision-making strategies influenced the results. There is no standard protocol for performing VE in our Institution, but the neurosurgeon was the same in all cases.

The literature has reported that SVZ localization of GBM is a poor prognosis predictor [43–46] and is associated with a high rate of LMD. According to our data, GBMs not transgressing the ventricular wall (without apparent subependymal involvement) is not associated with a higher rate of post-surgical LMD ($p > 0.1$). This divergence is because there is an overlap in casting cases of VE and periventricular GBM. After all, the VE is achieved more frequently when GBM is periventricular to reach maximal EOR.

GBM genotype has also been considered in our analysis but based on our data, IDH or MGMT promoter status was not correlated to a higher risk of LMD.

Some features of our MRI analysis have to be discussed. Many of the patients in our study performed preoperative 1.5 T MRI and postoperative 3 T MRI. We have included these patients in our work because the tumor's morphological characteristics (volume, contrast enhancement) are similar between 1.5 and 3 T MRI [47]. Another point is the definition we adopted of LMD as a discontinuous abnormal FLAIR signal combined with a contrast-enhancing portion. Increased contrast enhancement detected by MRI just after or during treatment can be produced by several causes, such as postoperative changes, microischemic lesions, and treatment-associated inflammation [48]. Therefore, we considered combining FLAIR and T1-weighted contrast-enhanced MRI to have higher accuracy in identifying LMD.

T1-weighted contrast-enhanced MRI should be used within two days after surgery to assess the EOR and no later than 72 h after the operation. The immediate postoperative MRI in GBM is not routinely done in our Institution, and the early postoperative MRI is at least one-month post-surgery, thereby preventing an exact estimation of the EOR. We excluded patients with disease recurrence at early postoperative MR (i.e., a contrast-enhancing area or FLAIR signal alterations in the surgical cavity). Thus, since only patients with complete tumor removal at early postoperative MRI were considered, no relevant differences in EOR in VE and non-VE groups occurred, and both groups were homogeneous in this respect.

The correlation between VE and the EOR is a relevant aspect. In the literature, the role of gross total resection (GTR) over subtotal resection in progression-free and overall survival is accepted [9, 10], while the superiority of supra-total resection (SpTR) over GTR is less clear [11, 49–51] [57], but has given some promising results. In our series, GTR was the main goal in each case, and the VE has sometimes been performed in not-periventricular GBM, even if the tumor limits were not adjacent to the ventricular walls, to obtain a supratotal resection (SpTR). In the case of apparent subependymal involvement, the patient's prognosis is very scarce [52, 53]. The survival time would probably not be enough to evidence any LMD associated with the VE. In these cases, the maximal EOR could be a positive prognostic factor, and in the cases of SpTR, a possible VE should not be a limit for a wider EOR. However, there are borderline cases in which the VE should be avoided. For instance, in cases of periventricular localization of GBM, without an apparent subependymal involvement, neurosurgeons should be aware of the consequences of VE instead of the possible reach of the supra total resection. In our opinion, EOR must be the primary goal of GBM exeresis but avoiding VE when possible should be another relevant issue.

The principal limitations of our work are its retrospective, non-randomized nature and the insufficient number of patients' spine MRIs pre-or post-surgical exeresis of GBM: the latter point might have brought an underestimation of actual cases of LMD. However, spine imaging is not routinely done as a follow-up investigation in GBM patients unless spinal symptoms develop. Therefore, the topic of spinal LMD in GBM has received only limited attention in the neurosurgical and neuro-oncological debate.

The influence of all the variables investigated in this work on the patients' OS was not investigated. Many other factors, such as adjuvant therapy, molecular patterns, and the size of GBM, can influence survival rates. Despite this, the role of LMD as an adverse prognostic factor on OS is accepted [5, 15, 22].

Conclusion

According to our data, VE during surgical exeresis of GBM increases the rate of post-surgical LMD. Thus, neurosurgeons should avoid VE when feasible to prevent this disease progression, potentially influencing OS negatively. This statement does not override the need for maximal EOR, which must remain the goal of GBM surgery because as one of the foremost positive prognostic factors. Further studies should be oriented to the specific risk of LMD associated with GTR and SpTR groups of patients.

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Declarations

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424. https://doi.org/10.3322/caac.21492
2. Wirsching HG, Galanis E, Weller M (2016) Glioblastoma. Handb Clin Neurol 134:381–397. https://doi.org/10.1016/b978-0-12-802997-8.00023-2
3. Davis ME (2016) Glioblastoma: overview of disease and treatment. Clin J Oncol Nurs 20:S2-8. https://doi.org/10.1188/16.Cjon.S1.2-8
4. 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. https://doi.org/10.1158/1055-9965.Epi-14-0275
5. Wright CH, Wright J, Onyewadume L, Raghavan A, Lapite I, Casco-Zuleta A, Lagman C, Sajatovic M, Hodges TR (2019) Diagnosis, treatment, and survival in spinal dissemination of primary intracranial glioblastoma: systematic literature review. J Neurosurg Spine. https://doi.org/10.3171/2019.5.Spine19164
6. 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. https://doi.org/10.1056/NEJMoa043331
7. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T (2008) Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 62: 564–576; discussion 564–576. https://doi.org/10.1227/01.neu.0000317304.31579.17
8. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, Taylor LP, Lieberman F, Silvani A, Fink KL, Barnett GH, Zhu JJ, Henson JW, Engelhard HH, Chen TC, Tran DD, Sroubek J, Tran ND, Hottinger AF, Landolfi J, Desai R, Caroli M, Kew Y, Honnorat J, Idbaih A, Kirson ED, Weinberg U, Palti Y, Hegi ME, Ram Z (2015) Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. JAMA 314:2535–2543. https://doi.org/10.1001/jama.2015.16669
9. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95:190–198. https://doi.org/10.3171/jns.2001.95.2.0190
10. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, Patel AS, Rizk EB, Suki D, Sawaya R, Glantz M (2016) Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol 2:1460–1469. https://doi.org/10.1001/jamaoncol.2016.1373
11. Sanai N, Berger MS (2018) Surgical oncology for gliomas: the state of the art. Nat Rev Clin Oncol 15:112–125. https://doi.org/10.1038/nrclinonc.2017.171
12. Hallaert G, Pinson H, Van den Broecke C, Vanhauwaert D, Van Roost D, Boterberg T, Kalala JP (2020) Subventricular zone contacting glioblastoma: tumor size, molecular biological factors and patient survival. Acta Oncol (Stockholm, Sweden) 59:1474–1479. https://doi.org/10.1080/0284186x.2020.1794032
13. Ahmadipour Y, Jabbarli R, Gembruch O, Pierscianek D, Darkwah Oppong M, Dammann P, Wrede K, Özkan N, Müller O, Sure U, El Hindy N (2019) Impact of multifocality and molecular markers on survival of glioblastoma. World Neurosurg 122:e461–e466. https://doi.org/10.1016/j.wneu.2018.10.075
14. Arita N, Taneda M, Hayakawa T (1994) Leptomeningeal dissemination of malignant gliomas. Incidence, diagnosis and outcome. Acta Neurochir 126:84–92. https://doi.org/10.1007/bf01476415
15. Jiang H, Yu K, Li M, Cui Y, Ren X, Yang C, Zhao X, Lin S (2020) Classification of progression patterns in glioblastoma: analysis of predictive factors and clinical implications. Front Oncol 10:590648. https://doi.org/10.3389/fonc.2020.590648
16. Mistry AM, Kelly PD, Thompson RC, Chambless LB (2018) Cancer dissemination, hydrocephalus, and survival after cerebral ventricular entry during high-grade glioma surgery: a meta-analysis. Neurosurgery 83:1119–1127. https://doi.org/10.1093/neuros/nyy202
17. 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. https://doi.org/10.1007/s11060-014-1592-1
18. Elliott JP, Keles GE, Waite M, Temkin N, Berger MS (1994) Ventricular entry during resection of malignant gliomas: effect on intracranial cerebrospinal fluid tumor dissemination. J Neurosurg 80:834–839. https://doi.org/10.3171/jns.1994.80.5.0834
19. Grabb PA, Albright AL, Pang D (1992) Dissemination of supratentorial malignant gliomas via the cerebrospinal fluid in children. Neurosurgery 30:64–71. https://doi.org/10.1227/00006123-199201000-00012
20. Young JS, Gogos AJ, Pereira MP, Morshed RA, Li J, Barkovich MJ, Hervey-Jumper SL, Berger MS (2021) Effects of ventricular entry on patient outcome during glioblastoma resection. J Neurosurg. https://doi.org/10.3171/2020.7.Jns201362
21. Zhang K, Yang Y, Zhuang J, Guo G, Chao X, Zhang Z (2022) Intracranial dissemination of glioblastoma multiforme: a case report and literature review. J Int Med Res 50:3000605221112047. https://doi.org/10.1177/03000605221112047
22. Bae JS, Yang SH, Yoon WS, Kang SG, Hong YK, Jeun SS (2011) The clinical features of spinal leptomeningeal dissemination from malignant gliomas. J Kor Neurosurg Soc 49:334–338. https://doi.org/10.3340/jkns.2011.49.6.334

23. Cahill DP (2021) Extent of resection of glioblastoma: a critical evaluation in the molecular era. Neurosurg Clin N Am 32:23–29. https://doi.org/10.1016/j.nec.2020.09.006
24. Revilla-Pacheco F, Rodríguez-Salgado P, Barrera-Ramírez M, Morales-Ruiz MP, Loyo-Varela M, Rubalcava-Ortega J, Herrada-Pineda T (2021) Extent of resection and survival in patients with glioblastoma multiforme: Systematic review and meta-analysis. Medicine 100:e26432. https://doi.org/10.1097/md.0000000000026432
25. John JK, Robin AM, Pabaney AH, Rammo RA, Schultz LR, Sadry NS, Lee IY (2017) Complications of ventricular entry during craniotomy for brain tumor resection. J Neurosurg 127:426–432. https://doi.org/10.3171/2016.7.Jns16340
26. 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. https://doi.org/10.1093/neuros/nyz144
27. Sanai N, Tramontin AD, Quiñones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, Lawton MT, McDermott MW, Parsa AT, Manuel-García Verdugo J, Berger MS, Alvarez-Buylla A (2004) Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature 427:740–744. https://doi.org/10.1038/nature02301
28. Sanai N, Alvarez-Buylla A, Berger MS (2005) Neural stem cells and the origin of gliomas. N Engl J Med 353:811–822. https://doi.org/10.1056/NEJMra043666
29. Berendsen S, van Bodegraven E, Seute T, Spliet WGM, Geurts M, Hendrikse J, Schoysman L, Huiszoon WB, Varkila M, Rouss S, Bell EH, Kroonen J, Chakravarti A, Bours V, Snijders TJ, Robe PA (2019) Adverse prognosis of glioblastoma contacting the subventricular zone: biological correlates. PLoS ONE 14:e0222717. https://doi.org/10.1371/journal.pone.0222717
30. 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. https://doi.org/10.1007/s11060-017-2562-1
31. Molinaro AM, Hervey-Jumper S, Morshed RA, Young J, Han SJ, Chunduru P, Zhang Y, Phillips JJ, Shai A, Lafontaine M, Crane J, Chandra A, Flanigan P, Jahangiri A, Cioffi G, Ostrom Q, Anderson JE, Badve C, Barnholtz-Sloan J, Sloan AE, Erickson BJ, Decker PA, Kosel ML, LaChance D, Eckel-Passow J, Jenkins R, Villanueva-Meyer J, Rice T, Wrensch M, Wiencke JK, Oberheim Bush NA, Taylor J, Butowski N, Prados M, Clarke J, Chang S, Chang E, Aghi M, Theodosopoulos P, McDermott M, Berger MS (2020) Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma. JAMA Oncol 6:495–503. https://doi.org/10.1001/jamaoncol.2019.6143
32. Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, Berger MS, Parsa AT (2012) Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg 117:1032–1038. https://doi.org/10.3171/2012.9.Jns12504
33. Piper RJ, Senthil KK, Yan JL, Price SJ (2018) Neuroimaging classification of progression patterns in glioblastoma: a systematic review. J Neurooncol 139:77–88. https://doi.org/10.1007/s11060-018-2843-3
34. Rapp M, Baernreuther J, Turowski B, Steiger HJ, Sabel M, Kamp MA (2017) Recurrence pattern analysis of primary glioblastoma. World Neurosurg 103:733–740. https://doi.org/10.1016/j.wneu.2017.04.053
35. Weller M, van den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, Bendszus M, Balana C, Chinot O, Dirven L, French P, Hegi ME, Jakola AS, Platten M, Roth P, Rudà R, Short S, Smits M, Taphoorn MJB, von Deimling A, Westphal M, Soffietti R, Reifenberger G, Wick W (2021) EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 18:170–186. https://doi.org/10.1038/s41571-020-00447-z
36. Castro BA, Imber BS, Chen R, McDermott MW, Aghi MK (2017) Ventriculoperitoneal Shunting for Glioblastoma: Risk Factors, Indications, and Efficacy. Neurosurgery 80:421–430. https://doi.org/10.1227/neu.0000000000001263
37. Müther M, Stummer W (2020) Ependymal fluorescence in fluorescence-guided resection of malignant glioma: a systematic review. Acta Neurochir 162:365–372. https://doi.org/10.1007/s00701-019-04144-4
38. 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. https://doi.org/10.1097/00006123-199010000-00002
39. de Groot JF, Fuller G, Kumar AJ, Piao Y, Eterovic K, Ji Y, Conrad CA (2010) Tumor invasion after treatment of glioblastoma with bevacizumab: radiographic and pathologic correlation in humans and mice. Neuro Oncol 12:233–242. https://doi.org/10.1093/neuonc/nop027
40. Lu KV, Chang JP, Parachoniak CA, Pandika MM, Aghi MK, Meyronet D, Isachenko N, Fouse SD, Phillips JJ, Cheresh DA, Park M, Bergers G (2012) VEGF inhibits tumor cell invasion and mesenchymal transition through a MET/VEGFR2 complex. Cancer Cell 22:21–35. https://doi.org/10.1016/j.ccr.2012.05.037
41. Marquardt G, Setzer M, Lang J, Seifert V (2002) Delayed hydrocephalus after resection of supratentorial malignant gliomas. Acta Neurochir 144: 227–231; discussion 231. https://doi.org/10.1007/s007010200030
42. Mistry AM, Hale AT, Chambless LB, Weaver KD, Thompson RC, Ihrie RA (2017) Influence of glioblastoma contact with the lateral ventricle on survival: a meta-analysis. J Neurooncol 131:125–133. https://doi.org/10.1007/s11060-016-2278-7
43. Chaichana KL, Pendleton C, Chambless L, Camara-Quintana J, Nathan JK, Hassam-Malani L, Li G, Harsh GRT, Thompson RC, Lim M, Quinones-Hinojosa A (2013) Multi-institutional validation of a preoperative scoring system which predicts survival for patients with glioblastoma. J Clin Neurosci 20:1422–1426. https://doi.org/10.1016/j.jocn.2013.02.007
44. Comas S, Luguera E, Molero J, Balaña C, Estival A, Castañer S, Carrato C, Hostalot C, Teixidor P, Villà S (2021) Influence of glioblastoma contact with the subventricular zone on survival and recurrence patterns. Clin Transl Oncol 23:554–564. https://doi.org/10.1007/s12094-020-02448-x
45. Yang W, Xu T, Garzon-Muvdi T, Jiang C, Huang J, Chaichana KL (2018) Survival of ventricular and periventricular high-grade gliomas: a surveillance, epidemiology, and end results program-based study. World Neurosurg 111:e323–e334. https://doi.org/10.1016/j.wneu.2017.12.052
46. Chaichana K, Parker S, Olivi A, Quiñones-Hinojosa A (2010) A proposed classification system that projects outcomes based on preoperative variables for adult patients with glioblastoma multiforme. J Neurosurg 112:997–1004. https://doi.org/10.3171/2009.9.Jns09805
47. Tselikas L, Souillard-Scemama R, Naggara O, Mellerio C, Varlet P, Dezamis E, Domont J, Dhermain F, Devaux B, Chrétien F, Meder JF, Pallud J, Oppenheim C (2015) Imaging of gliomas at 1.5 and 3 Tesla - A comparative study. Neuro Oncol 17:895–900. https://doi.org/10.1093/neuonc/nou332
48. Zikou A, Sioka C, Alexiou GA, Fotopoulos A, Voulgaris S, Argyropoulou MI (2018) Radiation necrosis, pseudoprogression, pseudoresponse, and tumor recurrence: imaging challenges for

the evaluation of treated gliomas. Contrast Media Mol Imaging 2018:6828396. https://doi.org/10.1155/2018/6828396
49. 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. https://doi.org/10.3171/2011.2.jns10998
50. Wykes V, Zisakis A, Irimia M, Ughratdar I, Sawlani V, Watts C (2021) Importance and evidence of extent of resection in glioblastoma. J Neurol Surg Part A 82:75–86. https://doi.org/10.1055/s-0040-1701635
51. 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. https://doi.org/10.3171/2015.5.Jns142087
52. Parsa AT, Wachhorst S, Lamborn KR, Prados MD, McDermott MW, Berger MS, Chang SM (2005) Prognostic significance of intracranial dissemination of glioblastoma multiforme in adults. J Neurosurg 102:622–628. https://doi.org/10.3171/jns.2005.102.4.0622
53. Ramakrishna R, Barber J, Kennedy G, Rizvi A, Goodkin R, Winn RH, Ojemann GA, Berger MS, Spence AM, Rostomily RC (2010) Imaging features of invasion and preoperative and postoperative tumor burden in previously untreated glioblastoma: correlation with survival. Surg Neurol Int. https://doi.org/10.4103/2152-7806.68337