STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR LOW GRADE GLIOMAS

The lay-template may be adjusted to bring the document in line with other disease specific standard clinical practice documents.

General remarks:

The recommendation for brain tumours will finally consist of a general roadmap and nine tumour specific sections for (LGG, HGG, medulloblastoma, rare embryonal tumours, ATRT, ependymoma, GCT, craniopharyngioma, CPT).

The general roadmap includes sections on neurosurgery, neuroradiology, neuropathology, radiotherapy, endocrinology, neuroophthalmology, neuropsychology, and survivorship/ quality of life.

- *Take all international European, national and working group guidelines on your tumour entity into account for this document*
- *Focus only on criteria specific for your tumour entity; general requirements, for example for neurosurgery or radiology, are mentioned in the "general roadmap".*
- *If you have general criteria in mind for different chapters, which you think are important, please add them in a separate section (as bullet points) and they can later be integrated in the general part.*
- *Besides describing what should be available/done, it is also important describe what should not be done any more (if important)*
- *Focus on first line treatment*
- *General description/ characteristics of chemotherapeutic agents will be part of roadmap – describe in this tumour-type specific part the combinations used and dose modifications in case of adverse events, toxicities or allergic reactions*

INTRODUCTORY PAGE

Name of tumour entity: Low grade gliomas

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1. BACKGROUND AND RATIONALE

Paediatric low-grade gliomas (pLGG) are a heterogenous group of different WHO grade I and II tumours. They are the most common brain tumours in childhood, accounting for approximately 35% during the first year of life and up to 50% in older children.[1] Prognosis is generally excellent, with a 10-year overall survival between 85-96%. However, pLGG survivors often suffer from functional, neurological, visual and endocrine complications as a result of their disease or treatment, implying that pLGG is often a chronic disease.

Surgical resection, when feasible, is considered the mainstay of treatment. The CCG9891/POG9130 study reported a 5-year PFS and OS of 94% and 99% respectively in children with confirmed gross total resection.[2] However, many tumours are not amenable to complete resection because of anatomical location and /or metastatic disease.

The carboplatin and vincristine regimen remains the standard first line systemic treatment for patients with pLGG, with the SIOP LGG 2004 Trial showing a 5-year overall survival and progression-free survival of 89% and 46.1% respectively.[3] Carboplatin and vincristine using a different schedule and dosages have also been validated by the Children's Oncology Group (COG) resulting in similar findings (39% EFS for non-NF1 patients).[4] Vinblastine monotherapy as first line treatment for patients with pLGG needing chemotherapy is considered the standard of care for the Canadian Group (5-year PFS 42% in non-NF1 patients).[5-7]

Historically, radiotherapy was the treatment of choice for symptomatic patients with unresectable pLGG. However, in the context of a low-grade tumour, potential sequelae associated with radiotherapy were a major concern, especially in young children demonstrating serious endocrine, neurocognitive, neurologic or vascular abnormalities as well as risk for second malignancy.[8-11] The risk for late effects depends on the radiation field and is considered higher, if radiotherapy is given to the left temporal lobe, left hippocampus or the hypothalamic-pituitary region.[12] Furthermore, Fisher's series showed that overall survival of the patients receiving radiotherapy immediately following incomplete resection and those with radiation following progression was the same after 5 and 10 years.[13] Moreover, progression free survival did not differ by management (P 0.32). PFS after 3 and 5 years was 58%±5% and 48%±5% for observation alone, 56%±6% and 48%±6% with immediate irradiation, and 43%±13% and 36%±13% with immediate chemotherapy.[13] Additionally, a Canadian population based retrospective study of 1202 pLGG patients (median follow-up 12.73 years) raised major concerns regarding the association of upfront radiotherapy with delayed increased overall and tumour-related late deaths.[14]

During the past decade the involvement of the mitogen-activated protein kinase (MAPk) pathway in pLGG became evident, and gave the opportunity to investigate targeted therapies. MEK inhibitors (including selumetinib and trametinib) and recently also RAF-inhibitors have been investigated in phase 1 and 2 trials, and are continuing to be studied in upcoming randomized trials.[15,16]

There are therefore several strategies from different disciplines for tumour control for paediatric low grade glioma, and a key aspect of overall management is to maintain visual, endocrinological and neurological function. Management strategy should therefore always be planned in the multi-disciplinary team setting.

2. PATIENT GROUP

Patients diagnosed with low grade glioma can be subdivided to different categories according to:

- **Location of the tumour**

Low-grade tumours characteristically are clustered anatomically to midline supratentorial structures in 39-40%, including the hypothalamus, optic chiasm and nerves, ventricular system, and other midline structures; the cerebellum in 32-36%; the cerebral cortex in 13.1-18.0%; the brainstem in 8.3-10%; and the spinal cord in 3.5-4.5%.[17,18]
Tumour location in combination with the grade of tumour and the potential risk of permanent neurological deficit determines resectability.

Hemispheric and **cerebellar** pLGGs are usually amenable to surgery, however there are considerations (see later under surgery)

Hypothalamic-optic pathway gliomas are sub-divided into NF1 related and sporadic tumours, with differences in the natural history and also imaging features. NF1 related tumours generally have a better PFS, and many do not require therapy. Both NF1 and sporadic tumours may lead to visual loss, endocrinopathies, hypothalamic symptoms such as diencephalic syndrome in young children and also hydrocephalus if third ventricle obstruction occurs. They are generally not amenable to complete resection via neurosurgery.

Thalamic pLGGs are rare, 1-2%, often presenting with hemiplegia and/or hemianopsia.[19,20]

Tectal plate gliomas are uncommon pLGGs, occurring predominantly in children and constitute 5% of paediatric brainstem tumours. They present with symptoms of raised intracranial pressure and usually require CSF diversion at diagnosis.[21]

Cervico-medullary pLGGs are slow growing tumours presenting with lower brainstem symptoms with high long term survival and high risk of progression / recurrence, even late ones. Therapy should be directed at achieving local tumour control while preserving and even restoring neurological function.[22]

Spinal LGGs: are rare and characterised by insidious nature. They can cause clear neurological deficit but also vague, generalized symptoms in young children. Thus, their diagnosis can be delayed until the intensity of symptoms becomes significant or debilitating.[23,24]Infiltration and indistinct margins with normal tissues often make complete resection difficult. Gross total resection when feasible appears to be the most important factor for PFS, (repeated) chemotherapy may contribute to reducing morbidity and seems to result in comparable tumour control compared with radiotherapy.[24,25]

- **Age**

In infants, pLGGs carry a unique clinical profile and additional management challenges. In general infantile gliomas are more common in the hypothalamic or optic pathway area (61-67%)[17,26], which limits resectability and they are more likely to be metastatic (23%) and progressive than LGG in older children.[26]

- **Underlying conditions**

Two cancer predisposition syndromes associated with paediatric LGG development have been described until now:

1. Neurofibromatosis type 1 (NF1) accounting for 10-20% of all paediatric LGGs, mainly optic pathway gliomas.[18,27]
2. Tuberous Sclerosis Complex (TSC) associated with Subependymal Giant Cell Astrocytoma (SEGA) development, accounting for 1-2% of pLGGs[18,28,29].

- **Presence of metastasis**

Leptomeningeal dissemination is seen in 4-12% of children with LGG either at diagnosis or progression and results in worse outcomes. [30,31]

- **Special considerations**

Infant CHG: < 1 year of age at diagnosis with any low-grade glioma histology **and** chiasmatic hypothalamic glioma location, independently from presence of neurologic and/or visual symptoms.

Diencephalic syndrome is defined as a syndrome of emaciation with normal to accelerated linear growth and BMI or weight for length ≤2 SD in young children with a tumour in the chiasmatic-hypothalamic region.

Incidentalomas: The rate of incidentally detected brain tumours in children is growing, due to availability and wide-spread use of neuroimaging for various indications. They are found in 0.2 – 5.7% of brain images and can pose a considerable burden for patients, their families and caregivers. In most cases where radiological suspicion of LGG is clear, observation seems to be the preferred management option unless the radiological features lose the LGG characteristics and / or symptoms present. [32,33]

All patients with LGG according to indication for management (see "Treatment details") form 2 groups: **Observation group** and **Treatment group.**

2.1 Diagnostic Criteria

2.1.1 Clinical presentation

It is highly dependent on the localization of the lesion. Patients with paediatric low-grade gliomas can present with one or combination of the following:

2.1.1.1 Symptom free via screening or other reason for CT or MRI

It is estimated that ~15% of children with NF1 are found to have an optic-pathway glioma often via screening, with almost 50% of them remaining asymptomatic or nonprogressive.[34]

2.1.1.2 Neurology[35]

pLGGs typically may present with:

- *Raised ICP and obstructive hydrocephalus* where lesions cause obstruction of the ventricular outflow, mainly in those with cerebellar and tectal lesions. Headache and nausea/vomiting are the most common complaints. In infants, increase in head circumference can be the only presenting sign.
- *Focal Deficits* such as weakness, sensory loss, language difficulty, cognitive difficulty, change of personality and decline in academic or athletic performance
- *Epilepsy*: tumour location influences the risk for epilepsy. Tumours involving the frontal, temporal and parietal lobes are more commonly associated with seizures compared to those involving occipital lesions. Infratentorial tumours rarely cause seizures. Cortical tumours have a higher incidence of associated epilepsy compared to non-cortical deeper lesions. Certain histological types are associated with chronic drug-resistant epilepsy i.e. gangliogliomas and dysplastic neuroepithelial tumours[36,37]

Cortical tumours usually present with focal neurological deficits including seizures and headache. Brain stem gliomas can present with fatigue, ataxia and multiple cranial neuropathies, whereas posterior fossa tumours usually present with cerebellar signs and signs of increased intracranial pressure.

2.1.1.3 Vision

Varying signs or symptoms of visual dysfunction from asymptomatic to severe visual loss can be observed in optic pathway gliomas. The severity of the symptoms depends on tumour location. Decreased visual acuity is the most common symptom observed. Furthermore, various visual field defects can be observed, such as central scotoma, bitemporal hemianopsia and peripheral contraction.

- Unilateral vision loss, strabismus and/or proptosis are described in tumours located in the anterior optic pathway
- Bilateral vision deterioration, vision field loss, nystagmus and eventually loss of visual acuity might be observed in patients with chiasmatic tumours
- Proptosis can also be observed and is more common in NF1 patients.

Visual assessment (visual acuity, visual fields and fundoscopy) plays a critical role for the management of these patients and is considered a significant challenge for young children and uncooperative patients.(See "ophthalmology section")

Risk factors for visual deficit are considered to be younger age at presentation, optic nerve atrophy at presentation and postchiasmatic involvement.[38,39]

2.1.1.4 Endocrine disorders

Abnormalities in weight, growth, precocious or delayed puberty and/or polydipsia/polyuria with diabetes insipidus may also be the presenting symptoms of low grade gliomas with hypothalamic involvement. (See "endocrinology section")

Diencephalic syndrome as described above, in which a disordered metabolism results in failure to thrive, severe emaciation and near absence of subcutaneous fat, mainly occurs in young patients.

2.1.2 Imaging

Magnetic resonance imaging is the modality of choice for evaluating central nervous system neoplasms. Contrast enhanced MR should be obtained at the time of tumour diagnosis. MRI studies of grade I Paediatric Low Grade Glioma show well-circumscribed lesions, with T1 hypointensity and T2- hyperintensity. Grade I astrocytomas often show homogenous enhancement with gadolinium administration, while grade II diffuse astrocytomas are typically non-enhancing, and possibly less circumscribed.

Computed tomography (CT) often first identifies an otherwise asymptomatic tumour when obtained for an unrelated reason, such as trauma. Unless there is some reason for which an MR cannot be obtained (such as a non-MR-compatible implant), any CT which is suspicious for a neoplasm should be followed by MR to better evaluate the anatomical borders and characteristics of the lesion.[40]

Based on the recently published imaging guidelines for paediatric low grade gliomas, the following are recommended:[41]

At diagnosis:

- All patients should have a **presurgical baseline MRI scan** to assess the tumour, and a **postoperative MRI scan** within 24-72 h after surgery to assess the amount of residual tumour.
- In cases where surgery is not indicated or only a small biopsy sample is taken, the diagnostic or prebiopsy scan could serve as baseline scan pretreatment.
- In situations where extensive parenchymal postoperative changes could obscure a residual tumour with urgent indication to treat, a **second MRI** approximately 2-3 weeks after surgery might better define residual disease according to RAPNO Working Group recommendations.[40]
- A **spine MRI** for patients with primary pLGG in their brain is recommended, when there is a concern for metastatic disease (i.e. symptoms that can indicate spinal disease or infants), before surgical intervention, or at 10-14 days after.
- For spinal LGG, a **baseline brain MRI** should be performed.

Imaging sequences and contrast agents

- **T2 and T2-FLAIR** are necessary sequences and are in general, considered the best sequences for assessing tumour changes in paediatric low-grade gliomas.
- **Postcontrast imaging (T1-weighted)** is necessary for pLGG assessment and as part of evaluating response.
- The safest available **contrast agents** (currently, macrocyclic gadolinium-based contrast agents) should be used, if possible, to reduce risk of nephrogenic systemic fibrosis and to minimise tissue deposition (i.e. brain deposition). Also, if possible, the same contrast agent should be used in the patient throughout their surveillance.

Currently, the standard practice is to use contrast agents during follow up of LGG patients regardless of time since diagnosis, complete resection, histological diagnosis or contrast enhancement of the tumour. Nevertheless, as per RAPNO working group comment, in the rare situation that a paediatric low-grade glioma is completely non-enhancing, imaging without contrast can be considered in follow-up surveillance.[40]

2.1.3 Histopathology

Low grade gliomas are a heterogeneous group of neoplasms that primarily encompass tumours of glial histology, including astrocytic and/or oligodendroglial, and tumours of mixed neuronal-glial morphology.

These tumours were considered grades I and II according to the previous WHO classification where they were distinguished from high grade glioma on the basis of specific morphologic features or, in the case of diffuse glioma, based on the absence of necrosis, mitoses and microvascular proliferation.[42]

According to the new 2021 WHO Classification for the CNS tumours, paediatric low-grade gliomas are now classified by histological and histogenetic similarities, even though molecular signatures vary, within the group *Gliomas, Glioneuronal Tumours and Neuronal Tumours*. Paediatric low-grade gliomas are found in 3 out of 6 families of the group and are summarized in the table below[42,43]:

New 2021 WHO Classification for low-grade gliomas		
Tumor class	**Tumor type**	**Grade**
Paediatric type diffuse low-grade gliomas	Diffuse astrocytoma,MYB- or MYBL1-altered	1
	Angiocentric glioma	1
	Polymorphous low-grade neuroepithelial tumor of the young (PLTNY)	1
	Diffuse low-grade glioma, MAPK pathway altered	NA
Circumscribed astrocytic glioma	Pilocytic astrocytoma	1
	Pleomorphic xanthoastrocytomas	2
	Subependymal giant cell astrocytoma	1
	Chordoid glioma	2
Glioneuronal and neuronal tumours	Ganglioglioma	1
	Desmoplastic infantile ganglioglioma	1
	Dysembryoplastic neuroepithelial tumors	1
	Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters	NA
	Papillary glioneuronal tumor	1
	Rosette-forming glioneuronal tumor	1
	Myxoid glioneuronal tumour	1
	Diffuse leptomeningeal glioneuronal tumour	NA
	Gangliocytoma	1
	Multinodular and vacuolating neuronal tumour	1
	Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	1
	Central neurocytoma	2
	Extraventricular neurocytoma	2
Adult-type diffuse gliomas	Astrocytoma, IDH mutant	2
	Oligodendroglioma, IDH mutant and 1p/19q co-deleted	2
	Oligondendroglioma NOS	2

Pathology work up of tissue for low grade gliomas includes:

-stainings of formalin-fixed, paraffin-embedded (FFPE) material with HE-, PAS-, Alcianblue- and Reticulin-staining,

-standard immunohistochemistry (IHC) encompasses a wider panel depending upon tumour differentiation (glial markers [GFAP, Olig2, S100 protein, vimentin], neuronal epitopes [synaptophysin, NeuN, chromogranin, neurofilaments; in case of glioneuronal differentiation], proliferation markers [Ki-67, phosphor-histone3], CD 68, CD 34, p53,Synaptophysin, p53,

Neurofilament; Chromogranine and NeuN in case of glioneuronal differentiation. phospho-ERK, phosphor-mTOR and phosphor-AKT in selected cases).[1]

Additional work up in selected cases includes:

- IDH 1(R132H) and BRAFV600E to distinguish gliomas with possible different biologic behaviour,
- H3K27M in case of midline tumours or spinal location to distinguish less expected high grade tumours (for details see "molecular pathology section");

The morphological features of pilocytic astrocytomas are distinctive and characterized by extensive vascular proliferation, biphasic architecture, Rosenthal fibers, eosinophilic granular bodies, and occasionally, regions of limited calcification.

Gangliogliomas are another low grade glioma (grade I) of mixed neuronal-glial subtype, also characterized by granular bodies and regions of calcification, and also exhibit binucleated neurons and cystic degeneration can bear BRAF V600Emutation.

Angiocentric gliomas that occur predominantly in children and young adults with refractory epilepsy as the leading clinical symptom, were initially included in 2007 WHO classification. Histopathologically they are characterized by monomorphous bipolar cells, an angiocentric growth pattern and immunoreactivity for EMA, GFAP, S-100 protein and vimentin, but not for neuronal antigens. MYB-QKI fusions are identified in 80-90% of angiocentric gliomas [43-45]

2.1.4 Molecular pathology[45-48]

Classification of low grade gliomas can be supported via methylation profiling.

The majority of paediatric LGG are driven by a single genetic event resulting in up-regulation of the RAS/MAPK pathway. The most common alterations in paediatric LGGs described so far are:

- **Neurofibromatosis type 1:** the first indication of RAS/MAPK involvement came from NF1 patients of whom 10-15% develops a low grade glioma within the optic pathway and an additional 3-5% arising outside the optic pathway. A recent study revealed that patients with NF1 and pLGG may harbor additional somatic genetic alterations[49]
- **KIAA1549-BRAF i**s the most frequent molecular alteration in pLGG and is significantly enriched in pilocytic astrocytoma and in tumours arising in the posterior fossa/cerebellum.
- **BRAFp.V600E:** the prevalence varies notably depending on histology and location and is frequently associated with additional alterations, most commonly deletion of CDKN2A. Patients with BRAFp.V600E mutated tumours have worse progression free survival compared to those with KIAA1549-BRAF. [48] Tumors with BRAFpV600E mutation and CDKN2A deletion have an increased likelihood of malignant behavior.[50]
- **FGFR1 alterations**, including point mutation and kinase domain duplications are more frequent in dysembryoplastic neuroepithelial tumors, other glioneuronal tumors and in midline brain structures. It is the second most commonly altered gene.
- **Alterations of MYB/MYBL1**, often seen in angiocentric glioma, seem to define a class of paediatric-type diffuse gliomas
- **Germline mutations in TSC1 and TSC2** are closely associated with subependymal giant cell astrocytoma, which occur in up to 20% of patients with tuberous sclerosis complex.[51]

A variety of relatively rare alterations of NTRK, RAF1, ALK, PTNP11 and others are also found in these tumours. The impact of these alterations in prognosis and response to treatment is still under investigation.

To distinguish unexpected high grade tumours, testing for absence of H3K27M mutations in brain stem and midline thalamic tumours and H3G34R/H3G34V in cerebral hemispheres, which are found in high grade gliomas is recommended.[52,53]

Finally, testing for IDH1 mutations-most frequently at position p.R132- is also recommended. IDH1 mutations although common in almost 70-90% of adult WHO grade II and III gliomas and 85% of secondary GBMs, [54] they are rare in paediatric gliomas accounting for only 0-17% of the cases.[45] COG reported a 16% incidence of IDH1 mutations in adolescents over the age of 14 years.[55] Recently, Ryall et al reported presence of IDH1p.R132H mutations in 0.8% of 1000 patients with paediatric low-grade gliomas with a median age of diagnosis at 15.7 years.[48] The clinical impact of these mutations in children is not yet clearly understood but it is likely that these tumours will not

behave as most other pLGG over the long term and could represent in fact adult malignancies that have been identified early.

Recent integrated molecular profiling has facilitated the delineation of additional diagnostic subclasses such as angiocentric glioma, polymorphous low-grade neuroepithelial tumour of the young (PLNTY), and isomorphic diffuse glioma.[56] Methylation profiling may aid in prediction of clinical behavior as recently supported by Sexton-Oates et al. [57]

Devising a simple recommendation concerning molecular testing/profiling for pLGG can be difficult. Ultimately, as proposed by Miklja et al, there are two primary approaches to the problem:

- Sequential testing of specific alterations in a tier based approach or
- Upfront NGS panels optimized for pLGG. [52]

In general, it is advised if possible to join the LOGGIC Core Bioclinical Data Bank currently recruiting patients with paediatric low-grade gliomas across Europe.

2.1.5 Neurological and visual function

2.1.5.1. Neurologist

Neurological examination at baseline is crucial, since it may define indication for treatment. This baseline information is used to determine treatment response: stable functioning, worsening or improvement.

2.1.5.2. Ophthalmologist

Visual functioning determined by fundoscopy, and age appropriate techniques for examination of visual acuity and visual field especially in case of tumours involving the optic pathway.

Visual symptoms / signs of OPG are influenced by factors like tumour extension, tumour volume, patient age, associated raised intracranial pressure and the presence / absence of NF1. The current recommendations used and published by the REiNS (Response Evaluation in Neurofibromatosis and Scwhannomatosis) and paediatric low-grade gliomas International Consensus paper should be followed when assessing visual outcomes.[40] Teller Acuity Cards and HOTV testing (using a standardised testing protocol that determines relative visual acuity for distance vision using a chart with the four letters H, O, T and V) should be the primary modes of assessing visual outcomes if possible, because together they can accommodate the widest range of developmental abilities. With small children, or children with developmental delays, testing can some-times be unreliable. It should be noted that, from birth to age of 3-4 years (earlier for some children), vision is a physiologically maturing process, and VA (visual acuity) of 0.3 logMAR is within normal limits at 2 years of age, while normal VA (0.0 logMAR) is only reached between 4-6 years of age (logMAR: the logarithmic scale of the angle subtended within the eye by a letter or Minimum Angle of Resolution). If it is unclear whether a noted vision change is due to true decline or poor patient cooperation, it is recommended that testing be repeated 1–2 weeks later to verify the change as best as possible

This baseline information is used to determine the indication for treatment as well as the response over time: stable functioning, worsening or improvement. Special consideration should be taken in systematic clinical examination of the different types of eye movements including eye position, range of eye movements, smooth pursuit, saccades, gaze-holding functions and optokinetic nystagmus as well as testing for different types of nystagmus (i.e. isolated dysfunction of vertical eye movements is due to a midbrain lesion). Infratentorial tumours may present with eye movement disorders.

3. TREATMENT DETAILS

Multidisciplinary tumour board

Decisions on treatment and/ or follow up in pLGG need multidisciplinary information, approach and interpretation. The multidisciplinary tumour board should consist of neurooncology, neurosurgical, neurology, neuroradiology, radiotherapy and neuropathology expertise and should meet at regular scheduled intervals in order to optimize diagnosis, follow up and treatment. [58,59] Involvement of other specialties including ophthalmology, audiology and endocrinology is extremely important.

Treatment indications

Indications to start non-surgical treatment in unresectable LGG
Radiologic criteria
- Increase of tumour volume of > 25 % (the increase of the diameter of the optic nerve should be indicated separately) as per RAPNO working group guidelines[40]
- Involvement of previously uninvolved areas
- Appearance of new lesions
- Increase of the number and/or size of metastases
Neurologic symptoms
- Diencephalic syndrome
- Focal neurologic deficits subsequent to tumour growth
- Drug resistant seizures with or without tumour growth
- (Focal) increased intracranial pressure subsequent to tumour growth
- Symptomatic metastases
Infants
– Infants below 12 months of age with chiasmatic-hypothalamic tumours
Ophthalmologic symptoms:
- Definitive loss of vision
- Borderline vision (“Threat to vision”)
- Reduction of residual low level vision/visual field
- Nystagmus as a result of visual impairment in infants
- Any visual loss in the second eye when the first eye is blind
- Visual deterioration on follow-up, a significant loss is defined as more than or equal to 0.2 LogMAR
“For patients with SEGA(s), therapy with an mTOR inhibitor is indicated when they require intervention but: 1. The tumour is not amenable to surgery 2. Surgery is contraindicated 3. Surgical approach does not allow complete resection 4. In case of bilateral fornix lesions.

3.1 Treatment

3.1.1 Radiotherapy

The introduction of chemotherapy aims to delay or obviate the need for radiotherapy to minimise cognitive, endocrine and vascular consequences[60] and development of later malignant neoplasms.[50] Patients younger than 5 years of age seem to be more at risk of sequelae following conformal radiotherapy with higher risk of moya moya, increasing deficits over time and greatest decline in cognition.[60,61] Thus, radiotherapy is delayed in young patients.

Radiotherapy had previously been the mainstay of treatment for incompletely resected pLGG but nowadays remains a standard as salvage treatment or as primary treatment in selected cases in which surrounding normal tissue can be optimally preserved. Modern high-precision radiotherapy techniques, including proton therapy, have the potential to limit the development of long-term toxicities. There is therefore an urgent need for prospective studies to compare the efficacy and safety of modern radiotherapy with systemic treatment in children with pLGGs.[62].

Up-front radiotherapy may be indicated following multidisciplinary tumour board agreement in:

- tumours where there are concerns regarding high risk of significant morbidity in the event of minimal tumour growth
- tumours where the risk of radiotherapy-related neurocognitive effects is felt to be low
- in children with disseminated disease craniospinal irradiation may be a treatment option, when chemotherapy has failed.[1]

Radiotherapy should not be given to children with NF1, as there is an increased risk of both second malignancy and vascular late effects in this patient group.

3.1.2 Chemotherapy

General requirements to start treatment are:

Good clinical condition (exception: infants with diencephalic syndrome) [63]	**all regimens**
Adequate bone marrow function:	**Carbo-VCR:** WBC> 2.0x10^9/L, ANC> 0.5x10^9/L, PLT >100x10^9/L (rising) [63] **Vinblastine:** ANC≥ 1.0x10^9/L, PLT ≥ 100x10^9/L[5] **Vincristine/Cisplatin/Cyclophoshamide:** WBC> 2.0 x 10^9/L, ANC > 0.5x10^9/L, PLT >80x10^9/L[63]
No hypersensitivity for carboplatin ≥ 3 CTCAE v5.0	**Carbo-VCR**
No hearing impairment ≥ grade 2 CTCAE v5.0	**Carbo-VCR** **Vincristine/Cisplatin/Cyclophoshamide***
No nephrotoxicity > grade 1 CTCAE v5.0	**Carbo-VCR** **Vincristine/Cisplatin/Cyclophoshamide***
No peripheral neuropathy ≥ grade 3 CTCAE v5.0 (exclude the possibility the neurological deficit is a result of the tumour itself)	**all regimens**

* in case of carboplatin allergy

3.1.2.1. First line treatment

3.1.2.1.1 Carboplatin-Vincristine regimen[63]

Treatment induction (Weeks 1-24)

WEEK	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	24
	V	V	V	V	V	V	V	V	V	V			V	V	V	V
	C			C			C			C			C	C	C	
																MRI

- **Vincristine 1,5mg/m^2 (0,05 mg/kg BW,** if BW<10kg) **[max dose:2 mg]** as **bolus or** a **short iv infusion**
  During induction, on day 1 of weeks 1 -10, and then on day 1 of weeks 13, 17 and 21

During consolidation, on day 1, 8 and 15 of each cycle

- **Carboplatin 550mg/m^2 (18,3mg/kg BW,** if BW<10kg) in 200 ml Glucose 5 %, as a **1h iv infusion**
  During induction, on day 1 of weeks 1, 4, 7, 10, 13, 17 and 21
  During consolidation on day 1 of each cycle.

For children below the age of 6 months additionally to the rules above further dose reduction of 1/3 is recommended. In case they do not experience relevant toxicity, dose adaption (increase) to full dose/kg body weight can be considered.

Consolidation therapy (Weeks 25-85):10 6-week cycles

WEEK	25	26	27	31	32	33	37	38	39	43	44	45	49	50	51	54
	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	
	C			C			C			C			C			
																MRI
WEEK	55	56	57	61	62	63	67	68	69	73	74	75	79	80	81	85
	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	
	C			C			C			C			C			
																MRI

Therapy could start with vincristine as short term infusion followed by carboplatin 1 hour later.

3.1.2.1.2. Vinblastine regimen[6]

Following Hypersensitivity reactions to carboplatin (HSR), first line treatment may continue with Vinblastine until total duration therapy of 70 weeks.

The following should also be taken into consideration:

- Vinblastine monotherapy is used as first line treatment in some expert European centers, especially in NF1 and in older patients although no randomized trial comparing carboplatin-vincristine vs vinblastine has published results so far.
- The recommended dosage for vinblastine in published series was 6mg/m^2 although in almost 70% of the patients a reduced dosage was required, due to hematological toxicity.[6] The proposed starting dosage, although not tested in protocols with published data as well as dose modifications are shown below:

Treatment (weeks 1-70)

If BSA <0.6m^2:

- **Vinblastine: 0,17 mg/kg BΣ iv push, weekly**

If BSA ≥0.6m^2:

- **Vinblastine: 5 mg/m^2 (max 10mg/dose) iv push, weekly**

3.1.2.1.3. Vincristine/cisplatin/cyclophosphamide regimen

Following hypersensitivity reactions to carboplatin (HSR), alternating courses of cisplatin/vincristine (A) with cyclophosphamide/ vincristine (B) every 6 weeks can also be administered. The two combinations shall be given a maximum of 5 times each (i.e. 10 x 6 week chemotherapy cycles in total) to limit cumulative doses. However, treatment **must not** continue beyond week 81 from start of chemotherapy.

NOTE: -Infants are at higher risk of cisplatin induced electrolyte imbalances

- For patients with significant visual impairment it is NOT recommended to use Cisplatin due to the risk of additional ototoxicity.

Consolidation scheme A: 6-week cycles

WEEK	1	2	3	4	5	6
	V	V	V			
	Cis (x2)					

Consolidation scheme B: 6-week cycles

WEEK	1	2	3	4	5	6
	V	V	V			
	Cy					

Consolidation scheme A:

- **Vincristine 1,5mg/m² (0,05 mg/kg BW,** if BW<10kg) **[max dose:2 mg]** as a **bolus or a short iv infusion**
  On day 1, 8 and 15 of each cycle
- **Cisplatin 30mg/m² (1mg/kg BW,** if BW<10kg) in 200 ml Glucose 5 %, as an **iv 3h infusion**
  On day 1 and 2 of each cycle.

Consolidation scheme B:

- **Vincristine 1,5mg/m² (0,05 mg/kg BW,** if BW<10kg) **[max dose:2 mg]** as **bolus or** an **iv short term infusion**
  On day 1, 8 and 15 of each cycle
- **Cyclophosphamide 1500mg/m² (50mg/kg BW,** if BW<10kg) in 200 ml Glucose 5 %, as a 1h **iv infusion**
  On day 1 of each cycle.

For children below the age of 6 months further dose reduction of 1/3 is recommended. In case they do not experience relevant toxicity, dose increase back to full dose/kg body weight can be considered.

3.1.2.1.4. Everolimus for patients with SEGA

If age ≥ 1year and <3years:

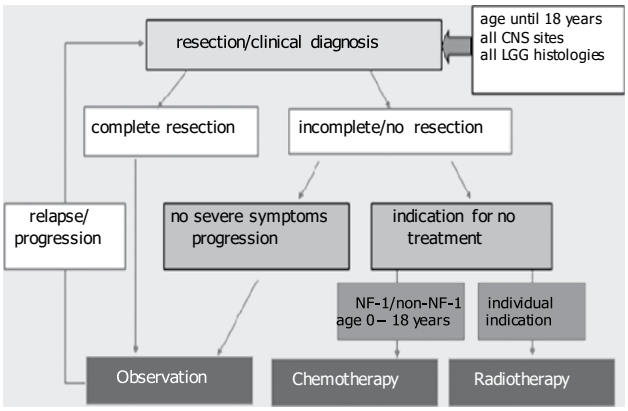
- **Everolimus: 7 mg/m² BSA po, once daily**

If age >3 years:

- **Everolimus: 4.5 mg/m² BSA po, once daily**

Trough levels of everolimus should be monitored aiming to 5-15ng/ml

Proposed diagram for follow up (Adopted from Gnekow et al)



3.1.3 Other

3.1.3.1.Surgery

In general, **surgical resection** remains the mainstay of treatment in low-grade gliomas, when feasible surgical management is guided by anatomical location, demarcation on imaging, histology and NF1 status.[58]

A multidisciplinary tumour board is essential for making decisions concerning biopsy or resection at the time of diagnosis and progression, taking into consideration the potential risk of surgery vs the therapeutic benefit as well as elucidating the histologic and molecular subtype of the tumour. Gross total resection is the initial therapeutic approach for cerebellar tumours, if applicable, the risk of cerebellar mutism syndrome, cerebellar cognitive affective syndrome and cranial nerve dysfunction should also be addressed in the MDT setting. For tumours located in the midline supratentorial region, the optic pathway/hypothalamus and the brainstem, partial resection or open or stereotactic biopsy is often a more appropriate approach, where optic nerve and pituitary and hypothalamus are all eloquent areas. Thus, it is recommended that biopsy or surgical resection of tumours in eloquent brain regions should only be undertaken by paediatric neurosurgeons with experience of operating in these regions.

Currently, typical intrinsic optic pathway tumours in association with NF1, do not require biopsy at the time of diagnosis, unless they are being managed in a clinical trial that involves a relevant biological stratification/question or they present with atypical features.[64]

For cerebral low-grade epilepsy associated tumours (LEATs) the decision for surgical treatment is made based on radiological appearance, resectability and refractoriness of epilepsy.[65] Shorter duration of symptoms, partial/focal seizures and gross total excision were predictors of a good seizure-outcome.[65-67] This patient group also is treated in dedicated neurosurgical teams for epilepsy neurosurgery.[68]

Regarding surgery of pLGG with relations to eloquent areas, neurosurgical strategies such as the use of intraoperative MRI or monitoring may be appropriate and surgical second opinion/discussion may be relevant.

3.1.3.2 Targeted therapy

Currently, targeted therapy as first line therapy for paediatric low grade gliomas is only acceptable in the context of clinical trials. Taking into consideration recently published data, possible benefits of targeted therapy could however be discussed for BRAFV600E mutant LGG[70,71]

3.2. Assessments

3.2.1 At diagnosis, before start and after end of treatment:

	At diagnosis	At end of therapy
Physical and neurologic examination	**X**	**X**
Anthropometric measurements	**X**	**X**
Neurology	**X**	**X**
Blood count including neutrophils	**X**	**X**
Electrolytes, create, SGOT, SGPT, Ca,Mg,P, Bil	**X**	**X**
MRI brain (+MRI spinal)	**X**	**X**
Opthalmology	**X**	**X**
GFR	**X**	**X**
Audiometry (in selected cases with anatomical predilection)	**X**	**X**
Endocrinology	**X**	**X**
Neurocognitive assessment	**According to institutional policy**	

3.2.2 During therapy

	Time	Comments
Physical and neurologic examination	**Before each course**	
Anthropometric measurements	**Before each course**	
Neurology	**Before each course**	
Blood count including neutrophils	**Before each course**	The application of vinblastine after the first 6 doses can be based upon blood counts obtained prior to the administration of the previous week's treatment. After a dose reduction, again after the first 6 doses after the dose reduction, the application can be based upon blood counts obtained prior to the administration of the previous week's treatment unless the patient has no signs of viral infection.
Electrolytes, create, ALT, AST SGPT, Ca,Mg,P, Bil	**Before each course**	
MRI brain (+MRI spinal)*	**at week 24,54 and 84** or according to institutional policy every 3 to 6 months until end of therapy	Consider performing MRI at week 12 in infants and patients with visual threat
GFR	**Every 6 months**	
Ophthalmology	**Every 3 months**	only when tumour involves optic pathway, or earlier if clinically indicated
Audiology assessment (in selected cases with anatomical predilection as well as patients treated with carboplatin)	**Every 6 months**	Pure Tone Audiometry if over three years; OtoAcoustic Emissions if under three years)
Endocrinology	**Every 6 months**	For all patients with tumors of the chiasmatic-hypothalamic region

*** During treatment**

3.2.3 For patients with SEGA/TSC:

Baseline investigations prior to start of everolimus	Full blood count & neutrophils, Urea, Electrolytes, Liver enzymes, Fasting Glucose, TGL, Chol, Urine dipstick for proteinuria , Hepatitis serology, APTT, PT
During initial dose (finding dose)	**Every 2 weeks:** Full blood count & neutrophils differential,trough everolimus level **Every 6 weeks:** Urea, Electrolytes, fasting glucose, triglyceride and cholesterol, urine dipstick for proteinuria
During continuation (once dose established)	**Every 6-12 months (more often if clinically indicated)** Full blood count neutrophils, trough everolimus level*, Urea, Electrolytes, AST, ALT, Bilirubin (conjugated/unconjugated),Fasting glucose, triglyceride, and cholesterol,Urine dipstick for proteinuria *or earlier if clinically indicated
Subsequent MRI	At 3 months and 6 months and 12 months, then yearly. (earlier if clinically indicated)

3.3 Summary of known adverse events

Drug	Toxicity	Comments
Carboplatin	*Dose dependent cumulative myelosuppression with a nadir between day 15 to 21.Grade 3 and 4 bone marrow toxicity is commonly described [1,3].* *Ototoxicity[72].* *Nephrotoxicity with loss of magnesium[1,73].* *Hypersensitivity reaction-Allergy to carboplatin/ Nausea-vomiting*	
Vincristine	Can lead to *peripheral neuropathy*, which can cause constipation as described above. Complaints of spontaneous pain in the jaws, hands and / or feet are seen, for which acetaminophen or eventually tricyclic antidepressants can be effective. *Motor neuropathy* can be seen in areflexia and difficulty lifting the feet, for which splints can be very helpful. Physiotherapy can be very useful in children with shortened Achilles tendon(s). *Rarely ptosis or vocal cord paresis* is seen due to neuropathy. Dose reduction should be considered. Vesicant.	It is **contraindicated** in children with Charcot-Marie-Tooth disease
Vinblastine	Mild alopecia Myelosuppression mainly leucopenia Moderate nausea and occasional vomiting Peripheral neuropathy, less commonly than vincristine. Vesicant.	
Cisplatin	Tubular-interstitial nephropathy Neurotoxicity: especially irreversible high frequency auditory impairment, peripheral poly-neuropathy Nausea, vomiting Hypocalcemia, hypomagnesemia Inappropriate secretion of ADH (SIADH) Coombs-positive hemolytic anemia Anaphylactic reactions	
Cyclophoshamide	*Myelosuppression,* *Hemorrhagic cystitis, Renal water retention.Nephropathy.* *Nausea-vomiting.* *Mucositis* *Alopecia.* *Cytotoxic alveolitis.* *Cardiotoxicity.* *Changes of taste.* *Syndrome of inadequate secretion of ADH (SIADH). Anaphylaxis.* *Bronchospasm.* *Dermatitis, Stevens-Johnson-syndrome,* *Neurotoxicity.* *Liver toxicity.* *Dose dependent infertility*	

3.4 Dose Modifications and delays

3.4.1 Carboplatin-Vincristine Regime

Drug	Toxicity	Dose modification
Carboplatin	WBC<2,0 x10^9/L or ANC<0,5x10^9/L or PLT <100x10^9/L at start of each course	**Delay treatment for 1 week.** If requirements are not met after 1 week delay: **25% reduction for the next** dose of Carboplatin
	Repeated sepsis during neutropenia	**25% reduction for the next** dose of Carboplatin
	Progressive Ototoxicity at 1-4 kHz (Brock grading system>grade 2)	**Omit Carboplatin**
	Nephrotoxicity >grade 1	**Dose calculation according to the modified Calvert's formula**
Vincristine	Peripheral neuropathy grade 3 or 4	**Omit the following dose/course of VCR** If neuropathy ameliorates resume therapy at **1,0mg/m^2 (max dose 1,5mg)**
	Convulsions SIADH	**Omit the following dose/course of VCR** If no further convulsions or symptoms of SIADH occur, resume therapy at **1,0mg/m^2 (max dose 1,5mg),** (continuing any concurrent anticonvulsive treatment). If no further convulsions occur, following doses of VCR can be given according to schedule at **1,5mg/m^2 (max dose 2mg)**
All drugs	Following severe neutropenia (ANC<0,5x$10^{9/L}$) associated with fever and sepsis and or severe infection and /or severe thrombocytopenia (<10x$10^{9/L}$ for >5 days)	**Decrease dose 25%** for the next course Consider G-CSF for acute severe infection

3.4.2 Vinblastine monotherapy

Drug	Toxicity	Dose modification
Vinblastine	ANC<0,75x10^9/L but ≥0.5x10^9/L and/or PLT<75x10^9/L but ≥50x10^9/L	Reduce the dose to **4mg/m^2 for BSA≥0.6m^2 or to 0.13mg/kg for BSA<0.6 m^2.**
	ANC<0.5 x 10^9/L and/or PLT < 50 x 10^9/L	**Withhold** vinblastine until recovery to neutrophils ≥ 0.75 x 10^9/L and platelets ≥ 75 x 10^9/L. **Resume** vinblastine at **4 mg/m^2 for BSA ≥ 0.6m^2** or at **0.13 mg/kg for BSA < 0.6 m^2.**
	Patients who at a reduced dose of 4 mg/m^2 for BSA ≥ 0.6m^2 or 0.13 mg/kg for BSA < 0.6 m^2 **still demonstrate** objective evidence of haematological toxicity affecting the weekly schedule	**Decrease** subsequent dose **to 3 mg/m^2 for BSA ≥ 0.6m2 or at 0.10 mg/kg for BSA < 0.6 m^2.**
	Non-Haematological Toxicity 1: Reversible grade 2 CTCAE v5.0 that requires dose reduction or grade 3 CTCAE v5.0 felt to be related to vinblastine	Resume with a **20% dose reduction** once the toxicity has recovered to baseline.
	Non-Haematological Toxicity 2: ≥ grade 4 CTCAE v5.0	Consider **alternative treatment regimens**.
	Peripheral neuropathy ≥ grade 3 CTCAE v5.0	**Omit** the following dose of vinblastine. If neuropathy ameliorates, resume vinblastine at 4 mg/m^2 or at 80% of the originally prescribed dose for BSA < 0.6 m2.

3.4.3 Vincristine/cisplatin/cyclophosphamide Regime

Drug	Toxicity	Dose modification
Cisplatin	WBC<2,0 x10^9/L or ANC<0,5x10^9/L or PLT <80x10^9/L at start of each course	**Delay treatment for 1 week.** If requirements are not met after 1 week delay: **25% reduction for the next** dose of Cisplatin
	Ototoxicity (Brock grading system>grade 2) or Nephrotoxicity >grade 1 or Creatinine-clearance: < 70 ml/min/1,73 m²	**Consider alternative regimen**
Cyclophosphamide	WBC<2,0 x10^9/L or ANC<0,5x10^9/L or PLT <80x10^9/L at start of each course	**Delay** treatment for 1 week; if requirements are not met after 1 week delay: **25% dose reduction** for the next dose of Cyclophosphamide.
	Nephrotoxicity >grade 1	**25% dose reduction for the next dose of Cyclophosphamide.**
Vincristine	**As indicated in Carboplatin-Vincristine Regime**	
All drugs	Following severe neutropenia (ANC<0,5x$10^{9/L}$) associated with fever and sepsis and or severe infection and /or severe thrombocytopenia (<10x$10^{9/L}$ for >5 days)	**Decrease dose 25%** for the next course Consider G-CSF for acute severe infection

3.5. Supportive treatment

In case of absence of institutional policies, the following are suggested:

3.5.1 Anti-emetic therapy

Antiemetic therapy should be administered according to institutional policy, Selective blockade of central 5-HT3 receptors, e.g ondansetron 5mg/m² (maximum single dose 8 mg) p.o/ i.v every 8-12 hours starting before chemotherapy is suggested for carboplatin administration. Application of additional anti-emetics like dexamethasone / aprepitant can be necessary. However, since pre-clinical evidence suggests anti-apoptotic as well as anti-senescence and proliferation inducing activity of dexamethasone in LGG, dexamethasone should be avoided if possible. [74]

3.5.2 Hydration

Carboplatin-Vincristine Regime: Concomitant hydration is not required for carboplatin, but is recommended if in agreement with institutional guidelines. Special consideration should be taken for infants with diencephalic syndrome and any child with diabetes insipidus in terms of sufficient hydration with careful monitoring of electrolytes, body weight and fluid balance during carboplatin infusion.

Vinblastine Monotherapy: Concomitant hydration is not required

Vincristine/cisplatin/cyclophosphamide Regime:
For Cisplatin:

- Diuresis 3000 ml/m² from 6-12 hours before the first until 24 hours after the second dose of Cisplatin with adequate substitution of Mg and Ca
- Mannitol-bolus 40 ml/m² Mannitol 20 % as a 10-15 min.-infusion before each dose of Cisplatin, parallel-infusion of Mannitol 20 % 40 ml/m²/24 h to enforce adequate diuresis.

- Avoid Furosemide

For Cyclophosphamide:

- Diuresis and prophylaxis of hemorrhagic cystitis: 3000 ml/m² for 24 h
- Mesna 500 mg/m² per dose iv., before and 4 and 8 hours after the start of the Cyclophosphamide infusion u 6 hourly registration of fluid balance
- Furosemide 0,5 mg/kg iv, if urinary production below 2 ml/ kg/hrs
- Controlling for hematuria (every portion of urine), in case of positive analysis for erythrocytes or dysuria the development of hemorrhagic cystitis is possible: increase hydration, increased/prolonged application of Mesna and pain therapy

3.5.3 Pneumocystis jirovecii prophylaxis

Cotrimoxazole is prescribed if on institutional protocol on two to three consecutive days per week (5-6 mg/bd TMP or 30 mgkg SMZ bid per day)

3.5.4 Laxatives for chemotherapy induced constipation

Weekly administration of vincristine is associated with higher risk for constipation[69], thus families should be given general measures to avoid constipation and laxatives, preferably macrogol, should be prescribed prophylactically.

3.5.5 Magnesium supplementation

Oral magnesium supplementation 7 mg/kg/day in 2-3 doses according to institutional guidelines in case of low magnesium; post carboplatin and cisplatin is recommended, and can be necessary as maintenance in part of the children.

3.5.6 Central venous catheters

Insertion of central venous catheter is recommended especially for infants and toddlers.

3.5.7 Use of G-CSF

The use of granulocyte colony stimulating factors is not routinely recommended.

3.6 Concomitant medication

Endocrine: Children with chiasmatic hypothalamic glioma can be dependent on substitution of hormones such as thyroid hormone, hydrocortisone, growth hormone and anti-diuretic hormone, and may also be treated for precious puberty. Hormonal therapy may be continued during chemotherapy without adjustments, however discontinuation of growth hormone substitute is decided according to institutional guidelines.

Epilepsy medication is generally also continued as indicated, some anti-epileptic drugs may have interactions and this should be checked, the same for supportive care medications, see below.

3.6.1 Carboplatin

It is recommended to avoid the use of ototoxic drugs (e.g. aminoglycosides and loop diuretics) in combination with carboplatin. Furthermore, it has been described that phenytoin plasma levels decrease when administered together with carboplatin.

Dexamethasone probably inhibits the effect of platinum compounds in glial cells.

3.6.2 Vincristine

Be aware of interactions with co-medications including ritonavir, nelfinavir, ketoconazole, itraconazole (increased polyneuropathy), erythromycin (decelerated elimination of vincristine), nifedipine, nefazodone, phenytoin (decreased plasma levels of phenytoin), isoniazid (increased neurotoxicity), digoxin (reduced effect of digoxin), G-CSF and GM-CSF.

3.6.3 Vinblastine

Be aware of interactions in co-medications including erythromycin (increased toxicity vinblastine), itraconazole (increased polyneuropathy), phenytoin (decreased plasma levels of phenytoin) and digitoxin (reduced effect of digitoxin).Importantly, also other drugs of the same class as the ones listed above and herbal remedies (e.g. St. John's wort) should be used with caution.

3.6.4 Cisplatin

Dexamethasone probably inhibits the effect of Platinum compounds in glial cells.

3.6.5. Cyclophoshamide

Interacts with Allopurinol, Cimetidin, Paracetamol, Barbiturates: increase of Cyc-effect and toxicity. Amphotericin B: hypotension, bronchospasm Insulin: increase of insulin-effect Narcotics: increase of effect of narcotics.

3.7 Patient follow-up

Follow up of patients with low grade gliomas depends on patient-related factors such as age and underlying diagnosis of NF1 and on tumour-related factors such as primary site, degree of resection, type of treatment, history and time from diagnosis in case of relapse Late relapses although rare may occur.[14,18,70,71] Krishnatry et al reported that radiation therapy was associated with late all-cause and tumour-related deaths in 1202 adult pLGG survivors.[14] Recently, Zaazoue et al suggested a less frequent imaging protocol for patients with gross total resection.[78] In this context, a less frequent imaging follow up than the proposed one below after the 5th year can be considered in patients with gross total resection.

For all treatment groups, the following are suggested:

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
Ophthalmology (mandatory for OPG)	Every 3 months	Every 3-6 months	Every 6(-12) months	Every 6-12 months
Neurocognitive assessment	According to institutional policy			

****For surveillance**

If spinal dissemination is identified at diagnosis, repeat surveillance spinal MRI at the same intervals as the primary intracranial lesion.

Additionally:

3.7.1 For observational group, without residual tumour or with stable disease, including stable residual tumour following surgery

	1st year	2nd year	3rd-5th year	6th-10th year
Audiometry	Every 6 months	Not indicated, if previously normal Regular assessments, if impaired[72]		
Endocrinology	Before growth is completed: annually, if clinically indicated more often After growth is completed: 3 to 5 yearly assessment in case of CHG			

3.7.2 For chemotherapy group, with stable residue after termination of therapy

	1st year	2nd year	3rd-5th year	6th-10th year
Audiometry	Every 6 months	Not indicated, if previously normal Regular assessments, if impaired[72]		
Renal function	6 months after end of chemotherapy	Yearly, if not otherwise indicated. May be deleted, if repetitively normal		
Endocrinology	**During treatment:** at beginning, 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			

3.7.3 For radiotherapy group with stable residue after termination of therapy

	1st year	2nd year	3rd-5th year	6th-10th year
Audiometry	Every 6 months	Not indicated, if previously normal Regular assessments, if impaired and/or acoustic nerve in RT field [73]		
Endocrinology	**After completion of radiotherapy:** at the end and one year after end of radiotherapy **Before growth is completed:** annually, if clinically indicated more often **After growth is completed**: 3 (to 5) yearly assessment but more frequently, if the pituitary hypothalamic region was in the RT filed			

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