



Overview of European standard clinical practice recommendations for multidisciplinary teams involved in the treatment of central nervous system tumours in children and adolescents – SIOPE Brain Tumour Group

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ABSTRACT

Tumours of the central nervous system (CNS) represent the most common group of solid tumours in children and adolescents up to the age of 18 years. They comprise several biological entities, subgroups, and subtypes. These subtypes and additional factors, including age at diagnosis, location, stage, or genetic characteristics of the tumours result in a very heterogeneous spectrum of treatment-relevant strata for risk-adapted multimodal treatment recommendations, clinical courses, and long-term outcomes. Multidisciplinary teams with highly

Abbreviations: ACTH, adrenocorticotrophic hormone; CN, cranial nerve; CNS, central nervous system; CPP, central precocious puberty; CT, computed tomography; FSH, follicle stimulating hormone; GH, growth hormone; HP, hypothalamic-pituitary; ICP, intracranial pressure; LH, luteinizing hormone; MDT, multidisciplinary team; MRI, magnetic resonance imaging; OCT, optical coherence tomography; OPG, optic pathways glioma; SIOPE, the European Society for Paediatric Oncology; TSH, thyroid-stimulating hormone; VA, visual acuity; VF, visual field.

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 quality of survival

experienced members are needed to treat these children and adolescents to achieve the best possible outcome in the short and long-term. This is particularly important for the new CNS tumour entities with no established standard of care. On behalf of the Brain Tumour Group of the European Society for Paediatric Oncology, we summarize the key statements of the involved disciplines that need to cooperate in the diagnosis and risk-adapted treatment of children with CNS tumours: neuroradiology, neurosurgery, neuropathology, radiotherapy, endocrinology, neuro-ophthalmology, and quality of survival professionals, covering what should be considered standard clinical practice for diagnostic assessments, treatment modalities, and follow-up of children with CNS-tumours.

1. Introduction

Tumours of the central nervous system (CNS) account for approximately one quarter of all neoplasms in children and adolescents up to the age of 18 years in high-income countries and represent the most common group of solid tumours. CNS tumours comprise several biological 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 a watch and wait strategy only, others can be treated with surgery alone. At the other end of the treatment-intensity spectrum are CNS tumours that need multi-modality treatment with surgery, (high-dose) chemotherapy, and radiotherapy. In addition, many of the newly identified CNS tumour entities described over the past decades have no established standard of care, nor any prospective clinical trial data to inform them. Therefore, multidisciplinary teams and exchange with expert panels are crucial to provide the best care for these children and adolescents.

During the last decades, remarkable advances have been made in diagnosing and treating CNS tumours in children and adolescents. This includes imaging with increasingly sophisticated magnetic resonance imaging (MRI) techniques, more precise preoperative planning of tumour surgery, advances in neurosurgery, improvement in examination of tumour tissue by moving from a morphology-based approach to integrated pathology using different immunohistochemical markers, genetic and epigenetic features, an avoidance or reduction in radiation doses and fields, and the increasing use of protons for radiotherapy. As a result of these improvements, the number of long-term survivors is increasing [4]. In parallel, the issue of late effects has been clearly recognised.

The Brain Tumour Group of the European Society for Paediatric Oncology (SIOPE-BTG) unites all experts in the field of paediatric neurooncology. It includes eight tumour working groups and nine discipline groups. This manuscript aims to provide guidance for professionals involved in the treatment of children and adolescents diagnosed with a CNS tumour, independent of the exact underlying diagnosis.

2. Methods

The European Reference Network on Paediatric Cancer (ERN Paed-Can) has asked the different European paediatric tumour groups, including SIOPE-BTG, to provide standard of care documents for their respective type of cancer in Europe. In this overarching manuscript we cover aspects of the treatment of CNS tumours in children and adolescents which are independent of the specific type of CNS tumour. Specific aspects and treatment modalities are covered in the separate manuscripts of each type of CNS tumour. The topics covered in this manuscript are based on the SIOPE-BTG discipline working groups. Each working group was represented by two to three experts. The disciplines included neuroradiology, neurosurgery, neuropathology, radiotherapy, endocrinology, neuro-ophthalmology, and survivorship care. The discipline working groups were asked to provide a summary covering essential and general aspects of their discipline, but also actions that should not be considered standard. They were not asked to perform a systematic literature search, but to support their summaries with current

literature. The final guideline was reviewed and approved by the respective working groups, ERN PaedCan, and the SIOPE board.

The use of chemotherapy, a core element in the treatment of CNS tumours, is not part of this manuscript because no separate discipline group exists and because chemotherapeutic approaches differ substantially between tumour types, including high-dose chemotherapy or intraventricular administration for some types. Chemotherapeutic approaches are therefore covered in the separate documents of each tumour group. In general, chemotherapy should only be delivered by experienced personnel and in an appropriate environment, experienced in the handling of cytotoxic agents, the management of acute and long-term toxicities. The term multidisciplinary team (MDT) refers in this manuscript to local or hospital-based structures and not national or international teams of experts.

3. Background

3.1. Epidemiology

The incidence rates of CNS tumours differ across Europe [5]. These differences might arise due to the data sources used to define the incidence, diagnostic and recording practices, or as true differences. Not all European countries have (childhood) cancer registries and if a registry exists, the registration process, coverage, and completeness differ [6]. The difference in coverage results from national or regional registries and different reasons for loss to follow up, such as migration, contribute to incompleteness. In addition, limited access to diagnostic techniques might lead to underdiagnosis in some countries and variabilities in outcome [7].

3.2. 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, chemotherapy, and genetic predisposition (Table 1), the latter which has been shown to cause approx. 8–19 percent of paediatric CNS-tumours [8]. Children and adolescents exposed to irradiation, e.g., cranial radiotherapy during leukaemia treatment, have a higher risk of developing secondary malignancies such as malignant glioma or meningioma.

3.3. Clinical presentation

The clinical presentation of CNS tumours depends on their location, the patients' age, and the grade of malignancy of the tumour [3, 9, 10]. Whereas high-grade CNS tumours usually have a symptom duration of a few days to weeks, symptoms of slow-growing low-grade tumours are often misdiagnosed and the diagnosis can be delayed for several years [11].

Up to half of CNS tumour patients present with raised intracranial pressure (ICP), most commonly with tumours of the posterior fossa [3, 12, 13]. Symptoms include headache and vomiting (typically, but not always early morning), changes in character, concentration disorders, weight loss due to anorexia and food refusal, fatigue, and lethargy [3, 12, 13]. Young children may develop increasing head circumference

Table 1

Cancer predisposition syndromes associated with central nervous system tumours (list not exhaustive; krebs-praedisposition.de/en).

Familial tumour predisposition syndromes	Mutation	CNS tumours
Li-Fraumeni	TP53 (17p13)	Medulloblastoma, Choroid Plexus Tumours, Glioblastoma
Multiple endocrine neoplasia type 1 (MEN1)	MEN1 (11q13)	Hypophyseal adenoma
Constitutional mismatch repair deficiency (CMMRD) syndrome	MLH1 (3p21), PMS2 (7p22), MSH6 (2p16)	Glioblastoma (all in Lynch syndrome)
Adenomatous polyposis coli (APC)	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
Neurofibromatosis type 1 (NF1)	NF1 (17q11)	Optic pathway glioma, other low-grade glioma
Neurofibromatosis type 2 (NF2)	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

before fusion of the cranial sutures. Other symptoms depend on the tumour location and may result from compression or infiltration of brain and spine structures (Table 2). Emergency situations in paediatric neuro-oncology include raised ICP, spinal cord compression, and cauda equina syndrome.

3.4. Multidisciplinary teams

The care of CNS tumours in children and adolescents is only possible within a multidisciplinary team (MDT) with early and ongoing communication between all involved disciplines. Regular MDT

Table 2

Clinical symptoms of central nervous system tumours depending on its location (list not exhaustive).

Location	Symptom
Brain stem / pons	Cranial nerve palsy (caudal nerves), contralateral spastic paresis
Cerebellum	Crooked head position, ataxia, nystagmus, intention tremor, dysdiachokinesia, dysmetria
Pineal region	Parinaud syndrome
Suprasellar / hypophyseal / hypothalamic region	Visual impairment, impaired visual fields, nystagmus, diencephalic syndrome with eating disorder and disturbed sleep-awake-rhythm, signs of endocrinopathy (short stature, hypothyroidism, diabetes insipidus, abnormal pubertal development, hypocortisolism, SIADH, central salt wasting, obesity)
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

meetings, including tumour boards, are essential to bring the expertise from multiple disciplines involved in the care of CNS tumour patients on the same knowledge level. Generally under the leadership of the paediatric neurooncologist, the following disciplines should be part depending on the timepoint of the treatment journey: neurosurgeons, neuropathologists, neuroradiologists, anaesthetists, intensive care specialists, neuro-ophthalmologists, endocrinologists, rehabilitation teams, psychologists, pharmacists, neurologists, physiotherapists, occupational therapists, paediatric oncology nurses, and other relevant subspecialty clinicians and teams specific to the care of each patient. Critical timepoints include initial diagnosis, pre- and post-operative, at suspected progression or relapse, and in case unusual findings and toxicities occurred. Within the European Reference Network for Paediatric Oncology Children and adolescents with cancer (ERN PaedCan), SIOPE-BTG members have been invited to run a virtual tumour board for children with CNS tumours [14]. In addition, two virtual tumour boards focusing on paediatric ependymoma and hypothalamic-pituitary tumours in the United Kingdom have been well-received.

4. Imaging in paediatric CNS tumours

Imaging evaluation of CNS tumours including possible CNS dissemination is core to their management. Standardisation of image acquisition is an essential pre-requisite across all centres who participate in paediatric CNS tumour studies. It facilitates comparisons of scans for individuals across various time points (pre-operative, post-operative, and follow-up imaging) and aids comparability across multiple centres by the central study coordinators and designated radiologists. The SIOPE Brain Tumour Imaging Working Group has developed an imaging consensus protocol based on evidence from earlier clinical trials [15]. The working group members consisted of neuroradiologists, imaging scientists, and clinicians with an interest in brain tumour imaging. 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 major improvements in quality of imaging on 1.5 T and 3 T MR scanners. Despite these advances, there is a huge variation in the capability of the scanner hardware and software across 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 include essential minimal and mandatory sequences to allow effective basic tumour evaluation. The protocol further provides recommendations on advanced, non-mandatory imaging methods including MR spectroscopy, diffusion tensor, and perfusion imaging. The Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group have developed consensus recommendations for response assessment specific for paediatric CNS tumours, including recommendations for MR imaging as part of the response assessment [16–21].

Institutional requirements to perform imaging in children and adolescents with cancer include the availability of a 1.5 or 3 T MRI scanners, trained imaging specialists (radiologist/ neuroradiologist trained in children and adolescents), and specialists able to provide imaging under sedation or anaesthesia (Table 3), and timely postoperative MRI within 72 hours after neurosurgery to avoid increased artefacts. The aspects of imaging sequences, tumour measurement, early post-operative and follow-up imaging, definition of residual tumours and response evaluation, and multi-modal imaging modalities in more detail are summarized in Supplemental S1.

5. Neurosurgery in paediatric CNS tumours

Neurosurgery in paediatric CNS tumours may include treatment of tumour-associated hydrocephalus, complete or partial resection of tumour, biopsy to determine oncological management, or a combination of these at different disease stages. Paediatric neurosurgical resources in terms of surgical expertise and access to modern equipment, are crucial

Table 3

“Must have”, “desirable” and “not to do” in children and adolescents with central nervous system tumours by discipline group.

All discipline groups
<p>Must have Being part of multidisciplinary teams to discuss every new patient at diagnosis, during treatment, and follow-up</p>
<p>Imaging</p>
<p>Must have All imaging studies must be performed according to the SIOPE-BTG neuroimaging protocol Pre-operative MRI plus contrast must be available for all patients Pre-operative 3D imaging acquisition should be done for surgery and radiotherapy purposes Early post-operative MRI plus contrast must be available for all patients within 72 h post-operative even in ventilated patients Scans must be reported according to protocol guidelines by designated specialists with experience in paediatric neuroimaging</p>
<p>Desirable Baseline spine MRI is recommended before surgical resection or biopsy, or 10–14 days after surgical resection or biopsy (minimise post-operative blood products and dural enhancement that might confound imaging interpretation) During the study, at each examination, the same Tesla-strength is recommended with comparable sequences on consecutive scans If post-operative 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.</p>
<p>Not to do Do not use CT for standard brain imaging in any childhood cancer tumour</p>
<p>Neuropathology</p>
<p>Must have Conventional histopathology and immunostaining (+/- FISH/MLPA) DNA methylation analysis, gene panel sequencing, and RNA sequencing (tumour and blood)</p>
<p>Desirable Whole-exome/whole-genome sequencing, proteomics</p>
<p>Radiotherapy</p>
<p>Must have 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 quality assurance process in all centres and should include peer reviewing of radiotherapy volumes and treatment plans</p>
<p>Desirable At least two clinical/radiation oncologists with appropriate specialisation in paediatric radiotherapy</p>
<p>Not to do Radiotherapy, both curative and palliative, should not be given by clinical/radiation oncologist with no special interest/experience in paediatric radiotherapy</p>
<p>Neuro-ophthalmology</p>
<p>Must have Careful history with questions about visual symptoms and physical including neurological and <i>fundoscopic examination</i> Referral for a baseline neuro-ophthalmological evaluation Multidisciplinary approach to the diagnosis and management of visual impairment Referral to a dedicated visual impairment rehabilitation</p>
<p>Desirable (Hand-held) optical coherence tomography (if available) in young children: Use of retinal nerve fibre layer/ganglion cell layer as surrogate measures of visual acuity in selected groups (e.g., OPG)</p>
<p>Not to do Omit or delay a baseline ophthalmology assessment in case of absent visual symptoms Discontinue ophthalmologic follow-up in children treated for a CNS tumour</p>
<p>Quality of survival</p>
<p>Must have Access to a qualified multidisciplinary team under the leadership of paediatric neuro-oncology and regular multiprofessional team meetings to discuss all aspects of care of the patients Access to physiotherapy, occupational therapy, speech therapy Access to neuropsychological and psychosocial support systems Experienced guidance for school, sibling and family, social environment during and after treatment Access to acute and long-term rehabilitation plan and rehabilitation facilities Access to Quality of Survival assessment at diagnosis and initial treatment Access to adolescent and young adult transition plan Access to palliative care</p>
<p>Desirable Neuropsychological evaluation should be performed standardized during regular follow-up visits Dedicated multidisciplinary follow-up care team</p>
<p>Not to do Follow-up visits that only evaluate medical condition (check also psychosocial, neuropsychological, school functioning)</p>

for a good outcome in emergency and elective situations. However, the provision of neurosurgical care, including paediatric neuro-oncological care, is diverse across Europe (**Supplemental S2**).

5.1. Paediatric neurosurgical volume and outcomes

The impact of provider caseloads on outcomes in paediatric neurosurgery is frequently discussed but has never been clear and has not led to major service re-organisations. However, studies highlight that the mortality rate is lower at high-volume hospitals (≥ 21 cases/year) compared to low-volume hospitals (≤ 4 cases/year) [22] and procedures performed by paediatric neurosurgeons had better outcomes than those

performed by general neurosurgeons [23].

5.2. Access to neurosurgical equipment

Trained and experienced paediatric neurosurgeons, anaesthetists, and a well-equipped operating room, including an operating microscope are essential for the provision of neurosurgical care.

Frameless image-guidance became established as a surgical adjunct in the late 1990s [24,25]. These systems have progressed and allow virtual preoperative planning and identification of the optimal approach. Image-guidance additionally allows a better understanding of the anatomical boundaries of a tumour and assists in obtaining a

maximal resection. Minimally invasive burr hole biopsies, by directing a biopsy needle along a pre-planned trajectory to a deep tumour, are now routine in most units. In practice, image-guidance systems are compromised by brain shift, related to loss of CSF, entry of intracranial air, and tumour resection during surgery. Despite these limitations, image-guidance is still considered essential for most brain tumour resections, particularly supratentorial and deep tumours.

The most common application of frame-based stereotaxy is the biopsy of brainstem tumours [26]. A possible alternative technique evolving with comparable accuracy is robotic assisted needle biopsies. This technique may be integrated in the frameless image guidance system and has the advantage that frame positioning, especially difficult in smaller children, can be avoided.

Intra-operative ultrasound allows real-time evaluation during surgery. It can be easily carried out by the surgeon at multiple times and allows some certainty that a large tumour component has not been left behind [27]. More recent technology allows navigated ultrasound, where the ultrasound probe is integrated in the frameless navigation system [28,29].

Intraoperative MRI is an expensive adjunct to neurosurgical practice as an alternative to intra-operative ultrasound and is usually available only in larger centres. The acquisition of an MRI scan during surgery allows confirmation that the extent of intended tumour resection has been achieved. It also corrects for the impact of brain shift during surgery and allows a re-evaluation of the relationships between the residual tumour and surrounding brain [30,31]. The limitations of intra-operative MRI relate to its time and cost. This can be mitigated 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.

Neuro-endoscopy is another neurosurgical adjunct essential in the management of brain tumours. It facilitates biopsy of intra- or paraventricular lesions or pineal tumours and is useful in the management of hydrocephalus [32,33]. Obstructive hydrocephalus can be treated at the same time as tumour biopsy with an endoscopic third ventriculostomy.

The ability to confirm the functional integrity of the cerebral cortex, cerebral tracts, and cranial and peripheral nerves by intraoperative neuro-monitoring, allows a safe and tailored tumour resection while preserving neurological function [34]. Neuro-physiological monitoring is used for the resection of spinal cord tumours, tumours involving or adjacent to the primary motor or sensory cortex, corticospinal tracts, cranial nerves, the brainstem and the cauda equina [35]. Intraoperative monitoring allows mapping by stimulation of functional relevant structures, particularly useful for cortical and brainstem tumours.

The availability of interventional radiology within an institution supports the management of large vascular tumours, particularly in infants and young children (e.g., choroid plexus tumours). Pre-operative embolization effectively reduces the vascularity of these tumours, and changes their consistency to facilitate a complete and safer resection [36].

5.3. Other specific requirements

Collaboration with neuropathology is crucial. Paediatric neurosurgeons need to view the technical aspects of a surgery not just to obtain the safest and most complete resection possible, but also to collect as much biological material as possible. From a molecular perspective, most tumours are heterogeneous, and multiple specimens should be obtained from various tumour parts. If possible, at least $1 \times 1.5 \text{ cm}^3$ or $3 \times 0.5 \text{ cm}^3$ specimens should be obtained. A pipeline for tissue processing, starting from the operating room to the laboratory, is essential and should be available seven days a week, and has been described in detail by SIOPE-BTG [37].

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.

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.

6. Neuropathology in paediatric CNS tumours

Integrated histological and molecular analyses are fundamental to render an accurate diagnosis and consecutively offer optimal treatment. Many studies have shown that morphological work-up alone does not sufficiently discriminate between histologically similar but biologically and thus clinically highly divergent tumours [10,38]. This applies for the entire spectrum of paediatric brain tumours and is most pronounced in tumour types in which only molecular data can identify prognostic or even predictive subtypes, e.g., posterior fossa ependymoma, medulloblastoma, or histological HGG, the latter by molecular means often found to be biologically low-grade [39–42].

Historically, the WHO classification has covered histological entities based on light microscopy, focusing on a “scale of malignancy” and giving an estimation on biological behaviour and the natural clinical course of the disease. This classification is regularly updated and started to include tumours and their subtypes based on molecular characterization. The most recent WHO classification 2021 has introduced novel CNS tumour types and subtypes [10]. It also has paved the way for molecular analyses to be considered essential to establish a WHO-conform diagnosis for most entities. The revisions of the WHO classification of paediatric brain tumours not only reflect the research effort into the molecular, genetic, and epigenetic characteristics, but also emphasize differences in treatment and prognosis within CNS tumour subgroups [10].

As a result of the importance of molecular markers, comprehensive work-up of tumour material is required and includes DNA methylation analysis. 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. Several tumour types have pathognomonic molecular alterations, mostly single nucleotide variants, small insertions/deletions or gene rearrangements (e.g., gene fusions, internal tandem duplications). 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 [43,44]. Thus, 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, additional RNA sequencing for fusion detection. Practically, it is desirable to test mutations somatically in the tumour and in the germline using the same approach, since at least 10% of childhood brain tumour patients harbour pathogenic germline variants in cancer-related genes [45].

If the required testing was not completely performed (e.g., lack of assay availability, 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 [46].

In some tumours, such as LGG, molecular data has led to tailored treatment regimens, such as MEK pathway inhibitors. This has increased the requirement for biopsy in tumours 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 essential.

6.1. Institutional requirements

In most European countries, neuropathology is not an established, officially regulated discipline with separate board certification. This regulatory aspect does not prevent regions without distinct neuropathologists from providing highest standards of care. 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. Basic infrastructure for preservation and assessment of brain tumour samples relies on coordination between (neuro-)surgery and neuropathology [37]. This interaction should allow for intraoperative evaluation of a fresh frozen section, preferably also a touch and smear preparation. Further, both disciplines should cooperatively ensure to retrieve and preserve high quality tissue for analysis, including archiving not only of formalin-fixed paraffin-embedded, but also fresh frozen tissue for all paediatric neuro-oncology patients.

6.2. Essential quality parameters

At least two experienced specialists in 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 (Table 3). The availability of at least two experienced specialists in neuropathology guarantees continuous access to this crucial diagnostic step. In case this is not feasible, established structures with reference neuropathologists or national structures should be available for every child or adolescent, also outside of trials.

7. Radiotherapy in paediatric CNS tumours

Radiotherapy is an integral component of the multidisciplinary management of paediatric CNS tumours. In children aged <12–36 months, radiotherapy may be delayed or avoided to minimize the risk of late effects, especially neurocognitive dysfunction. Indications for radiotherapy depend on the patient's age and the tumour's histological subtype (Table 4). Both factors also contribute to risk-adapted doses and fields.

Many countries are moving towards proton beam therapy (PBT). While PBT has the potential to reduce the risk of acute side effects and

Table 4

Summary of indications for radiotherapy in children and adolescents with CNS tumours (list not exhaustive).

Tumour type	Broad indication
Low-grade glioma	Indicated in patients with progressive disease following multiple lines of treatment (not first or second line approach)
High-grade glioma	All patients with high grade glioma
Medulloblastoma	All patients with medulloblastoma and aged >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 tumours	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	Radiotherapy depends on the specific subtypes and extent of resection.
Choroid plexus tumours (CPT)	Radiotherapy depends on the specific subtypes, extent of resection, and age of the patient

radiotherapy-induced late effects, conclusive evidence from large prospective studies is scarce. The option of PBT should be discussed within the multidisciplinary team for all children with CNS tumours. It is further encouraged to collect prospective outcome data on efficacy and toxicity following PBT using national or international protocols [47].

7.1. Institutional requirements

Every centre providing radiotherapy should have at least two clinical radiation oncologists and dedicated pre-treatment and treatment teams consisting of mould room staff, play specialists, nurses, anaesthetic staff, physicists, dosimetrist, and therapeutic radiographers [48]. New patient consultations and treatment should be done in an age-appropriate environment. All patients should be reviewed regularly during radiotherapy to provide continuous support and to address side effects. There should be established late effect follow-up clinics to proactively manage potential late sequelae [48].

7.2. Essential quality parameters

Clear radiotherapy pathways are needed to signpost the best radiotherapy approach for individual patients. Further, all patients should be treated with an appropriate advanced radiotherapy technique in keeping with national guidelines or clinical trial protocols. All radiotherapy departments should have externally validated quality assurance systems. Multidisciplinary radiotherapy planning processes involving clinical oncologist, radiographers, and radiotherapy physicists are needed. This goes in line with the need of well-established quality assurance for accuracy and reproducibility of daily treatment with modern imaging techniques (Table 3).

8. Endocrine aspects in paediatric CNS tumours

Hypothalamic-pituitary (HP) dysfunction can play a central role in long-term health of paediatric brain tumour survivors [49,50]. It can be present at diagnosis (e.g., in sellar or suprasellar tumours) or can subsequently develop [51,52]. Younger age at diagnosis, hydrocephalus, suprasellar and infratentorial tumour location, and radiotherapy, are risk factors for the development of HP dysfunction [51,52].

Peripheral endocrine dysfunction can be caused by the toxic effects of chemotherapy or radiotherapy on the thyroid gland or the gonads [53–55]. Off target effects of molecular therapies are also being recognised [56]. In paediatric brain tumour survivors, a well-functioning endocrine system is necessary for adequate recovery, development, growth, and optimal participation in daily life.

8.1. Different endocrine axes affected in paediatric CNS tumours

Of anterior pituitary axes, growth hormone (GH) deficiency is the earliest and most frequent pituitary disorder. The estimated prevalence of endocrinopathies in paediatric cancer survivors receiving HP irradiation was 40% for GH, 11% for TSH, 11% for LH/FSH, 3% for ACTH deficiencies, and 1% for central precocious puberty (CPP)[49]. In paediatric brain tumour survivors with and without radiotherapy, GH deficiency was present in 12.5%, CPP in 12.2%, and deficiencies of TSH, ACTH, and LH/FSH in 9.2%, 4.3%, and 4.2%, respectively [57]. Obesity is another issue in paediatric brain tumour survivors [50,58]. In a national cohort study of 661 survivors, one third (33%) had significant weight gain, overweight, or obesity after a median follow-up of 7.3 years [58]. Central diabetes insipidus is seen in children with damage to the hypothalamus, pituitary stalk, or pituitary gland.

8.2. Treatment-related risk factors and time of onset

Radiotherapy to the HP region is a risk factor for hypothalamic-pituitary insufficiency, with GH deficiency being most prevalent

Table 5

Overview and suggestion for follow-up of hypothalamic-pituitary dysfunction in children and adolescents treated for a CNS tumour.

Treatment	Potential late effect	Risk factors	Recommendation
Cranial radiotherapy	Overweight / Obesity	Age < 4 years	Monitor BMI yearly
		Radiation dose > 20 Gy	Dietary and physical exercise advice BMI > + 2 SD: consultation with endocrinologist
	Precocious puberty	Young age	Monitor Tanner stage in combination with growth velocity every 6 months
		Radiation dose pituitary region > 18 Gy	
	Central hypothyroidism	Young age	History for signs of TSH deficiency
		Radiation dose pituitary region > 40 Gy After starting treatment with GH	TSH, FT4 (yearly). Referral to endocrinologist when FT4 decreased on 2 separate occasions or declines with >20% over time
	LH/FSH deficiency	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 ACTH deficiency referral to endocrinologist	
Cervical/spinal radiotherapy	GH deficiency	Young age	Height, weight, sitting height, BMI every 6 months; referral endocrinologist if decline in growth chart
		Radiation dose > 18 Gy	
	Thyroidal hypothyroidism	Cervical (stray) irradiation > 20 Gy cranial	History for signs of T4 deficiency
	Thyroid nodule/carcinoma	Young age Cervical (stray) irradiation > 20 Gy cranial	TSH, FT4 (yearly). Referral to endocrinologist if low FT4 or high TSH Thyroid palpation (yearly). Referral endocrinologist if palpable nodule
	Thyroidal hypothyroidism	Same as for "cranial radiotherapy"	
Thyroid nodule/carcinoma	Same as for "cranial radiotherapy"		
Short stature	Young age	Sitting height every 6 months	

(Table 5). The risk increases with increasing dose and younger age at irradiation [49,59]. HP dysfunction can occur in the first year with an increase over time and shorter latency at higher doses [52,60]. Irradiation of the thyroid gland increases the risk for primary hypothyroidism, thyroid nodules and differentiated thyroid carcinoma [54]. Spinal irradiation may attenuate adult height due to premature fusion of the vertebral growth plates. Therefore, sitting height should be monitored alongside longitudinal height. Hydrocephalus has been associated with an increased risk for GH deficiency or CPP. There is no evidence that treatment with chemotherapy increases the risk for HP dysfunction, but alkylating agents may induce gonadal failure and pubertal delay [53, 55].

8.3. Surveillance

Table 5 summarizes the follow-up of HP dysfunction in children and adolescents after brain tumour treatment. All children with a tumour in the sellar or suprasellar region or with HP dysfunction at diagnosis should be referred to a paediatric endocrinologist at time of diagnosis. During follow-up, a decreasing growth velocity, abnormalities in pubertal progression, aberrant laboratory values, or a history suspicious for pituitary deficiency should also lead to a prompt referral [49].

8.4. GH treatment in childhood brain tumour survivors

GH deficiency during childhood may result in a decreased adult height, abnormal metabolic profile, poor bone health and muscle strength. Several cohort studies show that childhood cancer survivors treated with GH are neither at increased risk for recurrence or progression of the original tumour, nor for secondary tumours [61,62]. Recent guidelines recommend waiting until patients are disease free for at least one year before starting treatment, although this is based on little evidence [60]. Some patients may never be radiologically tumour free (e.g., LGG, craniopharyngioma). In these cases, benefits versus possible harms of GH treatment must be discussed by the paediatric endocrinologist, with the patient, parents, and the oncologist. There is however evidence that in patients with craniopharyngiomas, GH

replacement can be safely started early [63,64].

9. Neuro-ophthalmology

Brain tumours in children can alter the anatomy of the visual system and the physiological development, causing a variety of visual symptoms, including decreased visual acuity (VA), visual field (VF) defects, diplopia, and eye movement disorders (Supplemental Table S3.1) [12, 65–69]. The onset of neuro-ophthalmological manifestations depends on the tumour location and whether the visual pathway (afferent) or the cranial nerve (efferent) are involved. Complications (e.g., obstructive hydrocephalus, leptomeningeal dissemination, cerebral venous thrombosis) might cause raised ICP, resulting in a further threat to vision. Adult survivors of paediatric brain tumours are at risk for long-term visual sequelae, including unilateral or bilateral blindness, cataracts, and diplopia, which may jeopardize quality of life such as neuro-cognitive development, autonomy, driving eligibility, and education [65, 70, 71]. Despite this knowledge, many children with brain tumours are not referred for a baseline ophthalmology assessment [67].

9.1. Tumour location and specific manifestations at presentation

Visual symptoms and signs largely depend on the brain tumour location (Supplemental Table 3.2).

Visual deficits such as visual acuity (VA) or visual fields defects (VF) represent the most frequent symptoms of tumours infiltrating the visual pathway such as optic pathway gliomas (OPG) with 5–10% of them meeting the criteria for legal blindness [72,73]. OPG tend to present with a combination of uni- or bilateral VA and VF defects [72–74]. Isolated optic nerve gliomas and nerve sheath meningioma present with eye proptosis, and/or optic pallor/atrophy.

VA loss and VF defects, with uni- or bitemporal hemianopia with or without fundoscopic alterations are common (32%) in suprasellar tumours (e.g., craniopharyngioma), mainly due to external compression of visual structures, such as optic chiasm [75–77].

Posterior fossa tumours causing raised ICP can cause papilloedema, and if persistent or severe, optic atrophy and axonal death, resulting in

VA loss and/or VF defects [78]. Raised ICP can cause palsy of the sixth cranial nerve, presenting as esotropia, horizontal diplopia and head turn to maintain binocular vision [79]. Children with posterior fossa tumours also present with oculomotor signs (e.g., gaze palsy, strabismus, upbeat nystagmus, abnormal acuity) [78,79].

Tumours located in the occipital or temporal lobes, affecting the visual cortex, the geniculate bodies, or the optic radiations can cause VF defects (e.g., homonymous hemianopia).

Brain stem and/or pontine tumours present frequently with cranial nerve palsies including cranial nerves (CN)-III, CN-IV, or CN-VI leading to diplopia with exo-/esotropia, strabismus or other oculo-motor deficits. Torticollis can accompany parietic strabismus as an adjustment to maintain binocular vision.

Visual symptoms in pineal lesions or mesencephalic/tectal plate tumours include 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 [77].

Besides direct or indirect compression of the visual pathways, cranial nerves, or brainstem through tumour or hydrocephalus, it is good to realize that visual symptoms can also be the result of peri-operative complications, side-effects of chemotherapeutic agents, radiotherapy, and prolonged use of steroids. Also targeted drugs, like BRAF and MEK inhibitors can have ophthalmic side effects, which must be screened [80, 81].

9.2. Baseline visual assessment

A baseline neuro-ophthalmologic evaluation is recommended in all children and adolescents with a newly diagnosed CNS tumours (Supplemental Table S3.3 and S3.4). The RAFFO acronym provides a summary of the most relevant visual parameters to be assessed and include refraction test (R), visual acuity (VA), visual fields (VF), fundoscopic examination (F), and orthoptic assessment (O).

Best corrected VA assessed monocularly and if possible, from far and near distance, should be reported as logMAR, from -0.30–2.0 (Supplemental Table S3.5). If an accurate quantitative VA cannot be performed, observation of visual fixation may be useful and VA should be documented as hand motion, counting fingers or light perception. The appropriate VA testing method depends on child's age and cooperation. Vision rapidly mature in the first 2–3 years, reaching its full potential after 5 years of age.

Visual Fields should be measured age-appropriate and monocularly [82]. VF defects should be reported as symmetric (concentric) or asymmetric (homonymous) and as nasal/temporal restrictions ranging from 0° (full restriction) to no restriction. Supplemental Table S3.6 summarizes questions to parents and/or children which could help to unveil VF defects.

A dilated fundoscopic exam provides information on presence of papilledema which may be absent in case of subacute or chronic raised ICP. Therefore, its absence does not rule out an underlying CNS tumour causing ICP. When fundoscopy 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 retinal nerve fibre layer thickening [83].

9.3. Orthoptic examination

Examination of eye movement disorders (strabismus, cranial nerve palsies, gaze palsy, nystagmus etc) and pupillary light reflexes, cover test, and pursuit movements are recommended at baseline.

9.4. Recommended visual surveillance after treatment

Regular ophthalmological surveillance in children and adolescents diagnosed and treated for a CNS tumour is essential. Monitoring frequency and duration depend on various factors, including initial tumour

location, type of treatment, and presence, severity, and risk for further visual symptoms [84] (Supplemental Table S3.2, Table 3).

10. Quality of survival of children and adolescents with CNS tumours

Quality of survival refers to the presence and impact of the long-term neurocognitive, endocrine, ophthalmological, and other medical, behavioural, emotional, and adaptive functional sequelae of CNS tumour patients. Children and adolescents with a CNS tumour are at high risk to develop late effects because of the tumour and treatment-related factors – they do have the highest morbidity and mortality amongst all childhood and adolescent cancer entities. Due to increasing survival rates, the assessment and follow-up of these domains is crucial to support survivors and their families. A bio-psycho-social approach is recommended at diagnosis, during and after treatment. 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 [85]. A standardized assessment of patient reported outcomes (PROMS) would be desirable in CNS tumour patients and survivors but is not standard of care today. PROMS aim to assess the subjective health status of patients or survivors and enables continuous monitoring over time with the initiation of interventions if changes occur.

10.1. Institutional requirements

At diagnosis and during and after treatment each patient should have access to at least neuropsychological assessment as per international recommendations, endocrine assessment, ophthalmology assessment, hearing assessment, neurorehabilitation (in- or outpatient facility), physiotherapy, occupational therapy and speech therapy, adolescent and young adult transition, palliative care, vocational counselling/ social work/ child life specialist/ teachers, and age and risk adapted fertility preservation prior to start of gonadotoxic treatment.

10.2. Essential quality parameters

The International Guidelines Harmonization Group for Late Effects of Childhood Cancer is constantly developing new and updated guidelines on medical and psychosocial surveillance and support [86]. 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 [87] and PanCare [88]. All these guidelines are risk-adapted, based on the treatment received (surgery, chemotherapy, irradiation, haematopoietic stem cell transplantation) and cover multiple aspects of follow-up care. Table 6 gives an overview over the most relevant potential late effects in children and adolescents diagnosed with a CNS tumour, with a summary in Table 3 [53–55, 85, 89–99].

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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, focussing on general aspects and supportive care. The treating physician remains responsible for the application of any procedures and treatment to children and adolescents diagnosed with a CNS tumour.

Table 6
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 by IGHG and SIOPE QoS group (in addition to COG)
Paediatric CNS tumour	Adverse psychosocial/ quality of life effects	Educational and/ or vocational progress Social withdrawal	IGHG guideline [93]
	Mental health disorder	Regular psychosocial assessment (e. g. depression, anxiety, post – traumatic stress, suicidal ideation)	IGHG guideline [94]
	Fatigue, sleep problems	Psychosocial assessment	IGHG guideline [85]
Chemotherapy and cranial radiation	Dental abnormalities	Dental exam and cleaning	
Alkylating agents	Testicular hormonal dysfunction	Puberty development (Tanner stage, testicular volume), sexual function, monitor growth until mature, menstrual history, menopausal symptoms	IGHG guideline [52,54]
	Impaired spermatogenesis Ovarian hormone deficiencies Reduced ovarian follicular infertility		
Heavy metals	Ototoxicity	Audiological evaluation	IGHG guideline [86]
Antimetabolites	Reduced bone mineral density	Bone density evaluation	IGHG guideline [95]
	Neurocognitive late effects, clinical leukoencephalopathy	Neuropsychological evaluations, neurological exam	Jacola LM et al. [87] Limond J et al. [81]
Corticosteroids	Reduced bone mineral density, osteonecrosis	Bone density evaluation, Musculoskeletal exam	IGHG guideline [95]
	Cataracts	Visual acuity, Funduscopic 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	IGHG guideline [53,88]
Cranial radiation	Neurocognitive late effects, clinical leukoencephalopathy,	Neuropsychological evaluations, neurological exam	Jacola LM et al. [87] Limond J et al. [81]
	Cerebrovascular complications	Neurological exam	
	Hormonal deficiency, overweight, obesity, metabolic syndrome Cataracts, ocular toxicity Ototoxicity	Physical exam, endocrinological evaluations Visual acuity, Funduscopic exam Audiological evaluation	IGHG guideline in progress IGHG guideline [86]
Spine radiation	Artery disease Cardiac toxicity	Neurological exam Blood pressure, Cardiac exam, Echo and ECG	IGHG guideline [89]

Table 6 (continued)

Therapeutic exposure	Potential late effects	Periodic evaluations	Specific guidelines by IGHG and SIOPE QoS group (in addition to COG)
Brain surgery	Colorectal cancer	Colorectal cancer screening	IGHG guideline in progress
	Scoliosis/ kyphosis Neurocognitive deficits	Exam of back/ spine Neuropsychological testing	Jacola LM et al. [87] Limond J et al. [88] IGHG guidelines in progress
Spine surgery Pre-treatment	Hormonal deficiency, overweight, obesity, metabolic syndrome Scoliosis/ kyphosis	Physical exam, endocrinological evaluations Exam of back/ spine	
All	Fertility preservation		IGHG guideline [90–92]

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejcped.2024.100166](https://doi.org/10.1016/j.ejcped.2024.100166).

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