



*EndNote: Essential Medicine Converted*

## STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# BRAIN TUMOUR GROUP

## OVERVIEW AND DISCIPLINE GROUPS

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### **Disclosure:**

This document aims to provide a clinical practice guideline for the treatment of CNS tumours in children and adolescents in Europe. The treating physician remains responsible for the application of any procedures and treatment to children and adolescents diagnosed with a CNS tumour.

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## Background and Rationale

### 1. Introduction

Tumours of the central nervous system (CNS) represent the most common group of solid neoplasms in children and adolescents. CNS tumours comprise several histologic types and subtypes. These different subtypes and additional factors, such as age at diagnosis, location, disease stage or genetic characteristics of the tumours lead to a very heterogeneous picture of clinical courses and long-term outcomes (1-3). Some types can be followed-up with only a watch and wait strategy whilst others can be treated and cured with surgery alone. On the other end of the treatment intensity spectrum are CNS tumour types that need multi-modality treatment with surgery, chemotherapy (sometimes high-dose chemotherapy) and radiotherapy.

During the last decades, remarkable advances have been made in diagnosing CNS tumours in children and adolescents through imaging with increasingly sophisticated MRI, giving very detailed anatomical and other tumour characteristics. These improvements in imaging lead to more precise preoperative planning of tumour surgery. In parallel, there have been major advances in neurosurgery such as neuro-navigation, stereotactic surgery and intra-operative imaging (ultrasound and MRI) together with improvements in peri-operative supportive care.

Importantly, the examination of tumour tissue obtained by biopsy or resection became more sophisticated. It has moved from a morphology-based approach to an integrated diagnosis using different immunohistochemical markers, genetic and epigenetic features. This resulted in further sub-categorization of the tumour types and is reflected in the most recent version of the WHO classification of tumours of the central nervous system (4).

In addition to advances in diagnostic approaches and neurosurgery, great progress has also been made in radiotherapy. Efforts have been made to reduce radiation doses, to reduce radiation fields or to avoid irradiation completely. New radiotherapy techniques have been adopted including IMRT, Tomotherapy and Proton Beam Therapy.

The treatment of CNS tumours in children and adolescents requires a multi-disciplinary approach with early and ongoing communication between all involved specialty teams. The disciplines include paediatric (neuro)oncologists, neurosurgeons, neuroradiologists, radiotherapists, neuropathologists, neuropaediatricians, neuro-ophthalmologists, endocrinologists, rehabilitation teams and many more.

As a result of improvement in diagnosing and treating CNS tumours, the number of long-term survivors is increasing. In parallel, the issue of late effects has been clearly recognised. The awareness of these late effects influences up-front treatment to an increasing extent, but also long-term follow-up care after completion of treatment.

Disciplines needed in the treatment of children and adolescents diagnosed with a CNS tumour are reflected in separate chapters within this guideline as well as in the additional documents for specific CNS tumour entities. The link to the CNS tumours-specific documents can be found on the ERN PaedCan homepage (<https://paedcan.ern-net.eu/the-escp-project/>).

## 2. Epidemiology

Tumours of the central nervous system account for one quarter of all neoplasms in children and adolescents up to the age of 18 years in high-income countries. They represent the most common group of solid tumours. However, the incidence rates of CNS tumours differ between European countries (5). These differences might arise due to the data sources used to define the incidence, the diagnostic possibilities or as true differences. Not all European countries have (childhood) cancer registries and if a registry exists, the registration process and completeness of the registries may differ (6). In addition, limited access to diagnostic possibilities might lead to underdiagnosis in some countries and variabilities in outcome (7).

## 3. Classification of tumours of the central nervous system

The exact histopathological and molecular biological classification of CNS tumours in terms of tumour type and grade is essential to make treatment decisions and to treat patients on respective treatment protocols or to include in clinical trials. Tumour tissue collected through biopsy or surgery is processed by standardised conventional histological, immunohistochemical, and molecular-pathological procedures and classified according to the current WHO classification of CNS tumours (4). Historically, the WHO categories have covered histological entities based on light microscopy with a focus on a “scale of malignancy” giving an estimation on biological behaviour and the natural clinical course of the disease. This classification system is updated at regular intervals and is beginning to include tumour entities and their subtypes based on molecular characterization. The most recent version is from 2021 and includes major changes in terms of molecular diagnostic methods at diagnosis (4). This resulted in different and new approaches in the nomenclature and grading of CNS tumours. New tumour types and subtypes have been introduced, some purely based on novel diagnostic technologies (e.g. DNA methylation profiling).

This guideline covers the following types of CNS tumours in separate sections:

- Low grade glioma (LGG)
- High-grade glioma (HGG)
- Ependymoma
- Choroid plexus tumours
- Medulloblastoma
- Atypical teratoid rhabdoid tumours (ATRT)
- CNS Germ cell tumours
- Craniopharyngioma
- Rare CNS embryonal and sarcomatous tumours

## 4. Aetiology and risk factors

Most CNS tumours in children and adolescents develop sporadically through random mutations or epigenetic changes. Exceptions are tumours induced by irradiation and genetic predisposition. Children and adolescents exposed to irradiation, e.g. cranial radiotherapy for the treatment of acute lymphoblastic leukaemia, have a higher risk of developing second tumours such as malignant glioma or meningioma. Cancer predisposition syndromes associated with tumours of the CNS are listed in Table 1.

**Table 1:** Cancer predisposition syndromes associated with tumours of the Central Nervous System (list not exhaustive and focusing on CNS tumours; krebs-praedisposition.de/en)

<b>Familial tumour predisposition syndromes</b>	<b>Mutation</b>	<b>CNS tumours</b>
Li-Fraumeni	TP53 (17p13)	Medulloblastoma, Choroid Plexus Tumours, Glioblastoma
MEN type 1	MEN1 (11q13)	Hypophyseal adenoma
Turcot I	MLH1 (3p21), PMS2 (7p22), MSH6 (2p16)	Glioblastoma (all in Lynch syndrome)
Turcot II	APC (5q21)	Medulloblastoma (all in familial adenomatous polyposis)
Rhabdoid tumour predisposition syndrome	SMARCB1 (22q11.2)	ATRT, extracranial rhabdoid tumours, CPT, schwannoma, meningioma
DICER 1	DICER1 (14q32)	Pituitary blastoma, pineoblastoma, primary DICER1-associated CNS sarcomas and ETMR-like infantile cerebellar embryonal tumour
<b>Phakomatosis</b>		
Neurofibromatosis type 1	NF1 (17q11)	Optic pathway glioma, other low grade glioma
Neurofibromatosis type 2	NF2 (22q12)	Bilateral acoustic schwannoma, neurofibroma, meningioma, astrocytoma, peripheral schwannoma, spinal ependymoma, glial hamartoma
Von Hippel Lindau	VHL (3p25)	Cerebral and spinal hemangioblastoma
Tuberous Sclerosis	TSC1 (9q34), TSC2 (16p13)	SEGA, subependymal hamartoma, cortical tubera
Gorlin Goltz	PTCH1 (9q22), SUFU (10q24)	Medulloblastoma
Cowden syndrome	PTEN (10q23)	Dysplastic cerebellar gangliocytoma

## 5. Clinical presentation

The clinical presentation and symptoms of tumours of the CNS depend on their location, the patients' age and the "aggressiveness" of the tumour (3, 8). Whereas high-grade CNS tumours usually have a symptom duration of only of a few days to weeks, the specific symptoms of slow-

growing low-grade tumours are often misdiagnosed for a long time and the diagnosis can be delayed up to several years (9).

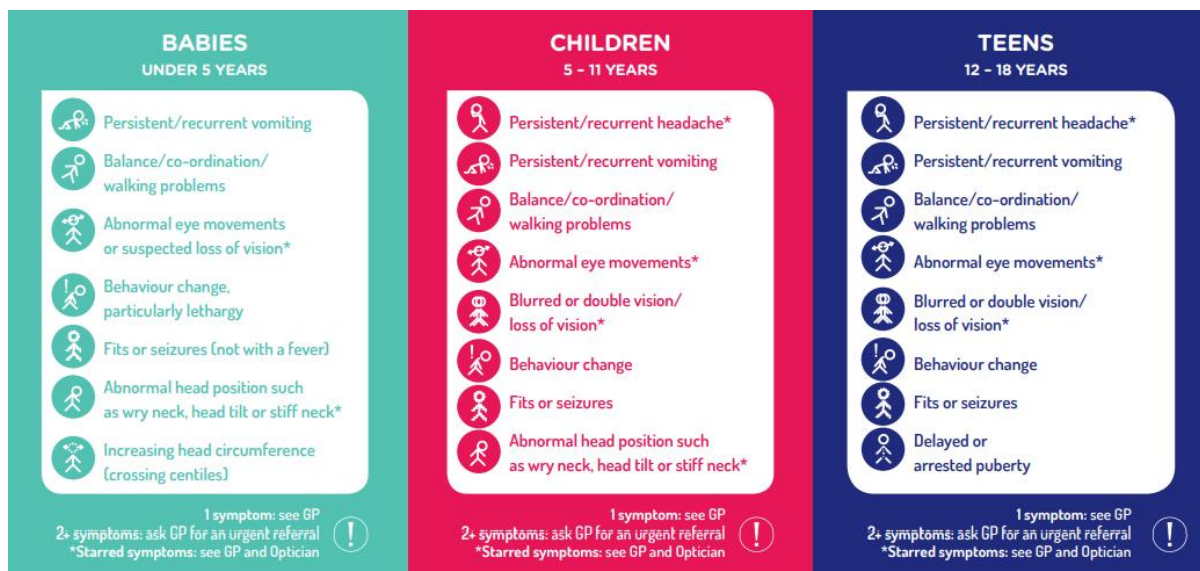
CNS tumours may present in with numerous signs and symptoms. Up to one half present with raised intracranial pressure due to obstruction of CSF flow most commonly in tumours of the posterior fossa. This is manifest as headaches and vomiting (typically but not always early morning), changes in character, concentration disorders, inappetence and food refusal, weight loss up to anorexia, rapid fatigability, lethargy and increased need for sleep (3, 10). Young children may develop increasing head circumference before fusion of the cranial sutures. Other symptomatology and signs depend on the tumour location and may result from compression or infiltration of brain and spine structures, examples of which are given in Table 2 (not an exhaustive list).

**Table 2:** Clinical symptoms of Central Nervous System tumours depending on its location

Location	Symptom
Brain stem / pons	Cranial nerve palsy (caudal nerves), contralateral spastic paresis
Cerebellum	Crooked head position, ataxia, nystagmus, intention tremor, dysdiadachokinesis, dysmetria
Suprasellar region	Visual impairment, impaired visual fields, nystagmus
Pineal region	Parinaud syndrome
Hypophyseal / hypothalamic region	Diencephalic syndrome with eating disorder and disturbed sleep-awake-rhythm, endocrinopathy (short stature, hypothyroidism, diabetes insipidus, abnormal pubertal development, hypocortisolism, SIADH, central salt wasting)
Hemispheres	Seizures, hemiparesis, hemiplegia, hyperaesthesia, visual impairment (visual pathway), aphasia, memory problems
Spinal	Scoliosis, signs of paraplegia (sensory, motor), ataxia, pyramidal signs, radicular pain, impaired function of bladder and intestine

In addition to tumour location, also the patients' age is an important factor and must be considered. Figure 1 summarizes red flags of clinical symptoms in infants/ preschool children and school children/ adolescents.





**Figure 1:** Red flags in infants, pre-school children and teens (<https://www.headsmart.org.uk/>)

## 6. Emergency situations

### Raised intracranial pressure

Possible clinical symptoms of raised intracranial pressure (ICP) include vomiting, headache, bradycardia, hypoventilation, altered level of consciousness, irritability, seizures, focal neurological deficits and (not mandatory) papilloedema. In these situations imaging of the head is urgently needed. The most common causes for raised ICP in children are infratentorial tumours compressing the fourth ventricle and preventing cerebrospinal fluid (CSF) from regular circulation. The treatment approach depends on the underlying cause and operability of the tumour. Circulation of CSF may be re-established through tumour resection, by way of CSF drainage either through internal or external drain or by way of endoscopic 3<sup>rd</sup> ventriculostomy. In addition to surgical approaches raised ICP can additionally be treated by steroids and mannitol.

### Spinal cord compression and cauda equina syndrome

Spinal cord compression (SCC) or cauda equina syndrome (CES) can be the initial symptom of a spinal tumour but can also develop during treatment. New metastasis or treatment complications e.g. bleeding after lumbar puncture, can cause SCC or CES during treatment. Early clinical symptoms of both syndromes may include back pain, urinary incontinence or retention, constipation or faecal incontinence. Motor weakness or paralysis and sensory impairment / loss are late symptoms of SCC (11). Neurosurgery should directly be contacted in case of a new intraspinal mass. High-dose steroids can improve symptoms by reducing the swelling. If debulking surgery is not feasible radiotherapy is an option and should be initiated as soon as possible. Even if the mass can be quickly removed, recover of neurological symptoms may take some time. Good pain control is needed together with treatment of urinary retention or incontinence, constipation and early initiation of physiotherapy.

## 7. Diagnostic modalities and staging – a short overview

Imaging is fundamental to patient care. Magnetic resonance imaging (MRI) has revolutionized CNS tumour management and is mandatory in the diagnosis of CNS tumours. The exception is a very small number of patients that require very urgent surgery following computer tomography (CT) scan.

MRI allows visualization of far greater anatomical information than CT and advances in MRI (e.g. diffusion, perfusion and MR spectroscopy) can provide additional information at diagnosis and in presurgical planning (e.g. tractography). During surgery, MR-linked neuro-navigation is a standard of operative care and intraoperative MRI is increasingly used to aid complete resection and avoid unnecessary re-resection. Following surgery, MRI is the standard technique in determining the extent of surgical resection with CT scan being no longer acceptable for this purpose.

Tumour staging with MRI of the whole head and spine is indicated at diagnosis in all tumour types (with the possible exception of craniopharyngioma). In selected cases (e.g. suspicion of craniopharyngioma) additional CT is needed to show calcification.

SIOPE has established MRI guidelines for imaging patients with CNS tumours (12). Further information on imaging can be found in the respective chapter of this document. Information on tumour staging approaches is outlined in the tumour-specific parts of this guideline.

## 8. Treatment modalities – a short overview

The efficacy of all treatment modalities needs to be balanced against the associated acute and long-term toxicities, including neuropsychological deficits (13). Surgery is an integral part in the treatment of all CNS tumours, but the extent of surgery depends on tumour location and its relation to vital structures. The goal and extent of surgery can therefore be classified into 3 levels:

1. obtaining tissue through biopsy to establish the diagnosis and to identify possible therapeutic targets
2. removal of a tumour mass or a cerebrospinal fluid accumulation to reduce pressure (intracranial or to the spinal cord) to eliminate a vital threat and to improve the quality of life - even if the tumour is not completely resectable
3. gross-total resection

Even though the prognosis of many children with CNS tumours depends on the success of the extent of surgery, in most cases the aim is to remove as much as possible without increasing morbidity and mortality. The prognostic relevance of the extent of resection is higher in CNS tumour entities for which less postoperative treatment options are available, while more radio- or chemosensitive entities may be curable even with limited resections. In addition, limited surgeries with second look procedures after neoadjuvant chemotherapy have proven beneficial in specific cases, for example in infants with large tumours in critical locations. Progress in neurosurgical techniques and pre-operative imaging has significantly increased the operability of CNS tumours.

Further information on neurosurgery can be found in the respective chapter of this document.

For chemotherapy, the agents used, and their combinations depend on the CNS tumour entity. For most entities, chemotherapy mainly consists of conventional chemotherapeutic agents. The blood-brain-barrier normally reduces the concentration of chemotherapeutic agents in the brain (14).

However, the expression and function of these transporter proteins is impaired at the ‘tumour-blood barrier’, as does the permeability of the endothelium and some systemically applied chemotherapeutic agents can therefore reach the tumour. For tumours that spread via the leptomeninges, intrathecal or intraventricular therapy (e.g. via an Ommaya reservoir) may be indicated.

The use of myeloablative chemotherapy with stem cell rescue may theoretically improve exposure of tumour to cytotoxic drugs and is used as a standard in some protocols and being investigated in ongoing clinical trials.

Our ever-increasing knowledge of tumour biology over recent years has led to the development of new agents targeting tumour specific receptors and pathways e.g. mTOR inhibitors in the treatment of SEGA and BRAF and MEK inhibitors in low grade glioma. The combinations of chemotherapeutics and targeted therapies used in each tumour group can be found in the respective section.

The third treatment modality for CNS tumours is radiotherapy. Even though its toxicity and potential to cause late effects is well known, radiotherapy can still not be omitted in the treatment of certain CNS tumour entities. The total dose of irradiation and its fractioning, planning target volumes, and irradiation technique are largely determined by the tumour type, the size of the tumour, the sensitivity of the tumour tissue to radiation, and the maturation state of the CNS. However, not only the radiation tolerance of the brain must be considered, but also the tolerance of the adjacent risk structures, especially the lens, the optic nerve, the optic chiasma, the brain stem, and the cervical medulla. International quality standards have been established to ensure correct, reproducible and high-quality irradiation. Further information on radiotherapy can be found in the respective chapter of this document.

Treatment approaches in case of progression or relapse of CNS tumours are very individual and not part of this guideline. However, for these occasions the respective contact persons for each CNS tumour entity can be contacted.

## 9. Follow-up care – a short overview

As a result of improvement in diagnosing and treating CNS tumours, the number of long-term survivors is increasing. Many of these long-term survivors suffer from significant and sometimes devastating late-effects. These may result from conditions that persist since diagnosis and do not resolve completely (e.g. visual impairment) or newly developing conditions due to the treatment (e.g. endocrine late effects after radiotherapy or hearing impairment after platinum agents). Early recognition and treatment (if possible) are crucial to prevent or mitigate late effects. Therefore, risk-adapted screening is recommended. Different long-term follow-up care guidelines help the clinicians to perform these risk-adapted screenings. Long-term follow-up care finally aims to improve quality of survival (QoS) of children and adolescents treated for a CNS tumour, but also to gain knowledge which helps to further improve front-line treatment. Further information on follow-up care and QoS can be found in the respective chapter of this document.

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## Discipline Groups

### Imaging Working Group

## STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# IMAGING WORKING GROUP

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### 1. Background

Imaging evaluation of primary tumours of the central nervous system (CNS) and possible CNS dissemination is core to their management in children. Given the infrequency of childhood CNS tumours, multicentre studies provide the best scientific evidence for their management. Standardisation of imaging acquisition therefore is an essential pre-requisite across all centres who participate in paediatric CNS tumour studies. Standardisation of imaging not only facilitates comparisons of scans for an individual subject across various time points (pre-operative, post-operative and subsequent follow-up imaging) but also aids comparability across multiple centres by the central study coordinators and designated radiologists.

The European Society for Paediatric Oncology (SIOPE) Brain Tumour Imaging Working Group has developed an imaging protocol based on consensus and evidence from earlier clinical trials (Avula S et al, European Society for Paediatric Oncology (SIOPE) MRI guidelines for imaging patients with central nervous system tumours. *Childs Nerv Syst.* 2021 Aug;37(8):2497–508). The members of the group consist of neuroradiologists, imaging scientists and clinicians with an interest in brain tumour imaging. The protocol has evolved over the past decade and is being updated in response to changes in imaging practices and the specific needs of the various clinical trials. The protocol is based on consensus among the group members either obtained in person and/or using e-mail surveys. This protocol was ratified by the group in December 2019.

The imaging protocol consists of sequences that are specific for the magnetic field strength (1.5 and 3 Tesla). Advances in MR technology have contributed to vast improvements in quality of imaging on 1.5T and 3T MR scanners. Despite these advances there is a huge variation in the capability of the

scanner hardware and software across various centres. The rationale for the sequences and parameters recommended is based on practicality, published evidence where available and the reliability of tumour assessment. The protocol has been tailored to consist of the minimal essential/mandatory sequences in order to allow effective basic tumour evaluation whilst allowing for the use of additional sequences including multi-modal advanced MRI.

We have provided recommendations on advanced imaging methods including MR spectroscopy (MRS), diffusion tensor imaging (DTI) and perfusion imaging. The advanced imaging recommendations are based on studies performed by the SIOPE group members and are aimed as a guideline and are currently not mandatory.

## 2. Institutional requirements

- 1.5 or 3T MRI scanners
- Trained imaging specialists (Radiologist/Neuroradiologist)
- Trained specialists able to provide imaging under sedation/anaesthesia if required

## 3. Essential quality parameters

- Designated radiologists/neuroradiologists for childhood brain tumours must be available for all patients

## 4. Contact Persons

Shivaram Avula (UK) Shivaram.Avula@alderhey.nhs.uk

Giovanni Morana (Italy) giovanni.morana@unito.it

## 5. Summary

<b>Must have</b>
All imaging studies must be performed according to the SIOPE-BTG neuroimaging protocol
Pre-OP MRI plus contrast must be available for all patients
Pre-OP 3D imaging acquisition should be done for surgery and RT purposes
Early post-OP MRI plus contrast must be available for all patients within 72h post-OP even in ventilated patients
Scans must be reported according to protocol guidelines by designated specialists with experience in paediatric neuroimaging
<b>Desirable</b>
Baseline spine MRI is recommended before surgical resection or biopsy, or 10-14 days after surgical resection or biopsy (to minimise postsurgical blood products and dural enhancement that might confound imaging interpretation).
During the study, at each examination, the same Tesla-strength is recommended

During the study, at each examination, comparable sequences on consecutive scans are recommended
If post-OP imaging shows extensive post-surgical changes that decrease the ability to assess residual disease, or that mimic tumour infiltration, a second follow-up MRI is recommended within 2-3 weeks after surgery.
<b>Don't do</b>
Do not use CT for standard brain imaging in any childhood cancer tumour

## 6. Appendix: Imaging protocol for patients in European SIOP Brain Tumour Studies

### 6.1 MRI protocol

#### Brain imaging

Essential sequences on 1.5T

Sequence	Technique	Plane
T1w	2D SE, TSE	Axial (along AC-PC axis)
T2w	2D SE, TSE	Axial
FLAIR	2D TSE	Axial or Coronal
T1w + Contrast	2D SE, TSE	Axial, Coronal and Sagittal
DWI with ADC	2D EPI	Axial

Essential sequences on 3.0T

Sequence	Technique	Plane
T1w	3D gradient echo	Axial or Sagittal
T2w	2D SE, TSE	Axial
FLAIR	2D TSE	Axial or Coronal
T1w + Contrast	2D SE, TSE	Axial
T1w + Contrast	3D gradient echo	Axial or Sagittal
DWI with ADC	2D EPI	Axial

3D gradient echo (GRE) sequence is the inversion recovery GRE sequence (IR TFE/FFE) 2D sequences: Slice thickness  $\leq 4$ mm and slice gap  $\leq 1$ mm (10 % of slice thickness is desirable). For very small lesions consider a slice thickness of 3mm or less.

3D sequence: Slice thickness  $\leq 1\text{mm}$  with no slice gap. An isotropic voxel resolution of  $1\text{mm} \times 1\text{mm} \times 1\text{mm}$  is desirable depending on scanner capability.

Resolution parameters: Field of view – 230 mm (range 220-250 mm depending on headsize); Matrix size - minimum 256 (512 is desirable for better resolution; 96- 128 for EPI sequences).

Some centres perform T1 FLAIR, T1 inversion recovery (IR) or T1 gradient echo instead of T1 SE sequence due to its suboptimal quality on 3.0T scanners. This is acceptable as long as the diagnostic quality of the imaging is not compromised and the same sequence is used consistently for the individual patient.

There are increasing concerns of long-term gadolinium deposition and the use of macrocyclic gadolinium-based contrast agents is recommended.

Sequences on 1.5T that may provide additional information:

Sequence	Technique	Plane
T1w	3D gradient echo	Axial or sagittal
FLAIR	3D gradient echo*	Axial or sagittal
Heavily weighted T2w	2D or 3D bFFE**	Axial or coronal or sagittal
Advanced MRI	DTI, perfusion & spectroscopy***	

Slice thickness for 3D sequences  $\leq 1\text{mm}$  with no slice gap. An isotropic voxel resolution of  $1\text{mm} \times 1\text{mm} \times 1\text{mm}$  is desirable depending on scanner capability.

\*3D FLAIR can be used instead of 2D FLAIR but not if 2D sequences have been used for the same individual on previous occasions.

\*\* The heavily weighted T2w sequence localized to a region of interest is useful in assessment of lesions (in particular poorly/non enhancing) within the extra axial space or along the parenchymal surface.

\*\*\* Please refer to section 6.6

## 6.2 Tumour measurement

As volumetric measurement tools are not available at all centres, the tumour volume is calculated using the (ellipsoid volume) formula  $A \times B \times C \times \frac{1}{2}$  where A, B and C are the maximum dimensions in the standard antero-posterior, transverse and cranio-caudal planes.

3D-volumetric calculations may be performed additionally. These volume calculations are the basis for follow-up evaluation and every effort should be made to ensure the highest possible accuracy.

It is desirable to save the measurements as annotated images if possible.

If there are multiple lesions, the sum of the 5 largest lesions must be obtained. This will need further validation and may change in the future.

Please note that the measurement guidelines may be altered in some trials where 2D measurements in the axial plane or different measurement methods for the 3 dimensions may be employed.



### 6.3 Early postoperative imaging

Optimal evaluation is made within the first 48 hours following surgery. As non-specific intracranial enhancement is often seen after 3 days following surgery the postoperative MRI must be obtained within this time. However, even within this time false positive nodular enhancement can be seen with haemostatic materials and following electrocoagulation. It is therefore prudent to carefully evaluate the pre- and post-contrast T1-weighted images in combination with the signal intensities on the T2-weighted and FLAIR sequences.

With increasing use of intraoperative MRI imaging the validity of the final intraoperative scan as baseline scan has been debated. Based on a single centre study and consensus it has been agreed that the final intraoperative MRI scan is acceptable as a base line provided it is from a 3.0T scanner (as it has been only validated on 3.0T), the SIOPE brain tumour protocol is followed, supervised by radiologist experienced in children's brain tumours and reported in consensus with the operating neurosurgeon. The preoperative and final intraoperative sequences must be comparable. On occasions where there has been further resection following the intraoperative scan, this will not qualify as a final intraoperative scan. A further scan after the extended resection with the full SIOPE protocol should be performed. The final decision to use intraoperative MRI scans rests with the national reference radiologist/radiology panel as the practices vary in different countries.

Comparability with the pre-operative MRI is essential for the detection of residual tumour. The size of a possible residuum has to be measured in all three planes. If the residuum is best visible on T2-weighted images a second plane incorporating a T2-weighted or FLAIR sequence must be employed.

A residuum is considered to be any area of persisting pathological signal and/or enhancement that is comparable with the appearance of the pre-operative tumour. DWI is helpful to demonstrate any local surgical or ischaemic injury, which may influence enhancement patterns and tumour evaluation on subsequent examinations.

For the evaluation of residual tumour seen on imaging, the surgical report is often valuable and should be available.

Sequences for cranial imaging: Please refer to section 6.1.

### 6.4 Follow-up MRI

Timing for follow-up MRIs should be planned according to the individual trial protocol. Please refer to section 6.2 regarding tumour measurements.

If the tumour enhances uniformly, the post-contrast T1 should be used for the measurement of the diameters. For heterogeneously, poorly or non-enhancing tumours the dimensions on T2/FLAIR or PD and pre-contrast T1 can be relevant. In some instances, therapy related reduction of enhancement disproportionate to the change in tumour volume may be encountered. The best sequence cannot be predicted at the outset in these tumours. In these circumstances, it is useful to choose the initial sequence on which the tumour was measured or change the sequence (e.g. due to a change in contrast behaviour) and compare the tumour dimensions with the same sequence on the previous staging MRI to assess response.

In instances where the MRI findings are equivocal for tumour progression/resolution (pseudo progression/pseudo response), an early follow up scan(s) may be required to evaluate for true progression/response. When true progression is confirmed, the initial scan which showed the

abnormality should be considered as time of progression. In the paediatric neuro-oncology setting, pseudo response mainly refers to reduction of enhancement following anti-angiogenic therapy and the response assessment in this setting is based on measurement on the T2 and FLAIR sequences.

### 6.5 Definition of residual tumour

The evaluation of early postoperative imaging for residual tumour can pose challenges. As very subtle residual tumours may not be visible on imaging the presence/grading of residual tumour should be made in consensus with the neurosurgical report.

Residual tumour will be defined as follows (applies only for early postoperative MRI):

- R0: No residual tumour on post-operative MRI in accordance with the neurosurgical report
- R1: No residual tumour on MRI but description of a small tumour residuum by the neurosurgeon or if the neurosurgical result is unknown.
- R2: Small residual tumour on MRI with the maximum diameter < 5mm in any plane or thin residual tumour covering the surgical margins like a ring or extending beyond the surgical margins.
- R3: Residual tumour measurable and  $\geq 5$ mm in all 3 planes.
- R4: Size of the residual tumour unchanged or only minimally changed from the pre-operative status (e.g. after biopsy).

A thin line of enhancement can be physiological or reactive on early post-operative MRI and correlation with the non-contrast sequences for evidence of haemorrhage/tissue injury and detailed comparison with pre-operative MRI may be required before considering the presence of residual tumour. If imaging is inadequate or the appearance of the surgical cavity is difficult to interpret the term "unclear" should be used. In some cases, early follow up imaging in 2-4 weeks with additional sequences, better resolution parameters and additional planes may be necessary for further clarification.

### 6.6 Definitions for neuroradiological response evaluation

#### 6.6.1 Measurable tumours

A measurable lesion is that which can be reliably followed-up allowing for the slight variations of the scan planes. The definition of measurable lesion is based on the historic practice of using 2D measurements on predominantly 2D imaging and mainly based on the RANO criteria. The current definition is based on the assumption that 2D sequences are pre-dominantly used in a number of centres. This may change in the future when the quality of volumetric imaging is more reliable for tumour measurement and performed in all centres.

#### **Measurable lesion**

Lesion visible in the 3 standard planes with a diameter of  $\geq 10$ mm in each plane. This is provided that the 2D image slice thickness + gap is  $\leq 5$ mm. If the slice thickness + gap is  $>5$ mm, then the maximum diameter should be  $\geq 2$  times the slice thickness + gap.

Non measurable lesion also includes lesions with poorly defined margins.

When there are multiple lesions, sum of the volumes of the 5 largest lesions are used.

### 6.6.2 Response criteria

- CR (complete response): no evidence of residual or recurrent tumour or meningeal dissemination.
- PR (partial response): Reduction of tumour volume  $\geq 50\%$  compared to the previous staging MRI.  
(The extent of meningeal dissemination can only be estimated and PR means considerable reduction of meningeal disease)
- SD (stable disease): Tumour volume between  $\leq 50\%$  decrease in size and  $\leq 25\%$  increase in size compared to the previous staging MRI (no significant change of meningeal dissemination)  
*NOTE: MR (minor response); This criterion is used in some trials for 50% to 25% decrease in tumour volume.*
- PD (progressive disease): increase of tumour volume of  $\geq 25\%$  or new lesion.

As highlighted in section 6.4, for measurable lesions, the sequence of choice for measurement cannot be predicted in advance and may require comparison of repeat measurement on the most reliable sequence on the current scan with a similar sequence on the prior/baseline scan for accurate response assessment.

Radiotherapy as a primary treatment may be associated with radiation induced reaction if there is measurable tumour growth after treatment. The combination with chemotherapy and radiotherapy may lead to temporary effects on imaging (enlarging contrast enhancing lesion, increased FLAIR/T2 abnormality) in up to 30-40% of cases, which are collectively known as pseudo-progression and may be mistaken for early true progression. If new enhancement or increase in residual tumour size occurs during the first 12 weeks after the end of irradiation and within the irradiated field, do not consider this a true progression unless otherwise confirmed (either by histology or on a short interval follow up scan – after at least 4-6 weeks). If there is confirmed growth on the follow-up MRI, then the date of progression is ascribed to the first time point when tumour growth was documented.

### 6.7 Multi-Modal Advanced MRI

There is increasing experience in the use of a number of advanced MRI techniques and these may add useful information to the conventional MRI. The individual techniques should be thought of as complimentary and as such a multi-modal approach is most appropriate.

We have developed and tested protocols which seek to provide a balance between quality of data and length of acquisition and at the same time give sufficient flexibility that they can be implemented on most MR scanners. MR spectroscopy (MRS) and Diffusion Tensor Imaging (DTI) methods are well established throughout the age range and the protocols for these are fairly well agreed. However, contrast injection perfusion imaging is less well established in children. We recommend Dynamic Susceptibility Contrast (DSC) – MRI at present, although there are still some areas of active development in the protocol particularly related to the contrast injection (see section below). The current protocols for these three methods are given in the parameter table below. We do recognise

that there are centres that will use more advanced protocols and would encourage anyone who is doing this or considering it to contact the SIOPE – Brain Imaging Group so that we can share experiences and further develop protocols. Examples are: 1) Arterial Spin Labelling for measuring perfusion without injecting contrast. Whilst this has generated considerable interest, we feel that further experience is required in applying this technique to children’s brain tumours, in particular its relationship with DSC-MRI, prior to recommending an international protocol. 2) Multi-b value DWI and the IVIM model for measuring perfusion without injecting contrast. 3) MRS imaging to investigate the heterogeneity of tumours. 4) Functional brain connectivity via a steady state fMRI protocol especially in diencephalic syndrome. We are keen to carry out limited centre studies of such techniques.

**Data Saving**

It is important that data is saved in a way that it can be analysed in a quantitative manner. DICOM headers should not be altered in a manner which renders the data uninterpretable, which can happen when images are sent to some PACS systems or anonymised. Please seek advice if you are unsure.

**Contrast Injection**

For DSC-MRI, contrast (usually Gd-DTPA or Gd-DOTA) injection should be via a pump injector. Most centres will not use these via a central venous line and so injection will need to be via an intravenous cannula placed prior to the scan. In order to reduce the T1 effects we recommend giving a pre-bolus injection which is half of the full amount (i.e. 0.05mmol/Kg Gd) at least 2 minutes prior to the main injection which should also be 0.05mmol/Kg Gd, so that the total dose is 0.1mmol/Kg Gd. The rate of injection is standardised at 3ml/sec. This protocol has been used successfully in infants although there can be problems with the pump injector in very small ones, the protocol is subject to further development particularly in this age group.

Multimodal Protocol											
22/ 09/ 2016 Version 2.3 SIOPE Brain Imaging Group											
Core Multimodal Protocol (Brain)											
Modality	MRS			Diffusion				Perfusion			
Description	SVS (short -TE)			D i				DSC- T1.			
Sequence	PRESS			EPI				GRE			
	Param	Value	Value	Param	Value	Param	Value	Param	Value	Param	Value
Fixed	Field	1.5 T	3 T	Field	1.5T	Field	3T	Field	1.5T	Field	3T
	TR (ms)	1500	2000	FOV (mm )	240	FOV (mm )	211	FOV (mm )	240x240x95	FOV (mm )	240x240x101
	Vector length	2048	2048	Aeq matrix	96x96	Aeq matrix	96x96	Aeq matrix	96x96x19	Aeq matrix	96x96x30
	TE (ms)	30		Resol ution	2.5i sotropie	Resol ution (m	2.2 i sot rop ie	Ori entat ion	axi al	Ori entat ion	axi al
				Coverage	whol e brai n	Coverage	whol e brai n	Sense	2	Sense	2
			b factor	1000	b factor	1000	Temp resol	1.49x60	Temp resol	1.86x60	
Variable	TE (ms)		30 - 35	TR (ms)	min	TR (ms)	min	Sequenee	FE-EPI	Sequenee	FE-EPI
	VOI (ml)	3.4 - 8 (to fit tumour)	2.2 - 8 (10 fit tumour)	TE (ms)	min (fi x BW?)	TE (ms)	min (fi x BW?)	TE (ms)	40m s	TE(ms)	40m s
	BW (kHz)	2 or 2.5 kHz	2 or 2.5 kHz	Grad dirs	15+	Grad dirs	15+	TR (ms)	min	TR(ms)	min
	Aves (WS)	128 - 256	64 - 196	NSA (b=0)	1(3)	NSA (b=0)	1 (3)	fti p angl e	20 d eg	fti p angl e	20 d eg
	Aves (W)	8 - 16	8 - 16	Speed-up	x2	Speed-up	x2	Inj ecti on rat e	3m l / s.e	Inj ecti on ra	3m l / s.e
				Parti al Fouri er		Parti al Fouri er		Gd-DTPA	0.1mmo l / Kg 50% as pre bolu s	Gd -D TPA	0.1mmo l / Kg 50% as pre bolu s
Time (mins)	Set -up		3					2		2	
	Acq		3.4 - 6.6		2.3 - 6.7			2		2	
	Total		6.4 - 9.6		5.3 - 9.7		5		3		4
---	<b>Total</b>										minimum at 3T - 8.3 min s + DSC

### 6.8 PET Imaging

There is growing interest and evidence in the use of PET imaging to assess brain tumours in children at diagnosis and /or surveillance. The following section aims to serve as a guidance for the usage of PET in paediatric brain tumours. PET imaging can supplement MRI using an amino acid tracer as O-(2-[<sup>18</sup>F]fluoroethyl-L-tyrosine (FET), L-[methyl- <sup>14</sup>C]methionine (MET), or 3,4-dihydroxy-6-[<sup>18</sup>F]fluoro-L-phenylamine (FDOPA). 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose (FDG) is a less useful tracer due to the high uptake in normal grey matter and will not be mentioned further. Four hours of fasting is recommended before tracer injection to ensure stable metabolic conditions. The use of a head holder is recommended to avoid motion artifacts.

Tracer	Dose MBq/kg	Examples of Scan times	Background region (healthy tissue)	Tumour-to background ratio	Physiological uptake
FET	3	20-40 min p.i. or 0-40 min p.i. (dynamic)	Cortical non-affected GM and WM	>1.6 (or >1.8)	Vascular structures, cerebellum, skin, basal ganglia, pineal body, venous anomaly
MET	10	10-30 min p.i. / 20-40 min p.i.	Cortical non-affected GM and WM	>1.3	
FDOPA	3	15-45 min p.i.	Contralateral striatum	>1	Basal ganglia, pituitary, skin, pineal body, venous anomaly
			Cortical non-affected GM and WM	>1.6	

p.i.: post injection, GM: grey matter, WM: white matter

Iterative reconstruction should be applied or alternatively filtered back projection. Corrections for attenuation, scatter, randoms, dead time, and decay should be applied. The use of point-spread-function reconstructions may give rise to artefacts and is not recommended. Voxel size < 3mm in all directions and a spatial resolution < 6 mm FWHM is recommended.

PET scans are co-registered to a recent (ideally < 2 weeks) MRI preferentially T1W + contrast or FLAIR. Note that automatic co-registration systems may introduce errors in children.

Integration of information obtained by MRI and PET should be performed by diagnostic imaging specialists in close collaboration of each other in order to offer clinicians a more comprehensive array of data. Tracer uptake is reported as maximal tumour-to-background ratio (TBR<sub>max</sub>) and metabolic active volume. In case of DOPA PET maximal tumour-to-normal striatum ratio (TSR<sub>max</sub>) should also be reported. Increased uptake can be seen in inflammatory lesions and after epileptic seizures.

For dynamic FET: an analysis with extraction of tumour time-activity-curves is possible and may be compared to that of healthy brain. The classification into increasing, decreasing or plateau may support the differentiation between inflammatory changes and tumour.

## Neurosurgery Group

### STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# NEUROSURGERY GROUP

This summary has been developed by Dr Kristian Aquilina<sup>1</sup>, Prof Ulrich-Wilhelm Thomale<sup>2</sup>

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## 1. Background and rationale

Brain tumours represent approximately 25% of paediatric cancers and account for the most frequent solid tumours during childhood and adolescence. They are clinically and biologically diverse entities and constitute the highest mortality and morbidity of all paediatric cancers. There is considerable variation in care and survival across Europe (1).

Neurosurgery is an integral component of the multidisciplinary management of these tumours, and may include treatment of associated hydrocephalus, complete or partial resection of the primary or recurrent tumour, biopsy to determine medical management or the combination of these at different stages. Children with brain tumours often present acutely as an emergency. Paediatric neurosurgical resources, both in terms of surgical expertise and access to institutional equipment and clinical care, are crucial to a good outcome both in the emergency and non-acute situations.

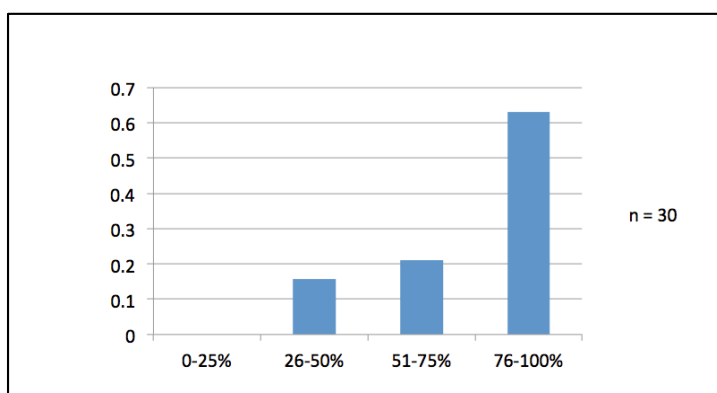
The provision of paediatric neuro-oncology care in general, and neurosurgical care in particular, is diverse across Europe. The brain tumour group within SIOP has been working with the European Reference Network to reduce this variation and enhance the appreciation of the need for a common standard of care in European countries. Several guidelines have been developed for the broad categories of brain tumours in children. This part of the document attempts to define paediatric neurosurgical best practice for these conditions.

## 2. Paediatric neurosurgical opinion in Europe

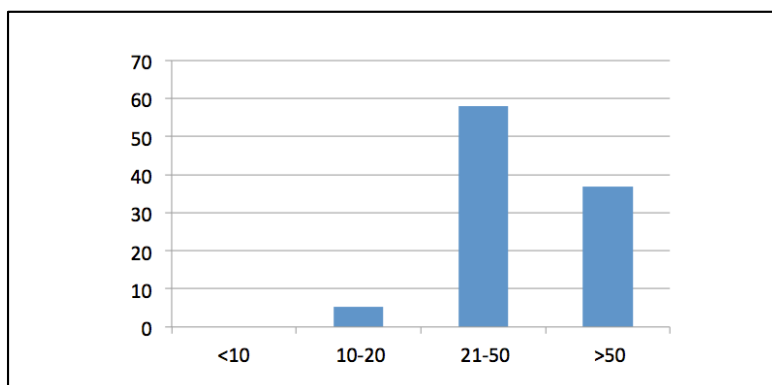
In an effort to provide an overview of views held by paediatric neurosurgeons across Europe on the way brain tumours in children should be managed, an online questionnaire was circulated between October and November 2017 to SIOPE BTG members, SIOPE members and other contacts from the ERN PaedCan database.

55 questions were included with the objective to evaluate the currently available structures and facilities in Europe and to define the potential fields for cooperation, interest for support and collaborative working and advice. There were 388 responders from 44 countries. Subsequently, a questionnaire was sent to paediatric neurosurgeons involved in the SIOP BTG and others attending the ESPN meeting in Bonn in 2018. There were thirty respondents.

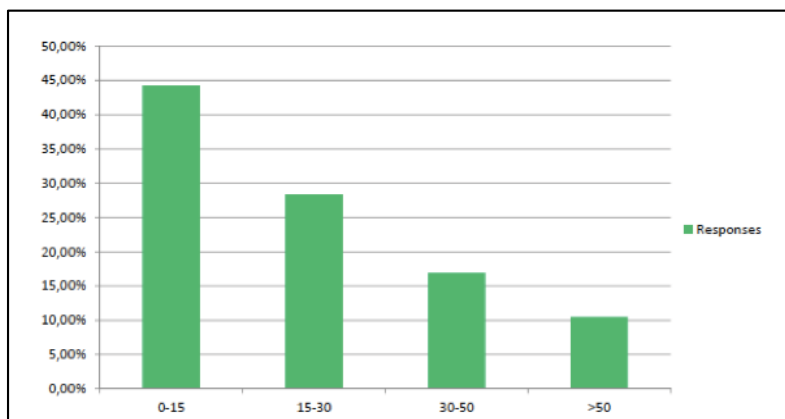
Just over two thirds of respondents stated that paediatric neurosurgical interventions constitute 76 to 100% of their personal practice. None of the respondents reported a proportion of paediatric interventions below 25% of their practice (Figure 1). 38% of respondents work within an institution that deals with over 50 paediatric brain tumour patients per year. The majority of respondents, almost 60%, work in institutions that deal with 21 to 50 cases per year (Figure 2). Almost 45% of respondents see up to 15 new paediatric brain tumours in their centre annually; 10% see more than 50 (Figure 3).



**Figure 1.** Graph showing responses from a cohort of neurosurgeons practicing in Europe to the question ‘What is the proportion of paediatric neurosurgical interventions in your practice?’



**Figure 2.** Graph showing responses from the same cohort to the question ‘How many paediatric brain tumour patients are treated in your neurosurgical institution per year?’



**Figure 3.** Graph showing responses from the same cohort to the question ‘How many newly diagnosed paediatric brain tumours are treated in your centre per year?’

A question on the requirements deemed necessary to perform neurosurgery for paediatric brain tumours was included. Of note, 100% of respondents stated that a multidisciplinary team, paediatric intensive care, and neuroendoscopy and an operating microscope in the operating room, are mandatory (Table 1).

	No	Desirable	Mandatory
<b>MDT</b>			100%
-pediatric neurooncology		5%	95%
-pediatric neuroradiotherapy		26%	74%
-pediatric neurologist	5%	63%	32%
-pediatric neuroradiology		21%	79%
<b>Specialties in same institution</b>			
-neuropathology		26%	74%
-pediatric neurooncology	5%	31%	63%
-pediatric radiotherapy	10%	63%	27%
-pediatric neurology		26%	74%
-pediatric neuroradiology		16%	84%
-pediatric endocrinologist		32%	68%
<b>Infrastructure</b>			
-pediatric IC			100%
-24/7 availability pediatric neurosurgeon	5%	21%	74%
-pediatric anesthesiology		10%	90%
-MRI under anesthesiology		26%	74%
<b>OR equipment</b>			
-microscope			100%
-Ultrasound aspiration		16%	84%
-Intraoperative US		42%	58%
-Intraoperative MRI	16%	79%	5%
-Intraoperative neuromonitoring		26%	74%
-Stereotaxy		21%	79%
-Neuroendoscopy			100%
<b>Registration</b>			
-standardized surgical report		79%	21%
-extend of resection		42%	58%
-complication		63%	36%

**Table 1.** Table showing responses from the same cohort to the question ‘What requirements should be met by a centre to perform neurosurgery for paediatric brain tumours?’

79% reported that a minimum number of paediatric brain tumours treated yearly per unit are a judicious requirement. Opinion, as to the minimum number of paediatric brain tumours that should



be treated yearly per unit varied. 37% of respondents stated thirty or more, and 26% stated at least twenty and a further 26% at least ten. The majority (61%) agreed that it would be helpful to define expert centres to which patients can be referred; 39% stated that consultation by a review panel alone is sufficient. Over 75% of respondents agreed that a review panel or referral centre would be helpful for craniopharyngioma, pineal region tumours, third ventricle tumours, optic pathway – hypothalamic tumours, brainstem tumours and tumours in children under one year of age.

### 3. Paediatric neurosurgical volume, patient numbers and outcomes

The impact of provider caseloads on outcomes in paediatric neurosurgery has never been clear and in general has not led to any major re-organisation of service provision. Literature specifically addressing paediatric brain tumours is scant. The largest study evaluates 4712 admissions for craniotomy for paediatric brain tumour, between 1988 and 2000, in 329 hospitals in the United States, under the care of 480 surgeons. In a multivariate analysis, the mortality rate was significantly lower at high-volume hospitals compared to low-volume hospitals, at an odds ratio of 0.52 for a ten-fold increase in caseload. The mortality rate was 2.3% in the lowest hospital volume quartile ( $\leq 4$  cases/ year) and 1.4% at the highest ( $\geq 21$  cases/ year). Adverse hospital discharge disposition was significantly less likely to be associated with high volume hospitals and surgeons ( $p < 0.001$  and  $p = 0.004$  respectively). The authors noted a move towards centralisation of these services during this 12-year study period, as well as an overall reduction in mortality from 2.7% in the first three years to 1.2% in the last four years (2). This study only address morbidity through adverse discharge disposition and does not evaluate overall oncological outcome.

A second study reviewed 732 children with malignant brain tumours, predominantly medulloblastomas and high-grade gliomas, recruited between 1986 and 1992 (3) . Although most procedures were performed by general neurosurgeons, those performed by paediatric neurosurgeons or members of the ASPN had better outcomes. Designated paediatric neurosurgeons and ASPN members were more likely to resect more than 90% of the tumour than general neurosurgeons. Neurological complications were least likely for ASPN members, at 18%.

### 4. Multidisciplinary set up

#### Components of the multidisciplinary team

Paediatric neuro-oncology is a complex field and paediatric neurosurgeons need to work within an environment that complements their skills. A complete multidisciplinary team typically consists of paediatric neurosurgeons, paediatric neuro-oncologists, neuro-radiologists, radiotherapists, pathologists, paediatric neurologists, endocrinologists, rehabilitation specialists, including physiotherapists and occupational therapists, and social workers. Regular discussion of all the cases at the presentation, diagnosis, post-operative, adjuvant therapy and recurrence phases is imperative. The neurosurgical treatment plan should be devised within the multidisciplinary group. The involvement of spinal surgical expertise is also required in the management of spinal tumours, especially where concerns about actual or potential deformity of the growing spine arise.

These meetings are typically chaired by a clinician and need to be frequent enough to allow timely discussion of all cases. Regular meeting times should be set aside throughout the year to review the function of the team and the meeting. The team should also designate separate sessions to review its outcomes, adverse events and complications.

### Neuroradiology

Safe neurosurgical practice needs accurate imaging of the tumour and its relationships to the surrounding brain. The Brain Tumour Imaging Working Group of the European Society for Paediatric Oncology has published guidelines on the essential imaging requirements pre- and post-operatively (4). These have been developed by consensus among its members and facilitate a consistent approach to image acquisition that optimizes care for the individual child and allows comparison between individual units. Although this group defines the ideal protocol that may only be available in some of the larger institutions, by adopting a pragmatic approach, similar to the North American experience, they also define the most essential components of the protocol that are required for basic patient care (5).

These publications also emphasize the importance of early post-operative imaging; the development of post-operative contrast enhancement even within 72 hours of surgery suggest that the ideal time for post-operative imaging is within the first 48 hours (4). Precise quantification of residual tumour is important within the context of the current algorithms for adjuvant therapy, particularly for ependymoma and medulloblastoma. The use of haemostatic material such as oxidized methylcellulose (Surgicel) causes early post-operative enhancement and should be avoided in paediatric brain tumour surgery.

The indications for surgery are often influenced by response to adjuvant therapy, particularly at recurrence; this requires consistent and accurate imaging to determine the extent of tumour growth. The Response Assessment in Pediatric Neuro-Oncology (RAPNO) group have published recommendations specific to paediatric brain tumours, defining both the requirements for tumour growth and the imaging needed to identify it (6)(7).

The availability of interventional radiology within an institution supports the management of large vascular tumours, particularly in small children and infants. The best example are the choroid plexus tumours, where complete resection is associated with a better prognosis, both for papillomas and carcinomas. Pre-operative embolization effectively reduces the vascularity of the tumour, changes its consistency to facilitate complete resection, and makes the procedure safer, particularly in a small child (8).

### Neuropathology

Recent revisions of the WHO classification of paediatric brain tumours not only reflect the vast research effort into the molecular, genetic and epigenetic characteristics of these tumours conducted over the last ten years, but also emphasize differences in treatment and prognosis within subgroups of brain tumours (9)(10). This continuously increasing complexity in tumour pathology has direct clinical significance, and close collaboration between neurosurgeon and neuropathologist has become even more important. While not all paediatric neurosurgical units may have access to state of the art molecular diagnostic techniques, collaboration with a laboratory that can provide this level of diagnostic detail is essential.

A recent expert review has underlined the importance of obtaining neuropathological, genetic and biological characterization of the tumour before the start of post-operative adjuvant therapy (11). In addition to its importance in research, this data is now also essential for each individual patient. Paediatric neurosurgeons need to view the technical aspects of a surgical procedure not just as a

way to obtain the safest and most complete resection possible, but also to collect as much biological material as they can. From a molecular perspective, tumours are often heterogeneous, and multiple specimens should be obtained from various parts of the tumour. This is particularly relevant to medulloblastomas (12). At least  $1 \times 1.5 \text{ cm}^3$  or  $3 \times 0.5 \text{ cm}^3$  specimens should be obtained in open procedures (11). A pipeline for tissue processing, starting from the operating room to the laboratory, is essential; as some neuro-oncology procedures are urgent, it is important that this pathway is available seven days a week.

In some tumours, such as low-grade gliomas, molecular data has led to specific tailored treatment regimens, such as MEK pathway inhibitors. This has increased the requirement for biopsy in tumour types that were previously only treated on a radiological diagnosis, such as optic pathway gliomas. These treatment decisions, based on molecular tumour data, may be outside the experience of smaller multidisciplinary groups, and collaborative access to a dedicated multi-centre molecular discussion group is relevant.

In addition to its diagnostic importance, tissue collection is also essential for research. This is a prerequisite for participation in some trials such as BIOMEDE, INFORM and the SIOPE-PNET5-MB trials (13). Outside of a trial, consent and ethical approval is specifically required in order to collect and store tissue for research. Facilities for biobanking are not available in all units, and material transfer agreements regulate the movement of tissue from one unit or country to another. As these tumours are rare, widespread collaboration across units and countries is of benefit to patients and should be encouraged and facilitated as much as possible.

## 5. Access to neurosurgical equipment

There is no question that a well-equipped operating room, as well as a trained and experienced paediatric neurosurgeon, is necessary for the provision of neurosurgical care. An operating microscope is essential for tumour resection in the brain and spine. Several other adjuncts are now also considered essential.

Frameless image-guidance became established as a surgical adjunct in the late 1990s (14)(15). These systems have now progressed through several iterations. In principle, they allow virtual preoperative planning and identification of the optimal approach. The craniotomy can then be sited in an optimal position in relation to the approach to the tumour. Image-guidance also allows a better understanding of the anatomical boundaries of a tumour and assists in obtaining a maximal resection. These systems also allow minimally-invasive burr hole biopsies, by directing a biopsy needle along a pre-planned trajectory to a deep tumour.

In practice, image-guidance systems are compromised by brain shift, related to the loss of cerebrospinal fluid (CSF), entry of intracranial air, and progressive tumour resection during surgery. Accuracy is greater near to a fixed anatomical point, such as the skull base or falx. Despite these limitations however, image-guidance is still considered essential for most brain tumour resections, particularly supratentorial and deep tumours, particularly if located within eloquent tissue.

Despite the development of frameless image-guidance systems, and their integration into neurosurgical practice, there is still a role for frame-based stereotactic surgery. In paediatric neuro-oncology the most common application of frame-based stereotaxy is in the biopsy of brainstem tumours. Although a biopsy is not usually considered necessary, at least in routine clinical practice, to make a diagnosis of diffuse intrinsic brainstem glioma, in other brainstem tumours the radiological diagnosis may be less clear. Stereotactic biopsy of these tumours has been shown to be

safe and effective(16). A possible alternative technique evolving with comparable accuracy is robotic assisted needle biopsies which may or may not be integrated in the frameless image guidance system and have the advantage, that frame positioning, especially difficult in smaller children, as well as additional need for imaging during surgery can be avoided.

Intra-operative ultrasound is another imaging modality that allows real-time evaluation during surgery. It can be easily carried out by the operating surgeon at multiple times, without the need for expensive equipment such as intra-operative MRI. Although it is difficult to be absolutely certain of a complete tumour resection using ultrasound alone, it allows some certainty that a large component of the tumour has not been inadvertently left behind (17). More recent technology has allowed improved visualisation of brain and spine tumours, as well as navigated ultrasound, where the ultrasound probe is integrated with the frameless navigation system(18)(19).

Neuro-endoscopy is another neurosurgical adjunct that is essential in the management of brain tumours. Endoscopy facilitates biopsy of intra- or paraventricular lesions and is often useful in the management of hydrocephalus associated with brain tumours. One particular example in children is the management of pineal tumours, where, in the context of a pineal tumour with negative tumour markers, a biopsy will determine whether surgical resection is required. Using an endoscope this can be performed through a frontal burr hole, under direct vision(20)(21). If the tumour is a germinoma, no further surgery is required. If however pathology confirms an astrocytoma or embryonal tumour, formal resection will be needed. Obstructive hydrocephalus, which often accompanies pineal tumours, can be treated at the same time with an endoscopic third ventriculostomy.

Intra-operative MRI is an expensive adjunct to neurosurgical practice and is usually available in the larger centres. Intra-operative MRI systems combine frameless image-guidance with real time imaging. The acquisition of an MRI scan during the procedure allows confirmation that the extent of intended tumour resection has been achieved. It also corrects for the impact of brain shift during the procedure and allows a re-evaluation of the relationships between the residual tumour and surrounding eloquent brain. Several publications have affirmed its usefulness(22)(23). The primary limitations of intra-operative MRI relate to its time and cost – in most hospitals, this is mitigated, to some extent, by using a two-room suite, where an MRI scanner adjacent to the operating room can function independently until an intra-operative scan is required. At this point, the patient is moved, without the need for head closure, from the operating room to the scanner, usually using a dedicated transfer system.

Intra-operative neuro-monitoring is another important adjunct to paediatric neurosurgical oncology(24). The ability to confirm the functional integrity of the cerebral cortex and tracts adjacent to a tumour, as well as that of cranial and peripheral nerves, allows a safe and tailored tumour resection that preserves neurological function. In current practice, monitoring is usually used for the resection of spinal cord tumours, as well as tumours involving or adjacent to the primary motor or sensory cortex, the corticospinal tracts, the cranial nerves, the brainstem and the cauda equina(25)(26). Typical paradigms involve monitoring motor evoked potentials, sensory evoked potentials, cortico-bulbar pathways, brainstem auditory evoked potentials, and, for spinal cord tumours, the D wave, which evaluates motor integrity across the operated spinal segment. Intra-operative monitoring also allows mapping by direct stimulation of functional relevant neural structures, particularly useful for eloquent cortical and brainstem tumours. The use of cranial nerve monitoring as well as direct stimulation in resection of a posterior fossa ependymoma that involves the cerebellopontine angle significantly increases the safety of the procedure.

## 6. Other requirements

### Paediatric anaesthesia and intensive care

Children are not small adults, and children undergoing brain tumour surgery need specialized anaesthetic expertise. This is particularly but not exclusively relevant to small children with large and vascular tumours. Intra-operative bleeding and rapid fluid shifts, as well as coagulopathy, can occur rapidly in these situations and expert paediatric anaesthesia is an essential component of a neuro-oncology service. Similarly, access to paediatric intensive care is also essential.

### Definition of high-risk cases and ability to collaborate

Some tumours in paediatric neuro-oncology practice are relatively rare or complex. These include brain tumours in infants, midline tumours such as craniopharyngiomas and pineal tumours, ependymomas and some recurrent tumours. It has been suggested that it may be helpful to develop opportunities to discuss the management of these cases within larger networks. The development of virtual tumour boards may in time facilitate this growth, and may even allow cross-border collaboration, particularly useful for smaller countries. The SIOP Ependymoma II trial has integrated and multi-disciplinary national panels to evaluate patients with residual tumour disease for possible second-look surgery (27). Although there is no clear or published evidence that this is consistently beneficial, two such efforts focusing on paediatric ependymoma and hypothalamic-pituitary tumours respectively in the United Kingdom have been well-received.

### Participation in research networks

Paediatric neuro-oncology units endeavour to collaborate with other units within research networks. The complexity, rarity and poor prognosis of many paediatric brain tumours would mandate that as many children as possible should be recruited to multicentre clinical trials. It is only in this way that new treatment algorithms are effectively evaluated within a reasonable period of time. The adoption of investigation and treatment algorithms embedded within trial protocols has the potential to reduce variability across units and countries, attract funding and clinical resources, as well as encourage best practice.

### Information management, discussion of complications

A database of procedures, adverse events and complications is an essential to the maintenance of a paediatric neurosurgical service. A complication database, with open discussion of complications, and a system to evaluate significant events, allows institutional learning and ongoing improvement. This approach is vital to a safe neurosurgical practice. It is facilitated by surgical and post-operative proformas that ensure comprehensive, accurate and contemporaneous data collection.

### Late effects clinic, rehabilitation, neuropsychology support

A paediatric neuro-oncology neurosurgical service also requires access to a late effects clinic, where the long-term impact of surgery can be evaluated together with the effects of chemotherapy and

radiotherapy. Access to rehabilitation and neuropsychological support is also important to ensure that children and their parents are given the opportunity to reach their best outcome and potential.

## 6. Conclusion

Paediatric neurosurgical care is a central component of paediatric neuro-oncology. Although variation in activity and neurosurgical resources across neurosurgical centres in Europe is unavoidable, a number of key elements remain essential to safe paediatric surgical neuro-oncology. Collaboration and networking across services and countries provide the necessary quality of care, opportunities to harmonise pathways and ensure that best practice is disseminated as far as possible.

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## Neuropathology

### STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# NEUROPATHOLOGY

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## 1. Background

### Role in paediatric oncology

Integrated histological and molecular analyses are fundamental to render an accurate diagnosis and consecutively offer optimal treatment. A multitude of studies have shown that morphological work-up alone does not sufficiently discriminate between histologically similar but biologically and thus clinically highly divergent tumours [1] [2]. This applies for the entire spectrum of paediatric brain tumours and is most pronounced in tumour types in which only molecular data are capable of identifying prognostic or even predictive subtypes, e.g., but not limited to posterior fossa ependymoma, medulloblastoma, or histological high-grade glioma, the latter by molecular means often found to be biologically low-grade [3-6].

Consequently, the WHO classification 2021 has introduced a variety of novel brain tumour types and subtypes [2]. It also has paved the way for molecular analyses to be considered essential to establish a WHO-conform diagnosis for most entities. Paediatric brain tumour types have thereby received the most substantial updates and classificatory changes among all entities, as further detailed in the respective subsections and summarized in Table 1.



**Table 1: WHO classification of paediatric CNS tumours*****Gliomas, glioneuronal & neuronal tumours****Paediatric-type diffuse low-grade gliomas*Diffuse astrocytoma, *MYB* or *MYBL1*-altered *new entity*

Angiocentric glioma

Polymorphous low-grade neuroepithelial tumour of the young *new entity*Diffuse low-grade glioma, MAPK pathway-altered *new entity**Paediatric-type diffuse high-grade gliomas defined by H3 status*Diffuse midline glioma, *H3 K27*-alteredDiffuse hemispheric glioma, *H3 G34*-mutant *new entity*Diffuse paediatric-type high-grade glioma, *H3*-wildtype and *IDH*-wildtype *new*Infant-type hemispheric glioma *new entity**Circumscribed astrocytic gliomas*

Pilocytic astrocytoma

High-grade astrocytoma with piloid features *new entity*

Pleomorphic xanthoastrocytoma

Subependymal giant cell astrocytoma

Astroblastoma, *MN1*-altered*Glioneuronal and neuronal tumours*

Ganglioglioma

Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma

Dysembryoplastic neuroepithelial tumour

Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (DGONC)\* *new entity*

Diffuse leptomeningeal glioneuronal tumour

Multinodular and vacuolating neuronal tumour *new entity**Ependymal tumours*

Supratentorial ependymoma

Supratentorial ependymoma, *ZFTA* fusion-positiveSupratentorial ependymoma, *YAP1* fusion-positive *new*

Posterior fossa ependymoma

Posterior fossa ependymoma, Group PFA *new entity*Posterior fossa ependymoma, Group PFB *new entity*Spinal ependymoma, *MYCN*-amplified *new entity*

Myxopapillary ependymoma

***Choroid plexus tumours***

Choroid plexus papilloma

Atypical choroid plexus papilloma

Choroid plexus carcinoma

***CNS embryonal tumours****Medulloblastomas, molecularly defined*Medulloblastoma, *WNT*-activated

Medulloblastoma, SHH-activated & *TP53*-wildtype

Medulloblastoma, SHH-activated & *TP53*-mutant

Medulloblastoma, non-WNT/non-SHH

*Medulloblastoma, histologically defined*

Medulloblastoma, histologically defined

*Other CNS embryonal tumours*

Atypical teratoid/rhabdoid tumour

Cribiform neuroepithelial tumour\* *new entity*

Embryonal tumour with multilayered rosettes

CNS neuroblastoma, *FOXR2*-activated *new entity*

CNS tumour with *BCOR* internal tandem duplication *new entity*

CNS embryonal tumour NEC/NOS

### ***Pineal region tumours***

Pineoblastoma

### ***Melanocytic tumours***

Meningeal melanocytosis and melanomatosis

### ***Tumours of the sellar region***

*Pituitary endocrine tumours*

Pituitary adenoma / PitNET

Pituitary blastoma *new entity*

*Craniopharyngiomas*

Adamantinomatous craniopharyngioma

As a result of the pivotal importance of molecular markers, comprehensive work-up is required and includes DNA methylation analysis for most tumour types. Despite some immunohistochemistry surrogate markers being available, the DNA methylation profile has the highest accuracy in identifying tumour differentiation. Hence, the WHO classification suggests epigenetic analysis as method of choice for most, especially otherwise diagnostically non-resolvable cases.

Similarly, several tumour types have pathognomonic molecular alterations, mostly single nucleotide variants, small insertions/deletions or gene rearrangements (e.g. gene fusions, internal tandem duplications). For many tumour types, an integrated diagnosis according to the WHO classification can only be rendered if these alterations are detected.

However, due to the promiscuity of some alterations (e.g. *BRAF* and *FGFR1* mutations, or *NTRK*-fusions occurring in a variety of tumour types) and co-occurrence (e.g. H3F3A and *BRAF* mutations), testing for a single alteration alone may not be conclusive [7] [8]. Thus, comprehensive work-up typically includes assessment of a variety of alterations by high-throughput analyses, namely DNA methylation profiling for tumour classification and copy-number-alterations, to some degree also covering rearrangements, DNA sequencing for a panel of brain tumour-related genes, and for select tumour types also RNA sequencing for fusion detection. Practically, it is also desirable to test mutations both somatically in the tumour as well as in the germline using the same approach, since at least 10% of childhood brain tumour patients harbour pathogenic germline variants in cancer-related genes [9].

If the required testing was not completely performed, due to lack of assay availability or sparse material, the most precise diagnosis based on the present data should be amended by “NOS” for “not otherwise specified”. If comprehensive testing was performed but yielded results that do not conform with any established tumour type in the WHO classification, “NEC” for “not elsewhere classified” should be added [10].

## 2. Institutional requirements

In most European countries, neuropathology is not an established, officially regulated discipline with separate board certification. Thus, the specialization of physicians and laboratories may vary more than for other medical disciplines. However, these regulatory aspects do not prevent regions without distinct neuropathologists from providing highest standards of care.

Basic infrastructure for preservation and assessment of brain tumour samples relies on coordination between (neuro-)surgery and neuropathology. This interaction should allow for interoperative evaluation of a frozen section, preferably also a touch and smear preparation. Further, both disciplines should cooperatively ensure the to retrieve and preserve high quality tissue for analysis, including archiving not only of formalin-fixed paraffin-embedded, but also frozen tissue for all paediatric neurooncology patients.

Platforms: basic histology, QC-regulated immunohistochemistry with most frequent markers of WHO classification, access to methylation analysis and NGS (tumour and blood), as surrogate FISH, MLPA etc.

## 3. Essential quality parameters

Outside of dedicated centres, submission of specimen from paediatric brain tumour for histopathological and molecular work-up are typically rare. In turn, regular scientific exchange and awareness for the limitations of the histological platforms is mandatory, especially since no European quality assurance measures are established. Typically, at least two experienced (i.e. > 5 years practise) specialists on neuropathology should be available, with full access to histology and immunohistochemistry facilities, and local or established referral access to DNA methylation platform and gene panel sequencing.

## 4. Contact centres/ networks

- Dept of Neuropathology, University Hospital Hamburg, Hamburg, Germany (contact Ulrich Schüller)
- Dept. of Neuropathology and Hopp Childrens' Cancer Center KiTZ, Heidelberg, Germany (contact Felix Sahm)
- Dept. of Neuropathology, University Medicine Berlin, Germany (contact David Capper)
- Dept. of Pathology, Great Ormond Street Hospital, London, UK (contact Tom Jacques)
- Dept. of Pathology, PMC Utrecht, Utrecht, The Netherlands (contact Pieter Wesseling)
- Neuropathology Service, GHU Paris, Paris, France (contact Pascale Varlet)

## 5. Summary

<b>Must have</b>
Conventional histopathology and immunostaining (+/- FISH/MLPA)
DNA methylation analysis
Genepanel sequencing (tumor and blood)
<b>Desirable</b>
RNA sequencing, whole-exome/whole genome sequencing, proteomics
<b>Don't do</b>
Prevent NOS diagnoses

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## Radiotherapy Group

### STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# RADIOTHERAPY GROUP

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## 1. Background

Radiotherapy is an integral component of the multidisciplinary management of paediatric brain tumours. In children aged less than 12-36 months, radiotherapy may be delayed to minimize the risk of long-term sequelae, especially neurocognitive dysfunction. Indications for radiotherapy generally depend on the age and histological subtypes of brain tumour and can be broadly summarised as below: A detailed account of the radiotherapy indicated is given in tumour specific section

- Gliomas:
  - o Low-grade glioma (LGG): Indicated in patients with progressive disease after surgery or surgery is not feasible
  - o High-grade (HGG): all children with high grade glioma
- Medulloblastoma: All patients with medulloblastoma and aged more 3-5 years should be considered for craniospinal radiotherapy
- Ependymoma: all patients aged >12 months should be considered for radiotherapy after surgical resection
- Germ cell tumour: All patients with germ cell tumours, except completely resected pure mature teratomas require radiotherapy as part of the multimodality treatment approach
- Craniopharyngioma: postoperative radiotherapy is considered on an individual risk based
- Rare embryonal tumours and ATRT: principles of radiotherapy generally follows that of medulloblastoma
- Choroid plexus tumours (CPT): Radiotherapy depends on the specific subtypes and extend of resection.

Many countries are moving towards proton beam therapy (PBT) as the technique of choice for children with primary central nervous system (CNS) tumours, especially those with a good chance of cure. While PBT has the potential to reduce the risk of side effects, particularly late radiotherapy effects, conclusive evidence from large prospective studies is scarce. Nevertheless, the option of PBT should be discussed within the multidisciplinary setting for all individual children with CNS tumours. In addition, it is encouraged to collect prospective outcome data on efficacy and toxicities following PBT using national or international protocols.

## 2. Institutional requirements

Treatment planning, delivery, and aftercare of radiotherapy for children are complex. Every centre providing radiotherapy should have at least two clinical oncologists and dedicated pre-treatment and treatment teams consisting of mould room staff, play specialists, nurses, anaesthetic staff, physicists, dosimetrist, therapeutic radiographers. An extended support team should also include paediatric psychologist and psychotherapist.

All patients requiring radiotherapy should be discussed in a specialised paediatric MDT with a core membership of clinical/radiation oncologist, paediatric oncologist, paediatric specialist nurses and play therapist.

New patient consultation should be done in an age-appropriate outpatient environment with radiotherapy team.

In general radiotherapy departments, children should be treated in a designated machine(s) in a child-friendly environment.

All patients should be reviewed regularly during radiotherapy to provide continuous support and to address any side effects.

There should be established late-effect follow-up clinics to proactively manage potential late sequelae.

## 3. Essential quality parameters

- Clear radiotherapy pathway to signpost best radiotherapy approach for individual patients, including pathways for referral to an external hospital for particle beam therapy.
- All patients should be treated with an appropriate advanced radiotherapy technique in keeping with national guidelines or clinical trial protocols.
- All radiotherapy department should have externally validated quality assurance system.
- Multidisciplinary radiotherapy planning process involving clinical oncologist, radiographers and radiotherapy physicists
- Well established quality assurance for accuracy and reproducibility of daily treatment with modern imaging techniques.

## 4. Contact centres/ networks

<https://siope.eu/SIOPE-Brain-Tumour-Group>

<https://siope.eu/activities/joint-projects/quartet/>

## 5. Summary

<b>Must have</b>
All patients treated with curative intent should have highly conformal radiotherapy
Selected patients should be referred to proton beam or particle beam therapy in keeping with national clinical guidelines.
There should be an established QA process in all centres and should include peer reviewing of radiotherapy volumes and treatment plans.
At least two clinical/radiation Oncologist specialising paediatric radiotherapy
<b>Desirable</b>
At least two clinical/radiation oncologist with appropriate site specialisation in paediatric radiotherapy
<b>Don't do</b>
Radiotherapy, both curative and palliative, should not be given by clinical/radiation oncologist with no special interest/experience in paediatric radiotherapy

## Endocrinology

### STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# ENDOCRINE SURVEILLANCE IN CHILDREN WITH BRAIN CNS TUMORS

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## 1. Background

The overall survival of children with tumours of the central nervous system has improved substantially, with a current expected 5-year overall survival rate of 73%. The mass effect of the brain tumour itself, as well as the treatment modality (neurosurgery, cranial radiotherapy [RT] and/or chemotherapy) can however result in serious adverse effects. Many survivors will face diverse lifelong health-related challenges after curative treatment of a childhood brain tumour. Hypothalamic-pituitary dysfunction can play a central role in long-term health and wellbeing of childhood brain tumour survivors<sup>1,2</sup>. In addition, peripheral endocrine dysfunction can be present due to the toxic effects of chemotherapy or radiation therapy on the thyroid gland or the gonads<sup>3-5</sup>. Endocrine disorders following cancer treatment may significantly influence health, especially during childhood. In children surviving a brain tumour, an adequate endocrine system is necessary for adequate recovery, for development and growth into adolescence and optimal participation in daily life. For this reason, the paediatric endocrinologist should be part of the multi-disciplinary neuro-oncology team<sup>6</sup>.

### *Anterior pituitary dysfunction*



Hypothalamic-pituitary (HP) dysfunction may be present already at diagnosis in children with a tumour located in the sellar or suprasellar region<sup>6</sup>. But also in children with a brain tumour without mass effect on the pituitary region, dysfunction of the hypothalamic-pituitary system may evolve in the years after treatment<sup>7</sup>. After treatment with radiotherapy, HP dysfunction may already occur in the 1<sup>st</sup> year, increasing in prevalence over time after exposure to radiotherapy<sup>7,8</sup>.

Childhood craniopharyngioma and its effect on the HP system will be discussed elsewhere. In this chapter we will focus on surveillance of HP dysfunction in children treated for a brain tumour, excluding craniopharyngioma.

In an analysis of the St. Jude Lifetime Cohort, after 27.3 years of follow-up, in 51.4% of adult survivors of any type of childhood cancer treated with cranial RT at least one anterior pituitary disorder was found<sup>9</sup>. In a nation-wide study of 718 Dutch childhood brain tumour survivors, 22.1% was diagnosed with at least one endocrine disorder within the first 5 years of brain tumour diagnosis<sup>10</sup>. Most endocrine disorders start appearing at a median follow-up time of only 2.2 years. Younger age at brain tumour diagnosis, hydrocephalus, suprasellar and infratentorial tumour site, as well as radiotherapy, have been shown to be independent risk factors for the development of HP dysfunction. Childhood brain tumour survivors who have received RT, with doses exceeding 30 Gy, are especially at increased risk of developing hypothalamic-pituitary dysfunction.

Of all anterior pituitary axes, GH deficiency is the earliest and most frequent pituitary disorder, affecting up to 22.2% of patients, followed by insufficiencies of the other axes. In a study of 3141 CCS with a median follow-up time of 24.1 years, a prevalence of 22.2%, 5.5%, 5.1%, and 4.1% was reported for GH, TSH, LH/FSH and ACTH deficiency, respectively. In those treated with HP radiotherapy, the estimated prevalence was 40.2% for GHD, 11.1% for TSHD, 10.6% for LH/FSHD, 3.2% for ACTHD, and 0.9% for CPP (n = 1089)<sup>1</sup>. In a cohort excluding craniopharyngioma followed for 6.6 years, growth hormone deficiency was present in 12.5%, precocious puberty in 12.2%, TSH deficiency in 9.2%, ACTH deficiency in 4.3%, and LH/FSH deficiency in 4.2% (Figure 1)<sup>10</sup>.

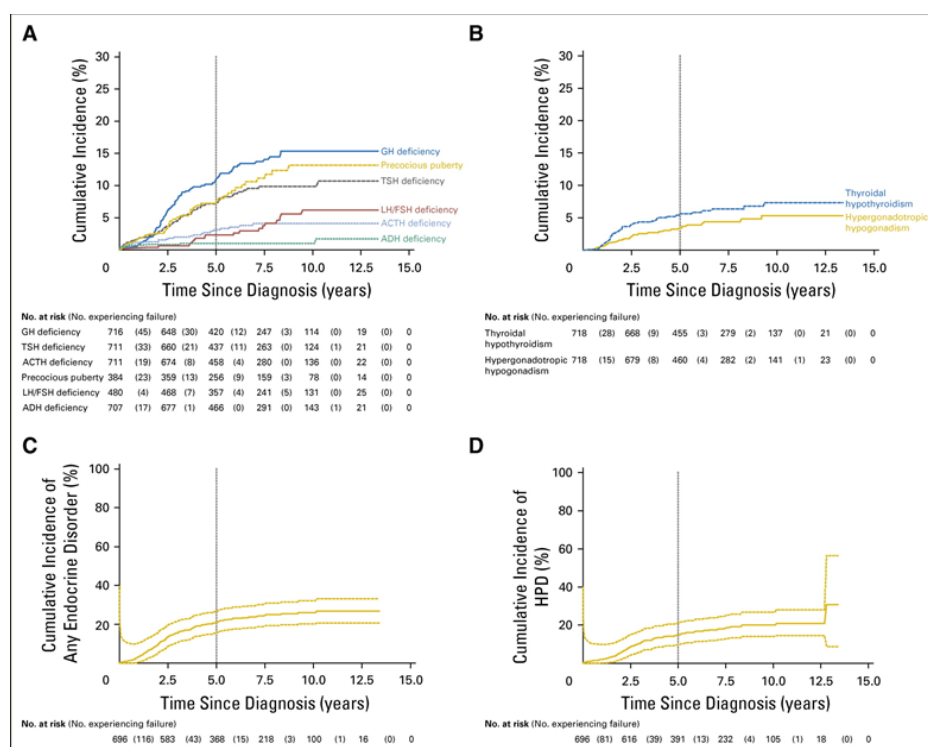


Fig 1. Cumulative incidence of all hypothalamic-pituitary axes in a Dutch cohort of 718 childhood brain tumour survivors, excluding craniopharyngioma (A), of thyroidal hypothyroidism and hypergonadotropic hypogonadism (B), and cumulative incidence and 95% CI (dashed lines) of any endocrine disorder (C) and hypothalamic-pituitary dysfunction (HPD; D). ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone <sup>7</sup>

### Weight gain and obesity

Children surviving brain tumours are also at risk for developing obesity <sup>2,11</sup>. Obesity during childhood increases the risk of serious morbidity in adulthood, such as diabetes mellitus and cardiovascular disease and therefore deserves special attention during follow-up. In a large nationwide cohort study including 661 childhood brain tumour survivors (CBTS), 33.1% had significant weight gain, overweight, or obesity after a median follow-up of 7.3 years. BMI SDS at diagnosis, diagnosis of low-grade glioma, diabetes insipidus, and central precocious puberty were associated with weight gain, being overweight, or obesity. The prevalence of other hypothalamo-pituitary hormone deficits was higher in overweight and obese CBTS compared to normal weight CBTS (Figure 2).

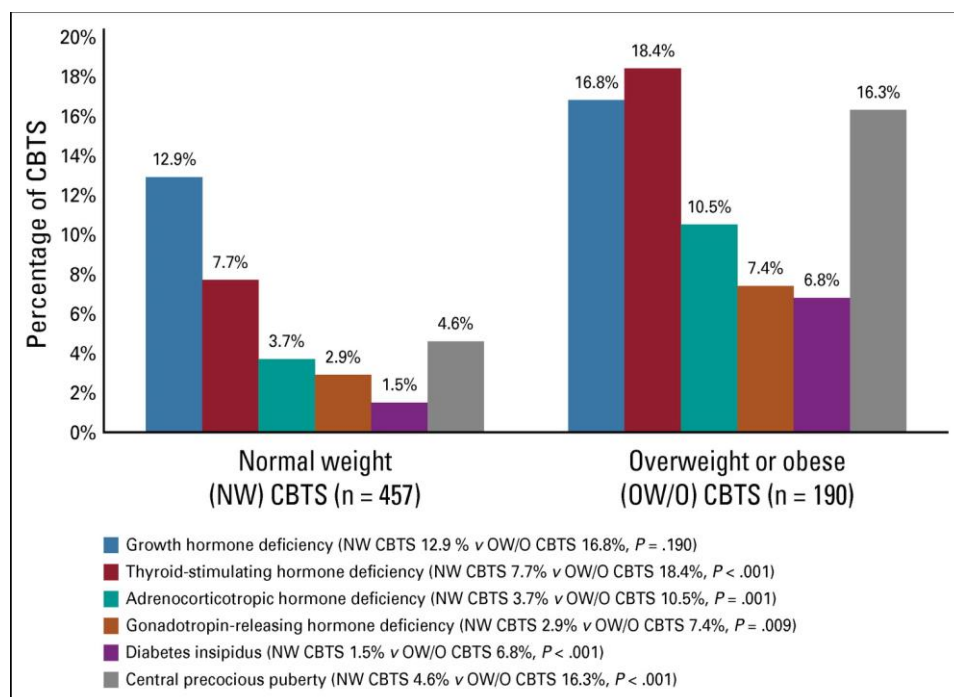


FIG 2. Prevalence of hypothalamic-pituitary disorders in childhood brain tumour survivors (CBTS) with normal weight, overweight, or obesity at follow-up. Endocrine disorders: GHD, TSHD, ACTHD, GnRHD, DI, and CPP. \*Percentage of CBTS with GHD, TSHD, ACTHD, GnRHD, DI, or CPP in normal-weight CBTS (n = 457) versus overweight or obese CBTS (n = 190) ( $\chi^2$  test). ACTHD, adrenocorticotrophic hormone deficiency; CBRS, childhood brain tumour survivors; CPP, central precocious puberty; DI, diabetes insipidus; GnRHD, gonadotropin-releasing hormone deficiency; GHD, growth hormone deficiency; TSHD, thyroid-stimulating hormone deficiency <sup>11</sup>.

### Posterior pituitary deficiency

Central diabetes insipidus (CDI) is the result of insufficient secretion of anti-diuretic hormone (ADH) from the posterior pituitary gland. CDI is seen in children with CNS tumours after damage to the hypothalamus, pituitary stalk or pituitary gland by localized CNS tumours or after surgical

procedures. CDI does not occur as a late effect of radiation therapy. Management of CDI requires an experienced paediatric endocrinologist and is in general very well managed with oral desmopressin. In rare cases, management can be difficult due to distorted thirst regulation and/ or concurrent ACTH deficiency, which is especially encountered in children with hypothalamic damage due to low grade glioma and craniopharyngioma. In such cases, regular monitoring of plasma sodium with monitoring of fluid intake is necessary.

## 2. Risk factors and time of onset

The most important risk factors to develop hypothalamic-pituitary dysfunction after treatment for a childhood brain tumour are:

- exposure to cranial radiotherapy
- suprasellar/ sellar tumour location
- hydrocephalus

### *Cranial radiotherapy.*

Exposure of the HP region to RT is associated with an increased risk of GHD. TBI has been associated with an increased risk for GHD, but not with TSHD, ACTHD, LH/FSHD, or CPP. The risk to develop HP dysfunction increases with RT dose and younger age at time of radiation therapy<sup>1,12,13</sup>. It is worth noting that CPP may be risk factor for subsequent LH/FSHD, and pubertal progression must be closely monitored in patients treated with GnRH analogues following cessation<sup>23</sup>.

### *Cranio-spinal radiotherapy*

Children who have been treated with cranio-spinal radiotherapy are at increased risk for HP dysfunction, similar to children who have had cranial radiotherapy alone. In addition, due to the fact that the thyroid gland usually lies within the radiation field, these children are at risk for primary hypothyroidism, thyroid nodules and thyroid carcinoma<sup>4</sup>. Often in such patients combined primary and central hypothyroidism is found with decreasing FT4 values and mildly elevated TSH concentrations. In addition, due to radiation of the spine, longitudinal height may be deprived as a consequence of decreased growth of the back, despite adequate GH and sex hormone replacement. This may be particularly attenuated in puberty, where most growth is in the spine. In such children, in addition to longitudinal height, sitting height should also be monitored.

### *Hydrocephalus*

Hydrocephalus has been associated with a higher risk to develop GH deficiency. In young children, hydrocephalus may also induce central precocious puberty.

### Chemotherapy

There is no evidence that treatment with chemotherapy increases the risk for HP dysfunction. However, chemotherapeutic agents are all designed to inhibit the growth of rapidly dividing cells, including at the epiphyseal growth plates. As such, there may be some loss of statural growth during periods of treatment despite adequate GH production as a result of effectively transient GH resistance. Treatment with alkylating chemotherapy may induce gonadal failure and pubertal delay/arrest<sup>3,5</sup>.

### Time of onset.

HP dysfunction after exposure to radiation therapy has been reported to occur as early as 0.1 years (GH deficiency) but can continue to evolve > 10 years (GH, TSH, ACTH, LH/FSH deficiency) after diagnosis. In children with medulloblastoma treated with radiation doses of 54 Gy, HP dysfunction is most often encountered in the 1<sup>st</sup> 3 years after radiotherapy, with > 80 % of survivors having HP dysfunction after 5 years of follow-up. Latency times are on average shorter after higher doses of radiation therapy.

### 3. Surveillance

Different surveillance schemes for HP dysfunction in children with brain tumours have been made such as the recommendations of the COG, the guidelines of the Dutch Childhood Oncology Group, the UK Children's Cancer Study Group Late Effects Group and the Scottish Group<sup>14-17</sup>. The International Guideline Harmonization Group (IGHG) is currently working on a harmonized recommendation.

### Hypothalamic-pituitary function screening

Here we provide an overview and suggestion for follow-up of HP dysfunction in children following treatment for a brain tumour. All children with a tumour in the sellar or suprasellar region or with HP dysfunction at diagnosis should be directly referred to the paediatric endocrinologist.

Treatment	Potential late effect	Risk factors	Recommendation
<b>Radiotherapy</b>			
<b>Cranial</b>	Overweight / Obesity	Age < 4 years Radiation dose > 20 Gy	Monitor BMI yearly Dietary and physical exercise advice BMI > + 2 SD: consultation with endocrinologist
	Precocious puberty (B2 <8 yr ♀, testes 4+ cc <9 yr ♂)	Young age Radiation dose pituitary region > 18 Gy	Monitor Tanner stage in combination with growth velocity every 6 months
	Central hypothyroidism	Young age Radiation dose pituitary region > 40 Gy	History for signs of TSH deficiency Lab: TSH, FT4 (yearly)

		After starting treatment with GH	- referral to endocrinologist when FT4 <reference interval on 2 separate occasions or declines with > 20 % in time.
	LH/FSH deficiency (B2 > 12 yr ♀, testes 4+ cc > 13 yr ♂)	Radiation dose pituitary region > 40 Gy	Monitor Tanner stage in combination with growth velocity every 6 months
	ACTH deficiency	Young age Radiation dose pituitary region > 40 Gy	History for signs of adrenal insufficiency 08:00 AM morning cortisol (yearly) – in case of suspicion of ACTHD direct referral to endocrinologist
	GH deficiency	Young age Radiation dose > 18 Gy	Height, weight, sitting height, BMI every 6 months - declining growth chart: referral endocrinologist
	Thyroidal hypothyroidism	Cervical (stray) irradiation > 20 Gy cranial	History for signs of T4 deficiency TSH, FT4 (yearly) - low FT4 or high TSH: referral endocrinologist
	Thyroid nodule/ carcinoma	Young age Cervical (stray) irradiation > 20 Gy cranial	Thyroid palpation (yearly) - when palpable nodule: referral to endocrinologist for thyroid ultrasound.
<b><u>Cervical/spinal</u></b>	Thyroidal hypothyroidism	Cervical (stray) irradiation > 20 Gy cranial	History for signs of T4 deficiency TSH, FT4 (yearly) - low FT4 or high TSH: referral endocrinologist
	Thyroid nodule/ carcinoma	Young age	Thyroid palpation (yearly) - when palpable nodule: referral to endocrinologist for thyroid ultrasound.
	Short stature	Young age	Sitting height every 6 months

### *Thyroid function screening*

Children who have been irradiated on the neck (craniospinal irradiation) should be screened yearly with thyroid function parameters (TSH and FT4) and neck palpation. Thyroid ultrasound may be considered as surveillance for presence of thyroid nodules or thyroid cancer. In 2018, the International Guideline Harmonization Group (IGHG) has published recommendations on thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer. Benefits of surveillance of patients at risk are the detection of DTC in an earlier stage, whereby the extent of surgery and/or additional radioiodine therapy may be reduced, possibly decreasing overall morbidity, recurrences as well as morbidity. Furthermore, if no cancer is found with surveillance, the high-risk patient can be reassured. On the other hand, there is uncertainty of the benefit of early treatment, since most DTC can be cured. Also, false positive results during surveillance, potentially leading to repeated neck ultrasounds and even FNA biopsies. This could cause anxiety, stress, and inconvenience for the patient, but also higher health-care costs, and the risk of complications of unnecessary biopsies or surgery. Surveillance could also lead to detection of indolent DTC, which may never have caused clinical problems, and may lead to overtreatment. Lastly, false negative results will lead to false reassurance of the high-risk patient. For these reasons, the IGHG recommends discussing the most optimal surveillance strategy (with regards to the frequency as

well as the method of surveillance (neck palpation or ultrasound), together with the patient (and parents) depending on the individual needs<sup>4</sup>.

### *Gonadal function screening*

CCSs diagnosed with a brain tumour and treated with toxic cancer therapies such as alkylating agents are at highest risk to develop ovarian or testicular failure<sup>18</sup>. It is worth noting, however, that even agents considered to be low-risk can impact fertility<sup>24</sup>. Clinical practice guidelines for both premature ovarian failure and testicular failure have been developed by the IGHG to provide long-term surveillance strategies for female and male cancer survivors<sup>3,19</sup>. Surveillance with monitoring of longitudinal growth, pubertal development and yearly LH/FSH/estradiol monitoring is recommended for female cancer survivors exposed to alkylating agents and radiotherapy to a field that includes the ovaries or to the hypothalamic pituitary region, which all have been shown to increase the risk for POI. In males, gonadotoxic therapies can result in impaired spermatogenesis, testosterone deficiency and sexual dysfunction. Counselling regarding male gonadotoxicity is recommended for male cancer survivors exposed to alkylating agents and radiotherapy fields involving the hypothalamic pituitary region or potential old spinal fields. In at-risk pre-pubertal and peripubertal male cancer survivors, monitoring of growth and pubertal development and progression (i.e. with Tanner stage) is recommended to screen for testosterone deficiency. In post-pubertal males, measurement of total serum testosterone in an early morning blood sample at clinically appropriate intervals is reasonable for surveillance of testosterone deficiency. Consideration should be made for the potential of fertility preservation techniques such as sperm, oocyte or ovarian tissue cryopreservation, ideally prior to administering gonadotoxic therapies.

### *Indications for referral*

Preferably, the paediatric endocrinologist is part of the multidisciplinary team of every child with a brain tumour enabling early detection and treatment of hypothalamic-pituitary deficiencies.

All children with brain tumours involving the hypothalamic-pituitary region should be referred to the paediatric endocrinologist directly at diagnosis for individual monitoring and, if necessary, treatment of endocrine deficiencies.

All children with decreasing growth velocity, failure of progression of puberty, aberrant laboratory values or a history suspicious for pituitary deficiency should be referred to the paediatric endocrinologist.

## 4. GH treatment in childhood brain tumour survivors

As discussed above, GH deficiency is frequent in brain tumour survivors after exposure to cranial radiation therapy. GH deficiency during childhood may result in deprived final height. In addition, an optimal GH state is necessary for an adequate metabolic profile, bone health and muscle strength. The safety of GH in childhood cancer survivors has been an issue of debate for many years. In several large cohort studies, CCS treated with GH were shown not to be at increased risk for recurrence of the original tumour, nor for a secondary tumours compared to CCS not treated with GH<sup>20,21</sup>. Future prospective studies are needed though to confirm these results and to answer the more difficult question upon the optimal time span to start GH therapy after achieving complete remission and

how to deal with children with ‘chronic’ low-grade glioma and GHD. Also, more studies are needed upon the optimal dosing of GH treatment <sup>22</sup>.

Most current recommendations advise that GH can be administered safely to brain tumour survivors in whom the diagnosis of GH deficiency has been established. Recent guidelines recommend waiting for GH therapy until patients are disease free for at least one year, although this is based on little evidence <sup>8</sup>. Some patients may never be disease free, however, such as those with low grade glioma, and in these individual cases the benefits versus the possible harms of GH treatment must be discussed by the paediatric endocrinologist, the patient and the parents and the oncologist.

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## Neuroophthalmology

### STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# VISUAL ASSESSMENT AND FOLLOW-UP OF CHILDREN WITH A CENTRAL NERVOUS SYSTEM NEOPLASM

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## 1. Background

Central nervous system (CNS) neoplasms in children can alter the visual system anatomy and physiological development and cause a variety of visual symptoms including a decreased visual acuity (VA), visual field (VF) defects, diplopia, and eye movement disorders as shown in **Table 1** (1-7).

The onset of neuro-ophthalmological manifestations is largely influenced by tumour location within the CNS and due to either visual pathway (afferent) or cranial nerve (efferent visual system) involvement. In addition, complications such as obstructive hydrocephalus, brain oedema, leptomeningeal dissemination, and cerebral venous thrombosis might cause raised intracranial pressure (RICP) with papilledema and further threat to vision (1 - 5).

Moreover, as visual system is under development in the first years, any additional visual input deprivation including refractive errors, keratopathy, cataracts, or strabismus occurring during this critical phase will lead to amblyopia and further visual loss. (1- 7)

Overall, adult survivors of paediatric CNS tumours have an increased risk of long-term visual sequelae, including unilateral or bilateral blindness (RR 14.8), cataracts (RR = 11.9) and diplopia (RR 8.8), which may ultimately jeopardize quality of life aspects such as neurocognitive development, autonomy, driving eligibility and education. (1, 8-11)

Series from large tertiary centres indicated that less than 50% of children with a newly diagnosed CNS tumour are referred for a baseline ophthalmology assessment, at a median time of 9 months (range 0-94 months) from diagnosis. (6) Initial evaluation might get delayed or missed for many reasons, including dealing with an acutely ill child and prioritisation of life-saving interventions, but also the risk of underreporting visual symptoms, which is particularly high in infants and young children or in case of VF defects. (1, 12)

Standard clinical practice recommendations for ophthalmological assessment and follow-up will hopefully contribute to a more accurate and standardized evaluation, a timely diagnosis, and earlier interventions to possibly mitigate or prevent irreversible visual loss in this group.

## 2. Tumour Location and Specific Manifestations

Neuro-ophthalmological manifestations due to infiltration and/or compression of the visual pathways (afferent) or cranial nerve/s (efferent visual system) are largely determined by location within the CNS. Most common visual symptoms and signs based on CNS tumour location are summarized in **Table 2**.

### **Posterior Fossa (PF)**

Tumours of the PF represent the most common CNS neoplasms in children, affecting visual function in several ways. RICP is common in PF masses leading to acute papilledema in the vast majority. While acute papilledema typically resolves if RICP is adequately treated, severe or prolonged RICP can result in vision loss due to optic atrophy and axonal death.

In very young children with PF fossa papilledema may be absent as incompletely fused cranial sutures compensate the mass effect by expansion of the head circumference in response to RICP.

At early stages papilledema causes limited visual symptoms, but enlargement of the physiological blind spot can be perceived, followed by nasal, arcuate or central VF defects. (13, 14) In addition, sixth cranial nerve (CN-VI) palsy can also occur, either due to compression of the dorsal pons, or brain stem displacement and nerve compression presenting as esotropia, horizontal diplopia and head turn to maintain binocular vision. (15)

Children with PF tumours also suffer from oculomotor signs, such as gaze palsy and strabismus (42%), upbeat nystagmus (23%) as well as abnormal acuity (15%), defined as VA below 20/40 (or > 0.3 logMAR) in one or both eyes. (13-16)

WHO grade IV Medulloblastoma (MBL), cerebellar (WHO grade I) pilocytic astrocytoma (PA), and ependymoma (EP) constitute the most frequent PF tumour types, with MBL and EP which have a greater risk of abnormal vision compared with cerebellar PA.

Overall survivors from MB or cerebellar PA suffer from frequent visual sequelae including persistent strabismus (25-29%) or nystagmus (12.5- 18%). (13-16)

Other histological subtypes such as ATRT and rare embryonal tumours have also been described in this location presenting with similar features.

### **Supratentorial Region**

Temporal, parietal and/or occipital lesions tend to present less often with visual symptoms, if compared with midline or PF tumours. However, neoplasm from the occipital or temporal lobes and involving the visual cortex or the geniculate bodies and/or optic radiations can cause VF defects such as homonymous hemianopia (see **Fig. 1**).

A variety of histologies can occur in tumours of this location, including high grade glioma (HGG), ependymoma, LGG, embryonal tumours, or other rare tumour entities.

### **Visual Pathways**

A visual deficit represents the main, and often sole symptom and sign of a CNS neoplasm infiltrating the visual pathways. Named as optic pathway gliomas (OPG) and histologically mostly low-grade glioma (LGG), OPG have a highly variable clinical course, ranging from stable and indolent to multiply progressive disease, potentially leading to severe visual sequelae. Overall, a significant proportion of children with OPG suffer from visual impairment, with 5 - 10% of them meeting the criteria for legal blindness. (17, 18)

Children with OPG tend to present with a combination of (uni/bilateral) VA and VF defects, influenced by tumour location along the visual pathway, as shown in **Fig 1**, and including homonymous or bitemporal hemianopia as the most frequent VF defects. (17-19) Infants below 1 year of age, and those with post chiasmatic OPG seem to carry a higher risk of VA deterioration. (20) Approximately 15% of children with Neurofibromatosis type 1 (NF1), a well-known cancer predisposition syndrome, present with OPG which is characterized by an indolent course in up to 70 - 85% but a more aggressive behaviour leading to visual deficits in about 15% - 30% of them (20, 21)

In addition to VA and VF defects, isolated optic nerve gliomas (IONG) with or without NF1 present with eye proptosis, and/or optic pallor/atrophy from chronic suffering of nerve fibres. Optic nerve sheaths meningioma which is commonly associated with Neurofibromatosis type 2 (NF2) presents with similar ophthalmological features of IONG.

Furthermore, optic disc abnormalities with papilledema can also occur in OPG, especially in large hypothalamic-chiasmatic OPG causing obstructive hydrocephalus and RICP.

### **Suprasellar (extra-optic)**

Visual loss is common in extra-visual pathways suprasellar region tumours, such as craniopharyngioma (CP), mainly due to external compression of the optic chiasm and other adjacent visual structures.

At diagnosis, and after treatment, about 30% of children with CP present or experience significant visual decline and about 10% are legally blind. Neuro-ophthalmological manifestations of CP include a combination of VA loss (43.9%) and VF defects (38%) of variable- but often relevant- severity and with uni- (13%) or bitemporal hemianopia (29.5%) as the most frequent VF defects. Blindness in one or both eyes has been reported in up to 13% of children with CP.

Fundoscopy alterations are also common (32%) in suprasellar tumour causing obstructive hydrocephalus and RICP with either papilledema (25.8%) or optic pallor/atrophy (44.8%).

Strabismus (16.5%), diplopia (14.5%) and see-saw, horizontal pendular or rotatory nystagmus (6%), as well as cranial nerve defects (13%) can also be unveiled at the orthoptic examination. (22 - 24)

Intracranial germ cell tumours (iGCT) such as germinoma, which also occur in the suprasellar region, can cause similar features including VF defects, and papilledema with associated RICP.

### **Brain Stem and Pons**

Brain stem and/or pontine tumours present frequent cranial nerve palsies including CN-III, CN-IV or CN-VI leading to diplopia with exo-/esotropia, strabismus or other oculo-motor deficits. Not infrequently, torticollis accompanies paretic strabismus as an adjustment to maintain binocular vision.

Amongst brain stem lesions, clinical course can be highly variable with both aggressive and relatively indolent tumours which tend to originate from the pons or the lower brain stem respectively. In general, an intrinsic pontine mass, associated with a shorter interval between symptoms onset and diagnosis (< 3-6 months) is more suggestive of diffuse intrinsic pontine glioma (DIPG) or H3K27M (WHO grade IV) diffuse midline glioma (DMG), while exophytic and dorsal brain stem lesions, causing a longer interval between symptoms and diagnosis are more suggestive of lower grade lesions.

### **Pineal/ Tectal plate**

Pineal lesions, which often occur in association with obstructive hydrocephalus and RICP, can lead to visual loss, including mainly papilledema (69%), optic atrophy (5%) and VF defects (4-5%). In addition, abnormal ocular movements with supranuclear paralysis of upward gaze and convergence together with light-near dissociation of the pupillary reflex, named as Parinaud's Syndrome, are typical of pineal or mesencephalic/tectal plate tumours. Convergence-retraction nystagmus is also found in association with Parinaud's syndrome and localizes the tumour to the dorsal midbrain/tectal plate. (25)

Most common pineal gland neoplasms mainly include malignant WHO grade IV pineoblastoma, and secreting or non-secreting germ cell tumours (GCT), while tectal plate/mesencephalic tumours are more often of low-grade histology (LGG).

### 3. Treatment-related Visual Impairment

Potential treatment complications and toxicities in children treated for a CNS neoplasm secondary to surgery, chemotherapy (CT), radiation (RT), and targeted treatments, can lead to visual impairment (VI) both acutely and long-term.

#### **Surgery/RICPTreatment**

Surgical intervention to resect a CNS tumour involving the chiasm, optic radiation as well as occipital lobes might eventually result in a variable degree of VF or VA post-operative deficits. Furthermore, surgery for posterior fossa ependymoma, or medulloblastoma might also results in cranial nerves (CN VI)- or gaze deficits and cause ocular misalignments or nystagmus.

A sudden and often irreversible VA or VF loss can be the consequence of perioperative complications such as optic nerve dissection, as well as an abrupt optic nerve vascular supply interruption after decompressive shunt procedures with rapid changes of intracranial pressure. (26)

#### **Chemotherapy and Targeted Agents**

Many of the standard CT agents used to treat CNS tumours have been described to cause visual-related complications, including optic neuritis, central and peripheral neuropathy, papilledema, maculopathy, cataracts, and overall visual loss. Alkylating agents used to treat selected CNS tumour types such as nitrosureas (CCNU), and platinum compounds (cisplatin) can cause dose-dependent retinal toxicity. Also, other common agents, such as vincristine (vinca alkaloid) and methotrexate have been rarely reported to possibly cause visual toxicity, such as uni/bilateral ptosis, optic neuropathy and, less frequently, posterior reversible encephalopathy syndrome (PRES) and visual loss. Prolonged use of steroids can also cause ocular toxicity with cataract. (26-28)

Targeted treatments which are increasingly used in children with various types of neoplasms can also cause visual toxicities. BRAF inhibitors can be associated with ocular toxicity, such as uveitis (41%), dry eyes, conjunctivitis, and photosensitivity in rare cases (4%).

Retinopathy has been described in association with MEK inhibitors, mainly in adults, ranging from intraretinal fluid accumulation - which is only visible at OCT - to retinal vein occlusion (RVO) leading to blurred vision and, albeit rarely, irreversible VA loss. It is not entirely clear if MEK-Retinopathy is also present in children. A regular assessment of VA and macular OCT/infrared funduscopy images can be helpful to monitor these potentially serious visual-side effects from MEKi, and guide decisions to interrupt or terminate treatment before irreversible visual loss occurs. (29, 30)

#### **Radiotherapy**

The use of RT in children with a CNS tumour constitute a significant risk factor of visual dysfunction including radiation-induced necrosis, retinopathy and amblyopia. Risk of cataract is associated with radiation doses (>30Gy) to posterior fossa, temporal lobes, as well as prolonged exposure to steroids, in particular prednisone. Moreover, a dose of 50Gy or more to the eye significantly increases the risk of cataracts, double vision, dry eyes, and blindness. Overall, between 5% and 8.5% of patients treated with  $\geq 50$  Gy bilaterally (chiasm or both optic nerves), for tumours of the suprasellar or the anterior optic pathway were at risk of VA decline. (31 - 34)

Cranio-spinal irradiation (CSI) which is still routinely used to treat children with medulloblastoma and other malignant CNS tumours has several short and long-term side effects, and associated with dry eye, retinal opacity, and posterior subcapsular cataract, which tend to occur at a median time of 27.6 months and in up to 28.8% of children after CSI. (35)

Finally, also non-visual tumour and/or treatment-related complications such as hearing loss, posterior fossa syndrome, or neurocognitive deficits need to be considered as might concur to worsen the functional outcome in this group. (14, 36)

#### 4. Recommended Baseline Visual Assessment - RAFFO

A list of visual parameters definition is available from **Table 3**.

Irrespectively from tumour location, a baseline (neuro)-ophthalmologic evaluation is recommended in all children with a newly diagnosed CNS neoplasm to include essential visual parameters with minimal requirements and best clinical practice methods and needed resources as indicated in **Table 4** (37)

The **RAFFO** acronym:

- **R**efraction
- Visual **A**cuity (**VA**)
- Visual **F**ields (**VF**)
- **F**undoscopic examination
- **O**rthoptic assessment

#### Refraction

Assessment of potential pre-existing or newly developed refractive error is paramount before assessing other parameters, to avoid confounding VA loss with a lens refractive problem, which might only require corrective lens.

#### Visual Acuity (VA)

VA reflects visual pathway integrity, still representing the most important measure in children with a CNS tumour, and it is defined as the size of detail that can just be resolved by an individual (visual resolution). It should be measured as the best VA corrected from refractive errors (BCVA), assessed monocularly - if possible, from far and near distance, and reported as the angular size of detail within the optotype at threshold that subtended by each part of the letter (logMAR), from 0.0 (normal vision) to 2.0 (see **Table 5**). Clinically relevant changes in VA are defined as a difference of 0.2 LogMAR VA or more. (38) In case an accurate quantitative VA cannot be performed, observation of visual fixation may still be useful to assess the presence or absence of visual perception and VA should be documented as Hand Motion (HM), counting fingers (CF), Light Perception (LP) or No Light Perception (NLP).

The most appropriate VA testing method depends on child's age and ability to cooperate. Teller Acuity preferential looking Cards (TAC) are most used to quantify VA in pre-verbal children and

infants, while Lea symbols, Cardiff Acuity Test, the Kays Picture Chart followed by reading charts (e.g. HOTV or Snellen) which can be used in older children. (38)

It is important to highlight that changing testing methods can lead to slightly under/overestimate VA over time. In addition, as vision rapidly matures in the first 2-3 years, reaching its full potential only after 5 years of age normal for age VA ranges should be used in this age group. (39)

### **Visual Fields (VF)**

Whilst VF measurement is not always feasible, due to young age and limited cooperation, an attempt to assess VF defects is considered essential in children with a CNS neoplasm.

VF should be measured monocularly if possible and with an age-appropriate testing method.

Confrontation or BEFIE test are used in children < 5 years of age (**Fig 2** and **Fig 3**), while Goldmann kinetic perimetry or -preferably- automatic perimetry (HFA 30-2 Sita Fast or Octopus) are recommended in older and more cooperative children thereby providing a more objective VF measurement. (40-42)

VF defects should be reported as symmetric (concentric) or asymmetric (homonymous) and as nasal/temporal restrictions ranging from 0° (full restriction) to no restriction. As VF are amongst the most underreported visual symptoms, we have formulated a list of questions to parents and/or children which could help to unveil VF defects (see **Table 6**)

### **Fundoscopy exam**

Papilledema, as well as other optic disc abnormalities (pallor/atrophy) are best assessed by dilated fundoscopic exam requiring a cooperative child. It is important to consider that papilledema may be absent in case of sub-acute or chronic RICP, and its absence does not rule out a CNS tumour. While at early stages only peripheral vision with visual fields (VF) defects is affected, visual acuity (VA) loss can also occur at later stages secondary to optic atrophy and axonal nerve fibres loss. (43, 44)

When funduscopy is not possible or results are inconsistent, OCT could be used as it may provide a more objective and reliable method to assess optic nerve disc swelling with RNFL thickening. (44, 45)

### **Orthoptic examination and eye movement disorder assessment**

Ocular alignment, eye movement and relative afferent pupillary defect (RAPD) can be assessed during the initial neurological examination of the oculomotor cranial nerves (CN III, IV and VI) and with pupillary light reflexes, cover test and pursuit movements ideally performed by an orthoptist. This examination may reveal strabismus, such as an exotropia or esotropia, which may be intermittent or continuous, as well as nystagmus or gaze palsies. Postural observation may reveal a head turn or torticollis, sometimes used by children with a CNS tumour to compensate abnormal eye movements and diplopia.

Non-essential, but still useful visual parameters to be evaluated in selected cases include the followings:

- Colour/contrast vision assessment
- Slit lamp (particularly if NF1 suspected)
- Optical Coherence Tomography (OCT) with RNFL and/or GCL-ILP measurement

In particular, the value and the emerging role of OCT and RNFL thickness is recognized in the daily clinical practice for many visual pathway disorders as more objective biomarkers compared with VA in OPG, as well as in other tumour types. A cut-off value (76  $\mu\text{m}$ ) has been used to define an abnormal OCT, with a change in circumpapillary RNFL thickness and/or macular GCL-ILP thickness of  $\geq 10\%$  as a significant change over time. (45) However, at present stage, no clear consensus exists on how to interpret OCT changes in relation to disease progression/response to treatment, and OCT results should be considered only together with other functional parameters. Also, RNFL measures are prone to subjective measurement, and can lead to frequent artifacts, which should be considered.

## 5. Recommended Visual Surveillance After Treatment

A significant proportion of children with CNS tumours can experience pre-existing or new visual impairment during or after treatment. Overall, we suggest continuing a regular ophthalmological surveillance in children diagnosed and treated for a CNS tumour. Monitoring frequency and duration should be determined by various factors, including the initial tumour location, type of treatment, and the presence, severity, and risk of further visual symptoms dysfunction. (46)

## 6. Must Have/Desirable/Not To Do Recommendations

MUST HAVE/DO	MAIN RESPONSIBILITY	MAIN TARGET POPULATION
A careful history with questions about visual symptoms and physical including neurological and <i>fundoscopic examination</i>	(Neuro)-Paediatrician	All children with suspected CNS tumour
Referral for a baseline neuro-ophthalmological evaluation	Ophthalmologist/orthoptist	All children with newly diagnosed CNS tumour
Multidisciplinary and comprehensive approach to the diagnosis and management of visual impairment	Multidisciplinary neuro-oncology team	All children with newly diagnosed CNS tumour and visual signs
Referral to a dedicated visual impairment rehabilitation	Neuro-(ophthalmologic) Rehabilitation service	All children with newly diagnosed CNS tumour and visual signs
DESIRABLE TO HAVE/DO	MAIN SUBJECT	MAIN TARGET
(Hand-held) OCT (if available) in young children: Use of RNFL/GCL as surrogate measures of visual acuity in selected groups (e.g OPG, CRP)	Neuro-ophthalmologist	Children with OPG and CP
NOT TO DO	MAIN SUBJECT	MAIN TARGET
Omit or delay a baseline ophthalmology assessment in case of absent visual symptoms	(Neuro)-Paediatrician	All children with diagnosed CNS tumour
Discontinue ophthalmologic follow-up in case of children treated for a CNS tumour	Neuro-ophthalmologist Neuro-rehabilitation services	All children treated for a CNS tumour















## 7. Tables and Figures


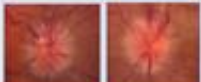








**Table 1: Visual Symptoms and Signs in Children with Newly Diagnosed CNS tumour**

Authors (ref)	Visual Symptoms	Neuro-ophthalmological manifestations					
		Papilledema	Optic atrophy	VA loss	VF defects	Strabismus (or CN palsy)	Abnormal eyes movements (nystagmus, etc.)
<i>Wilne</i> (3,4)	38%	38%	-	39% (blurred vision)	-	39% (diplopia)	6%
<i>Mole</i> (5)	-	30%	26%	-	-	25%	
<i>Liu</i> (6)	15%	35%	-	54%	19%	60%	
<i>Nujits</i> (7)	43%	44%	-	10%	55%	22%	66%

**Table 2** Visual Symptoms and signs *by* CNS Tumour Location

Tumor location most common histotypes	Visual symptoms and presentation	Ophthalmological findings	Visual fields (examples)	Fundus (examples)
Visual pathways LGG/OPG - Right optic nerve - Left optic nerve - Chiasm - Optic tract	- Blurred/reduced vision (OD/OS/ODS) - Visual field loss - Ocular misalignment - Diplopia - Wobbling eyes	- VA deficits - VF defects - Sectorial or total optic disc pallor - Disc edema - RAPD - Eye movement disorders (strabismus, nystagmus) - Proptosis - Color/contrast sensitivity deficits  - OCT RNFL alterations - OCT GCL - VEP	 optic nerve glioma OD   posterior left optic nerve lesion – anterior-chiasm   binasal hemianopsia   mid-chiasm lesion   posterior-chiasm lesion   homonymous hemianopsia – optic tract syndrome	 disc edema grade II OD   total optic atrophy OD           bow-tie atrophy OD
Suprasellar (extra-optic) Craniopharyngioma, germ cell tumours	- Blurred/reduced vision OD/OS/ODS - Visual field loss - Ocular misalignment - Diplopia - Wobbling eyes	- VA deficits - VF defects - Sectorial or total optic disc pallor - Disc edema - RAPD - Eye movement disorders (strabismus, cranial nerve palsies, nystagmus) - Color/contrast sensitivity deficits  - OCT RNFL alterations - OCT GCL	 bitemporal quadrantanopsia   bitemporal hemianopsia	 temporal optic nerve pallor

**Table 2** (continued)

Tumor location most common histotypes	Visual symptoms and presentation	Ophthalmological findings	Visual fields (examples)	Fundus (examples)
Posterior fossa Medulloblastoma, LGG, ependymoma, others	- Diplopia - Ocular misalignment - Wobbling eyes	- Disc edema - Eye movement disorders (nystagmus, cranial nerve palsies, gaze palsy, INO)		 disc edema grade III  disc edema grade IV  disc edema grade V
Temporal region HGG, ependymoma, others - optic radiation	- Visual field loss	- VF defects	 'pie in the sky'  quadrantanopia superior  quadrantanopia inferior  homonymous hemianopsia	
Occipital region HGG, others - visual cortex	- Visual field loss	- VF defects	 homonymous hemianopsia with macular sparing  quadrant scotoma inferior	
Brain stem and pons DMG, others	- Diplopia - Ocular misalignment - Limitation of gaze - Wobbling eyes	- Eye movement disorders (cranial nerve palsies, gaze deficits, INO, nystagmus)		
Pineal/tectal plate Germ cell tumors, LGG, others	- Limitation of gaze - Diplopia - Wobbling eyes	- Parinaud's syndrome - Disc edema		 disc edema grade I

**Table 3: Visual Parameters Definition and Unit**

Visual Parameters	Definition and Units
Papilledema	-Swelling of the head of the optic nerve, associated with raised intracranial pressure (RICP) -Quantitative grading methods (Modified Frisen Scale) from Stage 1 to 5
Visual acuity (VA)	- The ability of the individual to discriminate detail, and the size of detail that can just be resolved by an individual (visual resolution) - Continuous linear scale of VA loss measurement based on the logarithm of the angular size of detail within the optotype at threshold (Minimum Angle of Resolution or MAR) that subtended by each part of the letter, from 0.0 (normal vision) to > 2.0 logMAR
Visual Field (VF)	- The total area in which objects can be seen in the side (peripheral) vision focusing your eyes on a central point. - hemi/homonymous/concentric/nasal/temporal with degrees of deficit (with Goldmann perimetry or automated VF)
Strabismus	-Intermittent or constant deviation of ocular alignment
Nystagmus	-A condition in which there are frequent involuntary oscillations of the eyes that result in reduced visual function
Relative Afferent Pupillary Defect	-A condition in which pupils respond differently to light stimuli shone in one eye at a time due to unilateral or asymmetrical disease of the retina or optic nerve/s
Gaze deficits	-cranial nerve palsy (impairment of III, IV or VI nerve function causing abnormal eye movement and strabismus), -bilateral gaze palsy (impaired horizontal, vertical or combined movements in both eyes), -unilateral gaze palsy (internuclear ophthalmoplegia, one and a half syndrome)
Eye movement disorders	-Saccades (fast movements of the eyes), -smooth pursuits (slow, tracking movements of the eyes), -vergence (opposite movements of the eyes such as convergence where both eyes turn inwards symmetrically or divergence where both eyes turn outwards), -vestibulo-ocular and opto-kinetic reflexes (involuntary movements of the eyes in response to moving objects and movement of the head and body)
Optical Coherence Tomography (OCT)	-non-invasive imaging test which uses light waves to take cross-section pictures of the retina with its distinctive layers and thickness, Retinal Nerve Fiber Layer (RNFL) and/or Ganglion Cell Layer (GCL)

**Table 4: Essential Visual Parameters Minimal Requirement Vs Best Practice**

	Minimal Requirements*	Best Practice**
<b>Visual Acuity (VA)</b>	<b>Testing Methods</b>	
	Best corrected (from refractive errors)	Quantitative data using LogMAR
	Monocular	Use of OCT with RNFL and GCL-IPL measurement
	From near and far distances Age-appropriate tests (see text)	
	<b>Professional Resources</b>	
	Ophthalmologist	Paediatric (Neuro)-ophthalmologist
<b>Visual Fields (VF)</b>	<b>Testing Methods</b>	
	Direct confrontation test	BEFIE test or equivalent
	Kinetic Manual Perimetry (Goldmann)	Automated VF perimetry
	<b>Professional Resources</b>	
	Ophthalmologist	Technical ophthalmic assistant specialized in visual fields in children
<b>Optic disc (papilledema)</b>	<b>Testing Methods</b>	
	Direct funduscopy with dilated pupil	Use of OCT in selected cases
<b>Orthoptic assessment</b>	<b>Professional Resources</b>	
	Ophthalmologist	Orthoptist

\*Best Standard Practice = ideally recommended if available

\*\*Minimal Requirements: Needs to be performed and available in all Centres

**Table 5: Table for VA with LogMAR Values Conversion (38, adapted with permission)**

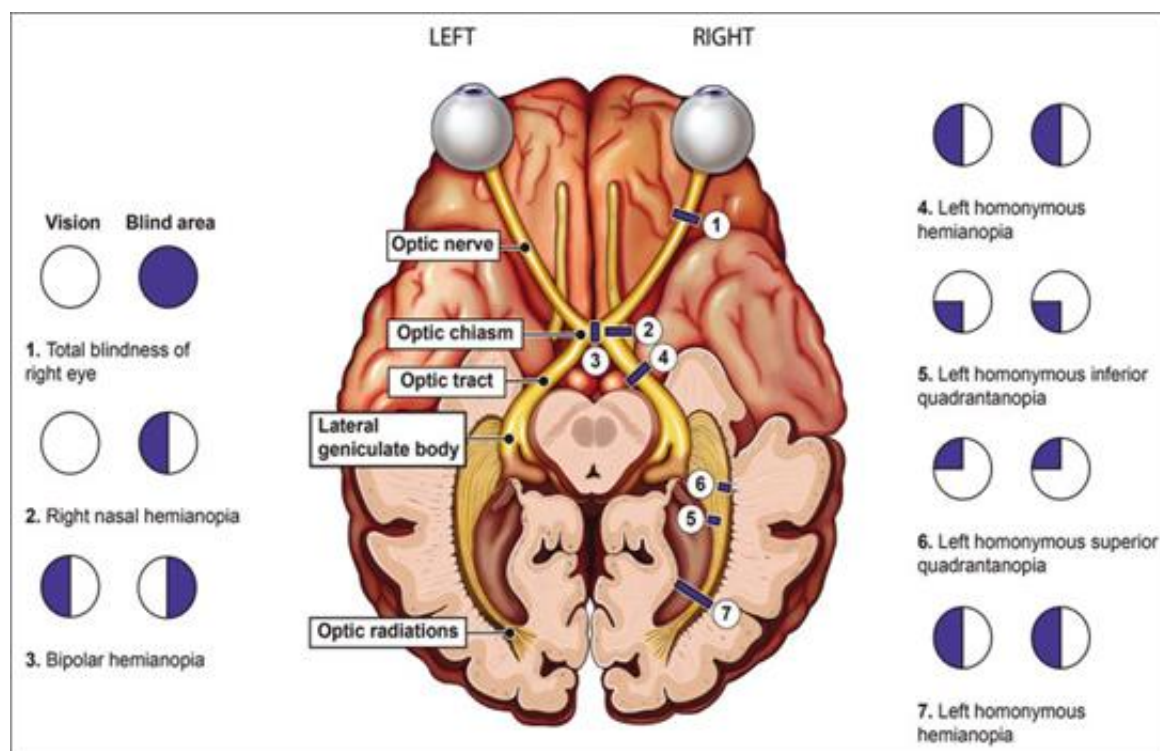
Decimals	Snellen (feets or meters)		LogMAR
	20ft	6m	
1.0	20/20	6/6	0.0
0.8	20/25	6/7.5	0.1
0.63	20/32	6/10	0.2
0.5	20/40	6/12	0.3
0.4	20/50	6/15	0.4
0.32	20/60	6/18	0.5
0.25	20/80	6/24	0.6
0.2	20/100	6/30	0.7
0.16	20/125	6/38	0.8
0.125	20/160	6/48	0.9
0.1	20/200	6/60	1.0
0.08	20/250	6/75	1.1
0.06	20/320	6/95	1.2
0.05	20/400	6/120	1.3
0.04	20/500	6/150	1.4
0.032	20/630	6/190	1.5
0.025	20/800	6/240	1.6
0.02	20/1000	6/300	1.7
0.016	20/1250	6/380	1.8
0.013	20/1600	6/480	1.9
0.01	20/2000	6/600	2.0
Counting Fingers	---	---	2.0
Hand Movements	---	---	2.5
Light Perception	---	---	3.0
No Light Perception	---	---	3.5

**Table 6: Possible questions for parents of children with suspected visual field (VF) loss**

Does the child have unexplained exotropia*?
Does the child have unexplained torticollis*?
Does the child tend to bump into people or things (objects)?
Does the child have difficulty finding words, difficulty reading as evidenced by missing words of hemifield slip, difficulty during tests as the result of skipping letters, not reading an entire line?
Does the child eat half of his plate?
Does the child colour half of a colouring page?
Has the child suddenly startled or shown fear in traffic?
Can the child find his parents in the schoolyard/playground?

\* with or without neurologic damage

**Fig 1: Visual Fields Defects Based on Visual Pathways Tumour Location (47 with permission)**



**Fig. 2: BEhavioural visual FIElds screening test for clinical use (48 with permission)**

Source: Porro, G., et al. A new behavioural visual field test for clinical use in pediatric neuro-ophthalmology. *Neuro-Ophthalmology* 19, 205–214 (1998).

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## Quality of Survival Working Group

### STANDARD CLINICAL PRACTICE RECOMMENDATIONS

# QUALITY OF SURVIVAL WORKING GROUP

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## 1. Background

Quality of survival (QoS) refers to the presence and impact of the long-term neurocognitive, endocrine and other medical, behavioural, emotional and adaptive functional sequelae of CNS tumour patients. Due to the increasing survival rates in children and adolescents treated for a CNS tumour the assessment and follow-up of these domains is crucial in order to support survivors and their families. Children and adolescents with a CNS tumour are at high risk to develop long-term sequelae because of tumour and treatment related factors – they do have the highest morbidity and mortality amongst all childhood and adolescent cancer entities. A bio-psycho-social approach is recommended at diagnosis, during and after treatment of a child/adolescent with a paediatric CNS tumour. This should be reflected in an interdisciplinary approach. As cognitive late effects are very common in paediatric CNS tumour survivors and these late effects can affect academic/professional functioning, independent living and quality of life, special attention needs to be paid to surveillance of neuropsychological functioning and required interventions to ameliorate QoS.

## 2. Institutional requirements

At diagnosis, during and after treatment each patient should have access to at least:

- Neuropsychological assessment as per international recommendations
- Endocrine assessment
- Ophthalmology assessment
- Hearing assessment
- Neuro-rehabilitation (in –or outpatient facility)
- Physiotherapy, occupational therapy and speech therapy
- AYA (adolescent and young adults) transition
- Palliative care
- Vocational counselling/ social work/ child life specialist/ teachers
- Age and risk adapted fertility preservation prior to start of gonadotoxic treatment

## 3. Essential quality parameters

### International follow-up guidelines

The International Guidelines Harmonization Group for Late Effects of Childhood Cancer is constantly developing new/updated guidelines on medical and psychosocial surveillance and support (<https://www.ighg.org/>). Each paediatric oncology centre should be aware of these guidelines and provide minimal standards to organize the medical and neuropsychological/ psychosocial surveillance and follow-up of these patients.

Other publicly available long-term follow-up guidelines are from the Children's Oncology Group (COG, <http://www.survivorshipguidelines.org/>) and PanCare (<https://www.pancare.eu/>).

All these guidelines are risk-adapted, based on the treatment received (surgery, chemotherapy and radiation therapy) and cover multiple aspects of follow-up care.

**Table 1:** Most relevant potential late effects in children and adolescents diagnosed with a CNS tumour. Potential late effects mainly based on the COG guidelines

Therapeutic exposure	Potential late effects	Periodic evaluations	Specific guidelines IGHG and SIOPE QoS group (in addition to COG; most freely available)
Paediatric CNS tumour	Adverse psychosocial/ quality of life effects	Educational and/ or vocational progress Social withdrawal	IGHG Guideline in progress
Paediatric CNS tumour	Mental health disorder	Regular psychosocial assessment (e. g. depression, anxiety, post – traumatic stress, suicidal ideation)	IGHG Guideline in progress
Paediatric CNS tumour	Fatigue, sleep problems	Psychosocial assessment	Christen S et al; IGHG psychological late effects group. Recommendations for the surveillance of cancer-related fatigue in childhood,

			adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group; Journal of Cancer Survivorship; 2020 (1)
Chemotherapy and cranial radiation	Dental abnormalities	Dental exam and cleaning	
Alkylating agents	Testicular hormonal dysfunction Impaired spermatogenesis Ovarian hormone deficiencies Reduced ovarian follicular infertility	Puberty development (Tanner stage, testicular volume) Sexual function Monitor growth until mature Menstrual history Menopausal symptoms	R Skinner et al; Recommendations for gonadotoxicity surveillance in male childhood, adolescent and young adult cancer survivors: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium; Lancet Oncology, 2017 (2)  W van Dorp et al; Recommendations for premature ovarian insufficiency surveillance for female childhood, adolescent and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium; Journal of Clinical Oncology; 2016 (3)
Heavy metals	Ototoxicity	Audiological evaluation	Clemens E et al; Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium; The Lancet Oncology; 2019 (4)
Antimetabolites	Reduced bone mineral density	Bone density evaluation	IGHG guideline in progress
Antimetabolites	Neurocognitive late effects, clinical leukencephalopathy	Neuropsychological evaluations, neurological exam	Jacola LM et al; Assessment and Monitoring of Neurocognitive Function in Pediatric Cancer; J Clin Oncol; 2021 (5)  Limond J et al; Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years; Eur J Paediatr Neurol; 2020 (6)
Corticosteroids	Reduced bone mineral density, osteonecrosis	Bone density evaluation, Musculoskeletal exam	IGHG guideline in progress
Corticosteroids	Cataracts	Visual acuity, Fundoscopic exam	

Plant alkaloids	Peripheral sensory or motor neuropathy	Neurological exam	
Radiation therapy	Secondary malignancy	Physical exam including neurological and skin exam, Consider CNS imaging in case of clinical findings	<p>Bowers DC et al; Surveillance for subsequent neoplasms of the CNS for childhood, adolescent, and young adult cancer survivors: a systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group; The Lancet Oncology; 2021 (7)</p> <p>Clement SC et al; Balancing the benefits and harms of thyroid cancer surveillance in survivors of Childhood, adolescent and young adult cancer: Recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium; Cancer Treatment Reviews; 2018 (8)</p>
Cranial radiation	Neurocognitive late effects, clinical leukencephalopathy,	Neuropsychological evaluations, neurological exam	<p>Jacola LM et al; Assessment and Monitoring of Neurocognitive Function in Pediatric Cancer; J Clin Oncol; 2021 (5)</p> <p>Limond J et al; Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years; Eur J Paediatr Neurol; 2020 (6)</p>
Cranial radiation	Cerebrovascular complications	Neurological exam	
Cranial radiation	Hormonal deficiency, overweight, obesity, metabolic syndrome	Physical exam, endocrinological evaluations	IGHG guidelines in progress
Cranial radiation	Cataracts, ocular toxicity	Visual acuity, Funduscopy exam	
Cranial radiation	Ototoxicity	Audiological evaluation	Clemens E et al; Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium; The Lancet Oncology; 2019 (4)
Spine radiation	Artery disease	Neurological exam	
Spine radiation	Cardiac toxicity	Blood pressure, Cardiac exam, Echo and ECG	Armenian SH et al; Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline

			Harmonization Group; The Lancet Oncology; 2015 (9)
Spine radiation	Colorectal cancer	Colorectal cancer screening	IGHG guideline in progress
Spine radiation	Scoliosis/ kyphosis	Exam of back/ spine	
Brain surgery	Neurocognitive deficits	Neuropsychological testing	Jacola LM et al; Assessment and Monitoring of Neurocognitive Function in Pediatric Cancer; J Clin Oncol; 2021 (5)  Limond J; Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years; Eur J Paediatr Neurol; 2020 (6)
Brain surgery	Hormonal deficiency, overweight, obesity, metabolic syndrome	Physical exam, endocrinological evaluations	IGHG guidelines in progress
Spine surgery	Scoliosis/ kyphosis	Exam of back/ spine	
<b>Pre-treatment</b>			
All	Fertility preservation		Mulder RL et al; Fertility preservation for female childhood, adolescent, and young adult patients with cancer: recommendations from the PanCareLIFE consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2021 (10)  Mulder RL et al; Fertility preservation for male childhood, adolescent and young adult patients with cancer: recommendations from the PanCareLIFE consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group; The Lancet Oncology; 2021 (11)  Mulder RL et al; Communication and ethical considerations for fertility preservation for childhood, adolescent, and young adult patients with cancer: recommendations from the PanCareLIFE consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group; The Lancet Oncology; 2021 (12)

#### 4. Contact centres/ networks

Quality of survival working group of SIOP-E brain tumour group (<https://siope.eu/european-research-and-standards/clinical-research-council/siopecrc/european-clinical-study-gr-2852/>)

## 5. Summary

<b>Must have</b>
Access to a qualified multidisciplinary team under the leadership of paediatric neurooncology – regular multiprofessional team meetings to discuss all aspects of care of the patients
Access to physiotherapy/ occupational therapy/ speech therapy
Neuropsychological assessments must be available
Psychosocial support systems must be available
Experienced guidance for school/ sibling and family/ social environment during and after treatment
Every patient must have an acute and long-term rehabilitation - plan and access to rehabilitation facilities
Assess Quality of Survival at diagnosis and initial treatment
AYA-transition plan must be available
Access to palliative care must be available
<b>Desirable</b>
Neuropsychological evaluation should be performed standardized during regular follow-up visits
Dedicated multidisciplinary follow-up care team
<b>Don't do</b>
Follow-up visits that only evaluate medical condition (check also psychosocial, neuropsychological, school functioning!)

## 6. References

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