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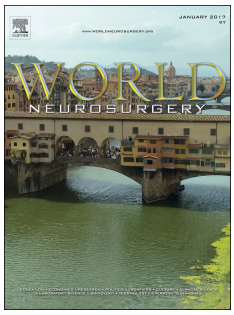


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## CRediT Statement

**Harrison Faulkner:** Methodology, Formal analysis. **Omar Arnaout:** Writing – Original Draft, Data Curation. **Reid Hoshide:** Formal analysis. **Isabella Young:** Writing – Review & Editing, Validation. **Jacky Yeung:** Validation, Visualization. **Michael Sughrue:** Supervision, Methodology. **Charles Teo**: Conceptualization, Supervision.

# The Surgical Resection of Brainstem Glioma: Outcomes and Prognostic Factors

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**Abstract**

*Object:* The management of brainstem glioma remains controversial, with increasing evidence supporting surgical resection as the primary treatment for a select subgroup of tumours. However, there remains no consensus on the specific benefits and risks, the selection of surgical candidates, and prognostic factors that may further refine surgical indications.

*Methods:* A retrospective, single-surgeon, chart review was performed for all patients who underwent surgical treatment for radiographically suspected brainstem glioma between 2000 and 2017. Pre-operative and post-operative radiographic evaluations on MRI were conducted. Survival outcomes were collected, and machine learning techniques were used for multivariate analysis.

*Results:* 77 patients with surgical treatment of brainstem glioma were identified, with a median age of 9 (range 0 – 58). The cohort included 64% low-grade (I and II) and 36% high-grade (III and IV) tumours. For all patients, the 1- and 5-year overall survival rates were 76.4% and 62.3%, respectively. Transient neurological deficit was present in 34% of cases, and permanent deficit in a further 29%.

*Conclusion:* The radical surgical resection of brainstem gliomas can be performed with acceptable risk in well-selected cases and likely confers survival advantage for what is otherwise a rapidly and universally fatal disease. Various radiographic features are useful during patient selection and may guide treatment selection.

## Introduction

Brainstem gliomas have a uniquely devastating potential given the eloquence and intrinsic structural complexity of the brainstem. As such, the natural history of these tumours is one of debilitating clinical progression and poor survival. For much of neurosurgical history the eloquence of the brainstem was considered an absolute contraindication to surgery, with Matson stating in his seminal text that "regardless of specific histology, brainstem gliomas must be classified as malignant tumours since their location in itself renders them inoperable".[1]

The advent of modern neuroimaging has since demonstrated the heterogeneity of brainstem gliomas, and improved surgical technology has contributed to the safety of their resection. For a select group of grade I tumours surgery is increasingly accepted as the primary mode of treatment. Conversely, it is well-established that a highly malignant entity known as diffuse midline glioma (DMG, previously diffuse intrinsic pontine glioma or DIPG) is truly inoperable and should be treated non-surgically. However, for tumours that lie between these extreme ends of the spectrum the role of surgical treatment remains unclear and controversial. For these tumours there is no consensus on the indications for surgery, and establishing the specific benefits and risks of resection is complicated by limitations within the literature including small and incomparable study populations and inconsistent outcome reporting. Further, the diagnosis of brainstem glioma often requires histopathological diagnosis, and with controversy surrounding the role of biopsy the pre-operative selection of surgical candidates presents an ongoing challenge.[2-5]

Given the devastating natural history of brainstem glioma and the limited efficacy of radiotherapy and chemotherapy treatments, elucidation of the role and benefit of surgical resection is of clinical significance. This study reviews a single surgeon's experience. Specifically, it aims to:

1) Report the outcomes of surgical resection for brainstem glioma
2) Improve the selection of surgical candidates by identifying prognostic factors

## Materials and Methods

*Study Population*

Review of a prospectively maintained database identified 77 consecutive patients who underwent surgery for brainstem glioma at the Centre for Minimally Invasive Neurosurgery in Sydney, Australia between 2000 and 2017. A subset of 38 patients with brainstem glioma deemed inoperable by the senior author (C.T), in which there was the presence of tumour invasion of pontine fibres and the lack of T1-T2 sequence equality (i.e. the T1 abnormality is volumetrically equivalent/similar to the T2 signal), was identified. Follow-up data for this group was unavailable, but it served as a useful point of objective comparison of pre-operative features. The diagnosis of brainstem glioma was based on radiographic characteristics of a neoplastic lesion located within medulla oblongata, pons or midbrain at the time of first presentation; rarely, the results of a prior biopsy were available. The radiographs were reviewed by two independent neurosurgeons (O.A and R.H) to confirm inclusion in the study, as well as to extract relevant information as detailed in *Data Collection.*

Exclusion criteria included insufficient pre-operative data or follow-up (n = 0), tumours of non-brainstem origin (n = 4) and extra-axial tumours (n = 3). Patients who the lead surgeon operated on abroad were also excluded due to insufficient follow-up records (n=6). Patients who underwent surgical procedures without resection, for example endoscopic third ventriculostomy, were also excluded.

*Data Collection*

Medical records from the study centre, as well as from external providers involved with patient care, were reviewed to obtain demographic, clinical, surgical, histopathological and follow-up data.

Surgical complications were defined and classified according to the system proposed by Landriel Ibañez et al.[6] Permanent neurological deficit was defined as focal deficit not present pre-operatively and persistent 1 year post-surgery. Disease progression was defined as clinical or radiographic evidence of tumour recurrence at or near the site of original pathology. All follow up is current as of September 1st, 2017.

*Imaging Protocol*

Two investigators (O.A and R.H), blinded to histopathology and clinical outcome, reviewed all MRI scans from the time of initial diagnosis. Recorded variables included location of tumour epicentre, vertical extension, ventral or dorsal origin, central or lateral origin, ventriculomegaly, tumour invasion of pontine fibres, basilar artery encasement, T1-T2 sequence equality (for which the T1 abnormality is volumetrically equivalent/similar to the T2 signal), size approximation, largest diameter, surface contact, exophytic component, gadolinium contrast enhancement pattern and cyst presence. Postoperative imaging was routinely obtained within 48 hours of surgery and was reviewed for extent of resection, which was classified as biopsy, subtotal (residual nodular enhancement), near-total (residual enhancement of the surgical cavity rim) or gross-total (no residual enhancement). For non-enhancing lesions, T2 signal intensity was used instead.

**Results**

*Patient Characteristics*

The population characteristics for the 77 operative patients are summarised in Table 1. The sample included 42 (55%) males and 35 (45%) females, with a median age at diagnosis of 9 years (range 0 – 58 years).

The most common presenting symptoms included ataxia (38%), diplopia (36%), headache (31%), nausea and vomiting (25%), and hemiparesis or hemiparaesthesia (19%). The median duration of symptom onset was 2 months (range 0.25 – 180). At the time of surgery, the symptom distribution was similar, though all deficits were more common and facial weakness was notably prevalent (38%). The median Karnofsky Performance Scale at the time of surgery was 70 (range 10 – 100).

Treatment prior to surgery at our centre was common. 28 (36%) patients underwent previous surgery, 25 (32%) had prior radiotherapy and 24 (31%) had prior chemotherapy. The time between diagnosis and surgery at our centre was a median of 8 months.

*Radiology Findings*

The most common tumour location was the pons (47%), followed by the midbrain (32%), cervicomedullary junction (12%) and medulla (9%). Tumours were commonly of dorsal origin (64%) and lateralised (71%), and predominantly made contact with the surface of the brainstem (96%). Few tumours displayed basilar encasement (15%), the presence of pontine fibre invasion (17%) or T1-T2 inequality (24%).

*Pathology*

The tumour type was predominantly astrocytic (76%). This included 24 (31%) juvenile pilocytic astrocytomas, 11 (14%) diffuse astrocytomas, 8 (10%) anaplastic

astrocytomas and 16 (21%) glioblastoma multiformes. Ependymoma accounted for 6 (8%) tumours, and other findings included 4 (5%) gangliogliomas, 1 (1%) oligogendroglioma, 1 (1%) primitive neuroectodermal tumour, 1 (1%) atypical neurocytoma, 1 (1%) granuloma, 1 (1%) pleomorphic xanthroastrocytoma, 1 (1%) rosette-forming glioneuronal tumour of the fourth ventricle, 1 (1%) embryonal tumour and 1 (1%) xanthoma. Stratified by WHO grade, 40% of tumours were grade I, 20% grade II, 17% grade III and 18% grade IV.

*Surgery*

All 77 patients underwent surgery. Biopsy with the aim of tissue diagnosis for clinical trial placement was performed in 3 (4%) cases. The remainder underwent aggressive resection with the goal of complete removal wherever possible, which was subtotal in 32 (42%) of cases, near-total in 18 (23%) and gross-total in 24 (31%).

Intraoperative complications occurred in 3 (4%) cases. In two instances surgery was halted, once due to bradycardia and hypotension and once due to desaturation, and in the latter case the surgery was performed at a subsequent date.

*Survival*

Figure 2 shows the overall survival (OS) and progression-free survival (PFS) of the cohort. The 1-year and 5-year OS/PFS rate for all tumours was 76%/70% and 62%/51%, respectively. The estimated mean OS/PFS was 170/138 months, and the median PFS was 70 months. Figure 3 and Table 2 summarise the survival rates stratified by tumour WHO grade.

*Follow-Up*

New neurological deficit was common – 26 (34%) patients experienced transient deficit in the immediate post-operative period and a further 16 (29%) suffered permanent

deficit persistent at 1-year. Common permanent deficits included ophthalmalgia and hemiparesis, both present in 9 cases. Severe debilitation occurred in 3 cases: 2 patients had long-term respiratory insufficiency and 1 suffered quadriplegia. Other post-operative complications (not including these foreseeable neurological deficits) occurred in 12 (16%) of cases, most commonly CSF leakage (6%), hydrocephalus (4%) and wound infection (3%). Details on further surgery and adjuvant radiotherapy and/or chemotherapy is detailed in Table 1. At the time of study conclusion 57% of patients remained alive.

## Discussion

This study aims to report the outcomes of resection, and to elucidate the indications for surgery. We present a large, single-surgeon series with exhaustive data collection and complete follow-up. We demonstrated prognostic factors associated with survival outcomes using a machine-learning method.

A growing body of evidence demonstrates the value of surgical resection for brainstem glioma, and while a group of diffusely infiltrative tumours truly are inoperable it is clear that many focal lesions benefit from surgical resection. However, the current state of the literature is limited by small sample sizes and by variability between populations, likely a result of the unclear indications for surgery. Differences in surgeon experience and skill are also likely given the relative rarity of brainstem surgery.

### *Patient Characteristics, Radiology Findings and Pathology*

The diverse range of patient demographics, clinical presentations, radiographic features and pathological entities within our series reinforces the now widely accepted conception of brainstem glioma as a heterogeneous group.[2,4,7-13] Further, it demonstrates that

some features commonly associated with diffusely infiltrative disease are present in patients with benign pathologies, for example a short duration of symptom onset (<3 months).

*Survival*

Several series (Table 3) have demonstrated the feasibility of surgery for brainstem glioma, and in recent years success has been achieved particularly in the setting of low-grade histology. Notably, with a large series of predominantly grade I tumours, Klimo et al.[14] reported 5- and 10-year OS rates of 98.0% and 89.6%, respectively. Direct comparison between series is complicated by inconsistent metrics and differing tumour populations. Regardless, our results reinforce the achievability of long-term survival among low-grade brainstem gliomas, with 2-, 5- and 10-year OS of 91%, 88% and 80%, respectively. While most low-grade series are comprised largely or solely of grade I tumours, our series contained a more diverse population and the preservation of good survival demonstrates the success of broader selection criteria. While it has been argued that grade II tumours lie on the biological spectrum of malignancy and should be considered diffuse by nature and therefore inoperable, our results demonstrate a survival advantage among this group too.[15]

The increasingly well-documented role of surgery represents an important step in the treatment of low-grade brainstem glioma. The conventional use of radiotherapy and/or chemotherapy has produced relatively poor outcomes, with reported survival rates ranging from 5-year OS of 55%[16] to 1-year OS of 63% for grade I tumours alone.[17]

Of greater controversy is the role of surgery in the treatment of malignant brainstem disease. Indeed, several authors have concluded that resection is beneficial only for low-grade tumours.[8,15,18] Comparison of our results with the notoriously poor outcomes of conventional radiotherapy and/or chemotherapy treatment is difficult given the divergent selection criteria: while our series excludes truly diffuse tumours, cohorts for traditional treatment typically

include and even focus on this group. However, among patients with grade III or IV tumours, our series has a 5-year OS of 27% and contains 3 patients with greater than 10 years survival. Although the sample size is small, this demonstrates the possibility of long-term survival in carefully selected patients and suggests that high grade pathology may not be an absolute contraindication to surgery.

*Prognostic Factors*

The results of our univariate analysis reinforce several previously-reported associations. The expected and well-established relationship between survival and WHO grade[15,18-25] was demonstrated, as was the benefit of exophytic extension or surface contact.[4,9,12,14,26-29]

Additional previously reported associations were also replicated, including between survival and duration of symptom onset[15,18,19,23,30,31] , diplopia[15] and basilar encasement.[15] It is hypothesised that a short onset of symptoms indicates rapid tumour growth and progression, while CN VI palsy and encasement of the basilar artery both reflect tumour presence in the ventral pons – the classical location of diffuse intrinsic brainstem glioma or DMG.[13,15] Basilar encasement demonstrated independent significance and so may play a further role, perhaps posing a technical barrier to complete resection or indicating aggressive tumour growth.

Various other prognostic findings within our series have not been previously described. The negative prognostic value of facial weakness has theoretical plausibility – CN VII follows a course through the ventral pons and the facial motor nucleus is located in the ventrolateral pontine tegmentum. As with CN VI palsy, the presence of this sign therefore indicates ventral pontine disease typical of diffusely infiltrative brainstem glioma. The presence of vertical extension is a likely surrogate of tumour size and growth rate, and so correlates negatively with survival. Visible invasion of crossing pontine fibers indicates

tumour infiltration as opposed to expansion, suggesting aggressive biology and difficulty of complete resection. The negative relationship between survival and radiotherapy pre- and post-surgery is not observed when other factors are controlled and is likely a reflection of malignancy.

Of particular importance is the survival advantage associated with extent of resection, which was significant at both the univariate and multivariate level. The need for radical surgery is well-established for tumours in other locations[32], however has remained controversial in the setting of the brainstem. Although some studies support the relationship[22,23,33,34] others have found no correlation.[14] Our series demonstrates the feasibility of radical resection (as illustrated in Figures 5 and 6), and suggest its benefit. However, at least some of the survival advantage is likely due to confounding effect – it is hypothesised that low-grade tumours with favourable biology and prognosis are more easily resected. The high rates of near- and gross- total resection achieved in our series (23% and 31% of cases, respectively) are mirrored in other recent studies: Klimo et al. achieved near- and gross-total resection in 33% and 17% of cases, respectively, Kestle et al. demonstrated gross- or near-total resection in 48% of cases combined and Lesniak et al. reported near-total resection in 28% of cases. [22,14,18]

*Selection Criteria*

Numerous schemes have been proposed for the radiographic classification of brainstem glioma, however few are surgically oriented and there remains confusion regarding the often-conflicting categories and their implications for management. In this context, we present the criteria used to select surgical candidates in this series. Based on previous literature, clinical experience, comparative analysis between the operative and non-operative cohorts and univariate analysis within the operative cohort, we define diffuse, inoperable

brainstem gliomas with several features. They are paediatric tumours arising in the ventral, midline pons, and are commonly large with vertical extension to surrounding structures. Distinctive radiographic features include T1-T2 inequality, visibility of crossing pontine fibres and symmetric encasement of the basilar artery and are exemplified in Figure 7.

*Follow-Up*

The rates of intra- and post-operative complication were aligned with, and in some cases lower than, those reported in the literature.[35,36] Conversely, the high rate of neurological deficit is significant. This is common among other brainstem series[18,37] and is not unexpected given the eloquence of the region.

In many cases, rehabilitation and further intervention (such as strabismus surgery) lessened the functional impact of ongoing deficit. Also, when considered in the context of the patient's pre-operative state, long-term neurological outcome was often positive. However, in patients with poor survival despite treatment there was often insufficient time for improvement. Therefore, the likelihood of deficit must be emphasised during patient discussions and the benefits of surgery must be considered carefully in light of this risk, the nature of possible deficit, the patient's pre-operative state and the wishes of the patient and their family.

*Limitations*

An important limitation of this study is the composition of the operative cohort, which likely suffers referral bias and contains many patients who underwent prior treatment. It is therefore difficult to establish causation (as opposed to correlation), and to make definitive claims of external validity. There is also no control population, such as non-operated patients, and comparison of our outcomes with other surgical and non-surgical series is difficult given

the differences in selection criteria. It would be reasonable to presume that patients who are not eligible for at least a biopsy were likely to fare similarly or worse as the biopsy cohort. The authors acknowledge that there may exist interplay among tumour grade, molecular pathology, and resectability, for which this study was not designed to address. The present report also only demonstrates a single-surgeon series, a larger-scale study utilising multiple surgeons may be necessary to confirm these results. Lastly, there are limitations inherent to all retrospective research, namely issues with the consistency, reliability and availability of collected data.

## Conclusions

There remains no doubt that brainstem glioma represents a diverse, heterogeneous population of tumours that are, in carefully selected cases, best treated with radical surgical resection. We present a single-surgeon series, with patients selected based on the exclusion of radiographically-defined diffuse tumours. This approach has achieved significant survival advantage, and notably when near- or gross-total resection is achieved long-term survival is possible even in the context of malignant disease. Our findings suggest that the historical nihilism surrounding brainstem gliomas should be re-considered, and that our focus should instead be on individualising patient selection so as to achieve the best possible outcomes.

## Disclosure

Michael E. Sughrue and Charles Teo are co-founders of Omniscient Neurotechnolgies. No products directly related to this are discussed in this paper. All other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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**FIGURE LEGENDS**

**Figure 1** – Flow diagram of study recruitment and exclusion

**Figure 2** – Kaplan-Meier survival curve showing OS for the 77 patients comprising the operative cohort

**Figure 3** – Kaplan-Meier survival curve showing OS for the 77 patients comprising the operative cohort, stratified by tumour WHO grade

**Figure 4** – Kaplan-Meier survival curve showing OS for the 77 patients comprising the operative cohort stratified by extent of resection

**Figure 5** – T1-weighted, post-gadolinium contrast MR images depicting pre-operative mid-sagittal (**a**) and axial (**c**) and post-operative mid-sagittal (**b**) and axial (**d**) planes. The midbrain tumour displayed no features of diffuse infiltration and was completely resected through a frontal, interhemispheric approach. The pathology returned as juvenile pilocytic astrocytoma and the patient is alive at study conclusion.

**Figure 6** – MR images depicting pre-operative T1-weighted, post-gadolinium contrast mid-sagittal (**a**) and T2-weighted axial (**c**) and post-operative T1-weighted post-gadolinium contrast mid-sagittal (**b**) and T2-weighted axial (**d**) planes. The medullary tumour features a significant exophytic component and was resected through a suboccipital approach. The pathology returned as diffuse astrocytoma and the patient is alive at study conclusion.

**Figure 7** – The characteristic radiographic features of diffuse, inoperable brainstem glioma. Pontine enlargement of ventral origin is evident in sagittal T2-weigthed (**a**) and T1-weighted non-contrast (**b**) sequences. The presence of crossing pontine fibres is best seen on T2-weighted axial cuts (**c**), as is symmetric encasement of the basilar artery (**d**). T1-T2 inequality indicates tumour invasion and is observed on comparison of T2- (**e**) and T1-weighted post-gadolinium contrast (**f**) sequences, in this case in the axial plane. Each of these tumours were deemed inoperable and treated with palliative radiotherapy.

Table 1 – Characteristics of 77 patients comprising the operative cohort

| Variable | Value |
|---|---|
| Patient characteristics | |
| Sex (%) | |
| Male | 42 (55) |
| Female | 35 (45) |
| Age at diagnosis (years) | |
| Mean | 16 |
| Median | 9 |
| Range | 0 – 58 |
| Clinical factors at diagnosis | |
| Duration of symptoms (months) | |
| Mean | 8 |
| Median | 2 |
| Range | 0.25 – 180 |
| Symptoms (%) | |
| Headache | 24 (31) |
| Nausea/vomiting | 19 (25) |
| Hemiparesis/hemiparaesthesia | 15 (19) |
| Diplopia | 28 (36) |
| Facial weakness | 11 (14) |
| Ataxia | 29 (38) |
| Bulbar signs | 12 (16) |
| Dizziness/vertigo | 8 (10) |
| Hearing loss | 5 (6) |
| Visual field defect | 3 (4) |
| Clinical factors at surgery | |
| Symptoms (%) | |
| Headache | 16 (21) |
| Nausea/vomiting | 9 (12) |
| Hemiparesis/hemiparaesthesia | 38 (49) |
| Diplopia | 37 (48) |
| Facial weakness | 29 (38) |
| Ataxia | 36 (47) |
| Bulbar signs | 23 (30) |
| Dizziness/vertigo | 8 (10) |
| Hearing loss | 11 (14) |
| Visual field defect | 6 (8) |
| KPS | |
| Mean | 60 |
| Median | 70 |
| Range | 10 – 100 |
| Prior treatment (%) | |
| Chemotherapy | 24 (31) |
| Radiotherapy | 25 (32) |
| Surgery | 28 (36) |
| Radiographic features | |
| Tumour location (%) | |
| Cervicomedullary junction | 9 (12) |
| Medulla | 7 (9) |
| Pons | 36 (47) |

| | |
|---|---|
| Midbrain | 25 (32) |
| Growth pattern | |
| Vertical extension (%) | 38 (49) |
| Anteroposterior origin (%) | |
| Ventral | 16 (22) |
| Dorsal | 46 (64) |
| Central | 10 (14) |
| Transverse origin (%) | |
| Lateral | 50 (71) |
| Midline | 20 (29) |
| Crossing cerebellopontine fibres (%) | 12 (17) |
| Ventriculomegaly (%) | 24 (35) |
| Basilar encasement (%) | 11 (15) |
| Volume approximation ($cm^3$) | |
| Mean | 33 |
| Median | 22 |
| Range | 1.9 – 135.4 |
| Largest diameter (cm) | |
| Mean | 3.6 |
| Median | 3.4 |
| Range | 1.4 – 8.5 |
| T1-T2 equality (%) | 34 (76) |
| Exophytic (%) | 50 (69) |
| Surface contact (%) | 71 (96) |
| Contrast enhancement (%) | |
| None | 14 (19) |
| Heterogeneous | 45 (66) |
| Homogenous | 10 (15) |
| Cystic (%) | 26 (36) |
| Histopathological features | |
| Type (%) | |
| Astrocytoma | 59 (77) |
| Juvenile pilocytic astrocytoma | 24 (31) |
| Diffuse astrocytoma | 11 (14) |
| Anaplastic astrocytoma | 8 (10) |
| Glioblastoma multiforme/Diffuse midline glioma | 16 (21) |
| Ependymoma | 6 (8) |
| Other | 12 (16) |
| WHO Grade (%) | |
| I | 31 (40) |
| II | 15 (20) |
| III | 13 (17) |
| IV | 18 (23) |
| Surgical factors (%) | |
| Extent of resection | |
| Biopsy | 3 (4) |
| Subtotal | 32 (42) |
| Near Total | 18 (23) |
| Gross Total | 24 (31) |
| Intraoperative complication (%) | 3 (4) |
| Clinical factors post-surgery (%) | |
| Postoperative complication | 12 (16) |

| | |
|---|---|
| Transient neurological deficit | 26 (34) |
| Clinical factors at last follow-up (%) | |
| Permanent neurological deficit | 16 (29) |
| Further treatment | |
| Chemotherapy | 9 (13) |
| Radiotherapy | 12 (17) |
| Surgery | 14 (18) |
| Alternative | 3 (4) |
| Alive at study conclusion (%) | 44 (57) |
| Length of follow-up | |
| Mean | 80 |
| Median | 71 |
| Range | 2 – 289 |

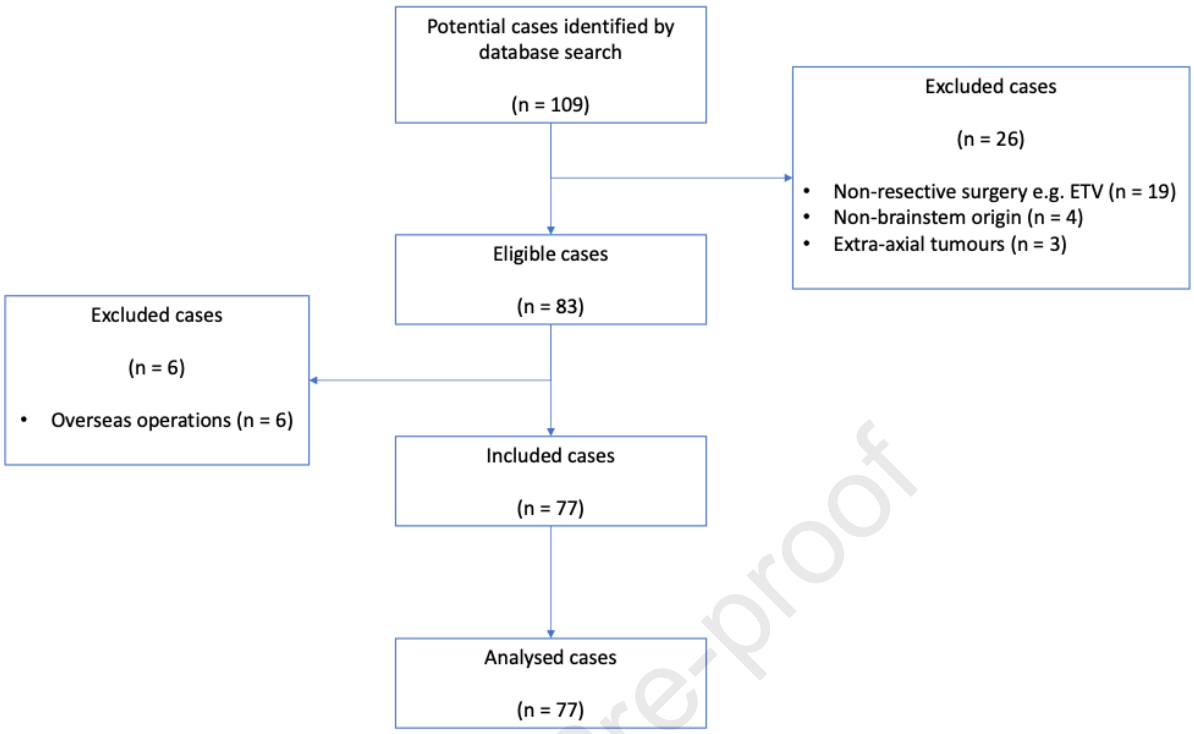
Table 2 - Survival outcomes stratified by tumor WHO grade

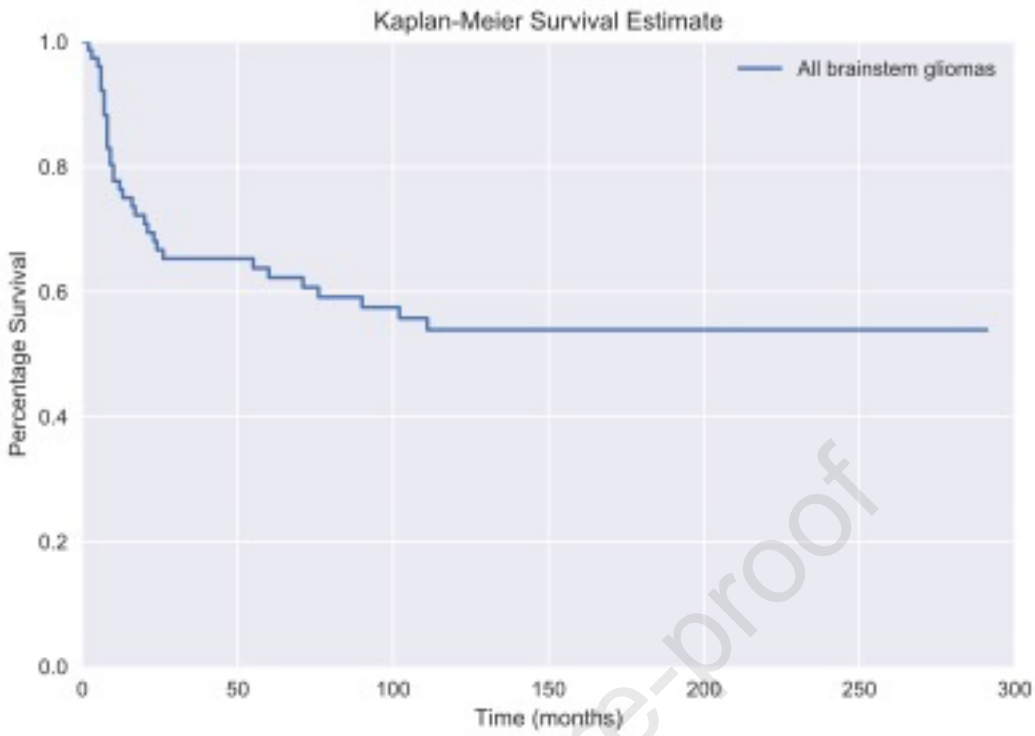
| **Tumour WHO Grade** | **1-Year OS/PFS (%)** | **5-Year OS/PFS (%)** | **Estimated Mean OS/PFS (Months)** | **Median OS/PFS (Months)** |
|---|---|---|---|---|
| I | 100/97 | 96/89 | 273/247 | -/- |
| II | 87/80 | 71/38 | 146/96 | -/54 |
| III | 74/67 | 46/38 | 71/56 | 26/20 |
| IV | 33/28 | 9/7 | 19/17 | 8/8 |

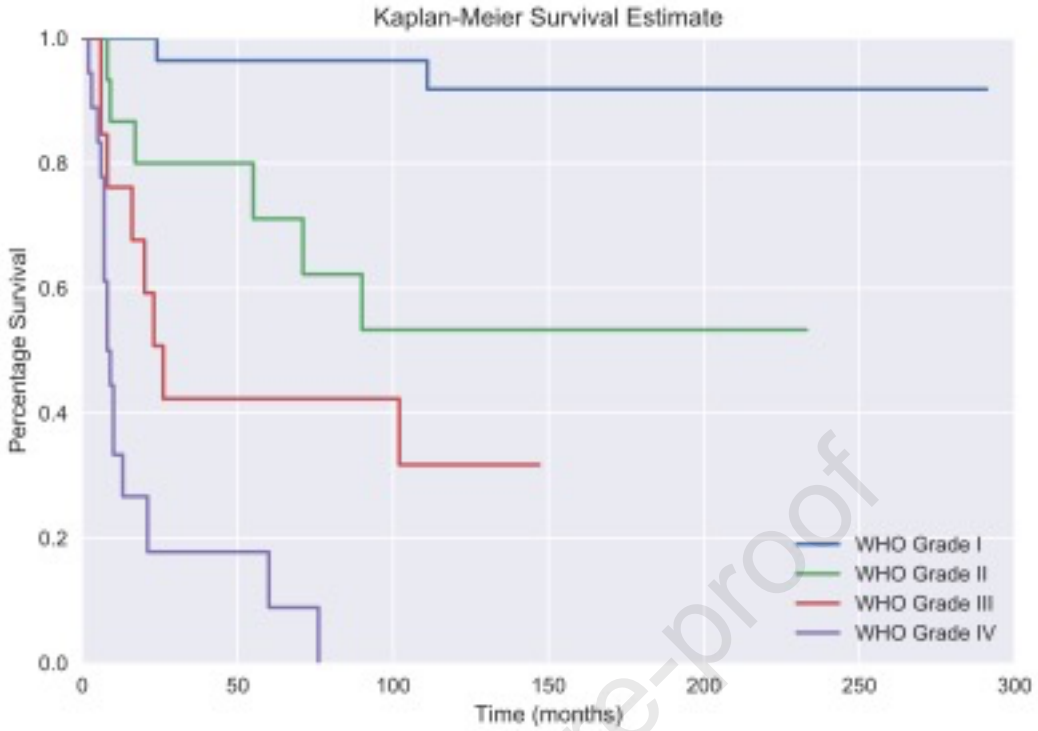
Table 3 - Summary of reported outcomes for the surgical treatment of brainstem glioma

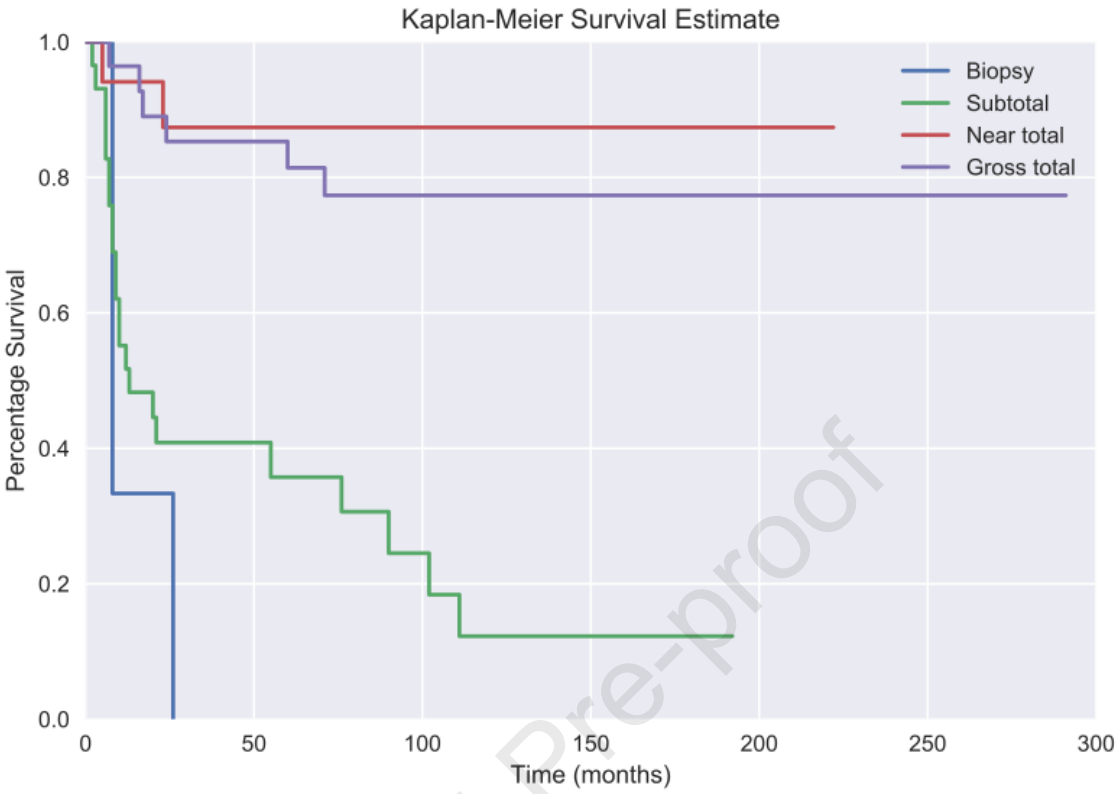
| Reference | n | Age | Classification | Histology | Outcomes |
|---|---|---|---|---|---|
| Epstein and McCleary [13] | 34 | Paediatric | Diffuse intrinsic<br>Focal intrinsic<br>Cervicomedullary | 32% low-grade<br>68% high-grade | • 1-year OS = 30% |
| Pierre-Kahn, Hirsch [50] | 75 | Paediatric | Focal intrinsic<br>Exophytic | 63% low-grade<br>29% high-grade | • 5-year OS = 55%<br>• 10-year OS = 49% |
| Xu, Bao [51] | 22 | Adult | Focal intrinsic<br>Exophytic<br>Cervicomedullary | 82% low-grade<br>9% high-grade | • Postoperative complication rate = 45% |
| Bricolo [52] | 175 | - | Diffuse intrinsic<br>Focal intrinsic<br>Exophytic<br>Cervicomedullary | 59% low-grade<br>41% high-grade | • 55% “good” outcome<br>• 15% “fair” outcome<br>• 30% “death” |
| Farmer, Montes [20] | 16 | Paediatric | Focal intrinsic<br>Exophytic<br>Cervicomedullary | 100% low-grade | • 2-year PFS = 64%<br>• 2-year OS = 100% |
| Lesniak, Klem [24] | 57 | Paediatric | Diffuse intrinsic<br>Focal intrinsic<br>Exophytic | 79% low-grade<br>21% high-grade | • 3-year PFS = 71.9%<br>• 5-year PFS = 45.6% |
| Kestle, Townsend [25] | 28 | Paediatric | Focal intrinsic<br>Exophytic<br>Cervicomedullary | 100% low-grade | • 5-year PFS = 51%<br>• 10-year PFS = 44%<br>• Postoperative complication rate = 71% |
| Mursch, Halatsch [48] | 16 | Adult | Diffuse intrinsic<br>Focal intrinsic<br>Cervicomedullary | 75% low-grade<br>25% high-grade | • Mean OS = 88.1 months<br>• Median OS = 34.5 months<br>• 5-year OS = 37.5%<br>• Postoperative complication rate = 68.8% |
| Miyamoto, Mikuni [53] | 2 | Paediatric | Focal intrinsic | 100% low-grade | • 2-year PFS = 100% |
| Sandri, Sardi [26] | 17 | Paediatric | Focal intrinsic<br>Exophytic<br>Cervicomedullary | 82% low-grade<br>18% high-grade | • 4-year PFS = 58.8%<br>• 4-year OS = 87.0%<br>• Postoperative complication rate = 18% |
| Mehta, Chandra [54] | 4 | All | Focal intrinsic | 68% low-grade<br>32% high-grade | • Postoperative complication rate = 25% |
| Klimo, | 52 | Paediatric | Focal intrinsic | 100% low- | • 5-year PFS = 58.9% |

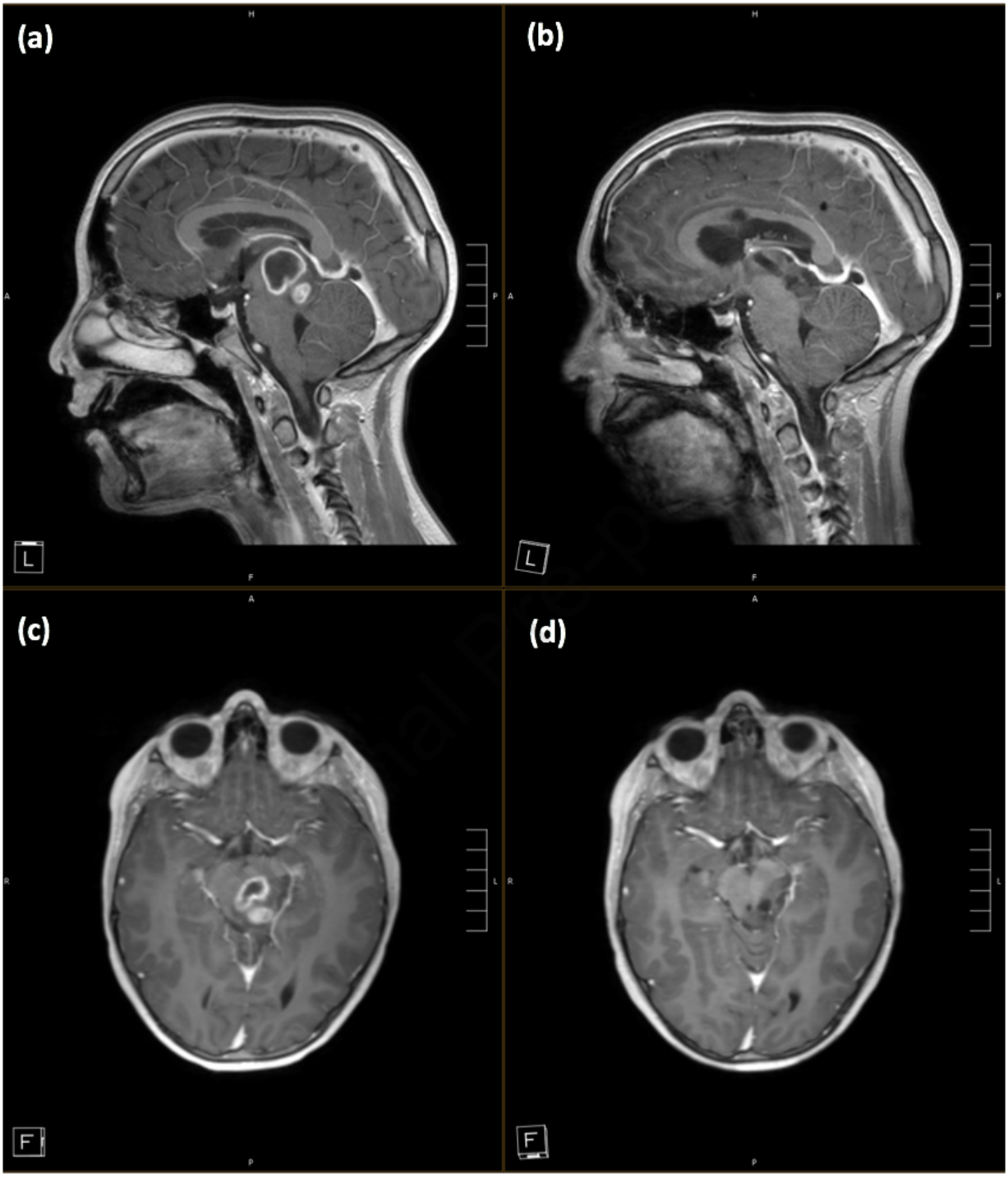
| | | | | | |
|---|---|---|---|---|---|
| Panandiker [19] | | | Exophytic | grade | • 5-year OS = 98%<br>• 10-year PFS = 52.1%<br>• 10-year OS = 89.6% |
| Garzón, García-Fructuoso [39] | 32 | Paediatric | Focal intrinsic Exophytic Cervicomedullary | - | • Mean PFS = 19.26 months<br>• Mean OS = 142.9 months<br>• Intraoperative complication rate = 40.6%<br>• Postoperative complication rate = 43.8% |
| Cavalheiro, Yagmurlu [5] | 207 | Paediatric | Focal intrinsic Exophytic Cervicomedullary | 85.5% low-grade 14.4% high-grade | • 5-year PFS = 92% (low-grade tumours)<br>• Median OS = 18 months (high-grade tumours) |







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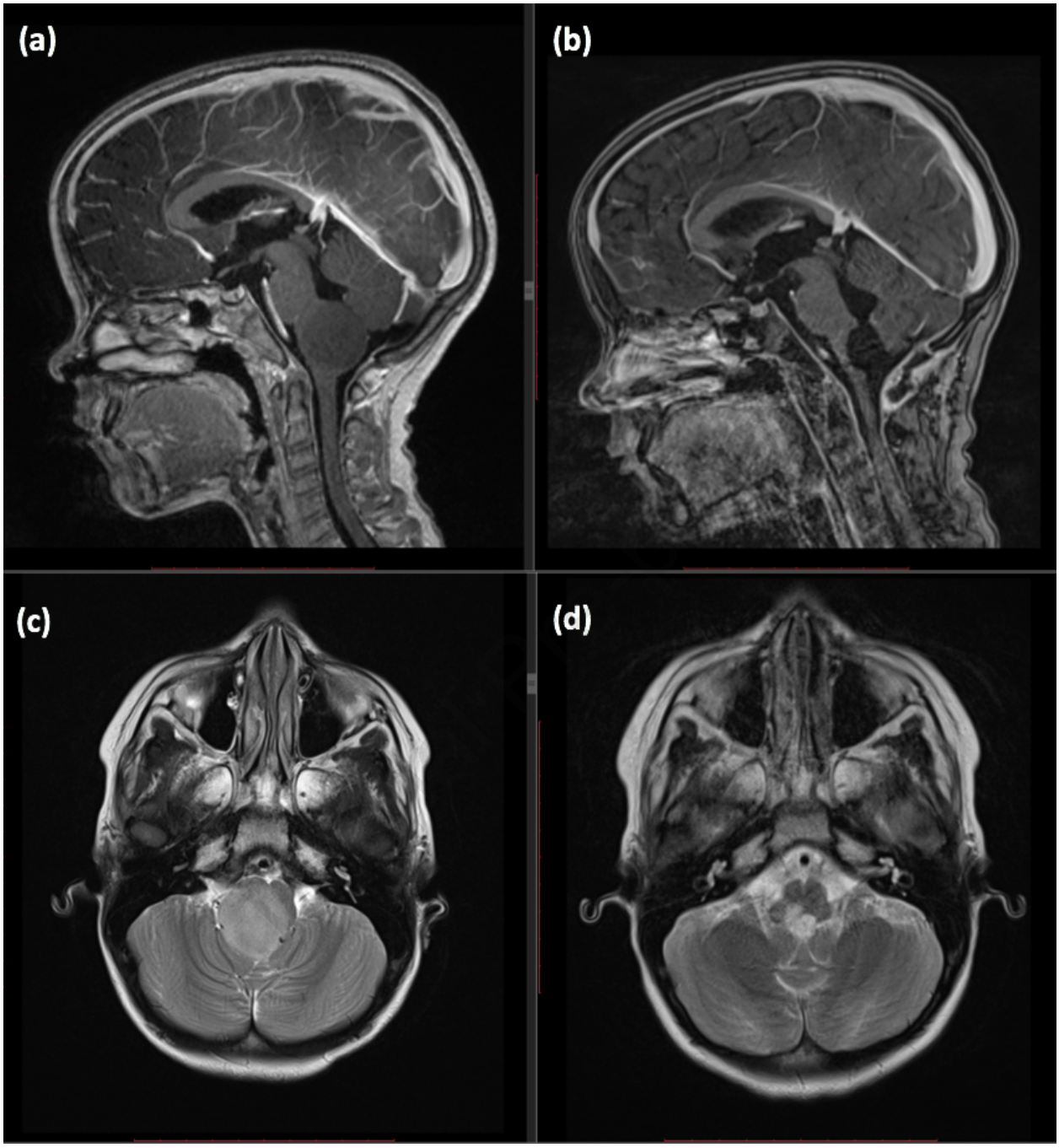
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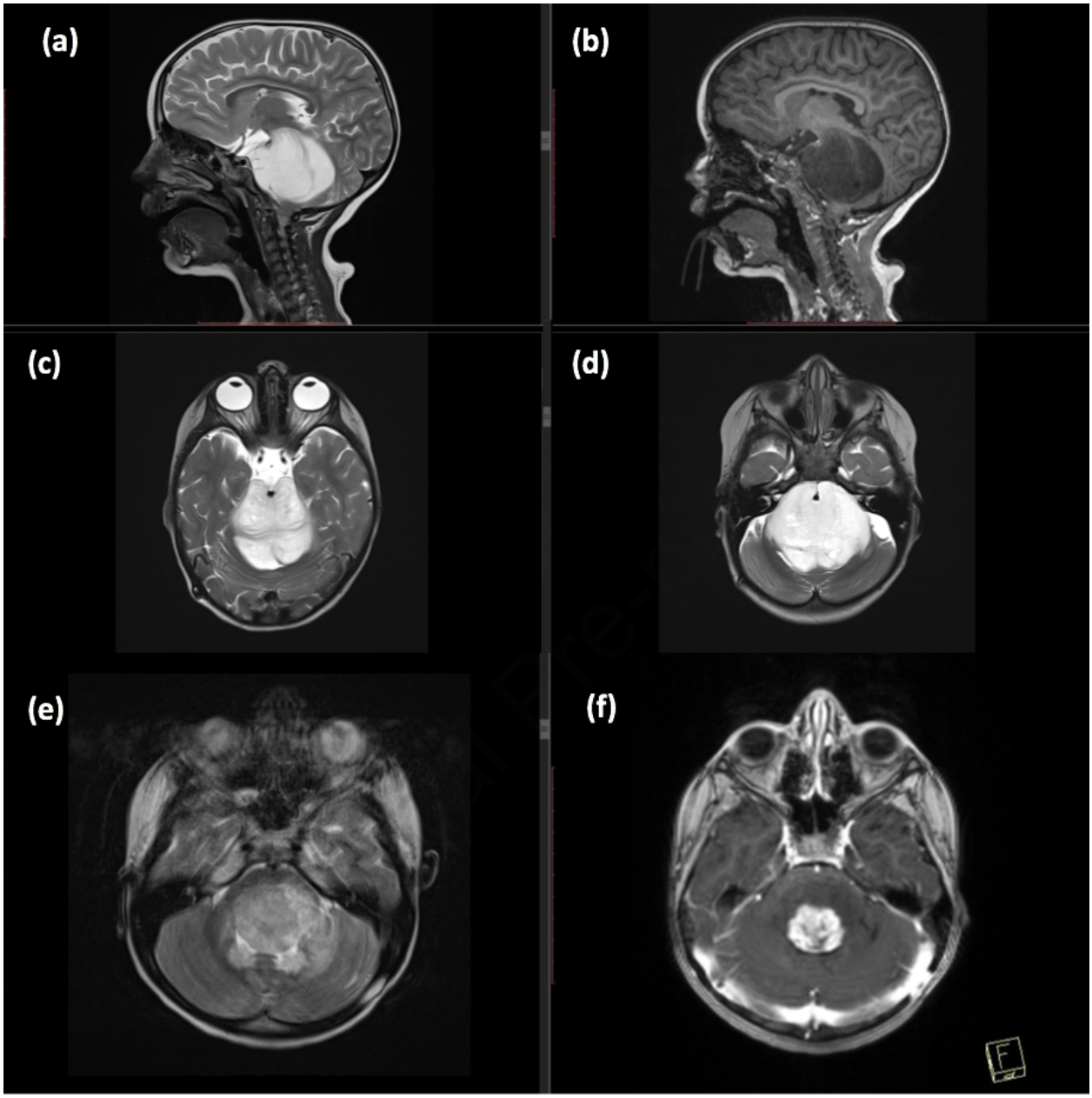
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## Abbreviations

DMG - Diffuse midline glioma

OS - Overall survival

PFS - Progression-free survival

**Disclosure**

Michael E. Sughrue and Charles Teo are co-founders of Omniscient Neurotechnolgies. No products directly related to this are discussed in this paper. All other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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