

## Management of Pediatric Glioma : Current Evidence & Guidelines



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## Introduction

- Brain tumors are 2<sup>nd</sup> most common tumor in children
- ~ 20% of all pediatric cancers
- Incidence is 5 cases/100,000 children per year
- 20% occur in children < 3years age
- ~60% occur in infratentorial brain exception is infancy <12months age 60% supratentorial</li>
- Gliomas are most common type of brain tumor in both children & adults derived from glial cells which are responsible for neuron cell support

#### **Broadly divided into 2 different entities**

- Low grade Gliomas (LGG)
- High grade Gliomas (HGG)
  - Diffuse Intrinsic Pontine Gliomas (DIPG)

About two thirds of total gliomas are LGG and localised however 5% can present with leptomeningeal dissemination esp. with hypothalamic and spinal tumors.

#### **Etiological factors**

- Etiological factors not well studied
- Prior exposure to irradiation : HGG gliomas
- Genetic and famililal syndromes syndromes Include Li-Fraumeni syndrome, Turcot syndrome, neurofibromatosis.

NF1 higher risk for developing JPA esp optic pathway.

Tuberous sclerosis, increased risk of LGG called subependymal giant cell astrocytoma (SEGA).

BRAF oncogene mutations and BRAF gene fusions : LGG gliomas

### **Clinical Presentation**

- Heterogeneous in presentation. Remain undiagnosed for prolonged period as patient in these age groups are not capable to effectively present their symptoms and some common symptoms might be non-specific such as headache
- Highly dependent on localization of lesion.
- Cortical tumors- Focal neurological deficits including seizures & headaches
- Brain stem- headache, fatigue, ataxia and multiple cranial neuropathies. Increase in tumor size can lead to obstruction of cerebral aqueduct and 4<sup>th</sup> ventricle causing obstructive hydrocepahlus
- Lower Brain stem lesions can present with failure to thrive d/t persistent dyspahgia, nausea and vomiting
- Optic pathway gliomas unexplained visual loss, monocular or asymmetric nystagmus, Diencephalic syndrome, optic atrophy

### **Diagnosis : Imaging**

• History and Physical examination

#### Imaging

Imaging	Remarks	Pros	Cons
CT scan	First line imaging modality	Good anatomic visualization Cheaper & Faster More widely available Can be used with metal objects	Limited reconstruction ability Exposure to ionizing radiation Poor resolution Contrast reaction
MRI	Gold standard imaging modality	Unparalleled resolution True multiplanar imaging No exposure to ionizing radiation	Susceptible to motion artifacts Cannot be used with metal objects Claustrophobic, noisy, long times Expensive
MR Spectroscopy	Assesses tumour metabolites	Useful for discriminating radiation necrosis from tumour	Limited utility near bone, vessels or air spaces Wide variability in interpretation
MR Perfusion	Assesses blood flow & volume	Generally correlates with grade Useful to distinguish radiation necrosis from tumour progression	Limited utility near bone, vessels

#### Others DTI, PET

#### **Imaging: Pilocytic Astrocytoma**



Large cyst with solid mural nodule within cerebellar hemisphere seen in 30-60% JPA MRI : cystic is hypointense on T1W Hyperintense on T2W

#### **Imaging : Brainstem Gliomas**



On MRI Diffuse pontine gliomas expanded pons, do not enhance Hypointense on T1W and hyperintense on T2W and FLAIR images

Focal midbrain types have variable enhancement Cervico-medullary type commonly enhances Dorsal exophytic type enhances homogeneously

Enhancement useful in followup response to therapy or recurrence

### **WHO Classification LGG**

Table 1 WHO low-grade glioma classification scheme.

#### Astrocytoma

Grade I

Pilocytic astrocytoma

Subependymal giant cell astrocytoma

Grade II

Diffuse astrocytoma (fibrillary, protoplasmic, or gemistocytic)

Pilomyxoid astrocytoma

Pleomorphic xanthoastrocytoma

Oligodendroglial tumour

Grade II

Oligodendroglial tumour

Neuronal and mixed neuronal-glial tumours

Grade II

Ganglioglioma

Gangliocytoma

Desmoplastic infantile ganglioglioma

Dysembryoplastic neuroepithelial tumour

- 25-30% of all childhood CNS tumors
- Peak incidence : first decade of life with no gender predilection
- Chiasmatic & Hypothalmic tumors more frequent in younger children
- Hemispheric tumors seen in older & adolescents.
- Pilocytic astrocytoma >15% common in posterior fossa
- IDH mutations are almost absent
- Malignant progression is extremely rare
- Linked to hereditary component
- SEGA associated with Tuberous sclerosis (20%)
- Optic pathway Gliomas with NF1

### LGG : Molecular genetic alterations based on location



Alteration in BRAF is found in majority of PA Pfister JCI2008

Genetic alterations in BRAF contribute to activation of MAPK pathway leading to either tumor growth, differentiation or oncogene induced senescence

Majority of BRAF alterations involve tandem duplication of gene of 7q34

### LGG : Molecular genetic alterations based on location (contd..)

- 100% PA habor alteration in MAPK axis , most commonly KIAA1549: BRAF fusions. Rx with MEK inhibitors— selumetinib, Trametinib in Ph II studies
- Additional alterations include RAF1 fusions, mutations, fusions or kinase domain duplications of FGFR1 and fusions of NTRK gene family
- BRAF fusions are exclusive for PA & associated with good prognosis.
- BRAF V600F mutations is seen pleomorphic xanthoastrocytoma , some PA, ganglioglioma. Rx with Dabrafinib promising result
- BRAF V600F mutant and 9p21 (CDKN2A/B)-deleted tumors (hall mark of pleomorphic xanthoastrocytoma) likely display increase propensity for progression and a worse outcome

#### **Pediatric HGG**

- ~ 20% of all primary CNS tumors in children
- ~ one half occur in Brain stem most frequently in ventral pons as DIPG
- Most supratentorial HGG located in cerebral hemispheres 35-50%, followed by thalamus 20-30% and basal ganglia
- Transformation from low grade to high grade is a rare phenomenon
- Same aggressive clinical behaviour and bad prognosis as adult
- Most series showing 3year event free survival 11-22% with majority succumbing to the disease

#### **Pediatric HGG : WHO Classification 2016**

Anaplastic astrocytoma, IDH-mutant Anaplastic astrocytoma, IDH-wildtype Anaplastic astrocytoma, NOS

Glioblastoma, IDH-wildtype Giant cell glioblastoma Gliosarcoma *Epithelioid glioblastoma* Glioblastoma, IDH-mutant Glioblastoma, NOS IDH 1 mutation & 1p19q codeletion uncommon in Pediatric gliomas

Diffuse midline glioma, H3 K27M-mutant

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted Oligodendroglioma, NOS

Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted Anaplastic oligodendroglioma, NOS

Oligoastrocytoma, NOS Anaplastic oligoastrocytoma, NOS

#### **Classification based on molecular subgrouping**



# Histone mutations have been identify unique driver of pHGG

Reclassification based on molecular subgrouping with significant clinical correlations with age , anatomical location, prognosis.





FIG. 4. Schematic illustrating the multiple subgroups of HGGs that differ based on lesion location, age at onset, and prognosis. In addition to the subgroup-defining alterations, such as *BRAFVence* and histone K27M mutations, timere commonly barbor according attended mutations (mut), amplifications (amp), deletions (del), and los: J Neurosurg Pediatr Volume 23 • March 2019

# **Treatment options**



Surgery Radiotherapy Chemotherapy Observation

### Surgery

- Primary object is to get tissue for diagnosis, removing / debulking tumor
- Factors actors that decide on surgery is patients clinical condition, age, hydrocephalus, surgeon assessment of risk of neurological sequalea and site of lesion
- Surgical excision GTR / maximal safe resection
   STR /no resection/ stereotactic biopsy

Radical resection correlates with longer survival when combined with RT

• Timing of Surgery in LGG : controversial topic & few conclusive studies (Craincross and Laperriere 1989 Archives of neurology46; 1238-39 and Recht 1992)

### **Radiation therapy**



- Conformal RT is imp component of treatment
  - Mostly given in adjuvant setting sometimes preoperatively, stand alone in inoperable case
  - Involves focal irradiation to tumor & surgical cavity with adequate margins

#### **RT Target volume : LGG**

- Tumors are difficult to see on CT as they often do not enhance, and are deeply infiltrative.
- MRI (T2 or FLAIR sequences) used for delineation
- CTV=1-1.5cm margin.
- Tumour extent modified at any geographical boundaries e.g. bone, falx, tentorium cerebelli as LGG tumours do not usually infiltrate these.
- PTV = 5-10mm margin around CTV
- Dose : 50.4-54Gy in 28-30 fractions

#### **RT Target volume : HGG**

EORTC treatment volumes (EORTC 22981/22961, 26071/22072 (Centric), 26981–22981, and AVAglio trials)

Phase 1 (to 60 Gy in 30 fractions)

GTV = surgical resection cavity plus any residual enhancing

tumour (postcontrast T1 weighted MRI scans).

CTV = GTV plus a margin of 2 cm<sup>\*</sup>

PTV = CTV plus a margin of 3–5 mm

RTOG treatment volumes (RTOG 0525, 0825, 0913, and AVAglio trials)

Phase 1 (to 46 Gy in 23 fractions)

GTV1 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans) plus surrounding oedema (hyperintensity on T2 or FLAIR MRI scans).

CTV1 = GTV1 plus a margin of 2 cm (if no surrounding oedema is present, the CTV is the contrast enhancing tumour plus 2.5 cm.

PTV1 = CTV1 plus a margin of 3–5 mm

Phase 2 (14 Gy boost in 7 fractions)

GTV2 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans)

CTV2 = GTV2 plus a margin of 2 cm

PTV2 = CTV2 plus a margin of 3–5 mm

M. Niyazi et al. / Radiotherapy and Oncology 118 (2016) 35-42

#### **Hyperfractionation in Brain stem Gliomas**

#### Table 1 Hyperfractionation—results of prospective studies

Study	Reference	No. of patients	Dose/fraction of radiotherapy	Total dose	ттр	MST	Survival 1 year	Survival 2 years	Survival 3 years
POG (8495)	[22] [22] [22]	38 57 57	1.1 Gy 1.17 Gy 1.26 Gy	66 Gy 70.2 Gy 75.6 Gy	6.5 m 6 m 7 m	11 m 10 m 10 m	48% 40% 39%	6% 23% 6%	3% 21% 6%
CHOP/NYU	[23] [24]	16 35	1.2 Gy 1 Gy	64.8 Gy 72 Gy	7 m 8 m	11 m -	48% -	- 28%	-
CCG (9982)	[16] [16]	53 66	1 Gy 1 Gy	72 Gy 78 Gy	5.5 m 8 m	9 m 9.5 m	38% 35%	14% 22%	8% 11%
UCSF	[25] [26]	20 36	1 Gy 1 Gy	72 Gy 78 Gy	36 w 8.4 m	51 w 10.8 m	-		_

TTP, Time to Progression; MST, Median Survival Time; m, months; w, weeks

#### **Dose constraints & recommendations for OAR**

Dose constraints and recommendations for intracranial organs at risk when conventional fractionation

OAR	Constraints for adults				
	Primary criteria	Secondary criteria			
Optic chiasma	D <sub>max</sub> < 54 [10,11]	D <sub>max</sub> < 60 [10]			
	D <sub>max</sub> < 55 [12]				
Cochlea	<i>D</i> <sub>mean</sub> ≤ 45 Gy [13,14]	Dmean < 35Gy children			
	D <sub>mean</sub> < 50 Gy [10]				
Hippocampus	Hippocampus				
	$D_{\rm max} \leqslant 6 \ { m Gy} \ { m and} \ V_3 \ { m _{Gy}} \leqslant 20\%$				
	Hippocampal avoidance volume				
	$D_{\rm max}$ < 25.2 Gy and				
	$V_{20 \text{ Gy}} \leq 20\% \text{ [21,22]}$				
	D <sub>max</sub> < 12 Gy [23]				
	V <sub>7.2 Gy</sub> < 40% [25]				
	D <sub>mean</sub> < 30 Gy [24]				
Brainstem	D <sub>max</sub> < 54 Gy [10,29]	$D_{\rm max} < 60  {\rm Gy}  [10]$			
		$D_{59 \text{ Gy}} < 10 \text{ cc}$ [29]			
Pituitary gland	D <sub>max</sub> < 50 Gy [34]	Dmean < 25Gy or 30Gy children			
	D <sub>max</sub> < 60 Gy [10]	Dmax< 42Gy children			
Retina	D <sub>max</sub> < 45 Gy [10, Yamazaki]				
	D <sub>max</sub> < 50 Gy [Shaffer]				
Lacrimal gland	$V_{30 \text{ Gy}} < 50\%$ [Sreeraman]				
	D <sub>max</sub> < 40 Gy [Jeganathan]				
Lens	$D \leq 6 Cy$ [Piroth]	Radiotherapy and Oncology 114 (2015) 230-			

#### Chemotherapy

- Chemotherapy has been to delay or avoid RT in LGG while in HGG it has been used in concurrent and adjuvant setting
- Choice of the optimal regimen is still controversial
- Combination of drugs like thioguanine, procarbazine, CCNU and vincristine (TPCV) or vincristine-carboplatin is preferred
- Alternative monotherapy with weekly vinblastine
- Other single agents- temozolomide, bevacizumab, irinotecan
- 5-year PFS in the range of 40–50% with CT in LGG

#### Randomized Study of Two Chemotherapy Regimens for Treatment of Low-Grade Glioma in Young Children: A Report From the Children's Oncology Group

Joann L. Ater, Tianni Zhou, Emiko Holmes, Claire M. Mazewski, Timothy N. Booth, David R. Freyer, Ken H. Lazarus, Roger J. Packer, Michael Prados, Richard Sposto, Gilbert Vezina, Jeffrey H. Wisoff, and Ian F. Pollack

#### Purpose

Surgery is curative therapy for pediatric low-grade gliomas (LGGs) in areas of the brain amenable to complete resection. However, LGGs located in areas where complete resection is not possible can threaten both function and life. The purpose of this study was to compare two chemotherapy regimens for LGGs in children younger than age 10 years for whom radiotherapy was felt by the practitioner to pose a high risk of neurodevelopmental injury.

#### **Patients and Methods**

Previously untreated children younger than age 10 years with progressive or residual LGGs were eligible. Children were randomly assigned to receive carboplatin and vincristine (CV) or thioguanine, procarbazine, lomustine, and vincristine (TPCV). Children with neurofibromatosis are reported separately.

#### Results

Of 274 randomly assigned patients who met eligibility requirements, 137 received CV and 137 received TPCV. The 5-year event-free survival (EFS) and overall survival (OS) rates for all eligible patients were  $45\% \pm 3.2\%$  and  $86\% \pm 2.2\%$ , respectively. The 5-year EFS rates were  $39\% \pm 4\%$  for CV and  $52\% \pm 5\%$  for TPCV (stratified log-rank test P = .10; cure model analysis P = .007). On multivariate analysis, factors independently predictive of worse EFS and OS were younger age and tumor size greater than 3 cm<sup>2</sup>. Tumor location in the thalamus was also associated with poor OS.

#### Conclusion

The difference in EFS between the regimens did not reach significance on the basis of the stratified log-rank test. The 5-year EFS was higher for TPCV on the basis of the cure model analysis. Differences in toxicity may influence physician choice of regimens.

#### PROSPECTIVE EVALUATION OF RADIOTHERAPY WITH CONCURRENT AND ADJUVANT TEMOZOLOMIDE IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA

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**Purpose:** To present outcome data in a prospective study of radiotherapy (**RT**) with concurrent and adjuvant temozolomide (**TMZ**) in children with diffuse intrinsic pontine gliomas (**DIPGs**).

Methods and Materials: Pediatric patients with newly diagnosed DIPGs were prospectively treated with focal RT to a dose of 54 Gy in 30 fractions along with concurrent daily TMZ (75 mg/m<sup>2</sup>, Days 1–42). Four weeks after completing the initial RT-TMZ schedule, adjuvant TMZ (200 mg/m<sup>2</sup>, Days 1–5) was given every 28 days to a maximum of 12 cycles. Response was evaluated clinically and radiologically with magnetic resonance imaging and positron emission tomography scans.

**Results:** Between March 2005 and November 2006, 20 children (mean age, 8.3 years) were accrued. Eighteen patients have died from disease progression, one patient is alive with progressive disease, and one patient is alive with stable disease. Median overall survival and progression-free survival were 9.15 months and 6.9 months, respectively. Grade III/IV toxicity during the concurrent RT-TMZ phase included thrombocytopenia in 3 patients, leucopenia in 2, and vomiting in 7. Transient Grade II skin toxicity developed in the irradiated fields in 18 patients. During the adjuvant TMZ phase, Grade III/IV leucopenia developed in 2 patients and Grade IV thrombocytopenia in 1 patient. Patients with magnetic resonance imaging diagnosis of a high-grade tumor had worse survival than those with a low-grade tumor (p = 0.001). Patients with neurologic improvement after RT-TMZ had significantly better survival than those who did not (p = 0.048).

Conclusions: T<u>MZ with RT has not yielded any improvement in the outcome of DIPG</u> compared with RT alone. Further clinical trials should explore novel treatment modalities. © 2010 Elsevier Inc.

### Poor outcomes of Paediatric HGG over past 30 years



EFS comparison of CCG945, ACNS0126, PCM945 parametric model

Cohen Neuro-Oncol2011

## Outcomes

- LGG : greater than 90% OS at 20 years
- HGG : AA 30% at 3 years

GBM- < 10%

#### Conclusions

- Pediatric gliomas are very diverse biologically and distinct entity
- Prognosis generally depends on grade, location
- Molecular driven classification and treatment strategies taking into account distinct biological differences are required to improve outcomes

# Thank you