Cover Letter for submission of Low-Grade Glioma Guidelines

To,
The President,
Pakistan Society of Neuro-Oncology (PASNO)
Pakistan.
October 15th 2021,

Dear Dr Ather,

Enclosed are the guidelines of Children and Adolescent with Low Grade Glioma for submission and approval of PSPO. These guidelines have been formulated by our Paediatric Neuro-oncology multidisciplinary team of oncologists, neurosurgeons, neuro-Radiologists, radiation Oncologists, neuropathologists, ophthalmologists, nurses, and endocrinologist across Pakistan. Dr Eric Bouffet has also reviewed it. These guidelines will surely help Pakistan`s health care professionals to give appropriate care for this most common brain tumour entity in Paediatric age group.
We have no conflicts of interest to disclose. Please address all correspondence concerning these guidelines to me. Thank you for your kind consideration.

Sincerely,

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Pakistan National Guidelines for the diagnosis and management of Paediatric and adolescent Low-Grade Glioma

(Extrapolated from current CCLG Guidelines for Diagnosis and Treatment of Children and Adolescents with Low-Grade Glioma)

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Contents

BACKGROUND

Low grade gliomas (LGGs) are a heterogeneous group of neoplasms comprising 30-40% of primary pediatric brain tumors. The cerebellum is the most common site of involvement (15-25%) followed by the cerebral hemispheres (10-15%) and the optic pathways (6%).

Histopathologically, LGG are recognized by astrocytic, oligodendroglial and mixed oligo-astro neuronal features. Children with Neurofibromatosis type 1(NF1) and tuberous sclerosis have a predilection to develop LGG. It is reported that 15–20% of NF1 patients will develop hypothalamic/chiasmatic/optic pathway gliomas (HCLGG) however these tumors often are more indolent than sporadic LGG in non-NF1 patients. Children with tuberous sclerosis are predisposed to develop subependymal giant cell astrocytoma (SEGA) that frequently respond to mTOR inhibitors. Treatment for children with LGG in low- and middle-income countries (LMIC) remains a challenge despite the excellent survival rates in high income countries (HIC). LGG treatment is dependent on tumor resectability, age of the child and the presence or absence of NF1. For tumors located in areas where gross total resection is possible, surgery is the most effective treatment with a 10-year progression free survival (PFS) of >90%. For tumors where resection can cause significant morbidities, a number of other strategies can be tried in the form of chemotherapy, radiotherapy or observation alone, and 5year overall survival (OS) is still >80%. Initially, radiation therapy was used as a single treatment modality for unresectable midline or progressive tumors and 5-year PFS was in the range of 60–80%. However, radiation may cause significant toxicities, particularly in young children. As a result, most Pediatric Oncology groups recommend the use of chemotherapy as first-line and reserve radiotherapy for recurrent or progressive disease and older children (currently 8 years of age and above in Europe and 10 years of age in North America) with non NF1-related LGG. Since children with LGG have a high probability of long-term survival, limitation of late effects is important. This is even more critical in developing countries where access to supportive care is scares or even nonexistent.

Despite the heterogeneous nature of LGG, these children usually need more than one treatment regimens. To address this, the SIOP Brain Tumor Group of Europe (SIOP-E BTG), in conjunction with the German Paediatric Oncology and Haematology Society (GPOH) and CCLG developed guidelines, to define a current standard of care for the diagnosis and treatment of children and adolescents with LGG. While all these guidelines are acknowledged as the backbone of this document, the authors of PSPO/PASNO have duly extrapolated the document for Pakistan National patient's cohort.

Reference:

1. Gnekow AK, Kandels D, van Tilburg C, et al. SIOP-E-BTG and GPOH Guidelines for Diagnosis and treatment of Children and Adolescents with Low Grade Glioma. *Klin Padiatr*. 2019;231(3):107-135.

CLINICAL FINDINGS

Neurological examination

The symptoms and signs of a LGG usually evolve slowly over a protracted period of time, although an acute onset (relating to raised intracranial pressure or intracranial bleed) can also occur. Site of the tumor is associated with specific clinical features suggesting the possibility of a space occupying lesion in the brain:

- Features of raised intracranial pressure – headaches, vomiting, cranial nerve palsies, papilledema, macrocephaly, ataxia, reduced consciousness.
- Tumors of the floor of the 3rd ventricle / hypothalamus – diencephalic syndrome.
- Tumor of the cerebral hemispheres – seizure activity.
- Tumors of the cerebellum – ataxia, incoordination.
- Tumors of the brainstem – long tract motor and/or sensory signs, cranial nerve palsies may include hearing loss.
- Tumors of the suprasellar area – visual and endocrine abnormalities (delayed/ precocious puberty, diabetes insipidus, obesity /short stature)
- Neurocutaneous syndrome features (NF1, TSC) Café au Lait spots, shagreen patches etc.

Ophthalmic assessment

LGG of the optic pathways, often termed OPGs, can lead to a spectrum of visual dysfunction ranging from asymptomatic to severe visual loss and / or blindness dependent on tumor location. Infants in particular are at high risk for visual loss due to often large Optic Pathway Hypothalamic Gliomas (OPHGs) frequently presenting with intracranial hypertension / hydrocephalus. They may also present with 'shaking eye' (nystagmus)

In the past many clinical trials reported treatment response in terms of tumour size reduction or progression-free survival. The forthcoming LOGGIC and ongoing COG trials have included vision as a primary outcome. Therefore, standardized methods to assess visual function in children with OPG have now been agreed. An ophthalmological examination by an experienced ophthalmologist should be included in the assessment of any child presenting with a visual pathway tumour according to these recommendations.

The following ophthalmic tests are recommended for the patients with OPG

1. Visual Acuity
2. Color vision
3. Visual Fields (ideally with Goldmann perimetry)
4. Pupillary reflexes
5. OCT (optical coherence tomography)
6. Anterior segment examination
7. Dilated fundal examination

Ophthalmic tests under following conditions

1) <u>If VA normal</u>: Un-dilated check for the presence of Lisch nodules to rule of NF-1, followed by dilated fundoscopy. Follow up if no concerns at:

i) Age 0 – 36 months = Review 3 monthly

ii) Age 36 months - 6 years = Review 6 monthly

iii) Age 6 - 8 years = Review once a year

iv) Age more than 8 years = discharge to their local hospital for annual review until aged 16

2) If VA reduced:
Check iris for Lisch nodules and pupils for relative afferent pupillary defect followed by dilated fundoscopy and cycloplegic refraction

In any event if Visual acuity is reduced by more than 1 line, need to recheck 2-3 weeks apart on 2 more occasions. If anisometropic and / or strabismus is identified, then amblyopia treatment trial should be considered (without refractive adaptation) for 6 weeks.

3) With newly diagnosed glioma

Visual acuity, color vision, OCT and visual fields test (ideally Goldmann when possible)

Check for pupillary reflexes followed by dilated fundoscopy

If VA reduced by more than 1 line, need to recheck 2-3 weeks apart on 2 more occasions before considering treatment. Refraction should be checked. If anisometropic and / or strabismus, then amblyopia treatment trial should be considered (without refractive adaptation) for 6 weeks before considering glioma treatment

4) Once glioma diagnosed and no treatment recommended

i) Age 0 – 36 months = Review 3 monthly

ii) Age 36 months - 6 years = Review 6 monthly

iii) Age 6 - 8 years = once a year review

iv) Age more than 8 years = discharge to local hospital for annual review until aged 16

Laboratory Investigations

Tumors of the sellar/ suprasellar area usually involves the hypothalamic-pituitary axis, therefore baseline pituitary function tests should be included in the management of LGG preferably done preoperatively. It includes serum TSH, Free T4, cortisol (morning) Sodium, IGF 1 (short stature) and urine/serum osmolality in children develop diabetes insipidus. LH, FSH, bone age?

RADIOLOGY GUIDELIENS

Prior to Surgery

MRI brain and spine (when possible)

MRI brain and spine (with contrast) should be done in all patients suspected of having low grade glioma,
a- Who are referred to your center prior to surgery.
b- In case surgery had been done in an outside hospital, all pre-surgery scans should be obtained and reviewed.

Imaging Technique:

BRAIN

All patients should undergo brain MR imaging at least at 0.5T.

Following sequences should be obtained:

- Axial and coronal T2 FSE (TR/TE, 2700/100 ms),
- Axial or Coronal FLAIR (TR/TE, 9000/120 ms; TI, 2200 ms),
- Precontrast T1 spin-echo and contrast-enhanced T1 spoiled gradient-recalled echo (TR/TE, 8/3 ms; 1-mm section thickness, 0 skip), followed by 2 planes of contrast-enhanced T1 spin-echo (TR/TE, 600–700/20 ms; 5-mm section thickness, 0.5 skip).
- All, patients should undergo DWI; b-value of 1000 s/mm2; 3 directions; 4-mm thickness, 0 skip) SWI/GRE/T2* is optional.

SPINE

All patients should undergo spinal cord MR imaging at least at 0.5T. but for more accurate imaging 1.5T is preferred.

Following sequences should be obtained

For Disseminated Brain Tumor

- Sagittal whole spine (entire dural sac): T1W + Contrast 2D SE/TSE, Slice thickness ≤3mm, Slice gap <0.5mm.
- Axial- suspicious areas: T1W + Contrast 2D SE/TSE or 3D GE, Slice thickness 4 mm, no slice gap.

For Spinal Tumor

- Sagittal whole spine (entire dural sac): T2W/T1W/T1W+Contrast 2D SE/ TSE, Slice thickness ≤ 3 mm should be done.
- Axial tumor volume T2W 2D SE/ TSE, Slice thickness 3-4 mm.
- Axial tumor volume T1W + Contrast 2D SE/ TSE or 3D GE, Slice thickness 3-4 mm (2D),1mm (3D).

Additional Guidelines for Assessment of the Spine:

Veins on the surface of the cord can be mistaken for nodules of dissemination and therefore axial slices without gaps are essential for all suspicious areas (slice thickness should be 4 or 5 mm).

Fat suppression often causes artefacts and is not necessary for the delineation of meningeal disease in spine; it should not be used routinely.

Additional Sequences Helpful in Certain Circumstances:

If tumor is poorly or non-enhancing a second plane is required to enable measurements in three dimensions. (T2W/ FLAIR Slice thickness + ≤ 4 mm, gap 10% Sagittal or coronal)

Small lesions may need thinner slices for reliable delineation of the tumor. (2D or 3D* T1W/ T2W/ FLAIR/ CISS/ FIESTA 2D slice thickness + gap =½ the lesion diameter, 3D ≤ 1 mm Sagittal and/or coronal and/or axial)

Additional Sequences Can Help in Differential Diagnosis:

For suprasellar tumors:

- The normal bright signal of the posterior pituitary lobe should be assessed by a sagittal T1W sequence.
- A fat suppression (STIR sequence) may be used, if the lobe signal cannot be discriminated from fatty bone marrow of the sella.
- The bright signal of the posterior pituitary lobe is preserved in optic pathway / hypothalamic gliomas of non-NF1 patients
- Whereas it is almost always lost in germ cell tumors and is often lost in craniopharyngioma invading the sella.
- Optic Pathway Hypothalamic gliomas

Note: "**Neuroradiologic diagnosis only**" is accepted for NF1 patients with an Optic Pathway Hypothalamic Glioma, and in non-NF1 patients with extensive involvement of the visual pathways, if the tumor is hypodense on an unenhanced CT-scan (routine CT-scanning is not generally recommended).

Nevertheless, consideration of (stereotactic) biopsy is recommended for non-NF1 patients and at all other sites.

Imaging interpretation:

All reports should comment on:

- Tumor location. It should be defined intra-axial or extra-axial.
- Tumor size should be given in three dimensions and try best to give volume. Formula for tumor volume is: Tumor volume= length x width2/2, where length represents the largest tumor diameter and width represents the perpendicular tumor diameter. Measurements should be taken on post contrast or T2W/FLAIR.
- Enhancement pattern should be defined as minimal/none if <10% was estimated to enhance, solid if >90% of the tumor volume was estimated to enhance, and heterogeneous if varying degrees of enhancement were seen in 10%–90% of the tumor volume on the basis of radiologist's visual assessments.
- Cysts/cavities, hemorrhage/ mineralization. Low signal on 2D gradient recalled-echo or bright on T1W should be used to detect hemorrhage/mineralization.
- Intracranial or leptomeningeal seeding should be mentioned.

- Tumor margin should be characterized as ill-defined if >50% of the margin could not be distinguished from the surrounding cerebellar parenchyma on the basis of all imaging sequences.
- Necrosis as suggested by ring-enhancement.

Post-surgery:

MRI brain with contrast and MRI spine with contrast should be performed within 48 hours. This is believed to minimize the chances of post-op change being confused with residual tumor.

If it's not done in the prescribed time the best time to get with resolved postoperative changes is 6 weeks.

- Pre- and post-contrast images should carefully be compared with the pre-operative MRI to detect residual tumor. (T1-weighted images in combination with the signal intensities on the T2- weighted and FLAIR sequences).

- The size of a possible residuum has to be measured in all three planes. If the residuum is best visible on T2-weighted images a second plane incorporating a T2-weighted or FLAIR sequence must be employed.
- Residual tumor is defined radiologically.

- A thin line of enhancement should be confirmed for physiological or reactive on early postoperative MRI with the correlation of non-contrast sequences for evidence of hemorrhage / tissue injury. Detailed comparison with preoperative MRI may be required before considering the presence of residual tumor.

Follow-up MRI

Technical comparability of follow-up MRIs has to be assured.

If a treatment-related reduction of enhancement disproportionate to the change in tumor volume is encountered, the most suitable sequence to visualize the tumor cannot be predicted. In this case the initial sequence on which the tumor was measured should be chosen and tumor dimensions should be compared on this same sequence with previous MRI to assess treatment response.

- **Pseudo-progression**

If MRI findings are equivocal for tumor progression / resolution (pseudo-progression / pseudo- response), an early follow-up scan(s) may be required to evaluate for true progression / response. In case of an increase in tumor volume during the first 12 weeks after the end of primary radiotherapy and within the irradiated field, a radiation-induced reaction has to be considered. (enlarging contrast enhancing lesion, increased FLAIR / T2 abnormality).

- **True progression**

When true progression is confirmed, the initial scan which showed the abnormality should be considered as time of progression. True progression has to be confirmed either by histology or on a short interval follow up scan – after at least another 4-6 weeks.

HISTOPATHOLOGICAL DIAGNOSIS

Pediatric-type low-grade gliomas (pLGG) are the most frequent, accounting for approximately 30% of all childhood brain tumors. According to World health organization (WHO) classification system these are grade I or II malignancies but include a number of histologically distinct histology's that can arise throughout the neuro-axis.[1]

Most recent Brain tumor classification in WHO CNS, 5th edition recognizes the clinical and molecular distinctions between those diffuse gliomas that primarily occur in adults (termed "adult-type") and those that occur primarily in children (termed "pediatric-type").[2] Paediatric diffuse gliomas morphologically resemble their adult counterparts; however, these demonstrate clear differences to adult tumours – including their incidence, location, risk of anaplastic transformation and genetic profiles.[3]

The current diagnostic list of tumour subgroups contributing to the paediatric and young adult low-grade glioma entity, according to the World Health Organization Histopathological Classification system, is displayed in Table 1.

Histological Diagnosis (WHO 2021 classification)	**WHO Grade**
Circumscribed astrocytic gliomas	
- Pilocytic astrocytoma	1
- Subependymal giant cell astrocytoma (SEGA)	1
- Pleomorphic xanthoastrocytoma (PXA)	2
- Chordoid glioma	2
Pediatric type diffuse low-grade glioma	
- Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	1
- Angiocentric glioma	2
- Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)	1
- Diffuse low-grade glioma, MAPK pathway-altered	1
Other glial / glioneuronal tumours	
- Ganglioglioma	1
- Dysembryoplastic neuroepithelial tumour (DNET)	1
- Rosette forming glioneuronal tumour	1
- Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	No yet assigned
- Desmoplastic infantile astrocytoma/ganglioglioma	1
- Papillary glioneuronal tumour	1
- Diffuse leptomeningeal glioneuronal tumour	Not yet assigned
- Gangliocytoma	1

Table 1: List of CNS glial/glioneuronal tumors that are seen in paediatric and young adult. According to WHO 2021 criteria[2]

Oligodendrogliomas and IDH mutant diffuse astrocytomas, are uncommon in children but can be seen young adults.

WHO CNS5[2] recommends use of the suffixes NOS (not otherwise specified) and NEC (not elsewhere classified) in order to clearly separate standard, well-characterized WHO diagnoses from those diagnoses that result from either (1) a lack of necessary diagnostic (eg, molecular) information or (2) nondiagnostic (ie, for a WHO diagnosis) or negative results.

Adding an NOS suffix indicates that the diagnostic information (histological or molecular) necessary to assign a specific WHO diagnosis is not available, providing an alert to the oncologist that a molecular work-up has not been undertaken or failed technically. An NEC suffix, on the other hand, indicates that the necessary diagnostic testing has been successfully performed but that the results do not readily allow for a WHO diagnosis. NEC diagnoses are what pathologists have termed "descriptive diagnoses,"
in which the pathologist uses a non-WHO diagnosis to categorize the tumor. In this regard, an NEC designation provides an alert to the oncologist that, despite an adequate
pathological work-up, the tumor does not conform to a standard WHO diagnosis. Like WHO diagnoses.[2]

WHO CNS5 advocates a layered structured report that has an integrated diagnosis (combined tissue-based histological and molecular diagnosis) followed by histological diagnosis, histological grade and molecular information.[2]

Tumour diagnosis and classification should be performed by pathologists who are well familiar with brain tumour reporting and updates. Moreover, review of the pathology by neuropathologists with specialist expertise in children's tumours is advocated whenever possible or if the need arises based on clinical and radiological assessment.

In the setting of LMIC setting, where molecular studies are not available, histology supported by relevant immunohistochemical studies can be sufficient in rendering a definitive diagnosis in most cases. GFAP, Ki-67, BRAFV600E, IDH1-1, ATRX, Olig-2, p53, S-100, CD34 and Synaptophysin are basic stains that are required for making a diagnosis[3].

When there is a doubt, whether it be scanty tissue, unhelpful Immunohistochemistry, unavailability of required immunostains or challenging histology, a second opinion either national or international center is recommended.

References:

1. Ryall S, Tabori U and Hawkins C: Pediatric low-grade glioma in the era of molecular diagnostics. Acta Neuropathologica Communications (2020) 8:30
2. David N. Louis, Arie Perry, Pieter Wesseling, etal. 2021 WHO Classification of Tumors of the Central Nervous System: a summary. NeuroOncol. 2021.23(8), 1231–1251, 2021 | doi:10.1093/neuonc/noab106.
3. Guidelines for the diagnosis and management of paediatric and adolescent Low-Grade Glioma (*extrapolated from current SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low-Grade Glioma: Klin Padiatr. 2019;231(3):107-135*)

SURGICAL GUIDELINES FOR LOW GRADE GLIOMA

Extent of resection remains strongly linked to survival for the majority of LGGs of the brain and spine. Within the literature, it has been demonstrated that achieving greater resection (90% or more) has a profound impact on progression-free survival (PFS) and overall survival (OS).(1) This is particularly true for hemispheric, cerebellar and intramedullary spinal cord tumors.

The decision to operate must be made and planned according to the patient's symptoms and radiological evidence of severity. Small lesions that do not compress adjacent structures may be either planned for elective surgery at a later date or observed for the time being with an emphasis on early follow-ups and repeat imaging. Larger lesions with signs of mass effect can be assessed according to the patient's symptoms: patients who are neurologically intact and not at risk for deterioration can be admitted for optimization and elective surgery.(2) With tumors causing hydrocephalus, urgent surgery is warranted. Resection of the tumor to both ameliorate hydrocephalus and treat the disease should be the goal of surgery. In situations where surgery has to be delayed due to a lack of facilities or need for patient optimization before surgery, a temporary strategy of CSF drainage can be employed via external ventricular drain (EVD) insertion. However, this comes with a caveat that drains should be removed within a few days. Otherwise, the patient is at risk for infection and shut dependency. Moreover, surgeons should be careful to emphasize to families of patients that CSF shunting is a temporary measure whereas surgical resection of the tumor is the definitive management.

In the perioperative period, Corticosteriods can be used as adjuvant therapy to decrease edema, especially perilesional edema noted on MRI imaging.
It is recommended that in the context of resource-constrained settings, complex cases be referred to pediatric neurosurgery specialists or surgeons with considerable experience with CNS tumors. Multidisciplinary teams can be engaged for input from oncologists and radiologists for a holistic approach. In the absence of any expertise in pediatric brain tumors, patients should be referred to a larger, higher-volume center with the appropriate equipment and expertise.

Surgical Plan

The goal of surgery is to extract sufficient tissue to reach a histopathological diagnosis, debulk or remove as much of the tumor as possible, and to ensure no new neurological deficits occur due to the surgical procedure. Even if the tumor is present in a subcortical area, there is a tremendous benefit in prognosis by removing as much of the tumor as is possible.(4) In particular, low grade gliomas within the superficial cerebrum and cerebellum can be resected completely with 90% or greater 10-year overall survival rates with rare recurrence.(5) For poorly circumscribed, non-pilocytic low-grade gliomas which infiltrate into eloquent regions, critical structures, or cross the midline, gross total resection may not be possible. In such circumstances, a debulking or neuro-navigation guided biopsy procedure may be more appropriate. When draining a cystic lesion, biopsy of the wall should also be planned. Cyst drainage may decrease mass effect of the tumor yet it is still necessary to obtain biopsy samples of the cyst wall for purposes of molecular and histopathological subtyping. Surgical specimens should be obtained both for formalin-fixed, paraffin-embedded standard histology and fresh-frozen samples for intraoperative diagnosis to confirm that no remnant tumor has been left behind. In adjunct to the surgical procedure, we can use functional MRI (fMRI), diffusion tensor imaging (DTI), and intraoperative functional mapping of eloquent areas (awake craniotomy procedures in children above 10 years of age) to achieve maximum cytoreduction without any new neurological deficits. However, these tools are not necessary particularly within LMIC settings, and surgeons should be cognizant of the financial burden this may have on a patient's family.
Operative notes should be reviewed by the lead surgeons for accuracy and consider the consistency, vascularity and extent of resection of tumor: whether gross total resection, near total resection (total volume of remaining tumor $< 1.5cm^3$), or partial resection (total volume of tumor remaining $\geq 1.5cm^3$).(6, 7)

Postoperative Outcomes

For children with low-grade gliomas who undergo total resection of the tumor (after confirmation by the surgeon's report and postoperative MRI with 24-48 hours of surgery), there is often no need for any further interventions. Management is then directed towards radiological follow-ups as well as routine clinical examinations for any neurological signs, particularly if tumor histology is concerning.(8)
Decisions on further intervention should first be brought before a multi-disciplinary neuro-oncology tumor board (NTB). Consensus is needed to decide whether the tumor shows pseudo-progression and requires a 'watch-and-wait' strategy or has progressed enough to merit surgery. In patients where subtotal resection was done, a repeat surgery may be considered later if the neurosurgeon feels it is necessary. However, it would be more practical to follow-up the patient with MRI scans at 3–6-month intervals and watch for signs of progression. If the tumor does not show measurable growth on imaging and the patient remains clinically stable, the decision to repeat surgery or adjuvant chemoradiotherapy can be delayed.

Special Considerations

For low-grade gliomas in the supratentorial midline, brainstem, and optic pathway, surgical resection is rarely considered an initial treatment plan. Observation until radiographic progression is acceptable for patients with minimal clinical symptoms. For optic pathway low-grade gliomas, tumor resection or debulking may be pursued when the tumor is unilateral with absence of vision preoperatively or painful proptosis.(9) Chiasmal and hypothalamic tumors can be debulked for relief of hydrocephalus due to third ventricle obstruction, mass effect, visual defects, and endocrinological disturbances. Therefore, early integration of an experienced pediatric endocrinologist is needed due to possible complex hormonal, electrolyte and fluid balance issues in the peri-operative period.
In brainstem gliomas and tectal glioma, the typical presentation is hydrocephalus – the appropriate treatment is to manage this conservatively and wait to decide on surgery until a MDT board has reached a decision for surgery. This is because while surgery can treat the lesion, the location of the tumor can result in significant morbidity associated with surgical intervention.(10) Resection of tumors in the cerebellum may carry the risk of postoperative cerebellar mutism syndrome, of which surgeons should be wary.

Surgery for tumor progression

Surgery for solid tumour progression

A further neurosurgery is indicated to reduce tumour volume Patients with progression of the solid tumour portion. Same guidelines apply as for primary resection.

Surgery for cystic tumour progression

For symptomatic cystic progression surgical management usually involve drainage of the cyst +/- insertion of a reservoir usually via open or endoscopic techniques. Consider debulking of the tumor. Repeat specimens of tumour should be obtained for further analysis.

Surgery for hydrocephalus

Primary tumor resection alone may not work for all, and patients may therefore require hydrocephalus treatment through an endoscopic third ventriculostomy or insertion of a ventriculo-peritoneal shunt25.

Extent of resection

The SIOP Brain Tumour Sub- Committee ratified the definition of extent of resection in 1995[26], with recent adaptations. The decision about the extent of resection should be made according to the following 2 factors

- post-operative MRI scan report (radiological judgement),
- surgical notes (surgical judgement)
- The final definition of the extent of resection integrates surgical and radiologic judgement

Total resection
A complete macroscopic / microscopic clearance of tumour reported by neurosurgeon in the operation notes and confirmed by a contrast-enhanced MRI scan performed within 48h (maximum 72h) of surgery.
Total resection requires concordance between surgical and radiological judgement).

Near total / subtotal resection
A small residue of tumour (total volume of remaining tumor < 1.5cm3) can remain. This may or may not be visible on a post-operative MRI scan performed within 48h (maximum 72h) of surgery.

Partial resection
The total volume of tumour remaining is ≥ 1.5cm3, confirmed by the post-operative MRI scan performed within 48h (maximum 72h) of surgery. The neurosurgeon has or has not recorded residual disease. The radiological and surgical reports may or may not agree.

Biopsy
This intends to only obtain tissue for diagnosis. No significant change in tumour volume on a post-operative MRI performed within 48h (maximum 72h) of surgery. Concordance between the surgical and radiological reports would be expected.

Post-operative Management Options

Following surgical intervention, the local multidisciplinary team must decide on further plan of management i.e., whether patient should be observed, or requires adjuvant therapy.

Observation group
If a complete resection is achieved patients should be observed clinically and radiologically.

Following *incomplete resection* or in case of a clinical-radiologic diagnosis only, a close observation with MRI imaging without treatment can be considered as long as they have no radiological tumour progression and no severe or progressive clinical symptoms.

Incompletely resected tumors have tendency to progress independent of location, but time to progression and proportion of patients progressing relate to the size of the postoperative residue with smaller residues progressing later and less frequently.

After a repeat-surgery in case of relapse / progression, observation-only is again considered only for patients without significant tumour-related symptoms.

Non-Surgical management

Indications to start non-surgical treatment:

- At diagnosis: Consider treatment after diagnosis if there are severe progressive neurological or visual symptoms. Infants under 12 months of age with chiasmatic/hypothalamic glioma, with or without Diencephalic syndrome and with residual tumour or metastatic tumour should be treated without a period of observation.

- Following observation: All other patients should enter into a period of observation with regular imaging and clinical review.

Treatment should be started in case of:

- Significant radiological progression of residual tumour
- Appearance of new lesions on MRI imaging not amenable to surgery
- Neurological or visual deterioration following initial observation.

Radiological progression

The decision to start non-surgical treatment based on radiological progression of an unresectable tumour must be carefully considered. Unless there is significant growth (greater than 25%) only observation is beneficial before a decision to start treatment is made. Neurological or visual impairment caused by tumour growth is a clear indication to start treatment.

Vision as an indication for non-surgical treatment

Visual impairment at presentation or visual deterioration are the most common indications for commencing non-surgical treatment. A reliable and quantifiable vision assessment is required in young children particularly with repeat testing although it is difficult. Visual acuity remains the most accepted measure for treatment decisions, mentioned more clearly in our opthalmological section.

A non-functional eye with no light perception (NLP) alone, in the absence of bilateral threat to vision, is not an indication for treatment. Other factors such a NF1 status, age and the extent of the optic pathway tumour should be taken into account when deciding whether to start treatment.

In patients with NF1 the radiological appearance of the optic pathway tumour may be very extensive and is often bilateral. Visual impairment at presentation with a history of deteriorating vision is an indication for an immediate start of treatment. Other signs of severe visual impairment in a young child include nystagmus, roving eye movements and relative afferent pupillary defect (RAPD). Exophthalmos, more often seen in NF1 may cause pain and can be an indication to start therapy.

References:

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Summary table of indications provided in the SIOP-E BTG guidelines (Table 2)

Radiological criteria
• Increase of tumour volume of > 25 % (the increase of the diameter of the optic nerve should be indicated separately) • Involvement of previously uninvolved areas • Appearance of new lesions • Increase of the number and/or size of metastases
Neurological criteria
• Diencephalic syndrome • Focal neurological deficits secondary to tumour growth • Drug resistant seizures subsequent to tumour growth • (Focal) increased intracranial pressure subsequent to tumour growth • Symptomatic metastases
Age criteria
• Infants below 12 months of age with Optic Pathway Hypothalamic Glioma
Ophthalmological criteria
• Definitive anamnestic loss of vision • Borderline vision ("Threat to vision") • Reduction of residual low level vision / visual field • Nystagmus subsequent to visual impairment in infants • Any visual loss in the second eye when the first eye is blind
Notes of value
• The presence of a (postoperative residual) tumour is no indication to commence first line adjuvant therapy on its own • At present there is no single molecular marker that is an indication to commence first line therapy on its own • A non-functional eye with no light perception alone is not an indication for treatment • Exophthalmos may be an indication to start therapy for cosmetic reasons • The presence of NF1 is not an indication to treatment on its own, but the visual pathways are more extensively and often bilaterally involved in NF1-associated tumours and may be associated with more severe visual impairment. Nevertheless, the presence of NF1 confers a better PFS [4,27-29], although long-term visual acuity may deteriorate in optic pathway glioma

Table 2: Indications to start non-surgical therapy in unresectable LGGs according to SIOP-E BTG guidelines.

CHEMOTHERAPY FOR LGG

The standard chemotherapy combinations are:

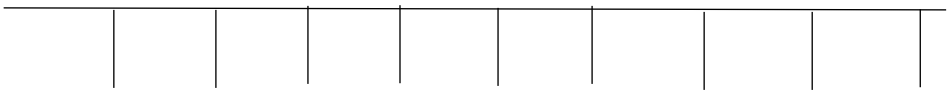
1. **First Line agent in non- NF1 patients**:

Weekly vinblastine for 70 weeks

For first line of treatment, we recommend weekly vinblastine as a slow IV bolus weekly for 70 weeks.

Dosage: Initial dose of 5 mg/ m² (as most patients needed dose reductions for hematological toxicity) Maximum dose 10 mg/m^2. If the child weighs below 10 kg (0.2 mg/kg)

Weekly Vinblastine (5mg/m^2)



Week 1 2 3 4 5 6 7 till 70

Date: Height, Weight, & BSA _____Height (cm) ____Weight (kg)____ BSA(m^2) _____

dose	Date due	Date Given	Vinblastine dose(mg/m^2)	Dose delivered	Delivery Status	Reason drug Altered/Not Given On Date Due	Comments	WBC	ANC	Hb	Plts

MRI Evaluation due Week 12 (+/- 2 weeks)		Delayed Given Modified Not given	Hematologic toxicity No documentation Patient non-compliant Protocol non-specified Change in pt weight Other	Required Observations: 1. Medical history 2. Physical exam e.g. height, weight, BSA 3. Performance status 4. Neurologic and eye assessment 5.CBC,RFTs.LFTs,Serum electrolytes

Assessments during this chemotherapy regime

- History, (including height & weight) clinical examination with neurological assessment should be performed at baseline and every three months on therapy.
- Ophthalmological assessment every three months during therapy in optic pathway gliomas.
- Full blood count and differential to be performed weekly for the first 12 weeks of chemotherapy then week one of a four weeks cycle of chemotherapy.
- Renal function tests, liver function tests and electrolytes, including calcium and urate should be monitored after every three months.

- Contrast-enhanced MRI scan of affected CNS site (brain, spine, or both) 3 months \until end of therapy.

Critical tests and dose modifications

Dose modification according to age/weight:
In children less than one year of age or weighing less than 10 kg, doses are calculated according to weight (0.2 mg/kg).

Dose modification according to CBC result (starting dose 5mg/m2):

- If neutrophil count is equal to or greater than 0.75 $x10^9$/L and platelet count is equal to or greater than 75 x 10^9/L, the next dose/cycle may be administered at full dose.
- If neutrophil count is less than 0.75 but equal to or greater than 0.5 x 10^9/L and/or platelet count is below 75 x 10^9/L but equal to or greater than 50 x 10^9/L, dose reduced to 4 mg/m2 or 20% of the originally prescribed dose for weight below 10kg.
- If neutrophil count is below 0.5 x 10^9/L and/or platelet count is below 50 x 10^9/L, withhold vinblastine until blood count recovery to neutrophil count = 0.75 x 10^9/L and platelet count = 75 x 10^9/L. Resume Vinblastine at 4 mg/m² or at 20% of the originally prescribed dose for children with weight below 10kg.
- Patients who at a reduced dose of 4 mg/ m² still demonstrate objective evidence of hematological toxicity affecting the weekly schedule will have their subsequent dose of the agent decreased to 3 mg/m² or to 33 % of the originally prescribed dose for weight below 10 kg.

2. Second line of agent in non- NF 1 patients:

Vincristine and Carboplatin

This combination is given in case of failed response to first line therapy or if there is significant residual disease or the disease has progressed > 25 %

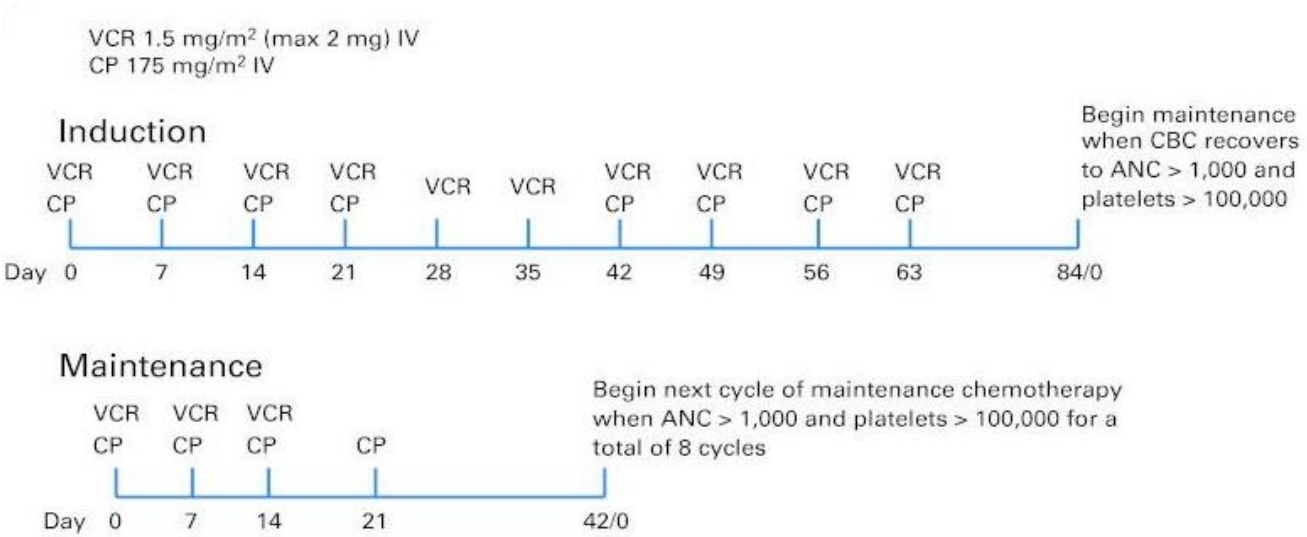
These are given as a 12-month chemotherapy regimen comprised of Vincristine and Carboplatin. This showed an improved outcome for patients with neurofibromatosis type 1 (NF1)-associated visual pathway glioma (NF1-VPG)

An intensified induction of 3-months
A reduced-intensity continuing phase of 9-months

Dosage
Vincristine (1.5 mg/m^2 max 2 mg)
Carboplatin (175mg/m^2)

Induction
Weekly vincristine and carboplatin for 4 weeks then only weekly vincristine for 2 other weeks followed by 4 other weeks of weekly vincristine and carboplatin repeat till day 84 from start of induction.
Begin maintenance when ANC > 1000 and platelets > 100,000

Maintenance
Monthly cycles of Vincristine and carboplatin at day 0, 7 and 14 and only Carboplatin at day 21.
Given for a total of 9 months.
Begin next cycle when ANC >1000 and platelets >100,000



Treatment schema for induction and maintenance therapy for low grade gliomas with carboplatin (CP) and vincristine (VCR)

Dose Modification for Toxicities

Vincristine Toxicity

Neurotoxicity

For seizures, hold one (1) dose, then reinstitute at 1.0 mg/m2 (1.5 mg maximum) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

Neurotoxicity Grade 3/4, foot drop, severe paresis, disabling paresthesias or ileus: hold one dose, resume vincristine at 1 mg/m2 (1.5 mg maximum) and then escalate to full dosage when symptoms resolve.

Jaw Pain

Treat with analgesics (not salicylates). Do not hold or reduce vincristine.

Hepatotoxicity

If total bilirubin is greater than 1.9 mg/dl, hold vincristine dose. If direct bilirubin is 1.5 - 1.9 mg/dl, administer vincristine at 1.0 mg/m2.

3. Third Line of agent in non-NF 1 patients:

PCV:

In case of unresectable low grade gliomas, a combination of Procarbazine, CCNU (Lomustine) and vincristine can be given as third line of agents: Give 6 cycles repeated every 6 weeks. Aim being to cover a period of approximately 10 to 11 months:

Procarbazine 60 mg/m² PO Days 8 to 21
Lomustine 110 mg/m² PO Day 1
Vincristine 1.4 mg/m² IV Day 1 & 22.

Toxicity and Dose Modification:

Hepatotoxicity:

If grade 3-4 toxicity develops (CTCAE v5.0), hold chemotherapy until toxicity is less than grade 2. If aetiology of toxicity is unexplained, the doses of vincristine, lomustine and procarbazine, should then be reduced by 25 %.

Neurotoxicity:
Peripheral neuropathy (grade 3 or 4; CTCAE v5.0) = omit VCR and if neuropathy resolves, resume dosing at 1 mg/m2. Convulsions / SIADH = the following dose/course of VCR should as well be omitted; if no further convulsions or symptoms of SIADH occur, therapy at 1.0 mg/m² VCR can be continued (continuing any concurrent anticonvulsive treatment). If no further convulsions occur, following doses of VCR can be given according to schedule.

Allergy: If an allergic reaction occurs during or following procarbazine, discontinue the medication for the rest of that cycle. If severe and clearly related to procarbazine, delete it from the remaining cycles.

Nephrotoxicity

If the creatinine clearance or GFR is 75% of baseline value, then the lomustine should not be administered. It should be held until the creatinine clearance rises above 75% of baseline value.

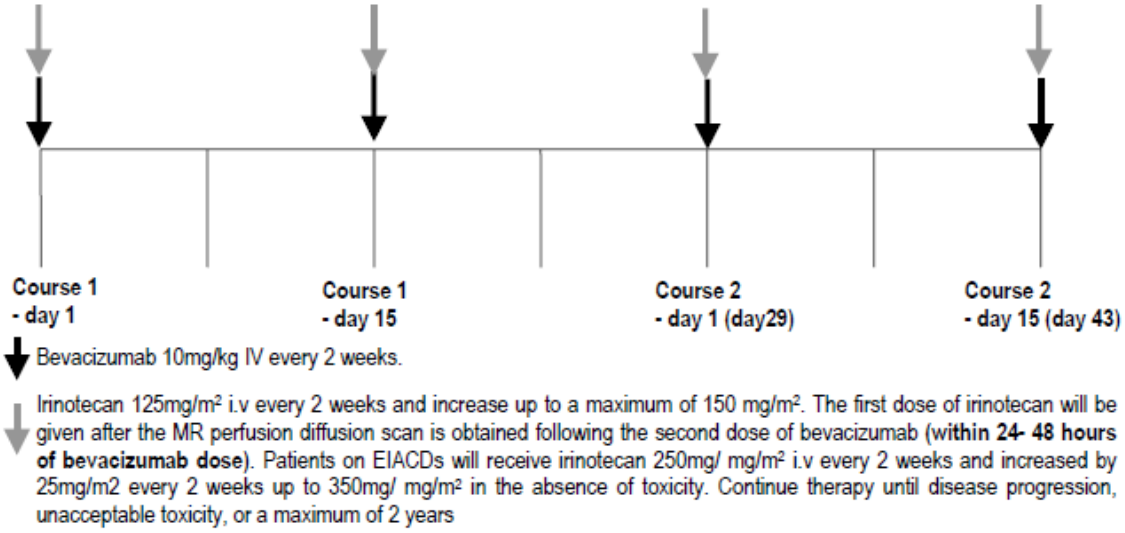
4. Fourth line of agent in non-NF 1 petients:

Irinotecan and bevacizumab

The combination of irinotecan and bevacizumab has shown tumour responses as well as clinical and visual improvement in small studies of progressive LGG in many developing countries but in Pakistan finances are major impediment to strart this regimen. We therefore recommend to start this chemotherapy with consensus of National Pediatric Brain tumor board. This regimen consisted of:

- Intravenous Bevacizumab at 10 mg/kg every 2 weeks and
- Intravenous Irinotecan at 125 mg/m² every 2 weeks. For maximum of 12 months.

Road map for Irrinotecan/Bevacizumab as fourth line of agent:



Assessments during this chemotherapy regime

- Clinical examination (including neurological assessment and blood pressure performed prior to commencing therapy and every two weeks prior to a course of therapy.
- Dipstick urinalysis for proteinuria prior to each course.
- Full blood count and differential, U&Es, liver function to be obtained at baseline and repeated every 2 weeks during therapy at discretion of local institution.
- Coagulation every 3 months.
- Ophthalmological assessment every three months during therapy if tumour involves optic pathway.
- Contrast-enhanced MRI scan of affected CNS site (bran, spine, both) 3-monthly until end of therapy.
- Knee x-ray for growth plate analysis 6 monthly. Patients with any new abnormality of the epiphyseal growth plate are required to have a MRI scan of the knee for confirmation.

Laboratory tests and dose modifications

Each cycle of irinotecan and bevacizumab can be administered if the following parameters are met:

- Full blood count: Absolute neutrophil count greater than 1.0 x 10^9/L, Platelets greater than 100 x 10^9/L
- Bilirubin below 1.5 upper limit of normal
- Urinalysis: below 1+ for protein
- No bleeding disorder.
- Normal BP (95^{th} centile for age and gender).
- Coagulation must be checked using a peripheral sample before the start of treatment and then every 3 months.

Dose Modifications:

Hematological toxicity:

- If the CBC parameters as mentioned above are not met, consider giving both bevacizumab and irinotecan at three weekly intervals.
- If the CBC parameters are still not normal in two different occasions reduce irinotecan doses by 20 %.
- If the CBC parameters remain unmet, delay the therapy by a further week and reduce all subsequent irinotecan doses by a further 20 % (60 % of original dose). Likewise, if, following a 20 % dose reduction of irinotecan, the CBC parameters initially recover but then are not met at a subsequent timepoint in the treatment course, delay the therapy by 1 week and reduce all subsequent irinotecan doses by a further 20 % (60 % of the original dose).
- If further episodes of myelosuppression were observed despite a 40 % dose reduction in irinotecan, discontinuing the chemotherapy regime should be considered.

Gastrointestinal toxicity:

If grade 3 and 4 diarrhoea (CTCAE v5.0) occurs despite maximum loperamide therapy:

- Await resolution, and then reduce the subsequent irinotecan doses by 20 %.
- If grade 3 or 4 toxicity persists beyond 2 weeks despite suitable symptomatic treatment, discontinue the chemotherapy regimen.
- If less severe diarrhea is ongoing at the start of next cycle, delay next cycle for up to 2 weeks until diarrhea resolves to below grade 1. If the diarrhoea does not resolve after this 2-week delay, the patient should discontinue the chemotherapy regimen.
- If diarrhoea occurs again in a subsequent timepoint in the treatment course, a further dose reduction of 20 % for all subsequent irinotecan doses can be considered (60% of original dose); all of the above guidance for a first occurrence would remain pertinent.
- If diarrhoea occurred again despite a 40 % dose reduction in irinotecan, the patient should discontinue the chemotherapy regimen.

Adverse events requiring delay in bevacizumab therapy:

Adverse events requiring a delay in bevacizumab therapy is detailed in Table 3. The delay in bevacizumab therapy should continue until these effects are resolved. Adverse events requiring immediate discontinuation of bevacizumab are given in Table 4.

Adverse event	CTCAE v5.0 Grade
Infusion / allergic reaction	Grades 1 – 2 / 3 (see Appendix 3; page 36)
Hypertension	Grade 2 – 3
Wound healing complications	Any Grade
Proteinuria	Grade 3
Venous thrombosis/embolism (including vascular access device)	Grade 3 and asymptomatic Grade 4
Any other clinically significant (CTCAE Grade 3/4) AEs that, according to the Clinician's discretion, could be related to Bevacizumab	Grade 3 or 4

Table 3: Adverse events requiring delay in bevacizumab therapy

Adverse events requiring discontinuation of bevacizumab therapy

Adverse event	CTCAE v5.0 Grade
Infusion / allergic reaction	Grades 3 / 4 (see Appendix 3; page 36-40)
Hypertension	Grade 4 (Hypertensive crisis) Hypertensive encephalopathy Medically significant hypertension not controlled with medication
Left ventricular systolic dysfunction	Grade 3 or 4
Heart Failure	Any grade
Gastrointestinal perforation	Any grade
Tracheoesophageal fistula	Any grade
Any non-tracheo-esophageal fistula	Grade 4
Recto-vaginal fistulae	Grade 3 – 5
Proctalgia	Grade 3 – 4
Haemorrhage: Non-pulmonary / non-CNS	Grade 3 – 4
Haemorrhage: Pulmonary / CNS	Grade 2 – 4
Proteinuria	Grade 4
Posterior reversible encephalopathy syndrome (PRES)	Any grade
Venous thrombosis / embolism	Grade 4
Any arterial thrombosis / embolism	Any grade
Myocardial infarction	Any grade
Cerebrovascular ischemia	TIA or CVA
Osteonecrosis	Any grade
Eye disorders	Grade 4
Necrotizing fasciitis	Any grade
Weight decrease	Grade 1 – 3

Table 4: Adverse events requiring discontinuation of bevacizumab

Contraindications of using Bevacizumab:

Bevacizumab is contraindicated in the following:

- Major surgical procedure, open biopsy or significant traumatic injury within 28 days.
- Minor surgical procedures within two days prior to the start of treatment (including the placement of a Central Venous Access Device (porta cath, picc line or Hickman lines).
- Non-healing surgical wound.
- A bone fracture that has not healed.
- Bevacizumab can be restarted after 10 days of shunt insertion, if patient's condition is satisfactory and does not present any wound healing or hemorrhagic complication.

Targeted biological agents:

LGG is now considered as a single pathway disease of the MAPK pathway, targeted treatment in particular with BRAF inhibitors for *BRAFV600E* mutated cases and MEK inhibitors are currently being studied in prospective clinical trials. Several MEK inhibitors are currently in development for paediatric oncology indications (trametinib, selumetinib, and cobimetinib). In Pakistan the ,main issue is the availability and access of these targeted agents but we are trying to get these by compassionate access program.-Future large-scale clinical trials are looking to incorporate these agents in randomised analyses against comparative first-line chemotherapy protocols upfront both for NF1 and non-NF1 patients.

Chemotherapy treatment pathway for Low Grade Glioma: NF1 patients

- Children with NF1 and LGG have a superior overall and progression free survival, supported by trial results of this patient subgroup using vincristine/carboplatin or single agent vinblastine regimens 4,8,27-29. They also have been reported to suffer more toxicity, particularly neurotoxicity with vincristine.

  1. Weekly Vinblastine as a mono therapy 5mg/m^2 IV bolus over 15 minutes for 70 weeks.
  2. Vincristine/Carboplatin. (mentioned previously).

- For patients with significant visual impairment it is not recommended to use cisplatin due to the risk of additional ototoxicity. The assessments required, critical tests and dose modifications for all of these regimens are as per non-NF1 patients and documented previously. The alternative chemotherapeutic regimens in the face of a carboplatin HSR, irinotecan / bevacizumab therapy should be considered as the third line chemotherapeutic option, remain as per non-NF1 patients.

SEGA (sub-ependymal giant cell astrocytoma):

SEGA are associated with Tuberous Sclerosis complex disease (TSC). It is autosomal dominant disorder associated with germline mutation in two tumor suppressor genes TSC1 (hamartin) and TSC 2 (tuberin) resulting in the development of low-grade tumours in multiple organ systems, including the brain, kidney, skin, heart, retina and lungs.
International recommendations for the management of SEGAs in the TSC population are published 37 and are summarised in the SIOP-E guidelines as below: 1

- TSC patients should be monitored for SEGA development every 2 years before the age of 20 years.
- Asymptomatic SEGAs with a diameter greater than or above 1 cm should be monitored every 6 months by MRI
- SEGAs may be treated by surgery if there are symptoms or documented tumour.
- mTOR inhibitor therapy for SEGA (everolimus, available in Pakistan)can be considered for children equal to or above 3 years of age with SEGAs requiring intervention but surgery is contraindicated, the lesion is not amenable to surgery, the surgical approach does not allow complete resection, or in case of bilateral fornix lesions.

Baseline investigations prior to commencing everolimus*:*

- APTT, INR
- Full blood count and differential, U & Es, LFTs (AST, ALT, Bili (conj/unconj))
- Fasting glucose, triglyceride and cholesterol
- Hepatitis serology
- Urine dipstick

- MRI brain for patients with SEGA (to be combined with MRI kidney if lesions are large, are growing fast or have unusual characteristics).Follow up scans for patients with SEGA:
    - At 3 months, 6 months and then yearly.

Dose of everolimus: Everolimus should be started at a dose of 7mg/m² for ages 1 to less than 3 years and a dose of 4.5 mg/m² for ages 3 years and above. It should continue for minimum of 6 months or until disease progresses.(2)

References:

1- Gnekow AK, Kandels D, van Tilburg C, et al. SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low Grade Glioma. *Klin Padiatr.* 2019;231(3):107-135.

Jozwiak S, Nabbout R, Curatolo P, participants of the TSCCMfS, Epilepsy M. Management of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC): Clinical recommendations. *Eur J Paediatr Neurol.* 2013;17(4):348-352.

RADIATION THERAPY GUIDELINES

Radiation Therapy is an effective treatment modality for non-resectable or partially resected low-grade gliomas. Radiotherapy in such situations may help achieve outcomes similar to gross total resection. Addition of radiation therapy to chemotherapy for partially resected tumors may help improve progression free survival but may not help in improvement of overall survival. Following things should be ensured for children with Low Grade Gliomas (LGG) being considered for treatment with radiation therapy.

- Decision to treat children with Radiation Therapy shall be taken in a multidisciplinary team tumor board meeting.
- Patient should have CT based radiotherapy planning.
- Availability of MRI imaging (Contrast enhance, T2 and FLAIR) sequences.
- Technical considerations for MRI images co-registrations with planning CT scan, standard contouring of targets and organ at risk, use of 3-D planning, immobilization devices, verification and accuracy of dose delivery and verification should be made.
- All radiation treatment volumes and plans should be 'Peer Reviewed' by expert radiation oncology team.

Equipment

Simulation:

Three-dimensional simulation is required. Both treatment planning CT and MR scans are required and must have slice separation and slice thickness of no more than 3 mm. The system must have the capability of coregistering MR and CT images so that the contouring of the target can be performed on the MR image.

Treatment Planning:
Any treatment planning system which can compute a dose-distribution on a point by point basis in 3 dimensional space that satisfies the criteria described below is acceptable. 3D conformal, IMRT, and VMAT are examples of allowed treatment planning. Standard treatment planning guidelines for the use of IMRT/VMAT such as those developed by the NCI in clinical trials should be followed in this study. (See QARC website, www.QARC.org)

Treatment Delivery:
A linear accelerator with nominal energy of at least 6 MV shall be used. All linear accelerators must be isocentric with a minimum source-axis-distance of 100 cm. All therapy units used for this protocol shall have their calibrations verified by the national regulatory body such as Pakistan Nuclear Regulatory Authority (PNRA). Multi-leaf collimators and a record-and-verify system are required for IMRT / VMAT treatment, but cerrobend blocking is allowed for patients treated with 3D conformal therapy

Target volume definitions

ICRU Definitions
The target volumes shall be defined as per International Commission on Radiation Units and Measurements (ICRU) report-50 definitions. In the ICRU terminology gross target volume (GTV) and clinical target volume (CTV) are anatomically defined and represent the extent of gross and microscopic disease respectively. The planning target volume (PTV) is geometrically, not anatomically, defined and is an expansion of the CTV intended to account for uncertainty in patient positioning.

- **GTV**

For all patients with enhancing tumors like pilocytic astrocytomas, the gross target volume (GTV) will include the entire tumor volume seen on gadolinium enhanced T1 MR imaging performed just prior to the start of irradiation plus any non-enhancing abnormality seen on T2 or FLAIR imaging at that time. All tumor cysts will be included in the GTV. For patients with diffuse tumors, the GTV will be the T2 or FLAIR abnormality seen on pretreatment MRI. All efforts should be made to have co-registration of MRI scan with the planning CT scan into the treatment planning system.

- **CTV**

For pilocytic astrocytomas, the CTV will be the GTV plus a 5 mm anatomically limited margin (e.g., the CTV will not extend into the calvarium, falx, tentorium cerebelli) as low grade gliomas do not infiltrate these structures. A wider margin of up to 10 mm could be taken in situations where patient has undergone multiple surgeries or when CT alone is used for delineation or when the available MRI scans do not provide clear delineation of tumor extent.

For adult-type diffuse LGGs, the recommended CTV margin is 15 mm, which may be reduced near organs at risk (OAR) to 10 mm where this might result in a clinically relevant dose reduction. In other LGGs, including paediatric type diffuse gliomas, a CTV margin of 10 mm is recommended.

- **PTV**

For all tumor types, the PTV will be the CTV plus a 3-5 mm (depending on institutional experience) margin to account for patient movement. For centers without regular portal imaging for verification the PTV margin should not be less than 5 mm. If there is doubt as to any of the accuracy measures, the PTV margin can be up to 10 mm. All effort should be made with the help of immobilization devices, portal imaging to minimize the institutional setup error.

All contours including those of Organ at Risks should be peer reviewed with other Radiation Oncologist in order to minimize the chances of missing the region of interest.

- **Localization**

A treatment planning CT scan with slice separation and thickness no more than 3 mm obtained with the patient in the treatment position is required. A treatment planning MR scan with slice separation and thickness no more than 3 mm is also required. The GTV must be contoured on the MR image and then the MR and CT images fused using the treatment planning system. A screen capture of the fused CT and MR images in three orthogonal planes should be available for recording for the Quality Assurance Documentation.

Timing of radiotherapy

Start of radiotherapy

Radiotherapy must start within 30 days of once the decision to treat the patient with radiation therapy has been taken by multidisciplinary tumor board meeting.

Interruptions and Delays

There are no planned rests or breaks. Once radiotherapy is started, treatment should not be interrupted unless the patient is too ill to receive treatment. No significant hematological toxicity is expected from these treatments and radiation therapy should continue in the face of decreased blood counts. For interruptions of more than 5 treatment days, please contact the primary pediatric oncologist and radiation oncology lead. The reason for any interruptions greater than 2 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation.

Target dose

Prescription

The standard dose being recommended is 50.4 to 54 Gy to be delivered in 28 to 30 fractions of 1.8 Gy each. Younger children (<5 years of age) shall be treated with a lower dose of up to 45 Gy. The treatment dose shall be prescribed to an Isodose surface that encompasses the PTV and that satisfies the dose uniformity requirements in Section X.4.3.

Following are some examples of dose prescription for some specific clinical situations (adapted from UK CCLG Guidelines for LGG):

Intracranial LGGs:

- For Optic Pathway Gliomas, 50.4 Gy in 28 fractions.
- For brainstem gliomas, a minimum of 50.4 Gy in 28 fractions, but 52.2 – 54.0 Gy in 29-30 fractions if achievable within optimal brain stem dose constraints.
- For Pleomorphic Xanthoastrocytoma (PXA, WHO grade II), 54 Gy in 30 fractions.
- For children aged under 5 years, 50.4 Gy in 28 fractions (except for PXA, which should preferably receive 54 Gy in 30 fractions); reduction to 45 Gy in 25 fractions may be considered in exceptional cases e.g. children below 3 years of age.
- For all other cases, 54 Gy in 30 fractions as standard; this may be reduced at the discretion of the Clinical Oncologist to a minimum of 50.4 Gy in 28 fractions, for example for a very large volume tumor in a young child, or a tumor the bulk of which is in close proximity to optic pathways.

Spinal LGGs:

- 50.4 Gy in 28 fractions as standard
- 50 Gy in 30 fractions may be used at the discretion of the Clinical Oncologist in selected situations (e.g. long length of cord in the volume, existing neurologic deficit, age below 5 years).

Disseminated cases - Craniospinal radiotherapy:
There is no standard dose recommendation for disseminate LGG. Craniospinal irradiation could be considered. Such cases should be discussed in mdt tumor board and offered treatment according to locally available resources.

Dose Definition

The absorbed dose is specified as Gy-to-muscle.

Dose Uniformity
The entire PTV should be encompassed within the 95% isodose surface. No more than 10% of the PTV should receive greater than 107% of the prescription dose, as determined by dose-volume-histogram. The maximum dose received by any point should be no more than 112% of the prescription dose. All points receiving ≥ 110% of the prescription dose should lie within the CTV.

Treatment technique

Patient Position:
Patients will usually be treated in the supine position. Immobilization with mask, neck rest and other system is required.

Sedation
General anesthesia is often required with young patients in order to achieve adequate immobilization. Propofol is a useful IV agent. Inhalation gases like Suvoflurane can be used

Bolus
No bolus is required or allowed.

Field Shaping
Field shaping shall be performed. Multi-leaf collimators (MLCs) are required for IMRT / VMAT treatment. Cerrobend blocking is allowed for 3D conformal therapy.

Normal tissue sparing

Radiation dose to critical structures such as the optic chiasm, optic nerve, pituitary/hypothalamus, and cochleae should be minimized. The optic chiasm dose should be limited to 54 Gy for patients with tumors arising from the optic apparatus or the hypothalamus and 50.4 Gy for others

Quality assurance documentation

For quality assurance purpose, the radiation therapy treatment plan should be available in digital format (either Dicom RT, RTOG format or other standard format) if possible. One can see the QARC website (www.QARC.org) for digital data submission information.

It is encouraged to compile the following documents:

- Copies of all diagnostic materials and surgical reports used in defining the target volume including (i) preoperative MRI and postoperative cranial MRI with and without contrast; (ii) All pre and post chemotherapy scans and serial scans done as part of follow up; (iii) operative reports.
- These would include enhanced and unenhanced T1 images as well as T2 and FLAIR sequences or others which best describe the extent of tumor.
- Copies of isodose distributions to demonstrate that the dose variation is within specification.
- The target volume, and the prescription point must be clearly shown
- A screen capture of the fused CT and MR images in orthogonal planes through the center of the target volume.
- Prescription Sheet for Entire Treatment
- A hard copy isodose distribution for the total dose plan in the axial, sagittal and coronal planes at the center of the planning target volume must be submitted. These dose distributions must include the following:
- A sufficient number of isodose contours should be shown to determine that the dose distribution conforms to the protocol guidelines. These isodoses should be superimposed over treatment planning CT images. However, if such hard copy presents difficulty, similar plots without gray scale image are acceptable if enough critical contours are identifiable to verify the dose distribution to target volumes and critical normal structures. Specifically, include those volumes for which there are dose volume histograms.
- Copies of simulator films and /or digitally reconstructed radiographs (DRR's) for each field.
- Copies of verification (portal) films (or hard copy of real time portal images) for each field.
- Photographs of the patient in the treatment position with the fields marked.
- Beam's Eye Views (BEV's) for all fields and showing the PTV (boost) and critical structures. BEV hard copies must be in color to enable reviewers to identify structures.
- A room view display of all fields should be submitted.
- Dose volume histograms in a standard format. If IMRT is used, a DVH shall also be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- Dose-volume histograms for the GTV, CTV and PTV as well as for the optic chiasm, left and right optic nerves and the pituitary/hypothalamus. The maximum and minimum doses in the target volumes shall be calculated and reported on the appropriate (RT-1/
- IMRT) Dosimetry Summary Form. These may be extracted from DVH's
- Documentation of an independent check of the calculated dose if IMRT is used.
- Color copies of isodose distributions to demonstrate that the dose variation is within specification.
- The target volume and the prescription point must be clearly shown.

- Documents verifying peer review and double checks from radiation oncologist, medical physicist and RTTs for all the phases of treatment for each patient.
- RT-1 Dosimetry Summary Formfor 3D-CRT / IMRT, whichever technique is used.
- RT-2 Radiotherapy Total Dose Record form.

Post treatment follow-up

The specific nature and extent of any follow-up will be tailored to the specific patient and incorporate local institutional policies:

- An '*observation*' group, without residual tumour or with stable residual disease
- A '*chemotherapy*' group, with stable tumour after termination of treatment
- A '*radiotherapy*' group, with stable tumour after termination of treatment

Tables 5- summarize these recommendations for each group.

	1st year	2nd year	3rd– 5th year	6th– 10th year
Physical and neurologic examination, auxology *	every 3 months	every 3–6 months	every 6 months	annually
MRI* (cranial and/or spinal)	every 3–6 months	every 3–6 months	every 6–12 months	annually, but optionally every 6
Ophthalmology (mandatory in VPG)	every 3 months	every 3–6 months	every 6 (-12) months	every 6–12 months
Audiometry (for brain stem LGG)	every 6 months	Not indicated, if previously normal; but regular assessments, if		
Endocrinology	Recommendations according to (►**Table6**)			
Neuro-cognitive follow-up	According to institutional policy			

Endocrinology follow-up is typically reserved for children with lesions of the hypothalamic-pituitary axis and other midline structures, or children who have received radiotherapy.

Table 6: Recommendations for endocrine assessments for relevant children with paediatric low-grade gliomas, (reproduced from Gnekow AK, Kandels D, van Tilburg C, et al. SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low-Grade Glioma. Klin Padiatr.

Schedule		
	Time point	**Timing of investigation**
Diagnosis	Before (or after) surgery	
Follow-up		

Observation group	Before growth is completed	Annually, but more often if clinically indicated
	After growth is completed	3 (to 5)-yearly assessment
Chemotherapy group	During treatment	At 6, 12 and 18 months of treatment for all patients with tumors of the chiasmatic-hypothalamic region, other patients at the beginning and end of treatment
	Before growth is completed	Annually, but more often if clinically indicated
	After growth is completed	3 (to 5)-yearly assessment
Radiotherapy group (cranial RT)	After completion of radiotherapy	At the end and one year after end of radiotherapy
	Before growth is completed	Annually, but more often if clinically indicated
	After growth is completed	3 (to 5)-yearly assessment, but more frequently, if the pituitary-hypothalamic region was in the RT field
Content of endocrine assessments		
	Time point	
Anthropometric data	Atdiagnosis	Parents' height, gestation (weeks), birth weight
	At all assessment points	Decimal age, standing height, sitting height, weight, occipito-frontal head circumference
Pubertal/reproductive data	At all assessment points (if relevant)	Tanner stages, testicular volume, date of menarche and/or of last menstrual period, regularity of menses
Biochemical data	At all assessment points (if relevant)	LH, FSH, DHEAS, Estradiol or Testosterone, free T4 and T3, TSH, IGF I and IGF-BP 3, and measurements of cortisol (institutional policy)
	At growth retardation	Bone age, growth hormone testing
	If the patient has thirst polyuria (especially at night), persistent or recurrent hypernatremia or othersymptomssuggestive of diabetes insipidus	Water deprivation test with measurement of urine and plasma osmolality

Appendix 1: Details of drug administration for chemotherapy regimes:

Vincristine and Carboplatin:

Vincristine IV bolus
Carboplatin IV infusion in 5% dextrose over one hour

The following fluid volumes are suggested but these are not critical and can be adjusted to the child's fluid requirements. The dextrose concentration must be greater than 0.5mg/ml.

Dose	Volume of 5% dextrose
25 – 250mg	50mls
251 – 500mg	100mls
501 – 1000mg	250mls

Irinotecan and bevacizumab

Irinotecan IV infusion over 1 hour in 0.9% sodium chloride or 5% dextrose
Suggested infusion volumes:

Dose Volume of 0.9% sodium chloride or 5% dextrose
2 – <4mg 5mls
4 – <10mg 10mls
10 – <62.5mg 25mls
62.5 – <125mg 50mls
125 – <250mg 100mls
250mg – <500mg 200mls

Bevacizumab IV infusion in 0.9% sodium chloride
Suggested infusion volumes:
Dose Volume of 0.9% sodium chloride
35 – <70mg 25mls
70 – <140mg 50mls
140 – 1650mg 100mls

First infusion to be administered over 90 minutes, second infusion over 60 minutes & third and subsequent infusions to be administered over 30 minutes

Appendix 2 - Carboplatin hypersensitivity reactions (HSRs)

Carboplatin may be associated with hypersensitivity reactions (HSR), which can present as a rash, itching, lip swelling, fever or in some cases life-threatening anaphylaxis. The incidence appears much higher in LGG treatment protocols than in other carboplatin containing regimens. The reaction is seen most commonly in consolidation phase. In SIOP-LGG 2004 study HSR of any grade was reported in 31/249 patients during induction and up to 117/192 during consolidation. HSR symptoms usually develop acutely during the infusion and only rarely hours or days later. Children receiving carboplatin have to be monitored throughout the infusion and for one hour thereafter. Recommendation for immediate management is shown in Table 7, below.

First line of management after clinical diagnosis of hypersensitivity reaction (HSR)

- STOP CARBOPLATIN INFUSION
- Monitor vital signs
- Rapidly assess and secure the airway
- Call for help (intensive care team needed?)

Treatment of Mild HSR

- Mild symptoms should be managed with anti-histamines (combination of H1 and H2 antagonists is superior), corticosteroids and ß2-sympathomimetic inhalations (in case of wheeze) according to local guidelines
- Examples:
  - H1 antagonists (e.g. chlorpheniramine) slowly i.v. in combination with
  - H2 antagonists (e.g. ranitidine) or PPI. Dosing according to local guidelines.
  - IV corticosteroids: hydrocortisone or dexamethasone – doses as per BNFC
  - ß2-sympathomimetic inhalations: e.g. Salbutamol inhaler or nebulized Salbutamol according to local guidelines

Treatment of Anaphylaxis

- Call resuscitation/intensive care team
- All the previous elements of care AND IM Adrenaline and fluid resuscitation according to local guidelines

General measures

- Provide supplemental oxygen if cardiopulmonary symptoms
- Position the patient in supine, or semi-reclining position of comfort and elevate the lower extremities (if dyspnoeic or vomiting or cardiopulmonary symptoms)

Recommendations for the continuation of chemotherapy following carboplatin HSR:
In children with mild HSR without overt anaphylaxis, carboplatin treatment can be continued with pre-treatment medication. Premedication with antihistamines (and corticosteroids) in combination with a prolonged infusion time up to a maximum of 6 hours can be considered.

Appendix 3 – Bevacizumab toxicity management guidelines

(Extracted from ITCC BEACON-Neuroblastoma Protocol_vn 6.0a_vd 16Jan2019): ClinicalTrials.gov Identifier: NCT02308527

. ***Infusion/ allergic reactions – CTCAE grades and actions***

CTCAE (v5.0) Grade	Action
Grade 1 *Infusion-related Reaction Mild transient reaction:* • Intervention not indicated *Allergic reaction:* • Transient flushing or rash; fever < 38°C • Intervention not indicated	If a Grade 1 infusion-related or allergic reaction occurs during the infusion, no treatment is needed. Supervise the patient, interrupt the infusion and complete bevacizumab infusion at a 50% rate. If no reactions occur, the next dose can be administered at a 75-100% rate. If reactions re-occur, challenge at a 75% rate and continue to use this rate if no reactions occur. If reactions re-occur at the 75% rate, use the 50% rate for subsequent administrations.
Grade 2 *Infusion-related and Allergic Reaction* (e.g. rash, flushing, urticarial, dyspnoea, fever > 38 ºC) • Intervention or infusion interruption indicated but responds promptly to symptomatic treatment; • prophylactic medications indicated for ≤24 hrs)	When a Grade 2 reaction occurs, stop the bevacizumab infusion. Manage the infusion reaction according to institutional guidelines. After recovery, resume infusion at 50% of the previous infusion rate for 15 minutes. If no further symptoms occur, complete the infusion at the reduced rate. Premedication should be given with the next infusion, but the infusion time may not be reduced. If a Grade 2 infusion-related adverse reaction occurs, all subsequent infusions should be administered over the shortest period that was well tolerated. For example: If an infusion-related AE occurred after the first infusion, the subsequent (i.e., the second) infusion must be administered over a slower infusion rate. If the infusion is then well tolerated with pre-medication, all subsequent infusions can be delivered over this extended infusion time. A possible gradual increase (i.e. from 50% to 75% infusion rate) is possible, provided that pre-medication is used. If grade 1 or 2 reactions occur at the increased rate, infusion should be continued at the previous tolerated rate for the whole treatment. If Grade 2 reactions occur at 50% rate despite appropriate pre- medications, further reduction in the infusion rate should be considered

Grade 3 *Infusion-related and Allergic Reaction* • Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) • Recurrence of symptoms following initial improvement • Hospitalisation indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates) • Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated as per institutional guidelines; allergy-related oedema/angioedema; hypotension	The bevacizumab infusion should be stopped and not restarted on that day. At the physician's discretion, bevacizumab may be permanently discontinued or reinstituted with pre-medication and at a rate half that when the reaction occurred. If the reaction occurred during administration at a 75% rate, initially re-challenge at a slower infusion rate (half of the rate when the reaction occurred) and gradually increase to 75% of the normal rate. When bevacizumab is re-started, the patient should be monitored, per physician's usual practice, for duration comparable to the duration of the initial reaction.
Grade 4 *Infusion-related and Allergic Reaction* • Life-threatening consequences • Urgent intervention indicated per institutional guidelines *Anaphylaxis* • Life-threatening consequences; • Urgent intervention per institutional guidelines	Permanently discontinue bevacizumab Maintain an adequate airway. Administer antihistamines, corticosteroids, adrenaline, or other medications as required. Continue to observe the patient, document observations, and administer further treatment according to the individual clinical case and clinical judgment.

Table 9: CTCAE grading and actions for Infusion-related / allergic reactions with bevacizumab

Proteinuria – CTCAE grades and actions

Screening dipstick urinalysis for proteinuria must be less than or equal to 1+ before bevacizumab is administered. Any patient showing greater than or equal to 2+ on urinary dipstick must have a urine sample sent for calculation of urine protein/creatinine ratio.

Urine protein/creatinine (Pr / Cr) ratio is calculated by dividing the concentration of protein in a spot sample by the concentration of creatinine in that sample. Both have to be measured in the same unit (mmol/L or mg/dl). Normal values: less than 0.2.

A referral to a nephrologist is recommended when a patient develops prolonged proteinuria.

Grade according to CTCAE (v5.0)	Action
Grade 2 2+ to 3+ on urine dipstick OR Urine Pr/Cr ratio = 0.5–1.9	Perform an early morning (first sample) Pr/Cr ratio or 24-hour urinary collection Delay bevacizumab if clinically significant proteinuria is present: • Pr/Cr ratio greater than 1.9 or • 24-hour urinary protein excretion greater than or equal to 0.5 g Resume bevacizumab when either • Pr/Cr ratio below 1.9 or • 24-hour urinary protein excretion below 0.5 g Permanently discontinue bevacizumab if bevacizumab therapy had to be delayed for longer than 6 weeks
Grade 3 Urine Pr/Cr ratio = greater than 1.9	

Table 10: CTCAE grading and actions for proteinuria with bevacizumab

Wound Complications (Non-Infectious) / Wound Dehiscence – CTCAE grades and actions

Grade according to CTCAE (v5.0)	Action
Grade 1 Incisional separation of ≤ 25% of wound, no deeper than superficial fascia	**Delay bevacizumab** until the wound has satisfactorily healed
Grade 2 Incisional separation of > 25% of wound, local care indicated	
Grade 3 Primary wound closure or revision by operative intervention is indicated	

Table 11: CTCAE grading and actions for wound complications / dehiscence with bevacizumab

Hypertension – CTCAE grades and actions

Age and sex-appropriate systolic and/or diastolic blood pressure that is persistently above the 95th percentile (ULN) requires further evaluation. It is strongly recommended that patients who develop hypertension during the study be evaluated in conjunction with a (paediatric) specialist.

In children, blood pressure varies with the age and is closely related to height and weight. Variability in blood pressure in children of similar age and body build should be expected, and it is recommended that serial measurements are obtained when a patient's blood pressure is assessed.

Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of infants and children as much as 40-50 mmHg greater than their usual level. Steroid usage (e.g., tumour-related intracranial pressure, allergic reaction, emesis, etc.) may also increase blood pressure and should be weaned off as soon as the clinical situation permits. Guidelines to age-specific percentiles of blood pressure can be accessed at *http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf*

Grade according to CTCAE (v5.0)	Action
Grade 2 Recurrent or persistent (≥24 hours) BP increase above the ULN; monotherapy indicated	**Delay bevacizumab administration** Initiate anti-hypertensive therapy Resume bevacizumab once systolic and/or diastolic BP for age and sex is below the 95th percentile
Grade 3 Requiring more than one antihypertensive drug or more intensive therapy than previously	
Grade 4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention required	**Permanently discontinue bevacizumab** Treatment as per institutional policy

Table 12: CTCAE grading and actions for hypertension with bevacizumab

<u>Venous thromboembolism (including vascular access device) – CTCAE grades and actions</u>

Grade according to CTCAE (v5.0)	Action
Grade 3 Thrombosis (e.g. uncomplicated pulmonary embolism (venous), non- embolic cardiac mural (arterial) thrombosis); medical intervention indicated	**Delay bevacizumab** Bevacizumab may be resumed once the patient has been fully anticoagulated and if the patient has not experienced a Grade 3 or 4 haemorrhagic event. Low-molecular-weight heparin should be prescribed and the treatment monitored in compliance with the approved product labelling or according to local clinical practice guidelines. Similarly, for patients on unfractionated heparin, the INR and APPT, respectively, should be within therapeutic range. **Permanently discontinue bevacizumab if the VTE worsens or recurs after resuming therapy**
Life-threatening (e.g.,pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	**Permanently discontinue bevacizumab** Treatment as per institutional policy

Table 13: CTCAE grading and actions for grade 3 and 4 venous thromboembolism with bevacizumab

References:

1- Guidelines for the diagnosis and management of paediatric and adolescent Low-Grade Glioma (*extrapolated from current SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low-Grade Glioma: Klin Padiatr. 2019;231(3):107-135*)

2- Laila Hassan*, **Naureen Mushtaq***, Nisreen Amyrali*, Eric Bouffet, Simon Bailey. SIOP PODC Adapted treatment recommendation for low grade gliomain Low and Middle income countries. (Pediatric Blood and cancer).Pediatr Blood Cancer. 2017;**64**:e26737