SIOP PODC Adapted Treatment Guidelines for Low Grade Gliomas in Low and Middle Income Settings.

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Abbreviations

LGG	Low grade glioma
LMIC	Low and middle-income countries
MRI	Magnetic resonance imaging
PODC	Pediatric Oncology in Developing Countries

CT	Computed tomography
HCLGG	Hypothalamic chiasmatic low grade glioma
TPLGG	Tectal plate low grade glioma
MDT	multi-disciplinary team
CTCAE	Common Terminology Criteria for Adverse Events
RT	Radiotherapy
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
PENTEC	Pediatric Normal Tissue Effects in the Clinic

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Abstract

Effective treatment of children with low grade glioma (LGG) requires a functioning multi-disciplinary team with adequate neurosurgical, neuroradiological, pathological, radiotherapy and chemotherapy facilities and personnel. In addition, the treating centre should have the capacity to manage a variety of LGG and treatment-associated complications. These requirements have made it difficult for many centers in low and middle-income countries (LMIC) to offer effective treatment and follow up. This article provides management recommendations for children with LGG according to the level of facilities available.

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Introduction

Low grade gliomas (LGGs) are a heterogenous spectrum of neoplasms comprising 40% of primary pediatric brain tumors.[1] The posterior fossa is the most common site of involvement (15-25%) followed by the cerebral hemispheres (10-15%) and the optic pathways (6%).[2, 3] LGG are graded according to the WHO grading system and include pilocytic astrocytoma and diffuse astrocytoma.[4] The grading system includes variants such as pilomyxoid astrocytoma, subependymal giant cell astrocytoma and pleomorphic xanthoastrocytoma. Histopathologically, LGG are recognised by astrocytic, oligodendroglial and mixed oligo-astro neuronal features.[5]

Children with Neurofibromatosis type 1(NF1) and tuberous sclerosis have a predilection to develop LGG.[6, 7] It is reported that 15-20% of NF1 patients will develop hypothalamic/chiasmatic/optic pathway gliomas (HCLGG) as well as glioma or LGG in other sites, however these tumors often behave more indolently 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.[8]

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). In HIC, 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 is not possible, a number of alternative strategies are possible in the form of chemotherapy, radiotherapy or observation alone, and 5 year OS is still >80%.[9] In LMIC,

treatment is dependent on accurate diagnosis of tumors, surgical expertise available, proximity and availability of local chemotherapy and/or radiotherapy, and sometimes on the ability of the family to pay for such treatment.

The optimal treatment for tumors that are not amenable to surgical resection remains controversial. One option for small tumors, and especially for children with NF1, is to observe closely with magnetic resonance imaging (MRI) scans, but this strategy is dependent on the availability and access to imaging facilities.[10] In a study of 128 NF1 patients with incompletely resected LGG, 58% had no evidence of recurrent/progressive disease 7 years after diagnosis.[11] Another prospective trial of Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) in 660 children reported a 5 year PFS of 45% for those children with residual tumour.[12] Initially, radiation therapy was used as a single treatment modality for unresectable midline or progressive tumors and PFS was in the range of 60-80% [13]. However, radiation may cause significant toxicity such as cognitive impairment, cerebral vasculopathy, endocrine dysfunction, hearing loss, and secondary neoplasms [14], especially in very young children and those with NF 1. As a result, most co-operative groups in HIC recommend the use of chemotherapy first-line and reserve radiotherapy for progressive disease and older children (currently 8 years of age in Europe and 10 years of age in North America) with non NF1-related LGG. Whether treating multiple relapses with sequential chemotherapy is superior to primary radiotherapy with respect to late effects is unknown. In LMIC, the age for considering radiation varies according to resources, compliance and availability of treatment modalities.

Since children with LGG have a high probability of long-term survival, limitation of late effects is important.[15] This is even more critical in LMIC where access to supportive care may be limited or even non-existent.

There are many challenges in treating children with low grade gliomas in LMIC. This document intends to provide guidelines for treatment of these children and details the minimum requirements considered necessary for comprehensive care.

SIOP PODC recommendations

The International Society of Pediatric Oncology (SIOP) has a committee named Pediatric Oncology in Developing Countries (PODC). The SIOP PODC Adapted Treatment Regimens Working Group produces recommendations for the management of childhood cancers in LMIC as defined by the World Bank and guidelines for implementation and continuous quality improvement based on local outcome data.[16] Service levels describing facilities and personnel required for the care of patients with LGG are defined in Table 1. Service level 1 is the minimal setting for surgery and chemotherapy and level 2 for radiotherapy.

Methods

A multi-disciplinary writing group was formed of neurosurgeons, radiation and pediatric oncologists, a medical physicist and neuroradiologists with experience in managing children with LGG in a LMIC setting. The recommendations were then circulated widely and

discussed at SIOP PODC meetings. The guidelines were ratified by the SIOP board. Online meetings were hosted by the Cure4Kids website (www.cure4kids.org).

Details of the literature search are provided in Supplemental Appendix S1. There is limited literature in the treatment of LGG in resource challenged countries and inferences have been drawn from results in HIC.

In an attempt to explore available neuro-oncology resources in LMIC we conducted a qualitative survey of 8 referral centres in Africa, Asia and central America during April and May 2016.[17] The survey highlighted the following issues. Most patients initially present to neurosurgeons whose expertise varies. There is a low rate of referral after surgery, amounting to an average of 5-10 patients per year (5% or less of all new childhood cancer patients in most of those centres). Computed tomography (CT) scans are generally available, and MRI for some patients who often have to pay out of pocket. There is no specialised pathology, no capacity to subtype and reports usually take 2-4 weeks. Most centres have onsite radiotherapy with patients taking 4-8 weeks to get to treatment. Most sites have a generalist radiation oncologist, but nearly half still have 2D planning and cobalt only. All centres have access to chemotherapy, but lomustine and temozolomide are seldom available. In most centres there is no multidisciplinary discussion at diagnosis or after surgery, and tumour boards for pediatric brain tumors are very rare. Supportive care drugs, palliative teams and telemedicine support are widely available. Most have access to pituitary hormonal testing, and many have endocrinology. Occupational and physio-therapy are available in some cases, as are wheelchairs. Few centres have access to hearing aids and there is little or no access to special schooling. Again, cost is a big limiting factor. Almost nobody has access to an educational psychologist for school placement.

Treatment Guidelines

Place of Treatment

Children with low grade glioma should be treated in a centre that has both the facilities to diagnose and treat them (Table 2 describes the setting suggested for different modalities of treatments for children and young people with LGG) and the experience of treating a number of these children each year. Consideration should be given to referral of these children to a regional or national centre with more expertise as this may offer a survival and outcome advantage.[18] This includes neurosurgical expertise, as it has been shown that outcome is linked to the number of procedures performed, [19, 20] centralised and expert pathological review [1, 21]and expert neuro-radiology [22]. It is our view that all LGG cases presenting at hospitals defined at setting level one and two, should be discussed at a regular meeting or teleconference with more experienced colleagues. In this way, capacity-building occurs in all settings, and risk can be assessed and discussed. High risk cases can then be referred and standard risk cases may be designated to remain in level 2 institutions, under guidance from the regional referral centre.(see table 2)

Diagnosis

Presentation

The first and critical step in the management of children with LGG is accurate diagnosis. Presenting signs and symptoms may be non-specific and are dependent on the site of the tumor and the presence or absence of raised intracranial pressure. Visual deficits ranging from nystagmus to visual field defects and blindness are common for optic pathway tumors, and seizures and motor deficits for supratentorial tumors. Several factors contribute to delayed diagnosis in countries with limited resources.[23] These include the traveling distance to medical centres, financial barriers and lack of radiological facilities.

Radiology

Radiological imaging is a cornerstone in the diagnosis of pediatric brain tumors. CT remains (level 2 radiology) the most widely available imaging modality around the world and is vital in diagnosing and assessing brain tumors, scans should include both pre and post contrast views. If available, multi-planar reconstruction is particularly helpful in evaluating certain tumors (for e.g. coronal plane for HCLGGs and sagittal plane for tectal plate low grade gliomas (TPLGG). CT lacks the resolution of MRI and may not provide the necessary detail to confidently differentiate LGG from other tumors. MRI (with and without contrast) also provides additional features such as diffusion imaging which may increase the level of confidence about diagnosis and can provide important additional information, such as relationship of tumour to visual pathway or surrounding blood vessels. Spinal metastatic disease may be seen in up to 10% of children with LGG, if possible an initial spinal MRI should be performed. Table 3 describes the suggested MRI sequences for imaging pediatric LGG. However, choice of imaging modality in the context of LMIC will depend on availability and potential for surgical resection.

There is a large variability in expertise available for interpreting the imaging of pediatric brain tumors. The radiologist should be part of a multi-disciplinary team (MDT) involving oncologist, neurosurgeon and pathologist. Where an on-site meeting is not feasible due to logistical constraints, a virtual MDT can be operated through electronic media.[24] Radiologists may also benefit from networking with sub-specialists such as pediatric radiologists or neuro-radiologists for particularly difficult cases.

Pathology

Biopsy should be considered for children with unresectable low grade gliomas where there is a doubt with regard to diagnosis. Certain tumors such as HCLGG and tectal plate gliomas may be reliably diagnosed on imaging alone. Where diagnosis is uncertain, it is vital that there is a reliable pathological service (preferably level 2 or above for pathology – see Table 2) to ensure accurate diagnosis. Molecular testing is not necessary to make a definitive diagnosis. For those tumors where the diagnosis is in doubt, a second opinion can be obtained via remote pathology systems or the specimen sent to a centre with appropriate expertise.

Visual assessment

Visual assessment is vital both in terms of deciding when to treat and as a monitoring tool during treatment for optic pathway LGG. Accurate visual assessment is always difficult in younger children. It is important to have a consistent approach, as visual deterioration may be the deciding factor in commencement of treatment.[25] It is worth noting that visual deterioration may occur in children with NF1 without any evidence of tumor growth and also that treating such a tumor may not result in arresting visual deterioration.[26]

Decision to treat

In a group of tumors where the potential for survival is excellent, treatment must be directed towards maximising quality of life by minimising late effects. The decision to use adjuvant treatment, and which treatment to offer should take into account the extent of resection, age of the child, location and size of tumour, NF1 status, endocrine function and visual acuity. Many incompletely resected tumors without evidence of endocrinopathy or visual deterioration can be managed expectantly. Observation of incompletely resected posterior fossa pilocytic astocytomas and optic pathway gliomas, especially in NF1 patients, should be the rule rather than the exception.

Although radiotherapy appears to demonstrate better PFS than chemotherapy (not in randomised trials) there is an increasing awareness of late neurocognitive toxicity in children who received radiotherapy to the brain with a result that chemotherapy has increasingly been used in younger children as first line treatment for subtotally resected LGGs. Radiotherapy is usually reserved as salvage in patients who progressed after primary chemotherapy [13] although more than 50 % of children with LGG will progress after chemotherapy[33, 34] and thus children may still require radiotherapy at some time. What however is still unclear is the degree of neurocognitive dysfunction attributable to chemotherapy alone and concerns have been raised that delaying radiotherapy with multiple courses of chemotherapy may increase visual and neurocognitive morbidity. It is also not known whether treatment with

radiotherapy after first line chemotherapy is as effective as primary radiotherapy. Some postulate that chemotherapy may render these tumors more radio-resistant whereas others suggest that the subset of tumors progressing after primary chemotherapy may be more aggressive. There is however no report showing a difference in PFS between patients receiving radiotherapy as primary treatment or those irradiated after tumour progression post chemotherapy.[46] It is also important to take into consideration the ability of a family to remain compliant with multiple protracted chemotherapy regimens and may play a role in LMIC where many children live far from oncology centres. Therapy in such cases must therefore be individualised through discussions with the family and MDT. (see Figure 1 for proposed initial treatment pathway and Table 2 for settings in which varying treatment options may be proposed)

The main debate therefore, is the timing and sequencing of the modalities of treatment.

Our recommendation is that observation alone is the preferred approach and that radiotherapy should be avoided as far as possible in all patients but especially those with NF1. Where treatment is indicated in children under the age of 8 years, they should receive chemotherapy. After that age, treatment choice can be individualised, keeping in mind that radiotherapy has better progression free survival, but will still cause additional unwanted late effects especially in centres where advanced radiotherapy techniques are not available.

Surgery

LGG comprises a heterogenous group of tumors. Surgical management of LGG is guided by anatomical location, demarcation on imaging, and histology. The following observations apply: Surgical expertise in resection of challenging tumors is essential. Most children will be long term survivors, so surgical morbidity must be minimised. Decisions about surgery should be made in an MDT, and resection of challenging tumors should be undertaken only by experienced surgeons in a referral centre (see Table 2), and preferably not by generalist neurosurgeons without specific expertise. Infrastructure and equipment, which maximise surgical safety and determine the ability for aggressive safe resection may not be available in LMIC. If aggressive resection of such tumors is contemplated, children should be referred to a regional centre of excellence (see Table 2). If neither surgical experience nor the necessary tools are available then the MDT may consider alternative treatment modalities.

There are some principles, which apply to certain typical subgroups of LGG:

LGG in hemispheric sites are usually surgically curable, depending on location. Complete resection may be achieved by most trained neurosurgeons although incomplete resection does not necessarily require further therapeutic intervention. These children may present with seizures, which often resolve after tumour resection.

Cerebellar tumors are often resectable and curable, but may be challenging. Even in the context of incomplete resection, these tumors do not necessarily require additional treatment and in this situation observation is the recommended approach.

HCLGG are difficult to manage surgically, with a high risk of morbidity including hypothalamic damage, endocrine deficits, visual deficit and/or neurological impairment. Chemotherapy and/or radiotherapy take precedence initially, although in centres with expertise and tools, meaningful debulking is possible with acceptable risk in selected tumors. Usually, surgery is limited to biopsy where necessary. Many of these tumors have a typical radiological appearance and may not require diagnostic biopsy/surgery.

Focal brainstem tumors are potentially amenable to resection but this is unusual and the risks are high. For tectal plate tumors, biopsy is usually unnecessary and outcome is usually good, however children often present with hydrocephalus and will frequently require a CSF diversion procedure. Definitive treatment is commenced only for documented progression.

Spinal cord tumors are potentially curable surgically but resection should be considered only where equipment and considerable expertise allow (usually level 3).

Several inflammatory or infectious conditions prevalent in many LMIC can mimic LGG tumors(18) and must be considered in the differential diagnosis. If possible, preoperative MRI may be helpful in distinguishing between these and neoplastic conditions and in determining whether biopsy is necessary. Difficult cases are best discussed with experienced regional colleagues (level 3 and above). If expertise and infrastructure are not available locally, patients should be transferred to an equipped regional centre if possible.

Chemotherapy

Chemotherapy has proven efficacy as an alternative to radiation in unresectable or incompletely resected tumors. During the last decades, several chemotherapy regimens have been reported.[27–31] The results of these experiences are relatively similar, with 5-year PFS in the range of 40-50%.

The choice of the optimal regimen is still controversial. Since children with LGGs have prolonged survival, long-term toxicities should influence the choice of chemotherapeutic agents. [32] In a randomized study, the Children's Oncology Group (COG) compared the vincristine-weekly carboplatin regimen and the TPCV combination (thioguanine, procarbazine, CCNU and vincristine) in non-NF1 children younger than 10 years. The 5-year PFS and OS for the whole group (274 children) were 45% and 86% respectively. Despite a 5 year PFS of 39%± 4% for the vincristine-carboplatin regimen and 52%±5% for the TPCV regimen, this difference was not statistically significant. The toxicity however appeared to be greater in the TPCV group.[33] In a HIT-LGG 1996 study of 216 patients given vincristine/ monthly carboplatin, 5 year PFS was 51%.[34] The use of the carboplatin-based regimen has been limited by the development of carboplatin hypersensitivity in up to 40% of patients.[32, 32, 35, 36] A widely used alternative is monotherapy with weekly vinblastine, which has been used both after carboplatin allergy and for progression or even as first line treatment. [37] This seems to offer similar results (42.3% 5 year PFS) but has the disadvantage of requiring weekly intravenous therapy for a year which may not be feasible for families or centres in LMIC.

Monthly carboplatin monotherapy was recently reported as an alternative to multidrug regimens. However, in this report, the number of children with NF1 (32%) was higher than in

other studies and younger children were excluded (treated with a separate protocol).[38] The 5-year PFS rate for HCLGG was lower than for comparable multidrug studies (34%). Other regimens include vinblastine and carboplatin (feasibility study) [39], vincristine and dactinomycin (62.5% 3 year PFS][27, 28], single agent temozolomide [40](49% 2 year PFS), bevacizumab and irinotecan (Pediatric Brain Tumor Consortium) (6- month and 2-year PFS of 85.54% and 47.8% respectively but with the vast majority of children progressing after the combination was stopped thus requiring maintenance therapy).[41] Several of these drugs are very expensive and not available in most LMIC.

Based on the available evidence, its widespread use and the ability to deliver chemotherapy reliably in a LMIC setting, vincristine and monthly carboplatin are recommended as first line treatment. This treatment regime is shown in Figure 2 and Table 4. In the case of carboplatin allergy as well as for second line chemotherapy weekly vinblastine is recommended at a dose of 6 mg/m^2.

It is important to observe and record chemotherapy toxicity and use this information in deciding whether dose modification or omission of certain drugs or courses is necessary. This is best done by using the Common Terminology Criteria for Adverse Events (CTCAE) grading system (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

During treatment, an early response assessment with MRI after three months can be confusing, since pseudoprogression has been reported. Treatment response to chemotherapy is therefore recommended after 26 weeks.

Radiotherapy

Radiotherapy (RT) is generally accepted as the most effective treatment modality for treatment of non-resectable or partially resected LGG with 10-year PFS in the range of 80%.[42–44] This is similar to gross total resection[45, 46]. For partially resected LGG, adding RT confers a PFS improvement of approximately 40% when compared with children who do not receive post-operative radiotherapy. However this benefit does not extend to overall survival (OS), which is > 90% in most series.[47]

In cases where radiotherapy is the treatment of choice as defined by the MDT, and because most children will survive LGG, every attempt should be made to minimise side effects. There are several technical considerations which must be considered even in the LMIC setting. These include delineation of targets and organs at risk using adequate imaging, the use of 3-D planning techniques, and verification and accuracy of dose delivery through appropriate immobilisation, treatment imaging and dose verification.[48]

For LGGs, we strongly recommend that the minimum requirement for radiotherapy is conformal radiotherapy where a CT- based 3-D technique is used for treatment

planning. This allows a conformal dose distribution around the tumour, providing better normal tissue sparing than 2-D treatment). Although additional conformality can be achieved with sophisticated techniques such as Intensity modulated radiation therapy (IMRT), [49] stereotactic irradiation techniques, [44, 50–52] or proton therapy [53] these are seldom available in LMIC and the exact benefit of these techniques in terms of late effects is unclear. Conformal 3-D radiotherapy is adequate to irradiate almost all LGG with a good dose delivery and acceptable toxicity if advanced techniques are not available. Although 3-D conformal RT is most commonly delivered by a linear accelerator, according to DIRAC 2017, 37.5% of low and middle income countries still use cobalt units. (Figure 3) Cobalt-60 machines should only be used for the treatment of LGG when 3-D planning with image-based position verification is available. Simple 2-D treatment plans based on X-ray simulation should not be used as this technique delivers wide fields, usually treated with parallel opposed beams meaning that large volumes of normal brain are treated to high doses. Accurate tumour and organ at risk (OAR) delineation is not possible. In centres with 2-D planning and cobalt machines, every effort should be made to transfer the patient to a better equipped radiotherapy centre. (Figure 4)

Treatment planning

Imaging

For radiotherapy planning purposes, CT scans are used for 3-D planning target delineation. The quality of the immobilisation device and CT scan determines the accuracy of the target and organ-at-risk delineation. A well-made mask/cast is critical. For younger children (<6

years) this requires sedation or general anaesthetic in order to minimise movement. If the tumour takes up contrast (e.g. JPA) then intravenous contrast should be used for the planning scan. If MR is available, then many 3-D planning systems do allow registration of MRI scans and fusion of planning CT and MRI which allows more accurate contouring and this is recommended.

Defining the target volumes

Target volumes are defined according to International Commission on Radiation Units and Measurements(ICRU) report-50 definitions.[54] If the patient has undergone prior surgery, then target delineation is based on post-operative imaging.

For WHO grade 1 tumors (JPA)

GTV (Gross tumour volume) = any cystic and/or solid tumour as viewed on CT/MRI.

CTV (Clinical target volume) = 5-10 mm margin around GTV. This margin takes possible uncertainties of tumour extent into account but should be modified at any geographical boundaries e.g. bone, falx, tentorium cerebelli as LGG tumours do not infiltrate these.

If CT alone is used for delineation, then the area at risk may be less obvious than with MRI, and a wider margin of 10mm is necessary. [13]

PTV (planning target volume) = 5-10 mm margin around CTV. This margin accounts for set up error and depends on the quality of the immobilisation device, the accuracy of radiotherapy equipment (e.g. gantry, couch and lasers) and the ability of centres to perform portal imaging for geometric verification during treatment.[13, 49] For centres without regular portal imaging for verification, the PTV margin should not be less than 5mm, and where there is any doubt as to any of the accuracy measures above, then the PTV margin should not be less than 10mm.

Organs at risk (OAR) should be identified and delineated, with every attempt made to limit critical structures to the minimum possible dose. Critical structures in close proximity to the target should also be assigned a PRV (planning risk volume) with the same margin as used for PTV.

There are various guidelines outlining suggested dose constraints for organs at risk. QUANTEC guidelines (Quantitative Analyses of Normal Tissue Effects in the Clinic) are the most widely used.[55] These guidelines are based on toxicity data from adult patients and do not necessarily reflect the radiobiology of the tissues in children. Currently, a collaborative group of physicians, physicists and epidemiologists are developing PENTEC (Pediatric Normal Tissue Effects in the Clinic) which is intended for use in children.

Treatment plan evaluation should include a conformity index(CI)[48]where:

The conformity index should be as close to 1 as possible. For CI's > 1.25, as in the case of 2-D planning, it implies that an unacceptably high volume of unaffected adjacent normal brain tissue is receiving a high dose, and an alternative plan should be used.

Radiotherapy dose

Although a dose/ response relationship has been investigated in adults, no such prospective randomised trials have been conducted in children. Small series show heterogenous dose distributions, with prescribed dose being influenced mainly by the age of the child, and site of tumour. Most trials however, have used doses ranging from 45- 54 Gy in 1.8 Gy per fraction. In HIT LGG 96 trial,[34] no difference was observed between a total dose of 50.4 Gy and 54 Gy and this has been confirmed in other studies.[49] 50.4 Gy in 1.8Gy per fraction is therefore the recommendation on current studies, with doses less than that(45Gy) reserved for younger children (< 5 years of age).

Quality assurance

This is a critical aspect of any radiotherapy program. Any centre treating children with brain tumors to radical doses should have a treatment planning system verification program according to internationally recognised protocols (IAEA). In addition, both dosimetric and geometric verification of treatment is required. [56] Machine calibration should be 2-3% of expected dose and appropriate treatment and position verification be in place in order to

ensure treated dose is within 5% of the prescribed dose. Institutional set up error is accounted for with a relative expansion margin used for PTV. Quality of casts, lasers and imaging all play a role.

Grade II astrocytoma

Grade II astrocytoma is less common in children than adults but has a much better prognosis than its adult counterpart.[34, 57] The outcome for this tumour in children is variable with some trials showing a distinctly worse outcome than for pilocytic astrocytoma, [21, 58] but other studies showing no difference.[30]

For planning purposes, these tumors are difficult to see on CT as they often do not enhance, and are deeply infiltrative. They are more easily visualised on MRI (T2 or FLAIR sequences) and therefore are better planned using this technology if available. A larger CTV(1-1.5cm) may be required.

LGG with leptomeningeal dissemination

This occurs in approximately 5% of pilocytic astrocytoma.[59] Although strong supporting evidence for use of craniospinal irradiation (CSI) in this group has still to be defined, [60] it is frequently used with some demonstrated benefit if there is a failure of chemotherapy.[52]

Relapse/Progression

Repeated relapse/progressive disease in children with LGG is common in incompletely resected/unresectable tumors. Children whose tumour involves the optic tract, those with multifocal tumors, those below 1 year of age and/ or those with evidence of dissemination at initial diagnosis tend to have a higher rate of progression than those with a single lesion.[34, 61, 62]

It is not always easy to determine whether progression or relapse should be treated immediately and if so, which modality to use. Each treatment decision in childhood LGG needs to be discussed amongst the multidisciplinary team. This should follow the same process as at initial presentation. Relapse of progression is determined by a 25% increase in the tumour, (measured by the sum of the product of the 2 largest perpendicular diameters of each target lesion) or by a combination of deteriorating visual or neurological signs in conjunction with radiology. Currently the RECIST criteria are most commonly used for radiological assessment. [63] The criterion for 25% progression as an indication for treatment should not be applied to cystic progression which may require separate surgical intervention. Care should be taken to ensure that changes related to treatment, especially post radiotherapy, are not due to necrosis. This may require surveillance and/or biopsy of the lesion. [64]

Surgical resection without significant morbidity remains the treatment of choice for surgically accessible tumors such as cerebellar astrocytomas.[65] Other treatment choices should follow the same guidelines as above for first diagnosis, although if radiotherapy has

not been used before then this may also be considered. If the child has already had radiotherapy, then chemotherapy is recommended. If chemotherapy is used, then the chemotherapy regimen chosen should generally be different to the previous regimen, The recommended regimens are as above. Re-irradiation is not considered routine for children with LGG.

Late effects of treatment

Late effects may occur as a result of the tumour or of its treatment. Important determinants of late effects are the site of tumour (cerebellar, cerebral, midline, or brainstem), modality of treatment received (surgical complications, type of chemotherapy given and whether radiotherapy was used) and recurrence. Detailed clinical examination, including neurological, ophthalmic and growth/ pubertal evaluation, is the corner stone in early recognition and in determining the need for further investigation. Monitoring TSH /T4 every 6 -12 months is encouraged to detect subtle hypothyroidism.

Late effects are best managed in a multidisciplinary setting and with access to a pediatric endocrinologist (level 3), but this is seldom available in LMIC. Table 5 lists the most common late effects seen in children with LGG and a suggested management approach. Where local expertise is not available, it is advisable to seek regional help. However a high index of suspicion is critical in order to correctly test for endocrine abnormalities, and relatively simple endocrine replacement may be life-changing. If necessary, expert opinion

may be accessible through teleconferencing with a regional centre or a twinning institution. Guidelines such as the Childrens Oncology Group Survivorship Guidelines may be a useful resource –(http://survivorshipguidelines.org)

Follow up

The frequency of surveillance is partly determined by the availability of local facilities, especially imaging. For completely resected lesions it is recommended that imaging is performed 6 monthly for 2 years and then yearly for up to 5 years. For incompletely resected tumors the children should be imaged 6 monthly for the first two years and then yearly for up to 10 years. For tumors affecting vision, imaging should also be accompanied by standardised ophthalmological assessment. Clinical assessment for late effects as outlined in table 5 should be undertaken at the time of imaging.

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References

1. Rickert CH, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 2001; 17: 503-511.

2. Pollack IF. The role of surgery in pediatric gliomas. J Neurooncol 1999; 42: 271-288.

3. Czyzyk E, Jóźwiak S, Roszkowski M, Schwartz RA. Optic pathway gliomas in children with and without neurofibromatosis 1. J Child Neurol 2003; 18: 471-478.

4. Louis DN, Perry A, Reifenberger G et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016; 131: 803-820.

5. Freeman CR, Farmer JP, Montes J. Low-grade astrocytomas in children: evolving management strategies. Int J Radiat Oncol Biol Phys 1998; 41: 979-987.

6. Guillamo JS, Créange A, Kalifa C et al. Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients. Brain 2003; 126: 152-160.

7. Campen CJ, Porter BE. Subependymal Giant Cell Astrocytoma (SEGA) Treatment Update. Curr Treat Options Neurol 2011; 13: 380-385.

8. Abdollahzadeh M, Hoffman HJ, Blazer SI et al. Benign cerebellar astrocytoma in childhood: experience at the Hospital for Sick Children 1980-1992. Childs Nerv Syst 1994; 10: 380-383.

9. Wisoff JH, Sanford RA, Heier LA et al. Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. Neurosurgery 2011; 68: 1548-54; discussion 1554.

10. Benesch M, Eder HG, Sovinz P et al. Residual or recurrent cerebellar low-grade glioma in children after tumor resection: is re-treatment needed? A single center experience from 1983 to 2003. Pediatr Neurosurg 2006; 42: 159-164.

11. Fisher BJ, Leighton CC, Vujovic O, Macdonald DR, Stitt L. Results of a policy of surveillance alone after surgical management of pediatric low grade gliomas. Int J Radiat Oncol Biol Phys 2001; 51: 704-710.

12. Shaw EG, Wisoff JH. Prospective clinical trials of intracranial low-grade glioma in adults and children. Neuro Oncol 2003; 5: 153-160.

13. Merchant TE, Kun LE, Wu S, Xiong X, Sanford RA, Boop FA. Phase II trial of conformal radiation therapy for pediatric low-grade glioma. J Clin Oncol 2009; 27: 3598-3604.

14. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol 2009; 27: 3691-3697.

15. Bandopadhayay P, Bergthold G, London WB et al. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. Pediatr Blood Cancer 2014; 61: 1173-1179.

16. Howard SC, Metzger ML, Wilimas JA et al. Childhood cancer epidemiology in low-income countries. Cancer 2008; 112: 461-472.

17. A D. Personal communication. 2016;

18. Zaghloul MS. Single pediatric neuro-oncology center may make difference in low/middle-income countries. Childs Nerv Syst 2016; 32: 241-242.

19. Albright AL, Sposto R, Holmes E et al. Correlation of neurosurgical subspecialization with outcomes in children with malignant brain tumors. Neurosurgery 2000; 47: 879-85; discussion 885.

20. Berry JG, Hall MA, Sharma V, Goumnerova L, Slonim AD, Shah SS. A multi-institutional, 5-year analysis of initial and multiple ventricular shunt revisions in children. Neurosurgery 2008; 62: 445-53; discussion 453.

21. Fouladi M, Hunt DL, Pollack IF et al. Outcome of children with centrally reviewed low-grade gliomas treated with chemotherapy with or without radiotherapy on Children's Cancer Group high-grade glioma study CCG-945. Cancer 2003; 98: 1243-1252.

22. Packer RJ, Gajjar A, Vezina G et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006; 24: 4202-4208.

23. Arnautovic A, Billups C, Broniscer A, Gajjar A, Boop F, Qaddoumi I. Delayed diagnosis of childhood low-grade glioma: causes, consequences, and potential solutions. Childs Nerv Syst 2015; 31: 1067-1077.

24. Mitra D, Kampondeni S, Mallewa M et al. Central nervous system lesions in Malawian children: identifying the treatable. Trans R Soc Trop Med Hyg 2012; 106: 567-569.

25. Avery RA, Bouffet E, Packer RJ, Reginald A. Feasibility and comparison of visual acuity testing methods in children with neurofibromatosis type 1 and/or optic pathway gliomas. Invest Ophthalmol Vis Sci 2013; 54: 1034-1038.

26. Zeid JL, Charrow J, Sandu M, Goldman S, Listernick R. Orbital optic nerve gliomas in children with neurofibromatosis type 1. J AAPOS 2006; 10: 534-539.

27. Rosenstock JG, Packer RJ, Bilaniuk L, Bruce DA, Radcliffe JL, Savino P. Chiasmatic optic glioma treated with chemotherapy. A preliminary report. J Neurosurg 1985; 63: 862-866.

28. Packer RJ, Sutton LN, Bilaniuk LT et al. Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. Ann Neurol 1988; 23: 79-85.

29. Lefkowitz IB, Packer RJ, Sutton LN et al. Results of the treatment of children with recurrent gliomas with lomustine and vincristine. Cancer 1988; 61: 896-902.

30. Packer RJ, Ater J, Allen J et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg 1997; 86: 747-754.

31. Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA. Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neurooncol 1997; 32: 235-241.

32. Lafay-Cousin L. Carboplatin Rechallenge After Hypersensitivity Reactions in Pediatric Patients With Low-Grade Glioma: How Far Should we Push. Pediatr Blood Cancer 2016; 63: 9-10.

33. Ater JL, Zhou T, Holmes E et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol 2012; 30: 2641-2647.

34. Gnekow AK, Falkenstein F, von Hornstein S et al. Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. Neuro Oncol 2012; 14: 1265-1284.

35. Dodgshun AJ, Hansford JR, Cole T, Choo S, Sullivan MJ. Carboplatin Hypersensitivity Reactions in Pediatric Low Grade Glioma Are Protocol Specific and Desensitization Shows Poor Efficacy. Pediatr Blood Cancer 2016; 63: 17-20.

36. Shah AC, Minturn JE, Li Y et al. Carboplatin Rechallenge After Hypersensitivity Reactions in Pediatric Patients With Low-Grade Glioma. Pediatr Blood Cancer 2016; 63: 21-26.

37. Bouffet E, Jakacki R, Goldman S et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 2012; 30: 1358-1363.

38. Dodgshun AJ, Maixner WJ, Heath JA, Sullivan MJ, Hansford JR. Single agent carboplatin for pediatric low-grade glioma: A retrospective analysis shows equivalent efficacy to multiagent chemotherapy. Int J Cancer 2016; 138: 481-488.

39. Jakacki RI, Bouffet E, Adamson PC et al. A phase 1 study of vinblastine in combination with carboplatin for children with low-grade gliomas: a Children's Oncology Group phase 1 consortium study. Neuro Oncol 2011; 13: 910-915.

40. Gururangan S, Fisher MJ, Allen JC et al. Temozolomide in children with progressive low-grade glioma. Neuro Oncol 2007; 9: 161-168.

41. Hwang EI, Jakacki RI, Fisher MJ et al. Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas. Pediatr Blood Cancer 2013; 60: 776-782.

42. Saran FH, Baumert BG, Khoo VS et al. Stereotactically guided conformal radiotherapy for progressive low-grade gliomas of childhood. Int J Radiat Oncol Biol Phys 2002; 53: 43-51.

43. Erkal HS, Serin M, Cakmak A. Management of optic pathway and chiasmatic-hypothalamic gliomas in children with radiation therapy. Radiother Oncol 1997; 45: 11-15.

44. Marcus KJ, Goumnerova L, Billett AL et al. Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. Int J Radiat Oncol Biol Phys 2005; 61: 374-379.

45. Youland RS, Khwaja SS, Schomas DA, Keating GF, Wetjen NM, Laack NN. Prognostic factors and survival patterns in pediatric low-grade gliomas over 4 decades. J Pediatr Hematol Oncol 2013; 35: 197-205.

46. Müller K, Gnekow A, Falkenstein F et al. Radiotherapy in pediatric pilocytic astrocytomas. A subgroup analysis within the prospective multicenter study HIT-LGG 1996 by the German Society of Pediatric Oncology and Hematology (GPOH). Strahlenther Onkol 2013; 189: 647-655.

47. Pollack IF, Claassen D, al-Shboul Q, Janosky JE, Deutsch M. Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. J Neurosurg 1995; 82: 536-547.

48. Nedzi LA, Choe KS, Pompos A and Ramirez E. Treatment Planning in Radiation Oncology. ED: Khan FM, Gerbi BJ. Philadelphia: Lippincott, Williams and Wilkins; 2012. p. 632

49. Paulino AC, Mazloom A, Terashima K et al. Intensity-modulated radiotherapy (IMRT) in pediatric low-grade glioma. Cancer 2013; 119: 2654-2659.

50. Weintraub D, Yen CP, Xu Z, Savage J, Williams B, Sheehan J. Gamma knife surgery of pediatric gliomas. J Neurosurg Pediatr 2012; 10: 471-477.

51. Boëthius J, Ulfarsson E, Rähn T, Lippittz B. Gamma knife radiosurgery for pilocytic astrocytomas. J Neurosurg 2002; 97: 677-680.

52. Kreth FW, Faist M, Warnke PC, Rossner R, Volk B, Ostertag CB. Interstitial radiosurgery of low-grade gliomas. J Neurosurg 1995; 82: 418-429.

53. Hug EB, Muenter MW, Archambeau JO et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. Strahlenther Onkol 2002; 178: 10-17.

54. ICRU Report 50, September 1993: Dose Specification for Reporting External Beam Therapy With Photons and Electrons. Washington, DC, International Commission on Radiation Units and Measurements,1993.

55. Marks LB, Yorke ED, Jackson A et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010; 76: S10-9.

56. International Atomic Energy agency. Setting up a radiotherapy programme. IAEA publication 2196. 2008: 46-47; 169 -171.

57. Stokland T, Liu JF, Ironside JW et al. A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702). Neuro Oncol 2010; 12: 1257-1268.

58. Fisher BJ, Lui J, Macdonald DR, Lesser GJ, Coons S, Brachman D, Ryu S, Werner-Wasik M, Bahary J-P, Hu C, Meht PM. A Phase II Study of a Temozolomide-Based Chemoradiotherapy Regimen for High Risk Low-Grade Gliomas: Preliminary Results of RTOG 0424. Journal of Clinical Oncology. 2013;31:Abstract 2008..

59. Chamdine O, Broniscer A, Wu S, Gajjar A, Qaddoumi I. Metastatic Low-Grade Gliomas in Children: 20 Years' Experience at St. Jude Children's Research Hospital. Pediatr Blood Cancer 2016; 63: 62-70.

60. Mazloom A, Hodges JC, Teh BS, Chintagumpala M, Paulino AC. Outcome of patients with pilocytic astrocytoma and leptomeningeal dissemination. Int J Radiat Oncol Biol Phys 2012; 84: 350-354.

61. Udaka YT, Yeh-Nayre LA, Amene CS, VandenBerg SR, Levy ML, Crawford JR. Recurrent pediatric central nervous system low-grade gliomas: the role of surveillance neuroimaging in asymptomatic children. J Neurosurg Pediatr 2013; 11: 119-126.

62. Gajjar A, Sanford RA, Heideman R et al. Low-grade astrocytoma: a decade of experience at St. Jude Children's Research Hospital. J Clin Oncol 1997; 15: 2792-2799.

63. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

64. Strenger V, Lackner H, Mayer R et al. Incidence and clinical course of radionecrosis in children with brain tumors. A 20-year longitudinal observational study. Strahlenther Onkol 2013; 189: 759-764.

65. Kaspera W, Majchrzak K, Bobek-Billewicz B et al. Reoperations of patients with low-grade gliomas in eloquent or near eloquent brain areas. Neurol Neurochir Pol 2013; 47: 116-125.

66. Willard VW, Conklin HM, Wu S, Merchant TE. Prospective longitudinal evaluation of emotional and behavioral functioning in pediatric patients with low-grade glioma treated with conformal radiation therapy. J Neurooncol. 2015;122:161-168.

67. Chojnacka M, Pędziwiatr K, Skowrońska-Gardas A, Perek-Polnik M, Perek D, Olasek P. Second brain tumors following central nervous system radiotherapy in childhood. Br J Radiol. 2014;87:20140211.

68. Steinbok P, Mangat JS, Kerr JM, Sargent M, Suryaningtyas W, Singhal A, Cochrane D. Neurological morbidity of surgical resection of pediatric cerebellar astrocytomas. Childs Nerv Syst. 2013;29:1269-1275.

69. Armstrong GT, Conklin HM, Huang S, Srivastava D, Sanford R, Ellison DW, Merchant TE, Hudson MM, Hoehn ME, Robison LL, Gajjar A, Morris EB. Survival and long-term health and cognitive outcomes after low-grade glioma. Neuro Oncol. 2011;13:223-234.

70. Turner CD, Chordas CA, Liptak CC, Rey-Casserly C, Delaney BL, Ullrich NJ, Goumnerova LC, Scott RM, Begley HC, Fletcher WJ, Yao X, Chi S, Kieran MW. Medical, psychological, cognitive and educational late-effects in pediatric low-grade glioma survivors treated with surgery only. Pediatr Blood Cancer. 2009;53:417-423.

71. Rea D, Brandsema JF, Armstrong D, Parkin PC, deVeber G, MacGregor D, Logan WJ, Askalan R. Cerebral arteriopathy in children with neurofibromatosis type 1. Pediatrics. 2009;124:e476-83.

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Legends

Figure 1. Flow diagram of suggested management strategy for children with low grade gliomas in LMIC.

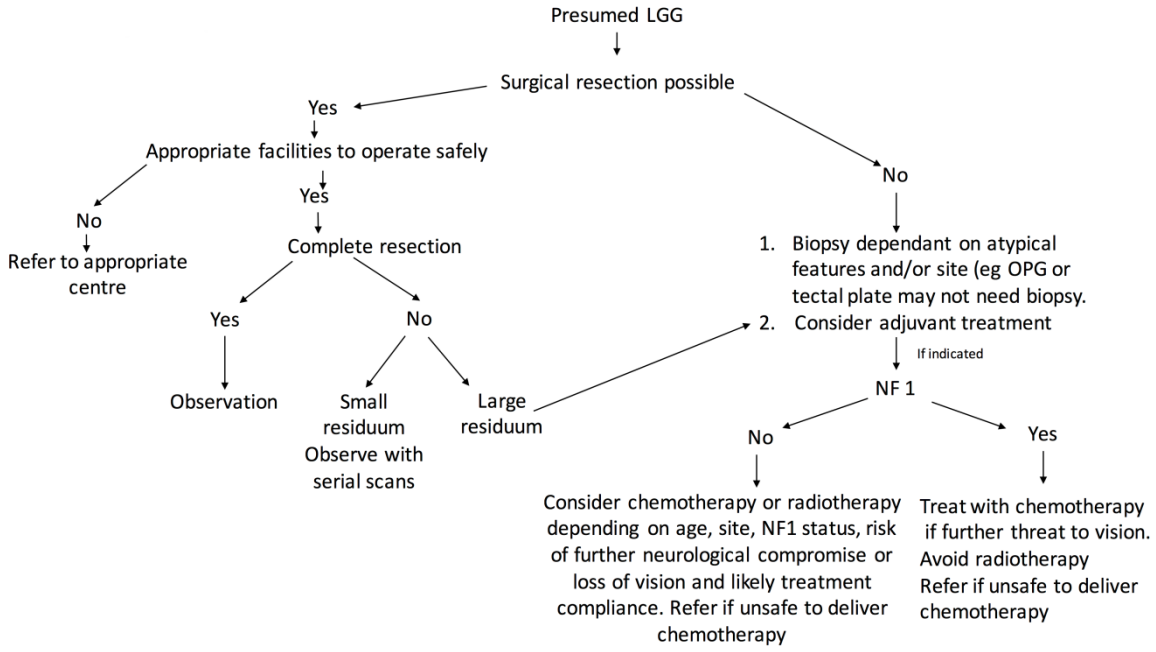

Figure 2. Chemotherapy protocol for vincristine and carboplatin for 1st line chemotherapeutic treatment of low grade gliomas in LMIC.

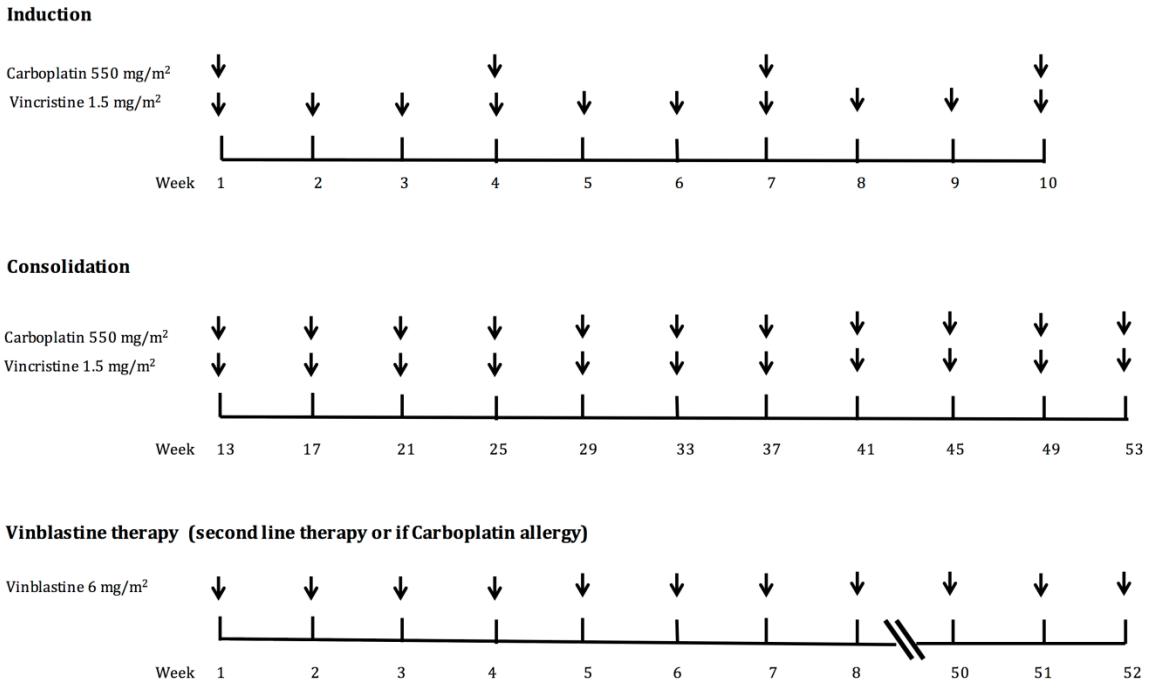

Figure 3. A comparison of cobalt and linac machine availability in LMIC in 2010 and 2017.

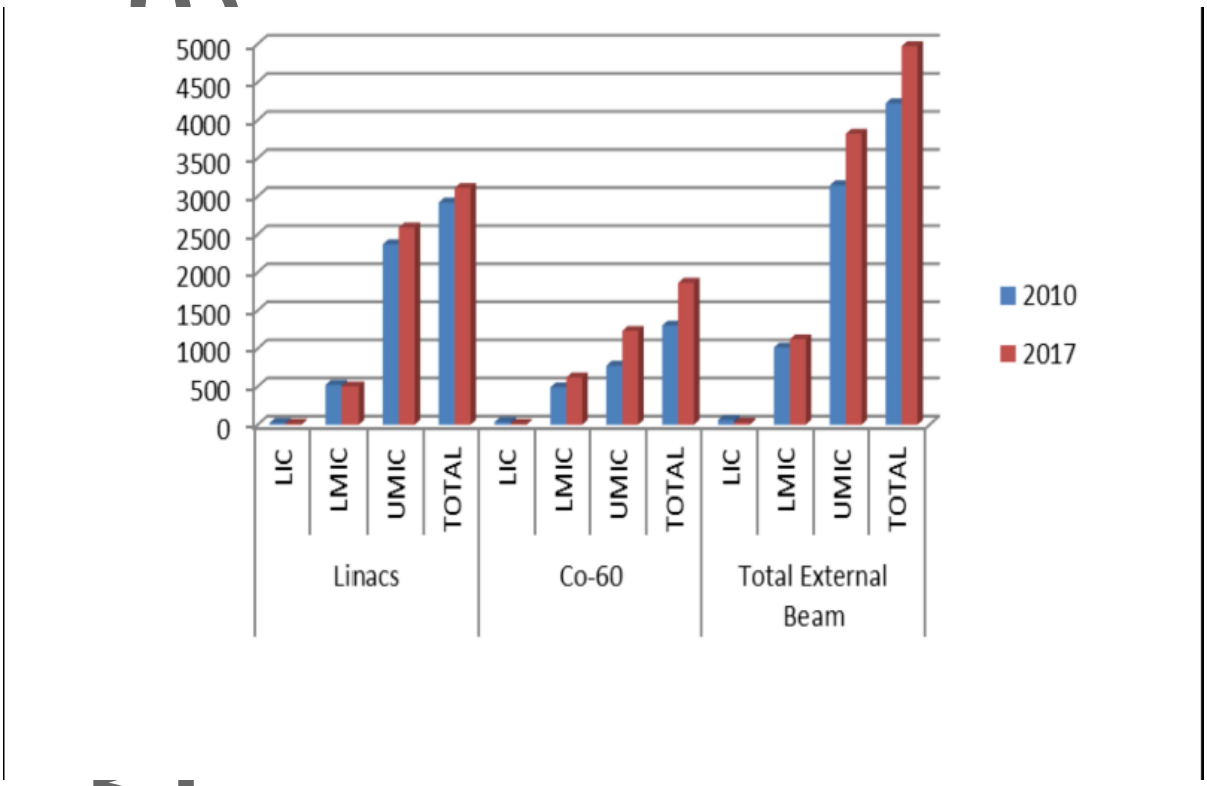

Figure 4. Comparative dose distribution of 2-D (A) vs. 3-D conformal(B), vs. VMAT(C) radiotherapy for JPA of optic pathway.

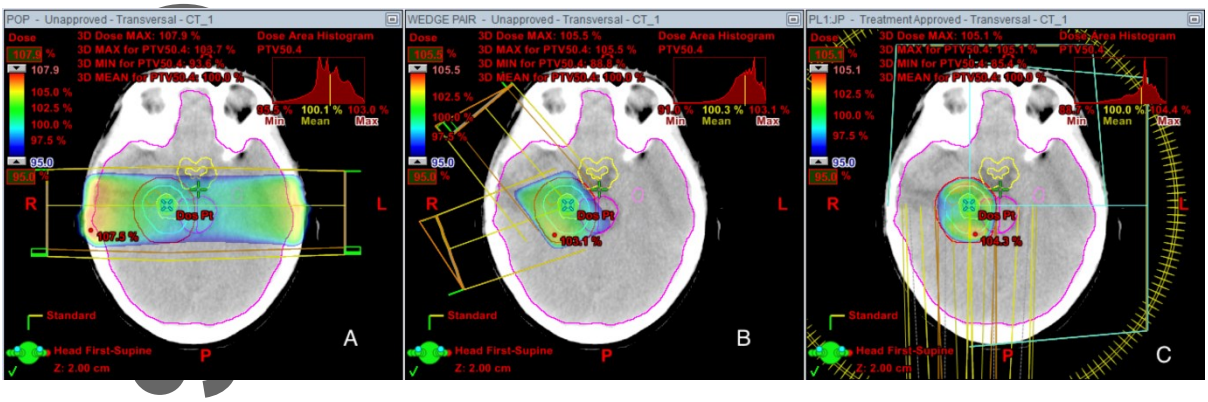

Table Legends

Table 1. Infrastructural and personnel service line levels for selection of SIOP PODC adapted treatment regimens for Low Grade Glioma.

Table 2. Treatment guideline for LGG in LMIC according to setting.

Table 3. Suggested MRI sequences for imaging pediatric LGG.

Table 4: Details of Administration and side effects of Vincristine/Carboplatin and Vinblastine Therapy.

Table 5. Late Effects related to tumour and management of Low Grade Gliomas.

Supplemental Appendix S1. Literature Search Strategy

Table 1. Infrastructural and personnel service line levels for selection of SIOP PODC adapted treatment regimens for Low Grade Glioma

Service	Level 0	Level 1	Level 2	Level 3	Level 4
Paediatric cancer unit description **(multidisciplinary team operates at all levels)**	Pilot project	Some basic oncology services	Established paediatric oncology program with most basic services and a few state-of-the-art services	Paediatric oncology program with all essential services and most state-of-the-art services	Paediatric oncology centre of excellence with all state-of-the-art services and some highly specialized services (e.g. proton beam radiation therapy, MIBG therapy, access to phase I studies)
Typical settings	LIC in disadvantaged areas	LIC in larger healthcare centres, lower MIC in disadvantaged areas	Lower MIC in larger healthcare centres, upper MIC in disadvantaged areas	Upper MIC in larger healthcare centres, Most centres in HIC	Selected tertiary and quaternary care centres in HIC
Medical facilities					
Ward	No paediatric oncology unit	Basic paediatric oncology service	Paediatric oncology unit available to most	Paediatric oncology unit with a full complement of	Specialized paediatric oncology units for

		available to some patients	patients; isolation rooms usually available for infected patients	fixed staff and available to all patients; isolation rooms always available for infected patients	particular groups of patients (e.g. transplant, neuro-oncology, acute myeloid leukaemia)
Diagnosis, staging and therapeutic capabilities					
Pathology	None	Microscope, H&E staining, CSF cytology	Limited immunohisto-chemistry panel (disease-specific), Cytospin for CSF samples	Complete immunohisto-chemistry panel, molecular pathology for most diseases	Research diagnostics, whole genome sequencing, molecular pathology for all diseases
Diagnostic imaging	None	Radiographs, ultrasound	CT scan, Bone scintigraphy, Gallium scintigraphy	Magnetic resonance imaging. PET-CT and MIBG may be available	Specialized imaging; advanced nuclear medicine applications, PET-CT and MIBG diagnostic
Antineoplastic availability	Access to a limited selection of oncology drugs	Access to a limited selection of oncology drugs	Access to almost all essential oncology drugs;[35] occasional shortages	Access to almost all commercially available drugs; rare shortages	Access to all approved drugs, plus phase I and phase II studies
Radiation therapy facilities	None	Cobalt source; 2D planning	Cobalt source or Linear accelerator; 2D or some 3D planning. Ability to	Linear accelerator; Full conformal therapy available. Intensity-modulated	Intensity-modulated radiotherapy. Proton beam facility

			deliver treatment on at least 4 days per week.	radiotherapy frequently available	
Personnel					
Oncology team leader	Primary care physicians care for cancer and many other diseases	Primary care provider with interest in oncology	Primary care provider with paediatric oncology experience or some training, medical oncologist without paediatric expertise	Paediatric oncologist or medical oncologist with significant paediatric experience or training	Paediatric oncologist with highly disease-specific expertise
Oncology unit medical, nursing, and pharmacy staff	A few staff members with basic training	A few oncology personnel with some oncology training; trainees responsible for many aspects of patient care	Generally adequate numbers of oncology personnel; consistent supervision of any trainees involved in patient care	Full complement of oncology physicians; specialized oncology nurses; pharmacists with oncology training	Full complement of oncology personnel, including specialized physician extenders (e.g. nurse practitioners, hospitalists)
Surgery and surgical subspecialties relevant for each cancer	No surgeon	General surgeon or adult subspecialty surgeon (neurosurgeon, ophthalmologist, other)	Paediatric surgeon or subspecialty surgeon (neurosurgeon, ophthalmologist, other)	Paediatric cancer surgeon or paediatric subspecialty surgeon (neurosurgeon, ophthalmologist, other)	Paediatric cancer surgeon or subspecialty surgeon with highly specialized disease-specific expertise
Pathology	No	Pathologist available for	Pathologist available for	Haematopathologist and	Pathologist with highly

	pathologist	some cases	all cases	paediatric pathologist available	specialized disease-specific expertise
Radiation therapy	None	Radiation therapists with adult expertise	Radiation therapists with some paediatric experience	Radiation therapists with paediatric expertise	Paediatric radiation oncologist with highly specialized disease-specific expertise
Radiology	No radiologist	Radiologist with adult expertise	Radiologist with paediatric expertise	Neuroradiologist with adult expertise	Neuroradiologist with paediatric expertise or full-time paediatric neuroradiologist

Table 2. Treatment guideline for LGG in LMIC according to setting

Service	**Level 0**	**Level 1**	**Level 2**	**Level 3**	**Level 4**
Paediatric cancer unit description **(multidisciplinary team operates at all levels)**	Pilot project	Some basic oncology services	Established paediatric oncology program with most basic services and a few state-of-the-art services	Paediatric oncology program with all essential services and most state-of-the-art services	Paediatric oncology centre of excellence with all state-of-the-art services and some highly specialized services

					(e.g. proton beam radiation therapy, MIBG therapy, access to phase I studies)
Role in Diagnosis of tumours (Pathology and Radiology)	If LGG is suspected referral or discussion with a level 2 or 3 unit	If LGG is suspected referral or discussion with a level 2 or 3 unit	Radiological diagnosis and pathological diagnosis of straightforward cases (e.g. posterior fossa pilocytic astrocytoma). Equivocal cases should be discussed with the referral centre in the monthly teleconference, and the the radiology or pathology specimen then referred to level 3 if necessary.	If difficulty in being certain of the diagnosis either radiologically, pathologically or both referral to level 4 centre.	Feedback to referral centre of cases, this may be the pathological specimen and/or radiology.
Role in managing LGG	Palliative care for very advanced tumours	Role as a satellite centre to a central referral hospital. All cases should be referred for	Management of straightforward LGG cases. Referral of difficult cases if possible to a level 3 or 4 centre Initial	Management of all LGG cases. Cases with specific needs could be referred to a level 4 centre if resources permit.	Management of referred cases from all levels. Feedback to referral centre.

		initial management to central referral hospital.(Level 2 or level 3) Monthly meeting of TC to discuss cases.	assessment and management planning of all referred cases. Management according to national protocol. Monthly meeting or TC to discuss cases.	Co-ordinate and distribute national protocol for management. Co-ordinate monthly meeting teleconferenc e with level 1 or 2 satellite centres to discuss cases.	
Resectable tumours	None	Surgery will be done at referral centre Follow up scans could be done at this centre but require reporting and discussion at central referral hospital	Surgery is determined by the experience of the local neurosurgeon. All cases that are being considered for surgery at level 2 should be discussed with the referral centre in the monthly teleconference . High risk surgeries should NOT be undertaken and should be referred to level 3 where an experienced paediatric neurosurgeon	Most Surgery will be undertaken at this level. Referral from levels 1 and 2 will be undertaken. Highly complex cases requiring specific expertise may be referred to level 4 if available.	Referred cases only

			is available.		
Unresectable tumours	None	Chemotherapy decision and initiation should be at central referral hospital. Subsequent chemotherapy could be done at this centre with advice from central hospital. 26 week review should take place centrally. No RT Follow up scans could be done at this centre but require reporting and discussion at central referral hospital	Chemotherapy decisions and initiation should be undertaken as per agreed national protocols. RT decisions may be made at this level. Patients receiving RT MUST have 3-D planning and a QA program in place. Referral of difficult RT cases to level 3. Follow up scans done at this centre.	Chemotherapy decisions, initiation will be undertaken. RT will be undertaken for all patients from level 1 and selected patients from level 2. 3-D planning and a QA program is mandatory. Follow up will be undertaken.	Referred cases only No follow up will be done in these centres

Spinal tumours	None	None	None	Spinal tumours will be assessed and managed at this centre.	Referred cases only

Table 3. Suggested MRI sequences for imaging paediatric LGG:

	MRI sequences	Comments
Minimum requirement (LIC/LMIC)	T1, T2 (different plane from T1), post-contrast in three planes	Provides the basic structural information about the tumour and its extent
Additional sequences if possible (LMIC/MIC)	FLAIR, diffusion-weighted imaging (DWI)	FLAIR useful for assessment of peri-tumoral oedema and differentiating tumour cysts from simple cysts, DWI helpful in differentiating cell-dense tumours such as medulloblastoma from radiologically atypical cerebellar LGG
Ideally (MIC)	Post contrast spine	LGG can rarely metastasise to spine

Table 4: Details of Administration and side effects of Vincristine/Carboplatin and Vinblastine Therapy.

	Details of administration	Side effects	Dose Modification
CARBOPLATIN	550 mg/m2 in 1 hour IV infusion Reconstitute lyophilized powder to concentration of 10 mg/ml with sterile water for injection, 5% Dextrose in Water, or 0.9% Sodium Chloride Injection. May further dilute in dextrose or sodium chloride containing solutions to a final concentration as low as 0.5 mg/mL. Carboplatin solutions, when prepared as directed are stable for 8 hours at room temperature. Aluminum can react with carboplatin, causing precipitate formation and potency loss. Do not use needles or IV administration sets containing aluminum parts that may come in contact with carboplatin for the preparation or administration of the drug.	**Immediate:** Within 1-2 days of receiving drug Nausea, vomiting Hypersensitivity reactions* (anaphylaxis, bronchospasm, hypotension), constipation, diarrhea **Within 2-3 weeks :** • Myelosuppression (anemia, neutropeniia, leukopenia, thrombocytopenia), • Electrolyte abnormalities (↓ Na, K, Ca, Mg) Delayed. • Hearing loss • Renal dysfunction	For infants less than 10 kg use 18.3 mg/kg. If under 6 months of age use a further 33.3% dose reduction Give if N > 1.0 x 10^9/L and platelets > 100 x 10^9/L If delay of > 1 week or repeated sepsis during neutropaenia then dose reduce by 25% If progressive ototoxicity at 1-4 kHz > grade II omit carboplatin If nephrotoxicity > grade I calculate dose according to the modified Calvert formula.
VINCRISTINE	1.5 mg/m2 given as an intravenous bolus injection. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the	**Immediate:** Jaw pain, headache Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm **Within 3 weeks:** Alopecia, constipation **Delayed**	For infants less than 10 kg use 0.05 mg/kg. If under 6 months of age use a further 33.3% dose reduction If peripheral Neuropathy grade III or IV then omit Vincristine and if neuropathy reverses then restart at 1.0 mg/m^2

	tubing of a running intravenous infusion.	Loss of deep tendon reflexes Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary. retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss. SIADH (rare):	If convulsion or SIADH occur then omit the following vincristine, if no further episodes then restart at 1.0 mg/m^2. If no further episodes occur at this dose then give subsequent doses at 1.5 mg/m^2 .
VINBLASTINE	6 mg/m2 given as an intravenous bolus injection. Vinblastine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.	**Immediate:** Nausea and vomiting, anorexia, metallic taste, jaw pain **Within 3 weeks:** Alopecia,constipation, myelosupression **Delayed** Loss of deep tendon reflexes Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait (rare). SIADH (rare)	If N < 0.75 but ≥ 0.5 reduce dose to 5mg/m^2 If N < 0.5 omit dose until N ≥ 0.75 then resume at 5mg/m^2 If persistent neutropenia reduce dose to 4mg/m^2 Once dose reduced no subsequent increase.

Table 5. Late Effects related to tumour and management of Low Grade Gliomas (14, 66-71)

Toxicity	Investigation	Suggested Management	Notes
Endocrine	**Ideally all endocrine disorders should be managed by a paediatric endocrinologist or paediatrician with experience in endocrine disorders of childhood** **Patient history, clinical examination including length, weight and pubertal stage are cornerstone of endocrine investigations**		Expected more with suprasellar tumours and post radiotherapy
Hypothyroidism	Serum Free T4/TSH	Oral thyroid hormone starting dose 50ug per m^2. Round off to nearest 12.5 µg. Dose needs to be adjusted according to serum levels.	
Central Diabetes Insipidus	Osmolarity and sodium level in serum and urine	Use of oral desmopressin Start as 0.05 mg twice daily. Dose range is 0.1 to 1.2 mg divided into 2 or 3 doses, monitor sodium level	
Growth hormone insufficiency	Growth chart showing crossing of growth centiles, IGF-1 and stimulation testing if possible	Synthetic growth hormone if available. The dose needs to be managed by a paediatric	

		endocrinologist.	
Hypoadrenalism (Adrenocorticoid insufficiency)	Early morning (pre-9.30am) Cortisol Synacthen testing if possible	Hydrocortisone replacement (7-8 mg /m^2/day in 3 divided doses) Triple if unwell, prednisolone at a quarter of dose can be used if hydrocortisone not available.	
Precocious puberty	Clinical examination, serum LH/FSH, testosterone or estradiol	LHRH antagonist, should only be managed in discussion with a paediatric endocrinologist	
Delayed puberty	Clinical examination, serum LH/FSH, testosterone or estradiol	Substitution of estradiol or testosterone should only be managed in discussion with a paediatric endocrinologist	
Infertility	Clinical examination, serum LH/FSH, testosterone or oestradiol, sperm testing when required or more specialised testing	Should be managed by endocrinologist or fertility expert.	
Visual impairment , poor vision, diplopia	Ophthalmic assessment (visual acuity and field,	According to the impairment, e.g. if	Expected with optic pathway tumours

with squint	fundus examination)	persistent strabismus may need surgery Quantify results to Logmar in order to obtain comparison at follow up	
Hearing loss	Auditory assessment	Usually permanent, some may benefit from hearing aids	Evaluate with use of carboplatin/ cisplatin or radiotherapy
Seizures	Clinical and neurological assessment	Correct underlying cause, use of antiepileptic drugs	Evaluate if underlying cause (e.g tumour relapse /progression or electrolyte imbalance)
Neurocognitive dysfunction (memory, concentration and processing speed are usually the predominant features)	Neuropyschometric assessment if available	Support at school is often required. Specialised schooling is necessary in severe cases.	This is worst in NF1 and / or children treated at <5 years with progressive suprasellar tumours or post radiotherapy
Nutritional status (obesity)	Regular assessment of growth parameters and BMI	Advice regarding proper caloric intake, regular physical exercise	Expect with suprasellar tumours

Neurological sequelae including ataxia	Clinical examination	Physiotherapy and occupational therapy	
Secondary tumours	Picked up on routine follow up scans or suspicion on clinical examination.	As per tumour type	Expect with use of alkylating agents or post radiotherapy
Vascular problems e.g. Arteritis, Moya-moya disease [	Clinical and neurological assessment. Angiography (either MRI, CT or formal angiography) is advised.	Thrombolytics, physiotherapy and occupational therapy, treat underlying cause	Expect with increasing age after use of radiotherapy, and in NF patients

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