# Management of paediatric glioblastoma

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## Abstract

Glioblastoma is rather uncommon in children, accounting for less than 5% of all paediatric brain tumours. Recent large sample size cohorts have clearly shown that extent of resection and adjuvant chemotherapy and radiotherapy impact survival. Unfortunately, this may not be the practice in a real world setting, especially in low-middle income countries (LMIC). The aim of this review is to summarize and highlight important findings from studies on paediatric glioblastoma.

**Keywords:** Pediatric glioblastoma, Extent of resection, Concurrent chemoradiotherapy.

## Introduction

The epidemiology and characteristics of malignant brain tumours differ sharply in paediatric and adult populations. Glioblastoma (GBM) comprises only 3% of all brain tumours in children, with 20% 5-year survival.[1] This is in contrast to adults, in whom it is the most common primary, intra-axial brain tumour, with poor 5-year survival of only up to 6%.[2] There is a lack of uniform guidelines for best treatment strategy in children with these tumours. Data from high grade glioma studies done in adults is often extrapolated to children, which may not be entirely applicable in the paediatric population.[3] Standard of care for adult GBM is gross-total resection (GTR) or maximum safe resection, followed by Stupp protocol and the same is advocated for children.[4,5] However, results from successive studies reported comparatively better prognosis in paediatric GBM than in adults, giving rise to the argument that there may exist a difference in the molecular make-up and histopathological features of this tumour between the two age groups.[6,7]

Few studies have reported immunohistochemistry markers for paediatric GBMs, such as IDH1, MGMT, Ki67, p53, PTEN and EGFR.[8] There is little agreement on best management and an ongoing debate whether extent of resection has an impact on survival, can tumour markers help prognosticate the outcome, and if chemotherapy and radiation have the same effect in prolonging survival as in adults.[9] In this study, we have reviewed the existing literature on paediatric GBM, and have aimed to summarize the current recommendations on the ideal treatment of this disease.

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## Review of evidence

### Extent of Resection

Historically, paediatric and adult GBM was believed to be the same entity due to their radiological and histological similarity and until recently both were treated similarly.[10] In 2012 Ansari et al. had reported a series of 23 cases in which GTR was noted to improve survival.[11] But most other studies since have reported promising results with GTR.[8,9,12-15] The largest retrospective case series on paediatric GBM was reported by Adam et al. in 2016.[15] They reviewed 342 cases operated over a 20 year period from the national database, and GTR was found to be an independent predictor of survival.[15] Similar findings were reported by Gupta et al. with a survival advantage of 6 months with GTR.[9] Liu et al. reported a series of 31 patients in whom GTR was a significant predictor of prolonged survival.[8]

### Adjuvant Treatment

Adjuvant chemotherapy with temozolamide is now widely practiced, but other chemotherapeutic agents such as cisplatin, carboplatin and lomustine have also been utilized.[16] However, Gupta et al. observed a statistically significant advantage of concurrent chemoradiotherapy followed by more cycles of temozolamide (Stupp protocol), over concurrent treatment alone with no cycles of chemotherapy after radiation, and reported median overall survival to be 41.9 months and 8 months in the two groups respectively.[9] Similar findings were reported by a retrospective observational study of 34 cases from South Korea.[17] A clinical trial conducted by Children's Oncology Group ACNS0423 evaluated dual agent adjuvant chemotherapy comprising of lomustine and temozolamide, and concluded that this regime improved survival outcomes, particularly in patients with MGMT overexpression and

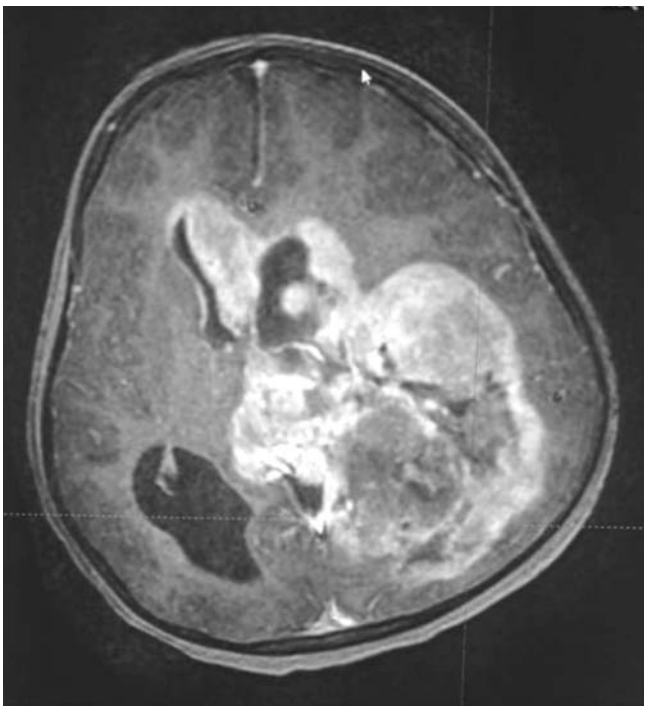

**Figure-1:** A sagittal section of MRI brain T1 post-contrast, showing a large intra-axial lesion in the frontal, parietal, temporal and occipital lobes, with heterogenous peripheral enhancement and central necrosis. There is meningeal enhancement as well at the skull-base, signifying leptomeningeal spread of the disease. Biopsy of this lesion was reported as Glioblastoma grade IV.

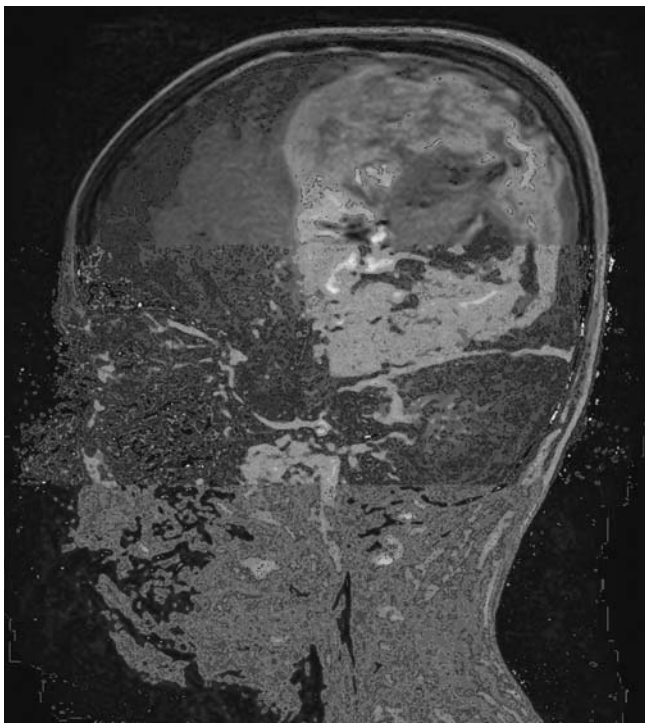

**Figure-2:** Axial section of MRI brain T1 post-contrast of the same patient, showing a large intra-axial contrast enhancing lesion in the left frontal, parietal and occipital lobes, extending into the corpus callosum, thalamus and ventricles, and is causing effacement of ipsilateral occipital horn of the lateral ventricle.

those who underwent GTR.[18] However, lomustine was associated with haematological toxicity, so its use was limited.[18] In another recently reported study, Lu et al. reported 40 cases of infant GBM, and found that extent of resection and chemotherapy were associated with improved prognosis.[19]

The infiltrating nature of GBM, and high tendency to recur even after GTR warrants radiotherapy post-surgery. Unlike adults, an optimal dose of radiations and the number of fractions has not been standardized for children. Some studies recommend a dose range of 5400 - 6000 cGy associated with better progression free survival, however, a standard protocol is still lacking.[20] Lately, there has been increasing interest in the efficacy of immune based treatment for malignant brain tumours. Levesley et al. recently studied the role of small molecule B-cell lymphoma 2 (BCL-2) and found that selective inhibition of BCL caused an increase in the efficacy of targeted chemotherapy agents.[21]

## Genetics and Molecular Markers

With innovations in genetic and molecular analysis, several specific markers have now been linked to the pathogenesis and treatment of high grade tumours in children.[22] PTEN gene expression has been noted to be associated with prolonged survival in GBM.[8] Paediatric GBM has also been found to be associated with histone H3.3 mutations, with different subgroups linked to different locations intracranially. H3.3K27 is associated with tumours located in midline including diencephalon, whereas H3.3G34 are associated with tumours located more laterally in the hemispheres. The latter group has better outcomes. With ongoing research in this area, the molecular basis of disease will play an important role in designing treatment strategy, and will serve as important predictors of outcomes than the conventional parameters, in few years.

## Conclusion

Paediatric GBM differs from the adult counterpart. Maximal safe resection with aim towards gross total resection, followed by adjuvant chemoradiation remains standard of care. Despite no level 1 evidence, we can safely conclude from the available literature that the treatment algorithm should include an attempt for GTR, followed by a standard adjuvant chemoradiation protocol. The neurosurgeon's role is particularly important in providing maximal safe resection which sets the stage for a successful adjuvant therapy response. In LMICs, paediatric high grade gliomas should be treated at specialized high-

volume centers with dedicated paediatric neuro-oncology teams to achieve best possible outcomes.

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