Childhood Intracranial Germ Cell Tumours

This document has been developed by Dr Manuel Diezi, Professor Barry Pizer, and Professor Matthew Murray

Document version and date : FINAL v1.1; 28th January 2025

Diagnostic assessments, therapeutic and supportive care procedures as well as follow-up recommendations mentioned in this document are based and adapted from the SIOP CNS GCT II protocol, Version 4, 16.03.2018. This overview of current European practice for the management of patients with intracranial germ cell tumours has been published recently [1].

Acknowledgements

We acknowledge all coworkers who were involved in writing and setting up the SIOP CNS GCT II protocol and trial which was adapted and formed the basis of this guideline. We thank members of the SIOPE Brain Tumour Group, CNS GCT Subgroup who contributed to this final document, in particular Gabriele Calaminus, James Nicholson, Thankamma Ajithkumar, Didier Frappaz, Claire Alapetite, Giovanni Morana, Herve Brisse, Dipayan Mitra and Maria Luisa Garre. We also thank Jason Fangusaro (US) and Ryo Nishikawa (Japan) for reviewing this document.

Table of contents

Patient Group

This document refers to paediatric (less than 18 years of age) patients with a diagnosis of a central nervous system germ cell tumour (CNS GCT), which can be subclassified as germinoma or non-germinomatous germ cell tumours (NGGCT). However, as these tumours occur throughout childhood and into early adulthood, this document is applicable to all patients with this tumour type, regardless of age.

Background

Germ cell tumours of the central nervous system (CNS GCT) represent a heterogeneous group of neoplasms including germinoma, endodermal sinus tumour (yolk sac tumour; YST), embryonal carcinoma (EC), choriocarcinoma (CHC), teratoma [mature (MT) or immature (IT)] and mixed tumours of these histological entities. Their incidence peaks during the second decade and there is a predominance of male patients. The incidence also varies globally, with higher rates in Japan and other Asian countries than in Europe and North America, suggesting genetic factors have a role.

Based on prognosis and current therapy intensity, CNS GCT are usually divided into (pure) germinomas (approximately two-thirds of malignant cases) and non-germinomatous germ cell tumours (NGGCT; comprising the malignant subtypes YST, EC, CHC (one-third of malignant cases) and teratoma. Mixed malignant GCTs (MMGCTs) contain more than one histological entity, and occur frequently within the CNS. It should be noted that NGGCT can include a germinoma component; what defines them as NGGCT is the presence of at least one of YST, EC, or CHC alone or in combination.

Due to their relative surgical inaccessibility, patients with typical radiology and secretion of tumour markers above specific thresholds, can pragmatically be diagnosed as ‘secreting’ malignant NGGCTs without biopsy, and treatment initiated accordingly (see below).

Markers

GCTs may secrete specific tumour markers including alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG). HCG measurement guidelines are reviewed in Appendix A.

AFP

- 70 kDa glycoprotein with a key fetal physiological protein binding function and produced by the embryonic/fetal yolk sac, liver and intestine (AFP production switches from AFP to albumin in the third trimester) [2]. Physiologically elevated serum levels thus found during gestation, both in the fetus and in the mother.
- Half-life 5-7 days [2].
- Consequently, after birth, serum levels continue to fall and should reach the reference range by 2 years of age [2].
- Used as tumour marker for liver tumours and predominantly YST components of malignant NGGCTs, but can also be produced by EC components [2].
- Measured by immunoassays and expressed in ng/ml or kU/L [2].
- **In Europe, AFP values > 25 ng/ml in serum and/or CSF are considered diagnostic of a secreting malignant NGGCT and treatment may be initiated without biopsy [3]**.

Unit	Conversion factor		Unit
IU/ml	x 1	=	kU/L
kU/L	x 1.205	=	ng/ml
kU/L	x 0.0012	=	µg/ml
kU/L	x 1	=	IU/ml
ng/ml	x 1	=	µg/L
ng/ml	x 0.83	=	kU/L
µg/L	x 1	=	ng/ml
µg/ml	x 830	=	kU/L

AFP unit conversion table

HCG

- 40 kDa glycoprotein composed of 2 subunits: α and β; the first structurally similar to other hormones (LH, FSH), while the second component is unique to HCG [2].
- Produced physiologically by the placenta or similar structures to maintain pregnancy [2].
- Half-life is 12-36 hours [2].
- **In Europe, HCG values > 50 IU/L in serum and/or CSF are considered diagnostic of a secreting malignant NGGCT and treatment may be initiated without biopsy [3].**
- Usually non-detectable in the CSF of healthy subjects.

Histological hallmarks of GCT subtypes.

For pathology diagnostic purposes, the most recent version of the WHO classification of CNS tumours should be followed [4].

Germinoma

Microscopically resemble primordial germ cells, composed of large, undifferentiated cells arranged in sheets, lobules or cords and trabeculae. The nucleus is round, centrally positioned and with prominent nucleoli. The cytoplasm is abundant and clear due to glycogen accumulation. Necrosis is uncommon. Most germinomas show a strong lymphocytic infiltration, which can make the diagnosis challenging, as malignant cells may be sparse. A full panel of immunohistochemical staining is therefore important to detect these cells in all suspected cases [KIT, POU5F1 (OCT3/4), PLAP, NANOG]. The presence of syncytiotrophoblastic cells within germinomas can result in some scattered positive HCG staining, and can therefore be associated with mild to moderate elevations of HCG in the serum and/or CSF.

Embryonal carcinoma

Composed of large cells arranged in nests and sheets and show large nucleoli, clear/violet cytoplasm, high mitotic count and some necrosis. Immunohistochemical staining for CD30 will identify these cells.

Yolk sac tumour

Typically composed of primitive-looking epithelial cells arranged in a loose network within a variably cellular, myxoid matrix. Immunohistochemical staining for AFP will identify these cells.

Choriocarcinoma

Characterised by cytotrophoblastic elements which show strong diffuse cytoplasmic immunostaining positivity for HCG.

Teratoma

Histology reveals either fully differentiated or incompletely differentiated elements, depending if it is a mature (MT) or immature (IT) form. They comprise ectodermal (epidermis, CNS tissue), mesodermal (muscle, bone, cartilage, adipose tissue) and endodermal (glandular, respiratory and enteric tissues) elements. Any immature tissue/s requires careful evaluation for classification as an immature teratoma (IT), as per WHO guidelines.

Mixed malignant GCTs (MMGCTs)

Frequently composed of a teratoma component and additional malignant GCT components (mostly YST and/or germinoma); the latter components can be present only in small areas. An intense search for such malignant GCT foci within teratomas with the help of specific immunohistochemical staining is critical because mixed malignant GCTs must be treated with more than surgery alone - with treatment determined by careful review of the pathology findings and in light of marker status. It is important to note that an MMGCT with the specific combination of teratoma and germinoma as the only malignant component results in treatment as for a germinoma (which includes consideration of when to perform any additional surgery and detail regarding radiotherapy dosing). MMGCTs with at least one of the malignant subtypes YST, EC, or CHC alone, with teratoma, or the YST/EC/CHC subtypes in combination with or without teratoma, results in treatment as for a NGGCT. Thus, treatment needs to be very carefully determined by full appraisal of pathology and marker status.

Minimal IHC panel for CNS GCT diagnosis in marker-negative cases

For marker-negative cases undergoing biopsy, histopathological diagnosis must be confirmed by specific immunohistochemical staining. Besides the established markers of AFP for YST, HCG for CHC, and placental alkaline phosphatase (PLAP) for germinoma, other markers are used which should be routinely assessed in GCTs [5]:

- POU5F1 (OCT3/4) and NANOG nuclear expression are restricted to germinomas and EC while PLAP and low molecular weight cytokeratins can show some cross reactivity with other GCT entities.
- While POU5F1 (OCT3/4) is specific for germinomas and EC, these entities can be distinguished by the expression of the transcription factor SOX2 which is negative in germinomas but expressed in EC.
- In addition, CD30 should routinely be evaluated in CNS GCT cases to rule in or out the presence of EC (CD30 positive in EC cases).
- The transcription factor POU5F1 (OCT3/4) is also helpful for the detection of sparse or single malignant GCT cells in lesions altered by strong inflammatory reaction and in CSF cytological preparations.
- Glypican 3 (Gly-3) and SALL4 stains are also very useful, in addition to AFP, in identifying small YST islands.
- For cases that remain uncertain despite the above comprehensive panel, second pathological review is warranted and further stains might be used.

The use of a marker panel is also important to differentiate GCTs from other undifferentiated tumours of childhood or tumours which can show various lines of differentiation, in particular in young children (e.g. atypical teratoid/rhabdoid tumour, choroid plexus carcinoma, ependymoblastoma, pineoblastoma, high grade gliomas) [4]. Hence, specific other panels of markers may need to be employed to rule in or out such other entities as determined by an individualised case-by-case assessment.

Histopathology	PLAP	Gly3 and SALL4	AFP	HCG	NANOG	POU5F1 (OCT-3/4)	SOX2	KIT	CD30
Teratoma	-	- (1)	+/- (2)	-	-	-	+	+	+
Embryonal carcinoma	+/-	-	-/+	-/+	+	+	+	-/+	+/-
Yolk sac tumour	+/-	+	++	-/+	-	-		-	-
Choriocarcinoma	+/-	-	-/+	++	-	-		-	-
Germinoma	+	-	-	-/+ (3)	+	+	-	+/-	-/+
PLAP: placental alkaline phosphatase; Gly3: Glypican 3; AFP, alpha-fetoprotein; B-HCG: beta-human chorionic gonadotropin									
(1) Immature neurotubules can express Gly3 (2) Immature liver/enteral tissue can express AFP (3) Single giant (syncytiotrophoblast) cells within germinoma can express HCG									

Molecular pathology and biological understanding of CNS GCT

There are currently no molecular pathology data used in the routine clinical setting to determine prognostication or alter patient management. Furthermore, we acknowledge that tumour banking itself is challenging, particularly where taking a biopsy is deemed unnecessary for diagnostic purposes in the presence of typical radiology and AFP and/or HCG markers raised above ‘secreting’ thresholds [5]. That notwithstanding, the collection of associated samples, such as serum and plasma, CSF and constitutional germline DNA is of crucial importance because in the future these specimens might provide a relatively non-invasive method, compared with neurosurgical biopsy, for identifying molecular changes representative of those in the tumours, thereby assisting diagnosis and risk stratification [5]. For example, specific short non-protein-coding RNAs, termed microRNAs, are known to be dysregulated in all malignant GCTs, including those in the CNS [6] and the same microRNAs have been shown to be raised in the circulation (serum and/or CSF) at diagnosis in patients with both extracranial and CNS disease. Latter examples of the potential utility of estimation of both serum and CSF microRNAs for CNS GCTs are described elsewhere [7, 8]. Furthermore, the mutational landscape of CNS GCTs has been described [9-11], highlighting potential genes and cellular pathways disrupted in CNS GCTs. Among altered signalling pathways, mutational activations of Kit, Ras/Raf/Erk- and Akt pathways have been reported in CNS GCT [12, 13]. Based on these, second-line targeted therapies have been used, unfortunately with limited success [14]. Further work will be required in this area to correlate biological findings with clinical outcome.

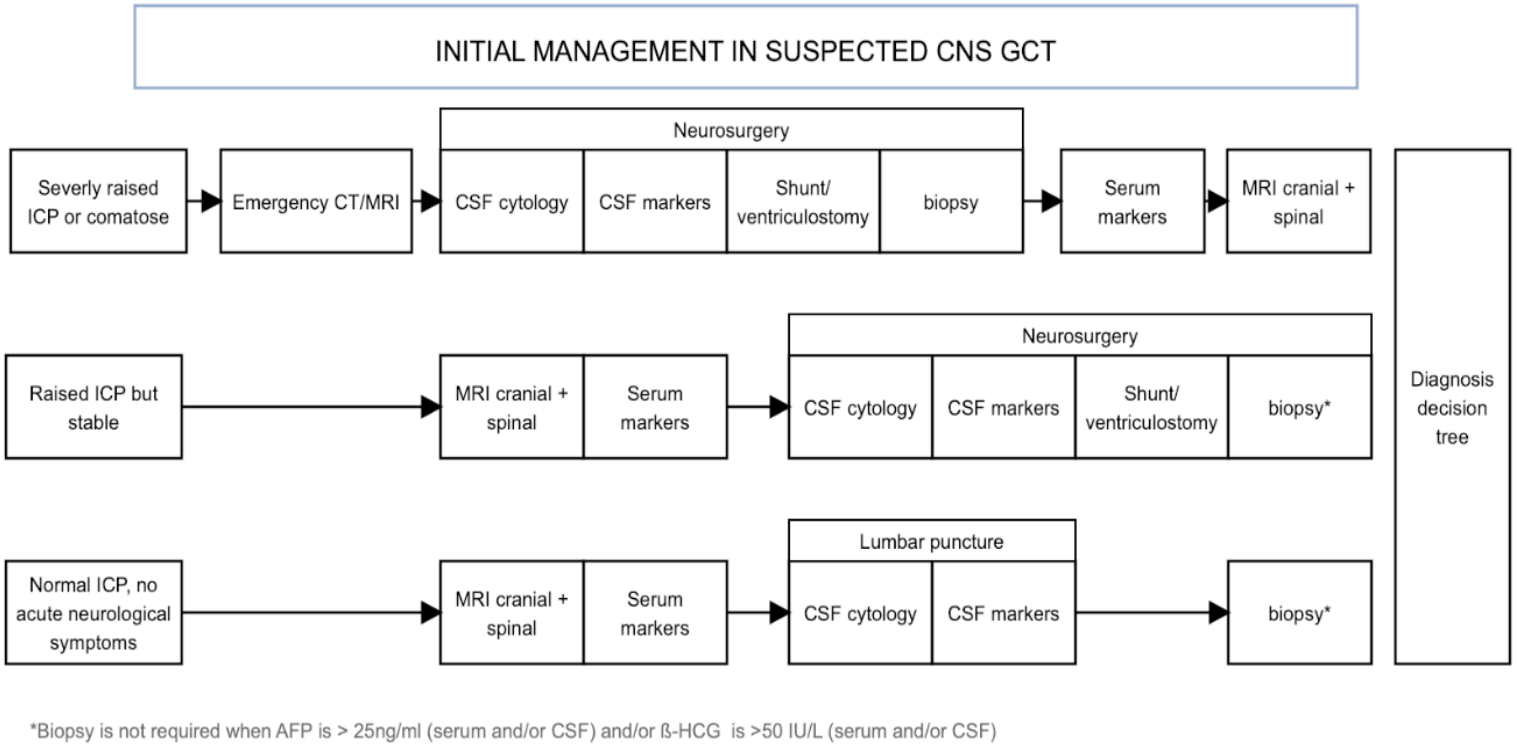
Consequently, the banking of available tumour tissue and associated serum/plasma and CSF specimens through national or international biobanks is very strongly encouraged, providing appropriate ethical consents have been obtained [15].

Initial presentation, diagnostic work-up and staging

- Patients can present at diagnosis with raised intracranial pressure (RICP), endocrinological and/or ophthalmological disturbances that must be managed appropriately.
- Among endocrine disorders, diabetes insipidus (DI) secondary to posterior pituitary involvement and secondary decrease in vasopressin (ADH) production requires immediate recognition and management.
- A bitemporal hemianopia and/or decreased visual acuity, without a satisfactory ophthalmological explanation, must lead to brain imaging.
- Radiologically, CNS GCT often affect the pineal gland, pituitary gland or both, sometimes with radiological or cytological dissemination, particulalrly to the ventricles.
- The sequence of diagnostic tests and neurosurgical management will depend on the presence of signs or symptoms of RICP.

Initial management of suspected CNS GCT

(as per SIOP CNS GCT II)



*Biopsy is not required when AFP is > 25ng/ml (serum and/or CSF) and/or ß-HCG is >50 IU/L (serum and/or CSF)

Signs & symptoms of raised intracranial pressure (RICP)

Symptoms and signs that suggest RICP include headache, vomiting, ocular palsies, altered level of consciousness, and papilloedema. The headache is typically worse on coughing, sneezing or bending and progressively worsens over time. There may also be personality or behavioral changes. Additional critically concerning signs may include pupillary dilatation, abducens palsies, and Cushing's triad (increased systolic blood pressure, bradycardia, abnormal respiratory pattern).

Patients with signs & symptoms of severe RICP

- In patients with severe RICP, emergency imaging (CT or MRI) should be performed.
- CSF cytology and markers should be collected during procedure for CSF diversion.
- If deemed secure and the neurosurgical team is experienced, a limited biopsy (aiming only to secure a diagnosis) could be considered during the same procedure.
- Serum markers are collected immediately after surgery.
- Further investigations such as spinal MRI and brain MRI if not already perfomed should be carried out therafter, ideally within 24h of neurosurgery.
- CSF cytology (together with markers) should ideally be repeated through a lumbar puncture when RICP has been adequately addressed and if safe and feasible to do so - this is optimal compared with ventricular sampling [5].

Patients with RICP but deemed clinically stable

- Brain and spinal MRI and serum markers should be collected before surgery for CSF diversion.

- CSF cytology and markers should be collected during the procedure for CSF diversion.
- If necessary for diagnosis, if deemed secure and the neurosurgical team is experienced, a limited biopsy (aiming only to secure a diagnosis) could be considered during the CSF diversion procedure.
- CSF cytology should ideally be repeated through a lumbar puncture when RICP has been adequately addressed and if safe and feasible to do so - this is optimal compared with ventricular sampling [5].

Patients with normal ICP & no acute neurological symptoms

- Brain and spinal MRI and serum markers should be collected before considering biopsy.
- CSF markers and cytology should be collected through a lumbar puncture - this is optimal compared with ventricular sampling [5].

For all patients

- With typical radiology and when AFP is > 25 ng/ml (serum and/or CSF) and/or HCG is > 50 IU/L (serum and/or CSF), biopsy is not mandatory and treatment may be initiated based on the diagnosis suggested by the markers.
- *Upfront neusosurgical resection is to be avoided for most tumours, unless teratoma is strongly suspected from the radiological appearances.*
- When diagnosis is not feasible based on serum and/or CSF markers, patients require surgical biopsy for pathological diagnosis, regardless of imaging findings.
- In Europe, the only potential exception to the above rule is when MRI imaging shows pineal and suprasellar ('bifocal') disease, markers are negative, the patient is >8-10 years of age AND central diabetes insipidus (DI) is present - then a diagnosis of germinoma can be assumed and treated accordingly [16]. This specific issue of 'bifocal' disease is addressed further in the global consensus manuscript [5]. If there is any doubt amongst the clinical team regarding the putative diagnosis, a low threshold for considering biopsy must be maintained, as rarely in this set of clinical circumstances, NGGCT may be

present: 3 of 89 cases (3.4%) in a recent large cohort [17]. Importantly, in this series of patients (all with bifocal lesions, DI and negative tumour markers), no tumours other than GCTs were identified [17]. Of note, none of the patients in the cohort developed permanent complications after endoscopic or stereotactic biopsy [17]. Thus, the decision to biopsy or not for bifocal lesions must be taken very carefully – if not biopsying, it should be noted that rarely NGGCTs occur in this scenario (which require more intensive treatment for cure) and therefore, if treatment response is not as expected, a low threshold for revisiting the diagnosis should be maintained.

- Biopsy procedures used for diagnostic purposes are summarised in Appendix B.

Surgical procedure for CSF diversion

- If urgent diversion is necessary, CSF should be collected for cytology and tumour markers (AFP, HCG).
    - CSF should be collected before proceeding to the diversion itself.
- An endoscopic third ventriculostomy (ETV), where feasible, is the favoured surgical intervention for obstructive hydrocephalus [5].
- If ETV is not possible, then placement of drain (EVD) is preferred over a definitive shunt. As CNS GCT are very sensitive to chemotherapy and radiotherapy, and such a drain can be expected to be removed relatively rapidly, an EVD is favoured over a permanent ventricular shunt [5].

Biochemical work-up

- Markers are elevated at diagnosis in the majority of patients with malignant NGGCTs (80% in the serum, >60% in CSF), and their presence, in conjunction with consistent MRI appearances, is sufficient for diagnosis, without the need for biopsy.
- CSF markers should be obtained, unless medically contraindicated, at the same time as serum markers.
- The site from which the CSF sample is obtained for markers (AFP & HCG) and cytology (lumbar/ventricular) should be documented. If marker levels are ≤ 25

ng/ml (AFP) and ≤ 50 IU/l (HCG) in both compartments, a biopsy should be performed (unless absolutely classical clinical and radiological features of 'bifocal' GCT disease are present).

Cytological staging

- As treatment decisions are based on the result of CSF cytology, its examination at diagnosis, and before treatment commences, is essential.
- Lumbar CSF is preferred to ventricular CSF [5], but see section on RICP above.
- In the absence of hydrocephalus and RICP needing urgent treatment, and if deemed safe, CSF should be obtained by lumbar puncture for markers and cytology. This should be undertaken prior to consideration of biopsy, whether or not serum markers are raised, as CSF markers may be increased in the presence of normal serum levels. Conversely, e.g. CSF AFP levels may be higher than serum levels and may place the patient in a 'high-risk' NGGCT group, so are critical to measure. Furthermore, the cytology result will determine the extent of subsequent radiotherapy fields.

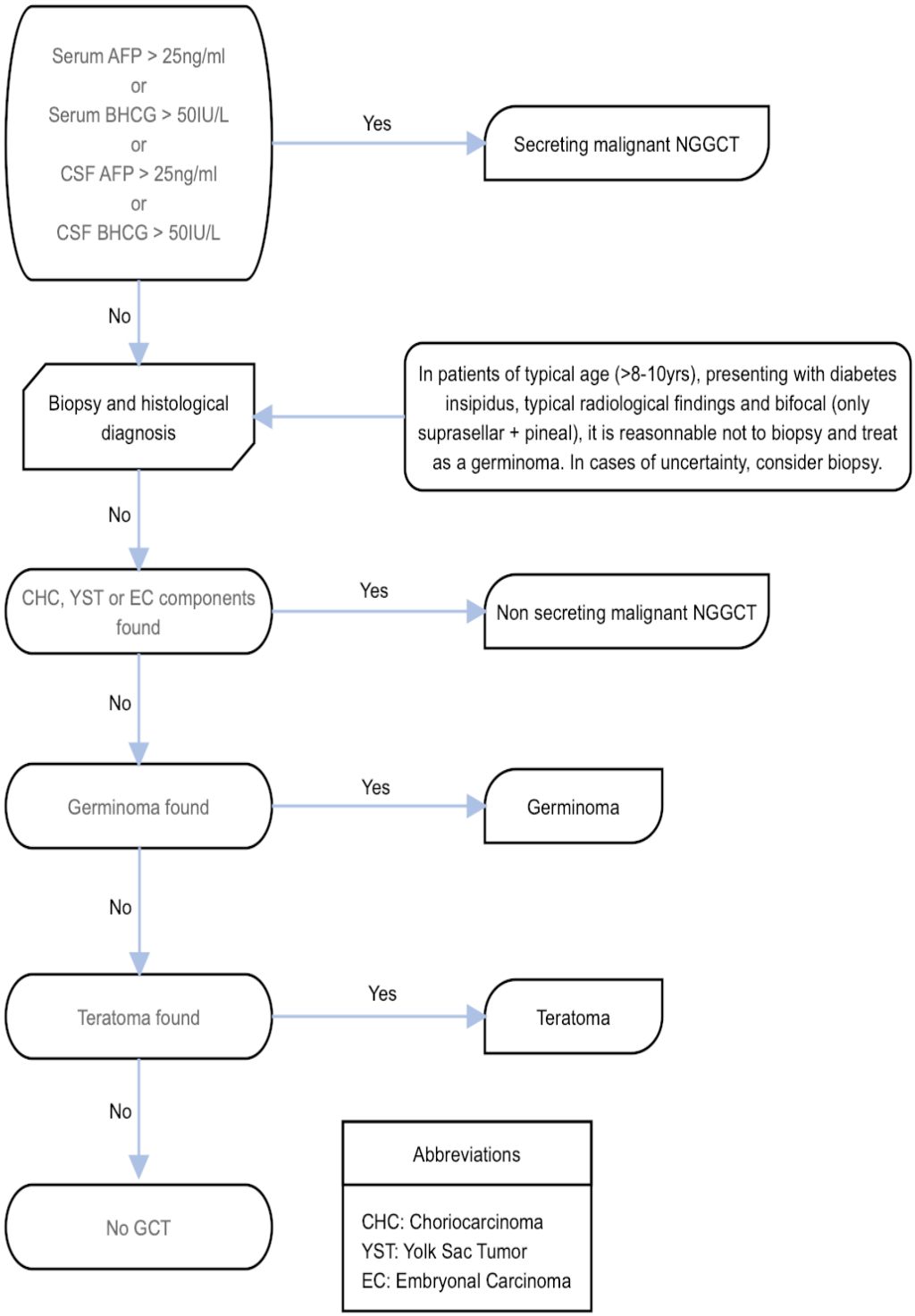
Imaging

- Although CT scan can contribute information on tumour cellular density and presence/absence of e.g. calcification, MRI is the preferred imaging modality.
- MRI appearances in typical locations (suprasellar, bifocal, pineal), in conjunction with expected clinical signs, are strongly predictive of the presence of a CNS GCT.
- A correct interpretation of imaging should take into account the MRI appearance of normal anatomy of pineal and suprasellar regions at different ages and of that of other benign or malignant lesions typical in these sites.
    - CNS GCT usually appear as a solid mass that is similar to grey matter and shows prominent enhancement following the administration of contrast.
    - The main distinguishing radiological features of pure germinomas relate to their typical sites of involvement, with up to 30% of cases bifocal and <10% metastatic, in which multifocal involvement is seen mainly within the ventricular system.

  - Both loco-regional and meningeal extension must be fully assessed [18].
  - The diagnosis of germinoma may be suspected because of pituitary disturbance, in particular DI, when the lesion is still small; in these cases, the MRI can show the lack of the bright spot of the neuro-hypophysis in T1 weighted images [19, 20].
- MRI should be performed before biopsy in all cases and within 24-48 hours following surgery if resection is performed, i.e. for suspected teratoma (not required after biopsy only).
  - As non-specific intracranial enhancement is often seen after 3 days following surgery, the postoperative MRI must be obtained within 72 hours and ideally within 24-48 hours postoperatively.
- Spinal MRI should ideally be performed before lumbar puncture and surgery and should include the full spine (including lower dural sac).
- Essential MRI sequences for brain and spine imaging, tumour measurement guidelines, post-operative residual tumour definitions and response criteria adapted from the recommendations of the SIOP-Europe Brain Tumour Group Neuroradiology Subgroup [21] are available in Appendix C.
- We recommend that in case of doubt regarding potential bifocal disease, cases should be discussed with neuro-radiologists' national GCT expert teams, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.
- Based on the results of full neuro-axis imaging, CSF cytology, biochemical marker work-up in both compartments (serum AND CSF), and biopsy results where indicated, patients can be stratified into diagnostic (germinoma *vs.* malignant NGGCT) and dissemination (localised *vs.* metastatic) treatment groups.

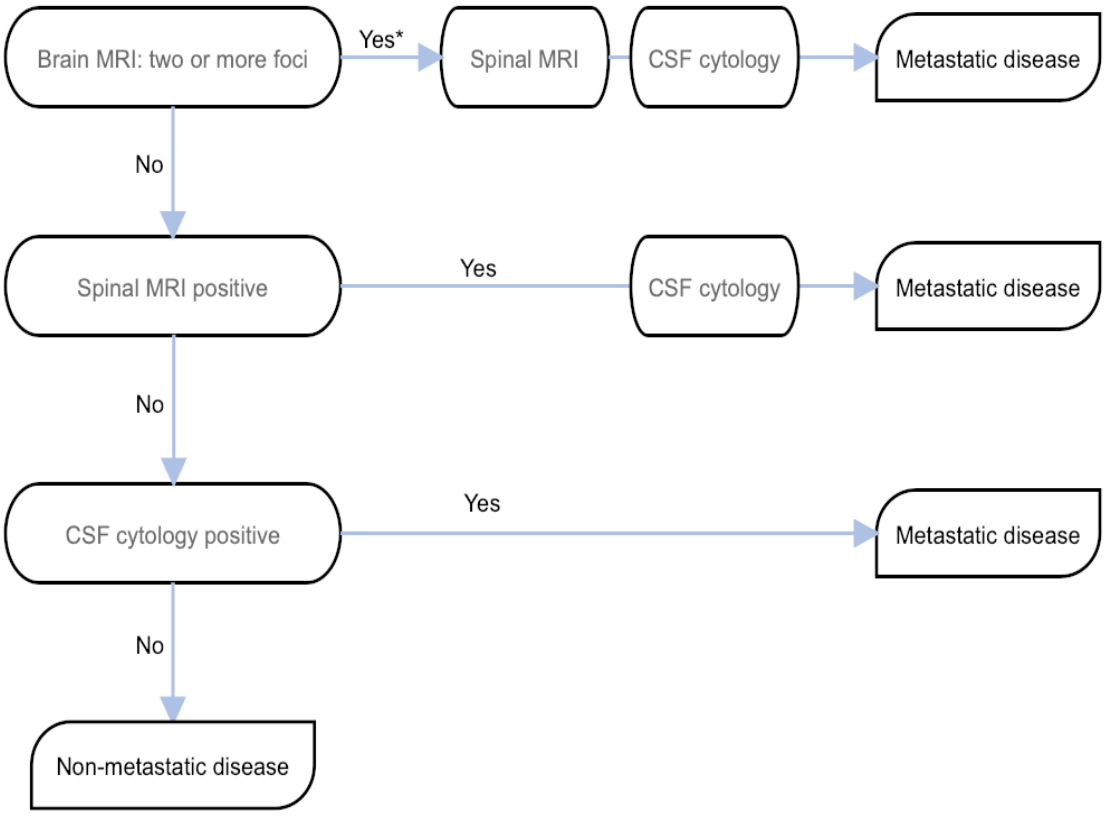
Diagnostic grouping

(as per SIOP CNS GCT II protocol)



- Serum and/or CSF markers above thresholds (AFP > 25 ng/ml and HCG > 50 IU/L are diagnostic of a secreting malignant NGGCT and treatment may be initated without performing a biopsy.
- In patients of typical age (>8-10yrs), presenting with diabetes insipidus (DI), typical radiological findings and bifocal localisation (i.e. only suprasellar and pineal site), it is reasonable not to biopsy and treat as a germinoma. In cases of uncertainty, consider biopsy [17].
- Histological findings of CHC, YST and/or EC are characteristic of non-secreting malignant NGGCT and treatment may be initiated accordingly

Grouping for dissemination



*In case of bifocal tumor (ONLY pineal+suprasellar) AND negative spinal MRI AND negative CSF cytology, disease is classified as non-metastatic

Diabetes insipidus (DI)

DI is a frequent symptom at initial presentation in CNS GCT patients with hypophyseal/suprasellar infiltration [22]. The involvement of endocrinologists is essential at diagnosis and during chemotherapy administration when hyperhydration is required. Guidance is provided in Appendix D, in order to:

- Provide emergency cortisol (usually hydrocortisone) cover during the perioperative period, if patient is not on high doses of corticosteroids for other reasons, namely management of RICP.
- Administer desmopressin (antidiuretic hormone; ADH) if the patient has DI prior to surgery.
- Monitor fluid intake and output, as well as blood sodium levels, closely during surgery and chemotherapy administration.

Treatment

Summary of available evidence for CNS GCT therapy

- Radiotherapy should be administered in all cases of germinoma and malignant NGGCT to achieve acceptable cure rates, except in the cases of very young children (<6 years) where a chemotherapy-only approach is often attempted to avoid long-term sequelae of radiotherapy.
- Chemotherapy is used for the treatment of both (non-metastatic) germinoma and all cases of NGGCT, with the goal of reducing radiotherapy fields and doses.

Germinoma

Germinomas are known to be particularly chemo- and radio-sensitive. Historically, craniospinal irradiation (CSI) has been the gold standard for treatment but, because of the long-term risks of radiotherapy, especially in growing individuals, neoadjuvant

chemotherapy has been introduced with the rationale to decrease the cumulative doses and fields of radiotherapy [16]. Conversely, chemotherapy alone is insufficient to allow for acceptable cure rates (~50% e.g. [23], compared with >90% with radiotherapy).

Non-metastatic germinoma, first-line treatment:

- A prospective North American trial evaluating chemotherapy prior to radiation to the tumour site in localised germinoma was conducted in the late 1990s [24]. Using a combination of chemotherapy (cisplatin, etoposide, cyclophosphamide, and vincristine) and radiotherapy [focal irradiation at 30.4Gray (Gy)], this trial showed a very good 3-year event-free survival (EFS) of 92+/-8%.
- Several groups observed an increased risk of relapse within the ventricles in those patients with involved field radiotherapy despite adjuvant chemotherapy, prompting recommendations of whole ventricular (WVI) rather than focal irradiation by the working groups in Europe, North America, and Japan [16, 25, 26].
- In Europe, the current European recommended dose from the SIOP CNS GCT 96 trial is WVI of 24Gy + 16Gy tumour bed boost (40Gy total dose) [16].
- Reductions of radiotherapy dosing to 18Gy + 12Gy tumour bed boost (30Gy total dose) in localised germinomas has been assessed in the ACNS1123 trial of the North American Children's Oncology Group, with pending results.
- The primary objectives of the European SIOP CNS GCT II trial (2012-2018) in germinoma patients were to maintain current high EFS rates using a risk-adapted approach. In localised disease, CSI was omitted and replaced by combined treatment with standard chemotherapy and WVI including the tumour bed (TB) area (WVI+TB) at 24Gy. Omission of the standard boost to the tumour bed at 16Gy (total dose 40 Gy) in patients with clinical remission (CR) after induction chemotherapy was an experimental question. Bifocal tumours (pineal + suprasellar) continued to be treated as non-metastatic disease, as in SIOP CNS GCT 96 [16]. In metastatic disease, the goal was to maintain excellent EFS with craniospinal irradiation (CSI) alone. Preliminary, unpublished results of the SIOP CNS GCT II study trial continue to show a very good outcome with a 3-year EFS of 96%.

- Following closure of the SIOP CNS GCT II trial in 2018, current European management guidelines for localised germinomas recommend chemotherapy with alternating cycles of carboplatin/etoposide and ifosfamide/etoposide for a total of 4 cycles, followed by 24Gy WVI+TB. The 16Gy tumour bed boost may safely be omitted from patients with localised, single site pineal or suprasellar disease, as well as for those with bifocal disease, in CR after induction chemotherapy [27, 28]. All other patients should currently continue to receive the boost. We recommend that in any cases of uncertainty, discussion with national GCT expert teams should take place, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.
- Although residual disease after chemotherapy and/or at the end of treatment is considered to be a risk factor for most malignant paediatric brain tumours, this is not the case for germinoma. Neither the presence (nor specifically the size) of such residual tumour was identified as an adverse prognostic factor in SIOP CNS GCT 96 [16]. Furthermore, it should be noted that metastatic CNS germinoma disease, following biopsy confirmation, is treated with CSI without recourse to surgical resection and these patients also have excellent outcomes [16]. Accordingly, a resection in cases of bulky residual disease after neoadjuvant chemotherapy should only be considered where there is concern of teratoma or remaining viable elements in situations where the risk-benefit balance is deemed favourable and the neurosurgical team is experienced, as described in the SIOP CNS GCT II protocol, namely:
    - *'Surgical excision should be attempted in cases of known germinoma plus teratoma, and cases of germinoma in which there is no apparent response to treatment. It should also be considered in cases of partial response, in which the radiological appearance at reassessment following chemotherapy is suggestive of teratoma.'*
    - *'The optimum timing of surgery is after the end of chemotherapy, but may also be considered following radiotherapy.'*
    - *For small residual masses in cases of germinoma that have responded to chemotherapy and/or radiotherapy, a watch and wait strategy should be adopted.'*

  - *We recommend that any complex case should be discussed with neurosurgeons' national GCT expert teams, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.*
- Of note, the term 'bulky' is not specifically defined for residual disease for the purposes described above, and needs to be assessed on an individual case-by-case basis, and will include, amongst other factors, the size/diameters of the lesion(s) at original diagnosis.
- We recommend that in any cases of uncertainty, discussion with national GCT expert teams should take place, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.

Metastatic germinoma, first-line treatment

- At diagnosis, around 20% of patients with germinoma present with radiological and/or cytological signs of disseminated disease [16].
- Current European standard-of-care for these patients remains CSI (24Gy) with 16Gy boost to metastatic sites (to a total of 40Gy) [16].

Germinoma relapse treatment

- Relapses in germinoma are rare and patients should be fully restaged with cranio-spinal imaging, serum and CSF markers and cytology.
- Among therapeutic options, both standard-dose chemotherapy (SDC) and re-irradiation OR high-dose chemotherapy (HDC) with stem-cell transplantation (SCT) (with or without further re-irradiation) have been used and represent valid approaches:
  - A retrospective study from UK and Germany describing relapse patients treated on the European protocol SIOP CNS GCT 96 as first-line therapy showed similar outcomes when retreated at relapse with either SDC + re-irradiation or HDC+SCT with/without re-irradiation [29].
  - Kubota *et al.* confirmed a very good outcome in relapsed germinoma patients with a combined approach of standard-dose platinum and ifosfamide-based reinduction chemotherapy followed by a melphalan-based HDC+SCT. Most of their patients thus avoided re-irradiation [30].

- Callec *et al.* recently reported a similar favourable outcome for relapsing germinoma patients treated with either SDC with re-irradiation or HDC+SCT with/without re-irradiation [31].
- We very strongly recommend that all relapsed intracranial malignant GCT patients are discussed with national GCT expert teams, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.

Non-germinomatous GCT (NGGCT)

Outcomes for patients presenting with CNS NGGCT are inferior to those with germinoma, as these tumours are more aggressive and less chemo- and radio-sensitive. As such, more aggressive combined chemo-radiotherapy approaches must be employed for cure.

NGGCT first-line treatment

- German experience using since 1986 a combined strategy with platinum-based chemotherapy (BEP: bleomycin/etoposide/cisplatin or VIP: vinblastine/ifosfamide/cisplatin) followed by craniospinal irradiation at 30Gy with a tumour boost of 24Gy showed a 5 year EFS of 67% [32].
- In Europe, patients with CNS NGGCT treated within SIOP CNS GCT 96 received a neoadjuvant chemotherapy with four cycles of dose-intense cisplatin-based chemotherapy (PEI: cisplatin, etoposide, ifosfamide), followed by radiotherapy to the tumour bed at a dose of 54Gy in non-metastatic cases and craniospinal irradiation at a dose of 30.6Gy with an additional 23.4Gy boost (total dose 54Gy) to the primary tumour and macroscopic metastatic sites, except for spinal cord sites where the boost dose is limited to 14.4Gy (total dose 45Gy), in metastatic patients. Five-year EFS and overall survival (OS) figures of 72% and 82%, respectively, were obtained in localised patients and of 68% and 75%, respectively, in metastatic patients [3]. The same study identified serum or CSF AFP levels greater than 1000 ng/ml at diagnosis, as well as residual disease after treatment, as significant unfavourable (‘high-risk’) prognostic factors [3].

- In Japan, patients have been stratified into two risk groups and treated with either neoadjuvant chemotherapy (etoposide and carboplatin or cisplatin) followed by local radiotherapy at a dose of 30Gy and further adjuvant therapy (intermediate-risk group) or with neoadjuvant chemotherapy with ICE (ifosfamide, cisplatin, etoposide) followed by cranio-spinal radiotherapy at 30Gy with a 30Gy boost to the tumour bed followed by adjuvant chemotherapy (high-risk group). This approach led to a moderate complete response rate at the end of first line treatment of 55.6% [25].
- In North America, NGGCT patients treated within the ACNS0122 trial received 6 cycles of carboplatin/etoposide alternating with cycles of ifosfamide/etoposide. As in European trials, second-look surgery was advised after this neoadjuvant chemotherapy if response was deemed insufficient (i.e. either partial response with ≥65% decrease in 3D measurments but positive markers or stable disease). Patients with residual disease (either unresectable or remaining after second-look surgery) received HDC (thiotepa/etoposide) followed by SCT. All patients received CSI at a dose of 36Gy with boost to the tumour bed and metastasis to a total dose of 54Gy and 45Gy, respectively. In this cohort, 5 years EFS and OS were 84% and 93%, respectively [33].
- In the recently closed European SIOP CNS GCT II trial, the primary objectives for patients with NGGCT were to improve EFS by dose escalation of chemotherapy in patients identified as high-risk at diagnosis [age <6 years,and/or diagnostic serum or CSF AFP >1000 ng/ml, and/or poor response to PEI chemotherapy (viable tumour at the time of delayed surgery)] and by standardising the surgical approach for residual disease after treatment.
- Preliminary, unpublished results for the SIOP CNS GCT II trial for malignant NGGCT patients show overall 3-year EFS and OS of 70% and 81%, respectively, similar to the SIOP CNS GCT 96 data.
- For NGGCT, patterns of relapse in SIOP CNS GCT II are not yet clear, and may require amalgamation with results from the previous SIOP CNS GCT 96 trial to help unravel the debate regarding the most appropriate radiotherapy fields. In the meantime, and in view of the concern regarding the potential risk of ventricular relapse from germinoma components within NGGCTs, and reports of distant metastases in the COG ACNS1123 trial [34], an updated consensus

is provided below. Whilst it has not been standard practice to date, it would be reasonable to consider extending the radiotherapy field for localised NGGCT cases where germinoma components may be present, to include the ventricles to a dose of 24Gy in 15 fractions (i.e. as per localised germinoma), with a boost dose to the primary tumour bringing the total tumour dose to 54Gy as before. Such cases would particularly include those where germinoma is present in any diagnostic biopsy/histology specimen, where ventricular seeding is directly visualised and documented by the neurosurgeons during a surgical procedure not detected on the preoperative MRI, or those cases with only modest HCG elevations above the 'secreting' threshold (e.g. 50-200 IU/L) which could be consistent with the presence of syncytiotrophoblastic cells within a germinoma component. As more results become available from SIOP CNS GCT II and other international trials, we anticipate greater clarity regarding appropriate fields and may be able to make more definitive recommendations internationally.

- For ‘high-risk’ NGGCT, based on diagnostic serum or CSF AFP >1000 ng/ml, poor response to PEI chemotherapy (viable tumour at the time of delayed surgery), and/or very young patients (<6y) in whom radiotherapy is to be avoided, there is not enough evidence to be able to recommend the dose intense (high-dose) PEI regimen as employed in SIOP CNS GCT II as clearly superior to standard PEI. It is very unlikely that, given the small number of patients in this group, there will be a clear-cut outcome, even after all of the data has been analysed, and any survival advantage of high-dose PEI chemo is unlikely to reach statistical significance. However, given that the 5-year EFS of this group was only 32% with standard treatment in SIOP CNS GCT 96 [3], and since high-dose PEI delivered in SIOP CNS GCT II was well tolerated with no serious adverse events reported, clinicians may feel that it is reasonable to offer/give dose intensified PEI with stem cell support (SCT) to such patients, with appropriate consent.

NGGCT relapse treatment

- Relapses in NGCCT are more common than for germinoma patients and prognosis is generally reported as poor, with only 14% 5-year OS [29, 30]. As

for germinoma, relapsing patients should be fully restaged and assessed before considering therapeutic management options.

- For curative intent, salvage treatment with HDC+SCT is imperative. Recently, in a cohort of 44 patients with relapsing CNS GCT including 25 NGGCT, Callec *et al.* reported a relatively good outcome with intensive salvage treatment including HDC [31]. Although patients included were treated over a long period, back as far as 1990, these results confirm that intensive treatment with HDC+SCT is absolutely necessary when the treatment intent is curative [31]. Regarding re-irradiation, Callec *et al* highlighted that although their series was relatively large, the limited sample size of each subgroup prevented a definite conclusive analysis in particular for fields, doses and timing of radiotherapy to be delivered at relapse, which would require better evaluation [31].
- We very strongly recommend that all relapsed intracranial malignant GCT patients are discussed with national GCT expert teams, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.

Teratoma

- Suspected teratoma is treated surgically, as it is almost completely resistant to chemotherapy and generally resistant radiotherapy. Radiotherapy may, however, be considered in patients with non-resectable residual disease and/or progression that cannot be controlled through repeated surgery. Additional treatment according to histology and resection status should be discussed and approaches for mature (MT) and immature teratoma (IT) needs to be individualised.
- Mature and immature teratomas are typically not chemotherapy- or radio-sensitive and complete surgical resection, where feasible, is the treatment of choice, although cases of occasional response to chemotherapy have been reported in immature teratomas [35]. In certain situations, malignant NGGCT tumours can differentiate into mature teratoma elements and increase in size on initiation of treatment with chemotherapy, with normalisation of tumour markers, a scenario known as ‘growing teratoma syndrome’ [36, 37]. Although

definitive surgical resection is the only known cure, some recent reports of patients treated with CDK4/6 inhibitors, such as Palbociclib, in this situation have described stabilisation of unresectable tumour residues [38, 39].

- Leaving large teratoma residues however risks future de-differentiation back into a malignant GCT or somatic transformation into non-GCT tissues such as sarcomatous change, which typically portends a dismal prognosis. Surgical resection of any teratoma and/or residual is thus strongly recommended in all cases, if at all feasible [40].
- We recommend that any such complex teratoma patients falling into the above categories are discussed with clinicians' national GCT expert teams, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.

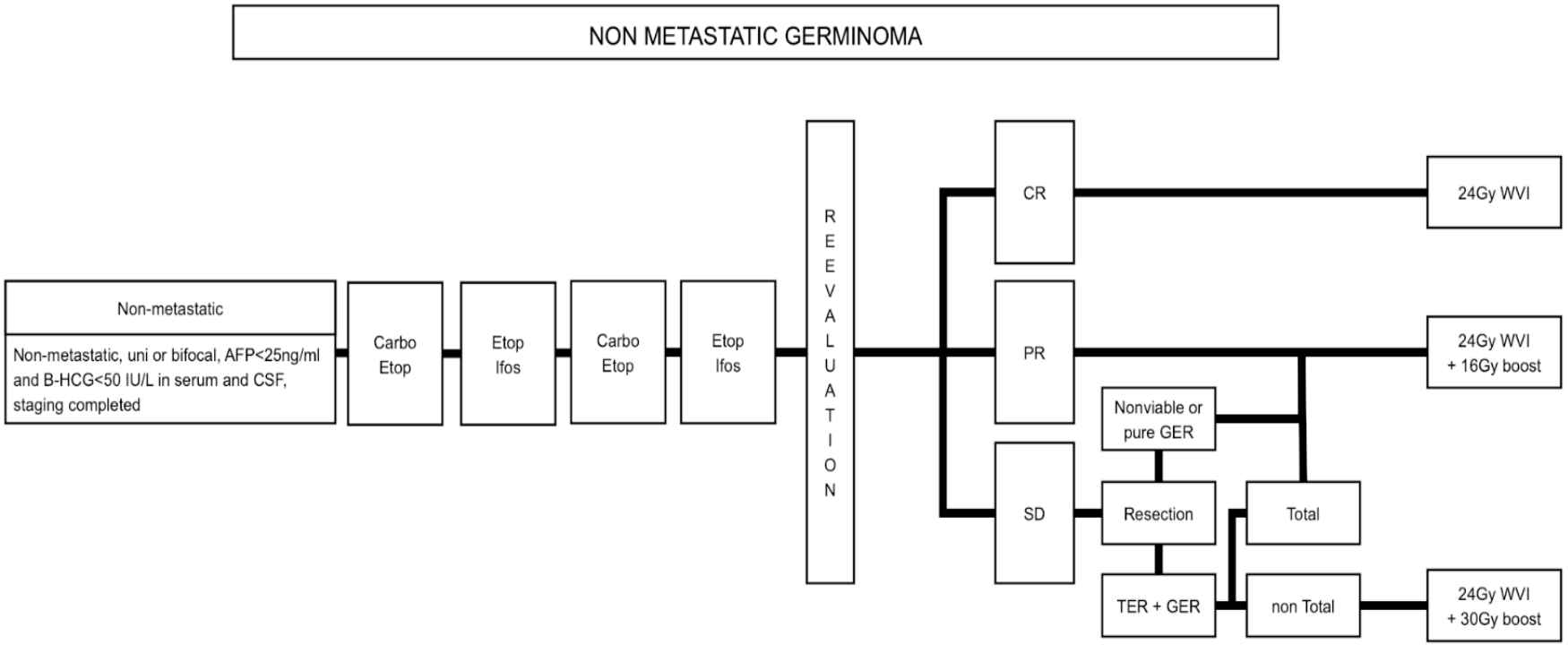
Overall management of CNS GCT

Germinoma

Based on current knowledge, all patients with intracranial germinoma should receive radiotherapy to maximise their chance of cure.

Localised germinoma, first-line treatment

For localised germinoma, platinum-based neoadjuvant chemotherapy is delivered first, which has allowed reduced doses of radiotherapy to be given. For localised germinoma, focal radiotherapy fields alone are insufficient, and therefore, radiotherapy should also include the ventricles [i.e., whole ventricular irradiation (WVI)] [16]. For localised patients with isolated suprasellar, pineal, or bifocal disease in CR after induction chemotherapy, the radiotherapy boost can be omitted and WVI is sufficient [27, 28].



SIOP CNS GCT II trial protocol - treatment arm for non-metastatic germinoma, including experimental arm for patients in CR after induction chemotherapy (see text for more details).

AFP: Alpha-fetoprotein, HCG: Human Chorionic Gonadotropin, Carbo: Carboplatin, Etop: Etoposide, Ifos: Ifosfamide, CR: Complete Remission, PR: Partial Remission, SD: Stable Disease, GER: Germinoma, TER: Teratoma, WVI: Whole Ventricular Irradiation

Chemotherapy consists of two courses of carboplatin/etoposide, alternating with two courses of ifosfamide/etoposide and should commence as soon as possible following diagnosis:

<u>Courses 1 and 3</u>		
Carboplatin	600 mg/m²/day (max 1200mg)	day 1
Etoposide	100 mg/m²/day	days 1, 2, 3
<u>Courses 2 and 4</u>		
Ifosfamide	1800 mg/m²/day	days 1, 2, 3, 4, 5
Etoposide	100 mg/m²/day	days 1, 2, 3

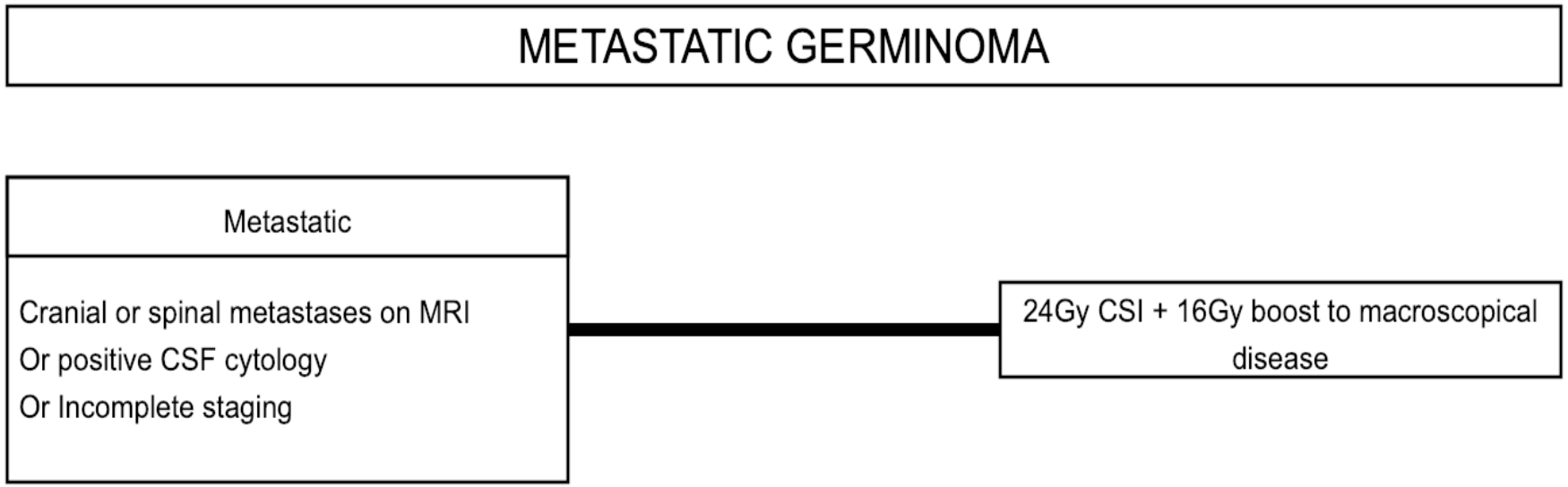
<u>Notes:</u>

- Details of chemotherapy administration for germinoma are given in Appendix E
- Courses of chemotherapy should be given at 21-days intervals, providing:
    - Haematological recovery from the previous course has taken place:
        - Neutrophils ≥1.0 x 10^9/L or WBC ≥ 2.0 x 10^9/L
        - Platelets ≥100 x 10^9/L and rising.
    - Both adequate glomerular and tubular function:
        - Glomerular filtration rate (GFR) >80ml/min/1.73m^2
        - Tubular reabsorption of phosphate (TRP) >85% (1-(urine phosphorus concentration/urine creatinine concentration) × (serum creatinine concentration/serum phosphorus concentration) × 100)
- Doses adaptations if the above criteria are not met are provided in Appendix H

Metastatic germinoma, first-line treatment

Metastatic and incompletely staged germinomas do not receive chemotherapy and should be treated with standard craniospinal irradiation (CSI) with boosts to macroscopic sites of disease.

If there will be a potential delay from diagnosis to delivery of CSI for patients with metastatic disease, potential use of a short period of 'holding' chemotherapy, e.g. carboplatin/etoposide, or e.g. vinblastine[41] could be considered, to prevent further disease-related co-morbidities developing, prior to definitive radiotherapy. This can be discussed with national GCT expert teams, and more widely (European-wide advice) if indicated/required, to ensure optimal patient outcomes.



SIOP CNS GCT II treatment arm for metastatic germinoma
CSI: cranio-spinal irradiation

Germinoma relapse treatment

All patients presenting with symptomatic or radiological germinoma relapse should be fully restaged and assessed, before considering management options. Among therapeutic options, both standard-dose chemotherapy (SDC) with re-irradiation or high-dose chemotherapy (HDC) and stem-cell transplant (SCT) with/without re-irradiation have been used and represent valid approaches [29-31].

We very strongly recommend that all relapsed intracranial malignant GCT patients are discussed with clinicians' national GCT expert teams, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.

Germinoma: assessments

Investigations before the start of chemotherapeutic treatment:

- Ophthalmological evaluation
- Endocrine evaluation
- Fertility preservation protocol should be discussed

Investigations before each course of carboplatin/etoposide and ifosfamide/etoposide chemotherapy.

- Clinical assessment, including neurological examination
- Weight
- Full blood count
- Blood biochemistry: electrolytes, urea, creatinine, ALT/AST, alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate

- Note: GFR estimated by radioisotope clearance, or other locally approved method, or by direct measurement of urinary creatinine clearance before first and third course
- Pure tone audiometry (before first course, with additional assessments based on local practice and if any concern regarding hearing)
- Pregnancy test, if applicable. If uncertainty in interpretation of HCG is likely due to elevated levels as a GCT marker, obstetric review and/or ultrasound should be considered.

Tumour reassessment after four courses of chemotherapy

- Clinical assessment, including neurological examination.
- MRI of the head with and without contrast.
- Serum markers; CSF markers in all cases of clinical doubt.

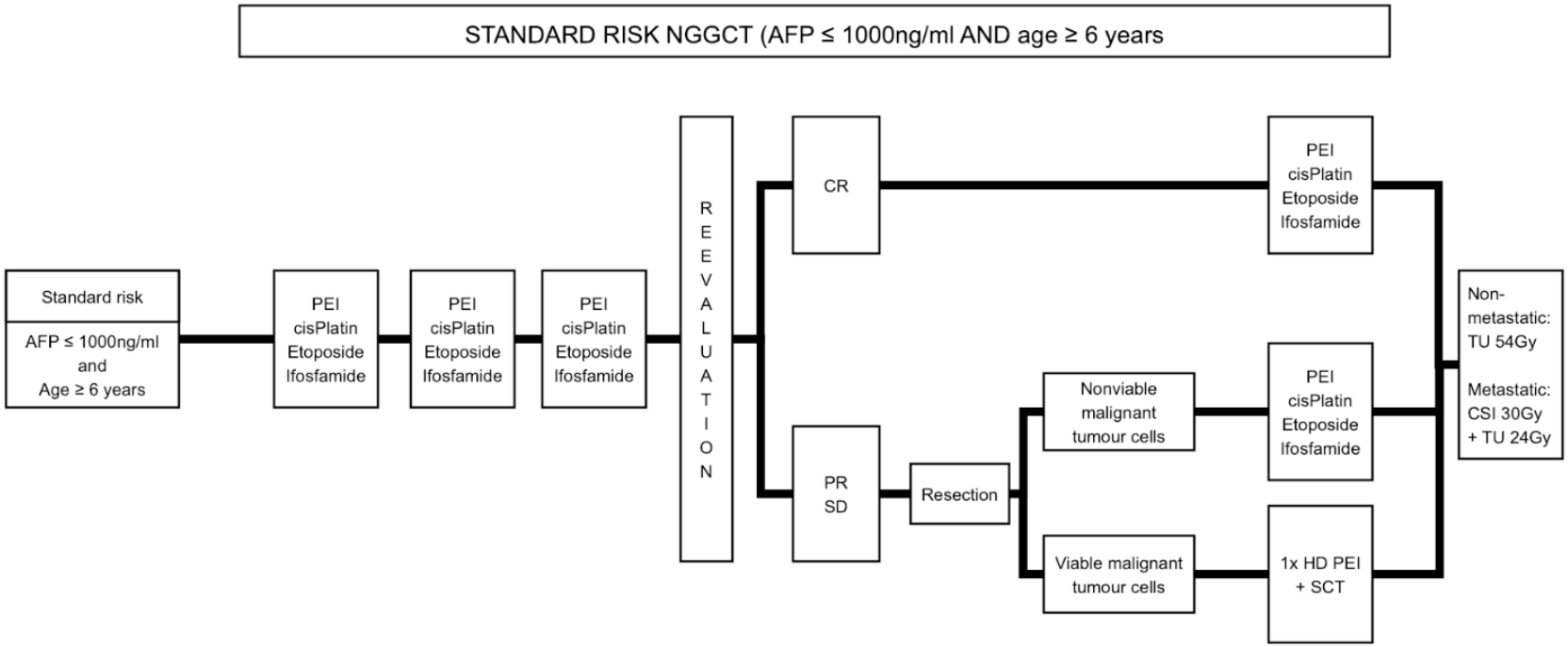
Non-germinomatous GCT

Patients with NGGCT should receive a combination of chemotherapy and radiotherapy, to maximise their chance of cure. Based on the diagnostic serum/CSF AFP level and patient age, patients can be stratified into two risk groups. Patients with AFP ≤1000 ng/ml and who are ≥6 years of age are classified as standard-risk patients. Those with AFP levels >1000 ng/ml and/or <6 years of age are considered high-risk patients [3].

For NGGCT, patterns of relapse in SIOP CNS GCT II are not yet clear, and may require amalgamation with results from the previous SIOP CNS GCT 96 trial to help unravel the debate regarding the most appropriate radiotherapy fields. In the meantime, and in view of the concern regarding the potential risk of ventricular relapse from germinoma components within NGGCTs, and reports of distant metastases in the COG ACNS1123 trial [34], an updated consensus is provided below. Whilst it has not been standard practice to date, it would be reasonable to consider extending the radiotherapy field for localised NGGCT cases where germinoma components may be present, to include the ventricles to a dose of 24Gy in 15 fractions (i.e. as per localised germinoma), with a boost dose to the primary tumour bringing the total tumour dose to 54Gy as before. Such cases would particularly include those where germinoma is present in any diagnostic biopsy/histology specimen, where ventricular seeding is directly visualised and documented by the neurosurgeons during a surgical procedure not detected on the preoperative MRI, or those cases with only modest HCG elevations above the 'secreting' threshold (e.g. 50-200 IU/L) which could be consistent with the presence of syncytiotrophoblastic cells within a germinoma component. As more results become available from SIOP CNS GCT II and other international trials, we anticipate greater clarity regarding appropriate fields and may be able to make more definitive recommendations internationally.

For ‘high-risk’ NGGCT, based on diagnostic serum or CSF AFP >1000 ng/ml, poor response to PEI chemotherapy (viable tumour at the time of delayed surgery), and/or very young patients (<6y) in whom radiotherapy is to be avoided, there is not enough evidence to be able to recommend the dose intense (high-dose) PEI regimen as employed in SIOP CNS GCT II as clearly superior to standard PEI. It is very unlikely that, given the small number of patients in this group, there will be a clear-cut outcome, even after all of the data has been analysed, and any survival advantage of high-dose PEI chemo is unlikely to reach statistical significance. However, given that the 5-year EFS of this group was only 32% with standard treatment in SIOP CNS GCT 96 [3], and since high-dose PEI delivered in SIOP CNS GCT II was well tolerated with no serious adverse events reported, clinicians may feel that it is reasonable to offer/give dose intensified PEI with stem cell support (SCT) to such patients, with appropriate consent.

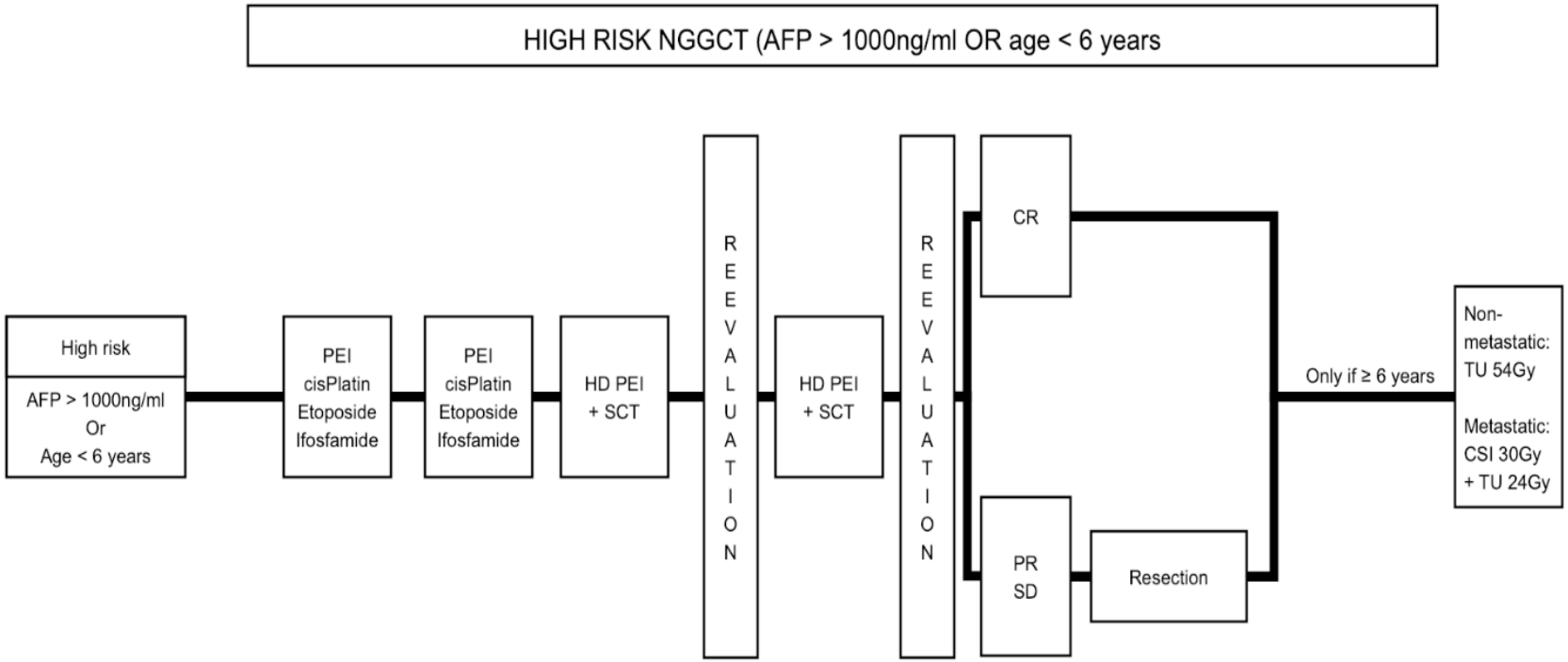
Standard-risk NGGCT first-line treatment



SIOP CNS GCT II trial protocol - treatment arm for standard-risk NGGCT

AFP: Alpha-fetoprotein, CR: Complete Remission, PR: Partial Remission, SD: Stable Disease, HD: High Dose Chemotherapy, SCT: Stem Cell Transplant, TU: Tumour bed, CSI: cranio-spinal irradiation, NGGCT: non-germinomatous germ cell tumour.

High-risk NGGCT first-line treatment



SIOP CNS GCT II trial protocol – <u>experimental treatment arm</u> for high-risk NGGCT

AFP: Alpha-fetoprotein, CR: Complete Remission, PR: Partial Remission, SD: Stable Disease, HD: High Dose Chemotherapy, SCT: Stem Cell Transplant, TU: Tumour bed, CSI: cranio-spinal irradiation, NGGCT: non-germinomatous germ cell tumour.

Chemotherapy is based on a combination of cisplatin, etoposide and ifosfamide (PEI), either at standard doses or in a dose-intense schedule followed by stem-cell rescue (SCT). Chemotherapy should commence as soon as possible following diagnosis.

In standard-risk patients, three initial courses of PEI are given followed by a radiological tumour reassessment following the third course. The fourth course is given after surgery in cases with resectable residual and is followed by radiotherapy. In the event that there is residual tumour at end of treatment/radiotherapy (radiotherapy for those patients ≥6 years), which is amenable to surgery, resection should be attempted at that stage.

For 'high-risk' patients [diagnostic serum or CSF AFP >1000 ng/ml, poor response to PEI chemotherapy (viable tumour at the time of delayed surgery), and/or very young patients (<6y) in whom radiotherapy is to be avoided], clinicians may feel that it is reasonable to offer/give dose intensified (HD-) PEI with stem cell support (SCT) to such patients (see more detail above), with appropriate consent.

Standard-dose PEI

Each course of PEI consists of:

Cisplatin	20 mg/m²/day	days 1, 2, 3, 4, 5
Etoposide	100 mg/m²/day	days 1, 2, 3
Ifosfamide	1500 mg/m²/day	days 1, 2, 3, 4, 5

Please note:

- It is also possible to use etoposide phosphate instead of etoposide in equivalent dose: 114mg etoposide phosphate equals 100mg etoposide.

- Ifosfamide dosing and administration differ from those used in treatment of germinoma.
- Courses of chemotherapy should be given at 21-days intervals, providing:
    - Haematological recovery from the previous course has taken place:
        - Neutrophils ≥1.0 x 10^9/L or WBC ≥ 2.0 x 10^9/L
        - Platelets ≥100 x 10^9/L and rising.
    - Both adequate glomerular and tubular function:
        - Glomerular filtration rate (GFR) >80ml/min/1.73m^2
        - Tubular reabsorption of phosphate (TRP) >85% (1-(urine phosphorus concentration/urine creatinine concentration) × (serum creatinine concentration/serum phosphorus concentration) × 100)
- Doses adaptations if the above criteria are not met are provided in Appendix H
- In case of replacement of cisplatin by carboplatin, the total equivalent dose of carboplatin is 600mg/m², given as one dose only on day 1.
- Peripheral blood stem cells should be harvested following the first and/or second course of standard PEI, if use of HD-PEI is being considered by the clinician.
- Details of PEI chemotherapy administration for NGGCT are given in Appendix F

High-dose PEI and SCT rescue

(reasonable for clinicians to consider for high-risk patients – see comments above):

Guidelines for preparation for stem cell collection:

- G-CSF (10 µg/kg/day s.c.) is administered after the first course of standard PEI chemotherapy, beginning on day 7 after start of chemotherapy and continued until leucocyte recovery or increase in CD34 positive cell count in the peripheral blood, followed by stem cell collection according to standard criteria, (i.e. 3 days leukocytes above 2000/µl or ANC above 1000/µl).
- The aim of stem cell collection should be to achieve a sufficient number of CD34 positive haematopoietic stem cells for reinfusion following 2 consecutive courses of high dose chemotherapy (HD-PEI) with stem cell support (i.e. >1 x

10^6 CD34 positive cells/kg body weight for each course). This is a lower dose than that conventionally used with truly myeloablative chemotherapy regimens.

- Stem cells should be harvested according to local institutional practice.

Each course of HD-PEI consists of:

Cisplatin	20 mg/m²/day	days 1, 2, 3, 4, 5
Etoposide	**300** mg/m²/day	days 1, 2, 3, **4, 5**
Ifosfamide	**2000** mg/m²/day	days 1, 2, 3, 4, 5

- Details of HD-PEI chemotherapy administration for NGGCT are given in Appendix G

NGGCT relapse treatment

All patients presenting with symptomatic, radiological or marker-detected NGGCT relapse should be fully restaged and assessed, before considering management options. Cases should be discussed with national or international experts, and for patients with malignant NGGCT relapse who are to be treated with curative intent, thiotepa-based HDC+SCT MUST be employed, with surgery and additional radiotherapy where feasible.

We very strongly recommend that all relapsed intracranial malignant GCT patients are discussed with clinicians' national GCT expert teams, and more widely (European-wide advice) if indicated/required (see Appendix K), to ensure optimal patient outcomes.

NGGCT: assessments

Investigations before the start of chemotherapeutic treatment:

- Ophthalmological evaluation
- Endocrine evaluation

- Fertility preservation protocol should be discussed

Investigations before each course of chemotherapy:

- Clinical examination, including neurological assessment
- Weight
- Full blood count
- Blood biochemistry – electrolytes, urea, creatinine, ALT/AST, alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate
- Serum markers (AFP and HCG)
- Pure tone audiometry (before first and third course, with additional assessments based on local practice and if any concern regarding hearing)
- GFR estimated by radioisotope clearance, or other locally approved method, or by direct measurement of creatinine clearance (before first and third course)
- Pregnancy test, if applicable. If uncertainty in interpretation of HCG is likely due to elevated levels as a GCT marker, obstetric review and/or ultrasound should be considered

Tumour reassessment after three courses of PEI chemotherapy

- Clinical assessment, including neurological examination
- Serum markers (AFP and HCG)
- CSF markers (AFP and HCG) – mandatory if raised at diagnosis
- CSF cytology - mandatory if positive at diagnosis
- MRI of the head with contrast
- MRI of spine with contrast - if involved at diagnosis

If there is residual tumour found by imaging after the third course of chemotherapy (3 x PEI), resection of the residual should be carried out, if possible, before radiotherapy. Either the presence of active malignant cells in the resected specimen or continuous rise of markers despite chemotherapy indicate poor response to treatment and should be discussed with National Lead(s).

Surgery role after neoadjuvant chemotherapy

After neoadjuvant chemotherapy, second-line surgery should be discussed and performed in the following circumstances, if at all feasible:

1. In NGGCT with any significant residual disease after 3 courses of induction chemotherapy.
2. In known cases of germinoma plus teratoma, germinoma with no response to treatment and in cases of germinoma with limited partial response (PR) to induction chemotherapy and imaging suggestive of teratoma. Note that in the SIOP CNS GCT II protocol, the only definition available for PR is >0% and <50% tumour volume response. Limited PR should therefore take into consideration the clinical/radiological scenario (suggestive of teratoma), the extent of PR, and the original tumour dimensions. No specific definition of limited PR is given and it should be assessed on a case-by-case basis.

GCT surgical resection should only be attemped by an experienced neurosurgical team. The neurosurgeon should operate according to his/her preferred method, using whatever technology is felt appropriate.

The extent of resection should be assessed by MRI performed ideally within 24-48 hours of surgery (and definitely within 72 hours) and categorised as gross total resection (CR) or partial resection (PR).

Dose modifications for young and for obese patients

- Chemotherapy for patients less than one year of age or weighing less than 10 kg should be prescribed on the basis of weight (kg). The dose is calculated from the dose in m^2 using the formula: $1m^2 = 30kg$
- In children less than 4 months of age, ifosfamide should be omitted and substituted by cyclophosphamide.
- There were no dose capping alterations or dose modifications for e.g. obese patients in the SIOP CNS GCT II trial protocol. It would be reasonable however for teams to consider dose capping/modification as per local protocols/guidelines.

Supportive Care

Anti-emetics, prophylactic antibiotics, use of GCSF etc should be employed as per local guidelines, unless otherwise specified within this document.

Patient follow-up

During and after the end of treatment, serum markers should be monitored every three months for one year, every 6 months for the second year and yearly up to 5 years afterwards, even when negative at diagnosis, as outlined in Appendix J. CSF markers/cytology are not mandated in follow-up but may be performed if indicated based on clinical/radiological status, particularly if positive at original diagnosis.

In general, it is recommended that patients should be followed up for a period of at least 5 years after the end of treatment with imaging, serum markers and clinical examination. Since recurrence of germinoma may occur later than this, clinical follow-up for at least 10 years is advised. Some clinicians may chose to follow patients up beyond 10 years as the potential risk of secondary cancers, cerebrovascular disease such as cavernous malformations/haemorrhage, and very late relapse of GCTs, remain beyond this time.

NGGCT relapses are seen most frequently in the first 2 years off treatment. Children with intracranial teratoma should be followed up every three months in the first year, including clinical assessment, serum markers and MRI. In the event of incomplete resection, clinical assessment and markers could be performed more frequently, as for malignant tumours.

Assessments for late-effects related to the tumour itself, associated hydrocephalus, surgery, chemotherapy and radiotherapy are essential in the long-term follow-up of patients with CNS GCTs. In particular, special consideration should be given to patient growth and other potential endocrinological deficits, as well as kidney and hearing impairments. In addition, neuropsychological functions should be monitored as well. Suggested follow-up is given in Appendix J.

Appendices

Appendix A: HCG measurement

The characteristics of HCG both in physiological and pathological conditions, the fact that it can be found as a dimer (= full molecule) or as fragments (beta subunits), and the pattern of secretion of HCG by GCTs, necessitates considerations of the specificity and sensitivity of different immunoassay methods. The following must be taken into account:

- HCG or intact HCG: reflects only the dimer HCG; measurement units are mIU/ml or IU/l
- Free β-HCG : reflects only the free ß sub-unit; measurement units are ng/ml.
- Total HCG or so called 'ß-HCG': reflects simultaneously HCG and various populations of β-HCG (free and nicked); measurement units are mIU/ml or IU/l.

Although earlier terminology used refers to β-HCG, total HCG, or just HCG, is now being used to reflect the levels of HCG (dimer) and β free subunits.

Several commercial kits are available for the detection of HCG; most measure both dimer and free β-HCG (total HCG). The value is expressed in mIU/ml. More specialised laboratories are able to measure dimer HCG (mUI/ml) and free β-HCG (ng/ml) separately, using highly sensitive methods. It is very important that each oncological centre treating intra- and extracranial GCTs is aware of the potential and limits of the kits used, and whether or not the kit is able to detect β-subunits (free or as a dimer), intact HCG, or both. A method which is limited to the detection of intact HCG, is not appropriate for GCTs, in particular germinomas. In addition, with a half-life of typically only 12-36 hours, HCG levels could be underestimated if a prolonged delay exists between sampling and assay performance. Furthermore, it is crucial that all assays refer to international standards.

Appendix B: Biopsy procedures for CNS GCT

Obtaining a biopsy for diagnostic purposes (only indicated in marker negative, non-secreting tumours, except for pineal and suprasellar bifocal disease, where a diagnosis of germinoma can be assumed if radiology and clinical presentation absolutely typical) could be performed using several approaches:

1. Endoscopic biopsy usually performed during the same procedure as for the management of raised intracranial pressure by either endoscopic third ventriculostomy (ETV) or insertion of an external drain. An endoscopic biopsy should only be performed by an experienced neurosurgical team. The priority is first to perform the ETV to control the ICP and hydrocephalus and then to proceed to endoscopic biopsy. Use of both rigid and flexible endoscopes has been described and successful ETV rates are usually good (70-90%). In certain situations, endoscopic inspection of the third ventricle can reveal lesions not seen on MRI and upstaging of CNS GCT disease to the metastatic group. Due to the treatment implications, this needs to be very carefully documented in the patient's operation/medical notes. The small sample sizes may not be representative.
2. Stereotactic biopsy remains the gold standard for small and deep-seated lesions, with a low complication rate and positive diagnostic yield of more than 95%. It nevertheless requires a separate procedure from shunt placement or endoscopic ETV. The relatively small samples size may still not be representative.
3. Open biopsy or resection, only to be considered in situations where pure teratoma is suspected and/or suspected tumour entities which may be different from GCT are being considered and warrant open surgical approaches and resection. Open surgery as a first line procedure may be considered for large tumours causing mass effect or compression of neural structures such as the visual pathways, in which timely institution of chemotherapy would not be felt to reverse these signs and symptoms.

Appendix C: Imaging in CNS GCT

(Adapted from [21])

Brain imaging, essential MRI sequences

1 to 1.5 tesla scanner

Sequence	Technique	Parameters	Plane
T_1W	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial (along AC-PC axis), sagittal
T_2W	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial
FLAIR	2D TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial or coronal
T_1W + Contrast	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial, coronal and sagittal
DWI with ADC	2D EPI	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable) b=0 and 1000. ADC maps reconstructed online	Axial

3 tesla scanner

Sequence	Technique	Parameters	Plane
T_1W	3D gradient echo (MPRAGE/IR, SPGR/Fats, SPGR/3D, TFE/3D, FFE)	Slice thickness ≤ 1 mm with no slice gap. An isotropic voxel resolution of 1mm x 1mm x 1mm is desirable depending on scanner capability	Axial or sagittal

T_2W	2D SE, TSE/FSE	Slice thickness ≤ 4mm and slice gap ≤ 1mm (10% of slice thickness is desirable)	Axial
FLAIR	2D TSE/FSE	Slice thickness ≤ 4mm and slice gap ≤ 1mm (10% of slice thickness is desirable)	Axial or coronal
T_1W + Contrast	2D SE, TSE/FSE	Slice thickness ≤ 4mm and slice gap ≤ 1mm (10% of slice thickness is desirable)	Axial
T_1W + Contrast	3D gradient echo (MPRAGE/IR, SPGR/Fats, SPGR/3D, TFE/3D, FFE)	Slice thickness ≤ 1 mm with no slice gap. An isotropic voxel resolution of 1mm x 1mm x 1mm is desirable depending on scanner capability	Axial or sagittal, to match pre-contrast
DWI with ADC	2D EPI	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable) b=0 and 1000. ADC maps reconstructed online	Axial

Spine imaging, essential MRI sequences

Sequence	Technique	Parameter	Plane
T_1W + Contrast	2D SE/ TSE	Slice thickness ≤3mm Slice gap <0.5mm	Sagittal whole spine (entire dural sac)
T_1W + Contrast	2D SE/TSE or 3D gradient	Slice thickness 4-5 mm No slice gap	Axial –suspicious areas*

Tumour measurement

As volumetric measurement tools are not available at all centres, the tumour volume is calculated using the (ellipsoid volume) formula A x B x C x ½ where A, B and C are the maximum dimensions in the standard anteroposterior, transverse and craniocaudal planes.

Imaging. 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.

Post-operative residual tumour definitions

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 ≥ 5mm in all 3 planes.

R4: Size of the residual tumour unchanged or only minimally changed from the pre-operative status (e.g., after biopsy)

Response criteria

CR (complete response): no evidence of residual or recurrent tumour or meningeal dissemination.

PR (partial response): Reduction of tumour volume ≥ 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 ≤50% decrease in size and ≤ 25% increase in size compared to the previous staging MRI (no significant change of meningeal dissemination)

PD (progressive disease): increase of tumour volume of > 25% or new lesion.

Note that very good radiological PR after chemotherapy is common in localised germinomas. Such situations may raise a debate between final classification of PR or CR, which are associated with different treatments (e.g delivery of radiotherapy boost

or otherwise). Such cases should be reviewed carefully by local multidisciplinary teams, and more widely if required, to ensure optimal patient outcomes. CNS GCT consensus recommendations from the European Society for Paediatric Oncology Brain Tumour Group (SIOPE-BTG) and North American Children's Oncology Group (COG) are currently under development to better standardise equivocal situations.

Appendix D: Management of DI and perioperative fluid in patients with CNS GCT. *Please note: discussion with and advice from a trained endocrinologist is advised for all such patients*

Post-operative guidelines

- Keep accurate 6-8 hourly fluid balance, inserting a urinary catheter if necessary. Where catheterized, hourly urinary output and specific gravity; otherwise, specific gravity on all urine samples.
- Check paired plasma and urine osmolality, plasma electrolytes and glucose immediately postoperative and 8 hourly thereafter. Changes in plasma sodium >5 mmol/L require more frequent measurements (4-6 hourly).
- Daily weight, at 08.00 am before breakfast.
- Establish whether there is thirst impairment once the patient regains consciousness.
- Commence oral fluid intake and remove intravenous infusion as soon as feasible.
- Continue to monitor fluid balance for at least 10-14 days as in inpatient postsurgical settings, a classical tri-phasic response in anti-diuretic hormone (ADH) secretion can occur.

This can also be associated with cerebral salt wasting:

- An initial phase of DI, possibly due to oedema, manifesting within 24 post-operative hours and lasting up to 2 days.
- A second subsequent phase of either normal fluid regulation or of inappropriate ADH secretion (SIADH) lasting 1-14 days. The latter is presumed to be due to surgically induced vasopressin neuronal necrosis.
- A third phase of permanent DI can follow, especially after severe and prolonged SIADH.

- Note: The above three phases may each also occur independently. Patients with DI at presentation may require higher desmopressin doses postoperatively.
- Cerebral salt wasting, due to over-secretion of atrial natriuretic peptide causing natriuresis and diuresis, can also develop as a primary (neuronal insult) or as a secondary response to SIADH (directly via ADH or through plasma volume expansion).

Management of DI during chemotherapy & hyperhydration

Initial management

Monitoring:

- Accurate 6 hourly fluid balance
- Volume specific gravity (SG) and glucose on all urine samples 8-12 hourly paired plasma and urine osmolality, plasma electrolytes. Changes in plasma sodium >4 mmol/L require more frequent measurements (4-6 hourly).
- Record daily weight, at 08.00 am before breakfast
- Check baseline biochemistry: i.e., liver function tests, calcium profile and thyroid function tests
- Ensure that normal endocrine replacement therapy and desmopressin preparations (oral/intranasal and parenteral) are available.

Fluid intake:

- Intravenous fluids according to chemotherapy protocol (2-3L/m^2). For patients with significant diuresis secondary to DI, the need for mannitol diuresis should be reviewed – it would be reasonable to withhold mannitol in the presence of a urine output >400ml/m^2 measured over 6 hours.

Desmopressin dose:

- During hyper-hydration, reduce desmopressin dose to 50% or 75% of maintenance. Further adjustments in desmopressin dose may be required according to fluid balance and serum electrolytes.

Hydrocortisone replacement:

- If the patient has cortisol deficiency and is on hydrocortisone replacement therapy, the oral maintenance dose may need to be doubled during cycles of chemotherapy, if neutropenia or sepsis is likely. Intravenous hydrocortisone should be given at a dose of 2 mg/kg of body weight (to a maximum of 100 mg per dose), 8 hourly if the patient is unable to tolerate oral intake

Thyroxine replacement:

- Patients with secondary hypothyroidism on thyroxine replacement should be clinically and biochemically euthyroid, with a normal serum FT3 and a serum FT4 value in the upper third of the reference interval.

Further management

- Neutral fluid balance (Intake within ± 10% of output)
- If fluid balance and weight is neutral and plasma sodium is normal and stable, continue with the same desmopressin and fluid regimen.
- NB allow for insensible losses: 250-300ml/m^2

Positive fluid balance (weight gain/intake >10% more than output)

Possible causes

- Excessive desmopressin replacement: In the presence of normal renal and cardiac function, a positive fluid balance is usually due to excessive desmopressin replacement. It is associated with dilutional hyponatraemia, weight gain, and urine/plasma osmolality ratio >1 (SG of urine >1015)
- Drug-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH): SIADH can be induced by chemotherapeutic agents such as Cyclophosphamide. This diagnosis will be suspected by the persistence of dilutional hyponatraemia despite withdrawal of desmopressin treatment.
- Relative hydrocortisone deficiency: adequate hydrocortisone cover is necessary to allow normal water excretion. Failure to increase cortisol replacement in cases of ‘stress’, causes water retention and dilutional hyponatraemia. If the patient is unwell, consider doubling oral hydrocortisone

dose but if unable to tolerate oral intake use hydrocortisone at a dose of 2 mg/kg 8 hourly intravenously.

- Partially/untreated hypothyroidism: partially/untreated hypothyroidism can also cause dilutional hyponatraemia.

Management (c.f. algorithm 1)

- Check paired plasma electrolytes and urine/plasma osmolality ratio
- If plasma sodium is <132mmol/L and/or it is decreasing at a rate >0.5-1 mmol/L/hour:
    - Omit a dose of desmopressin and change to a solution with a higher content of sodium chloride (i.e., 0.45% or N saline with dextrose).
    - Reintroduce desmopressin at a lower dose when urine output is more than 4-5 ml/kg/hour for 1- 2 consecutive hours and/or urine/plasma osmolality ratio is less than 1 (SG of urine < 1005).
    - Consider SIADH if hyponatraemia and positive fluid balance persist despite withdrawal of desmopressin and urinary sodium is >20 mmol/L with urine/plasma osmolality ratio >1. Fluid intake should be restricted, and chemotherapy regimen reviewed.
    - Ensure that the patient is biochemically euthyroid and that cortisol deficiency is adequately replaced, according to patient clinical status and ability to tolerate oral intake.
    - Due to the risk of pontine myelinolysis following precipitous correction of hyponatraemia, only symptomatic severe hyponatraemia, (seizures and/or coma), justifies partial correction by hyperosmolar saline infusion, i.e., 3% NaCl (500 mmol/L) at 1-2 ml/kg/hour, 0.5-1 mmol/kg/hour, for 2 to 3 hours) followed by conservative measurements to limit the rate of correction to less than 12 mmol/L per day.
- If plasma sodium is normal and stable from the previous measurement:
    - ensure that fluid balance is accurate. Repeat plasma electrolytes after 4 hours and reassess trend.

Negative fluid balance (weight loss/intake >10% less than output)

Possible causes

- Desmopressin under-replacement or under-replaced non-renal losses: Weight loss is usually caused by either inadequate desmopressin replacement or under-replaced non-renal fluid losses. The former is associated with hypernatraemia while the latter can be associated with either hypo/hyper/eunatraemia.
- Renal tubulopathy/diuretics/cerebral salt wasting: Natriuresis (urine sodium >20mmol/L) and polyuria can result from chemotherapy-induced renal tubular damage, diuretic use or cerebral insults causing cerebral salt wasting (CSW).

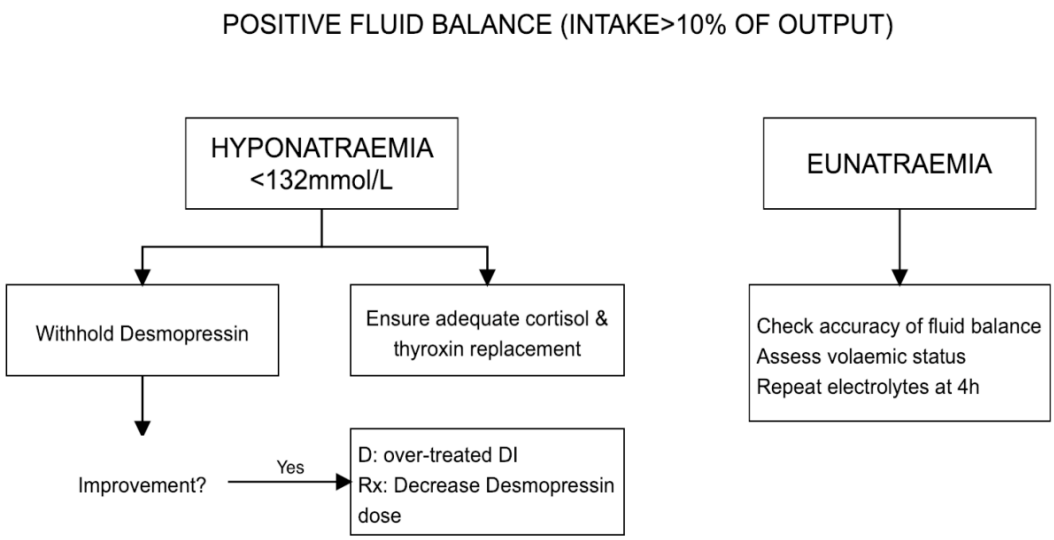
Management (cf Algorithm 2)

- Check plasma and urine electrolytes and osmolality:
- If plasma sodium is >150 mmol/L or it is increasing at a rate >0.5 mmol/L/hour, consider:
    - Under-replacement with DDAVP: give an extra dose of desmopressin and consider increasing desmopressin maintenance dose by 50%. Consider malabsorption of desmopressin (oral or intranasal). If the child is unable to tolerate/absorb desmopressin, consider SWITCHING oral to intranasal preparation or vice versa. NB strengths of these preparations vary 10-fold. Oral desmopressin takes 1-2 hours to be absorbed and take effect, intranasal much less. The latter preparation is 10 times more effective. Parenteral administration or intravenous infusion of desmopressin should only be given in exceptional circumstances and under the supervision of a Paediatric Endocrinologist.
    - Hypovolaemia: give 0.9% sodium chloride challenge (10ml/kg) and check response in terms of urine output
    - Desmopressin dose-adjustment: The dose of Desmopressin should be titrated according to the daily urine output, in turn dictated by the prescribed fluid intake. Insensible fluid losses (300ml/m^2/per day) should be allowed. Any excess renal or gastric losses should be replaced. Changes in hydrocortison or desmopressin regimen more often than every 24-48 hours should be avoided to establish trends.
- If plasma sodium is <132 mmol/L and urinary sodium is >20 mmol/L:

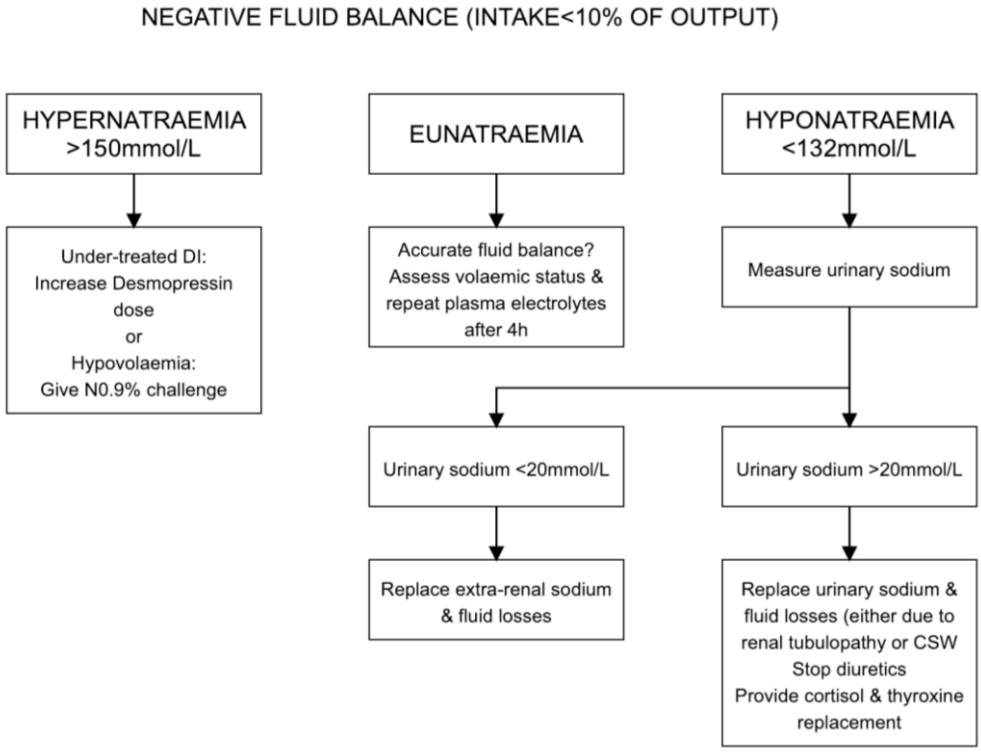
  - Fluid and sodium losses in excess of intake should be replaced by calculating and matching fluid and sodium balance at least 8 hourly (in arrears) and checking daily weight. In severe natriuresis with severe hyponatraemia, oral sodium chloride supplementation if tolerated or hypertonic saline solutions may be required. However, a rapid correction of hyponatraemia should be avoided as it can cause pontine and extrapontine myelinolysis.
- If plasma sodium is <132 mmol/L and urinary sodium is <20 mmol/L:
  - Replace extra renal fluid and sodium losses. Sodium chloride 0.9% may be required.
- If plasma sodium is normal and stable from the previous measurement, and the patient is clinically euvolemic:
  - Ensure that fluid balance is accurate. Repeat plasma electrolytes after 4-6 hours and reassess.
- DO NOT make changes in desmopressin regimen more often than once every 24-48 hours.

End of hyper-hydration

At the end of the chemotherapy, revert to pre-treatment fluid and desmopressin regimen. Continue to monitor fluid balance and electrolytes to ensure that the patient remains eunatraemic and euvolemic.



Algorithm 1: management of positive fluid balance



Algorithm 2: management of negative fluid balance

Appendix E: Administration of chemotherapy in germinoma

Carboplatin, etoposide/etoposide phosphate and ifosfamide should be diluted prior to infusion according to locally validated practice and/or procedures for the aseptic preparation of chemotherapy agents. The infusion fluids and volumes for infusion should be selected to permit the drug to be administered over the stated time.

A central venous catheter according to local practice is recommended for the delivery of this chemotherapy.

Etoposide (100 mg/m^2)/Etoposide phosphate (114 mg/m^2) (on days 1-3 of each cycle) should be given as an IV infusion over 1-4 hours, prior to carboplatin. *(If etoposide phosphate is used, 114 mg of etoposide phosphate = 100 mg etoposide.)*

Carboplatin [600 mg/m^2 on Day 1, Cycles 1 and 3 (maximum dose: 1200 mg)] should be given as an IV infusion over 1 hour.

Ifosfamide (1800 mg/m^2 on Days 1 - 5, Cycles 2 and 4) should be given as an IV infusion over 3 hours. Concurrent administration of hydration and MESNA is recommended to avoid urothelial toxicity. Ifosfamide dosing and administration differ from those used in treatment of NGGCT.

Notes:

- Other nephrotoxic drugs, including aminoglycoside antibiotics, should be used with caution with ifosfamide.
- Ifosfamide dosing differs from that used in the treatment of non-germinomatous GCT (NGGCT).
- MESNA should be given at a dose of 2200 mg/m^2/day (120% of the daily ifosfamide dose) and should be continued for at least 24 hours following completion of the last dose of ifosfamide. It is recommended that this is given as a continuous infusion, infused either separately or added into the hydration fluid according to institutional practice. On Day 1 an additional bolus infusion of

360 mg/m^2 (20% of the daily ifosfamide dose) should be given prior to the ifosfamide infusion.

- Hydration fluid should commence three hours before start of ifosfamide and run continuously until at least 24 hours following the completion of the last ifosfamide infusion.
- If the volume of the etoposide infusion on day 1 is used in place of the first three hours of hydration fluid, care must be taken, to ensure that the volume is sufficient to provide fluid at the specified rate. The hydration fluid used may be according to institutional practice and should be infused at a rate that provides, inclusive of the volumes of the chemotherapy and MESNA infusions, a total of at least 83 ml/m^2/hour (2L/m^2/day).
- Depending on the volume used for drugs, the total fluid volume is likely to be significant. Consideration should be given to capping this at 3L/m^2/day.
- In the rare event of haemorrhagic cystitis, MESNA or hydration should be increased, and diuretics added, according to institutional practice. Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.
- Note: If etoposide is used in place of hydration fluid, care must be taken to ensure that the volume is sufficient to provide fluid at the required rate.

Appendix F: Administration of chemotherapy in NGGCT

Cisplatin, etoposide/etoposide phosphate and ifosfamide should be diluted prior to infusion according to locally validated practice and/or procedures for the aseptic preparation of chemotherapy agents. The infusion fluids and volumes for infusion should be selected to permit the drug to be administered over the stated time

A central venous catheter according to local practice is essential for the delivery of this chemotherapy

Etoposide: 100 mg/m^2 (or etoposide phosphate 114 mg/m^2) on Days 1-3 of each cycle) should be given as an IV infusion over 1-4 hours, prior to cisplatin and ifosfamide.

Cisplatin (20 mg/m^2 on Days 1–5 of each cycle) should be given as an IV infusion over one hour. It must be accompanied by an adequate diuresis. In the absence of DI, this should be achieved with a forced mannitol diuresis, which should be administered as an infusion of Mannitol 15-20% according to national practice, 40 ml/m^2 over 1 hour, concurrently with each cisplatin infusion and approximately 3-4 and 6-7 hours after the cisplatin infusion. For patients with significant diuresis secondary to DI, mannitol is unlikely to be needed, and it is suggested that it should be omitted if a urinary output of at least 400 ml/m^2 over 6 hours is maintained.

Ifosfamide (1500 mg/m^2 on Days 1–5 of each cycle) should be given as an IV infusion over 3 hours, following cisplatin. Concurrent administration of hydration and MESNA is recommended to avoid urothelial toxicity. Other nephrotoxic drugs, including aminoglycoside antibiotics, should be used with caution with ifosfamide and cisplatin.

<u>Notes:</u>

- If etoposide phosphate is used, 114 mg of etoposide phosphate is equivalent to 100 mg etoposide.

- Please note: In case of replacement of cisplatin by carboplatin, the total equivalent dose of carboplatin is 600 mg/m².Given as one dose only on day 1, over 1 or 2 hours
- Please note: Ifosfamide dosing differs from that used in the treatment of germinoma.
- It is suggested that MESNA should be given at a dose of 1800 mg/m^2/24 hours (120% of the daily ifosfamide dose) and should be continued for at least 24 hours following completion of the last dose of ifosfamide. It may be given according to institutional practice, either as a continuous infusion (alongside, or added to the hydration fluid), or as bolus infusions of 600 mg/m^2 at times +0 h, +4h and +8 h, on Days 1–5 and as a continuous infusion on Day 6. On Day 1 an additional bolus infusion of 300 mg/m^2 (20% of the daily ifosfamide dose) should be given prior to the ifosfamide infusion.
- Hydration should commence at least three hours before start of cisplatin and run continuously until at least 24 hours following the completion of the last cisplatin infusion.
- If the volume of the etoposide infusion on day 1 is used in place of the first three hours of hydration fluid, care must be taken, to ensure that the volume is sufficient to provide fluid at the specified rate.
- The hydration fluid used may be according to institutional practice and should be infused at a rate that provides, inclusive of the volumes of the chemotherapy and MESNA infusions, a total of at least 125 ml/m^2/hour (3L/m^2/day). Depending on the volume used for drugs, the total fluid volume is likely to be substantial. Consideration should be given to capping this at 3.5L/m^2/day or 4L/m^2/day.
- In the rare event of haemorrhagic cystitis, MESNA or hydration should be increased, and diuretics added, according to institutional practice. Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.

Appendix G: Administration of HD-PEI

Etoposide (300 mg/m^2)/Etoposide phosphate (342 mg/m^2), (on days 1-5 of each cycle) should be given as an IV infusion over 1-4 hours, prior to cisplatin and ifosfamide.

Notes:

- if etoposide phosphate is used, 342 mg of etoposide phosphate is equivalent to 300 mg etoposide.

Cisplatin (20 mg/m^2, on days 1-5 of each cycle) should be given as an IV infusion over one hour. It must be accompanied by an adequate diuresis. In the absence of DI, this should be achieved with a forced mannitol diuresis, which should be administered as an infusion of Mannitol 15-20 % according to institutional guidelines, 40ml/m^2 over 1 hour, concurrently with each cisplatin infusion and approximately 3-4 and 6-7 hours after the cisplatin infusion. For patients with significant diuresis secondary to DI, mannitol is unlikely to be needed, and it is suggested that it should be omitted if a urinary output of at least 400 ml/m^2 over 6 hours is maintained.

Notes:

- In case of replacement of Cisplatin by Carboplatin, the total equivalent dose of Carboplatin is 600 mg/m^2 given as one dose only on day 1 over one or two hours.

Ifosfamide (2000 mg/m^2, on Days 1–5 of each cycle) should be given as an IV infusion over 3 hours, following cisplatin. Concurrent administration of hydration and MESNA is recommended to avoid urothelial toxicity.

Notes:

- Other nephrotoxic drugs, including aminoglycoside antibiotics, should be used with caution with ifosfamide and cisplatin.
- Ifosfamide dosing differs from that used in the treatment of germinoma.
- MESNA should be given at a dose of 2400 mg/m^2/24 hours (120% of the daily ifosfamide dose) and should be continued for about 48 hours following

completion of the last dose of ifosfamide. It may be given according to institutional guidelines, either as a continuous infusion (alongside, or added to the hydration fluid), or as bolus infusions of 800 mg/m^2 at times +0 h, +4h and +8 h, on Days 1 – 5, and as a continuous infusion on Days 6 & 7. On Day 1 an additional bolus infusion of 400 mg/m^2 (20% of the daily ifosfamide dose) should be given prior to the ifosfamide infusion.

- Hydration should commence at least three hours before cisplatin and run continuously until at least 48 hours following the completion of the last ifosfamide infusion.
- The hydration fluid used may be according to institutional practice and should be infused at a rate that provides, inclusive of the volumes of the chemotherapy and MESNA infusions, a total of at least 125ml/m^2/hour (3L/m^2/day). Note: Depending on the volume used for drugs, the total fluid volume administered is likely to be significant. Consideration should be given to capping this at 3.5L/m^2/day or 4L/m^2/day.
- In the rare event of haemorrhagic cystitis, MESNA or hydration should be increased and diuretics added, according to institutional practice. Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.

The treatment schedule of HD-PEI should be modified only in exceptional cases, e.g. high fever or documented significant toxicity (please contact national investigator / co-ordinator).

Reinfusion of stem cells

- Stem cell support will be administered on day 7 of HD-PEI therapy according to local guidelines.

Appendix H: Chemotherapy doses modifications for toxicities

Please refer to current Common Terminology Criteria (CTC) Adverse Events (CTCAE) for documentation of toxicities.

Haematological toxicity

Courses of chemotherapy should be delayed until haematological recovery from the previous course has taken place, defined by neutrophils ≥1x10^9/L or WBC ≥ 2x10^9/L, and platelets ≥100x10^9/L.

Ototoxicity

Audiometry should be performed prior to courses of chemotherapy. Modifications in treatment are based on SIOP-Boston scale (see Appendix I).

Nephrotoxicity

Both glomerular and tubular toxicity must be monitored before each course of cisplatin, carboplatine or ifosfamide.

1. GFR should be assessed using Schwartz's Formula[42]:

$$C_{creat}\ [mL/min/1.73m^2] = F \times height\ [cm] / Creat_{serum}\ [mg/dL]$$

Where F is proportional to body muscle mass, hence depending on age and gender:

Gender, Age	***F***
Infants, <1 year	0.45
Males, 1-16 years	0.55
Females, 1-21 years	0.55
Males, 16-21 years	0.70

2. Tubular function can be assessed according to local practice.

Suggested dose adaptations:

Matching CTCAE grading system

Drug Toxicity grade	GFR [ml/min/1.73m^2]	Action (apply worst grade)
Cisplatin		
1	≤ 60	- Delay for 1 week. - If GFR > 60, resume Cisplatin. - If GFR does not recover above 60, consider substituting for Carboplatin, dosed based on appropriate formula (e.g Calvert or Newall), targeting **AUC 7.9 mg/ml*min, d1**
Ifosfamide		
0-1	≥ 60	Ifosfamide dose at 100%
2	30-59	Ifosfamide dose at 70%
3-4	≤ 30	Consider using cyclophosphamide instead
Etoposide		
1	≤ 60	Etoposide dose at 70%

Note: dose adaptations above are illustrations based on single drug experience and not co-administration. Accordingly, especially in rare cases of severe renal toxicity (GFR≤60 ml/min/1.73m^2), caution should be used and doses adapted on individual bases, after consultation with nephrology and/or clinical pharmacology, and taking into account the disease risks. Tubular function can be assessed, but tubular dysfunction is not anticipated after only 2 cycles of ifosfamide-containing chemotherapy.

Neurotoxicity

If severe central neurotoxicity (CTC grade 3 or 4) occurs, follow institutional guidelines and discuss investigations such as brain imaging and coagulation profile. Consider the use of Methylene Blue (methylthionine chloride) 1mg/kg (max 50mg), 4 hourly as i.v. infusion. As the risk of haemolytic anaemia is increased in G6PD deficient patients, a G6PD screen is reasonable at the initiation of treatment. Prolong ifosfamide to 4-8

hours with the next application and infuse methylthionine chloride 1mg/kg (max 50mg) three times a day and for a duration as per institutional guidelines. In the subsequent course, apply methylthionine chloride one dose of 1mg /kg (max 50mg) 24 hours prior to ifosfamide. During ifosfamide give three-times daily methylthionine chloride as described above. If repeated severe neurotoxicity occurs, consider withholding ifosfamide and substitute cyclophosophamide.

Appendix I: SIOP-Boston ototoxicity scale

(adapted from [43])

Grade	Parameters
0	≤ 20 dB HL at all frequencies
1	> 20 dB HL (ie, 25 dB HL or greater) SNHL above 4,000 Hz (ie, 6 or 8 kHz)
2	> 20 dB HL SNHL at 4,000 Hz and above
3	> 20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above
4	> 40 dB HL (ie, 45 dB HL or more) SNHL at 2,000 Hz and above
NOTE. Scale is based on sensorineural hearing thresholds in dB hearing level (HL; bone conduction or air conduction with a normal tympanogram). Bone conduction thresholds are used to determine the grade in the case of abnormal tympanometry and/or suspected conductive or mixed hearing loss. Even when the tympanogram is normal, bone conduction is strongly recommended at the single frequency that is determining the ototoxicity grade to fully confirm that the hearing loss at that frequency is sensorineural. Temporary, fluctuating conductive hearing loss due to middle ear dysfunction or cerumen impaction is common in the pediatric population, and decreases in hearing thresholds that include conductive hearing losses do not reflect ototoxicity to the cochlea. Abbreviations: SIOP, International Society of Pediatric Oncology; SNHL, sensorineural hearing loss.	

Suggested dose adaptations:

Grade	Chemotherapy modification
0	None
1	None
2	None
3	Substitute carboplatin 600mg/m^2 for day 1 (in one dose) instead of cisplatin for 5 days
4	Omit any platinum

Appendix J: Follow-up assessments

Evaluations	End of treatment (EOT)	3 months	6 months	9 months	12 months	18 months	24 months	3 years	4 years	5 years
MRI head/brain	x	x	x	x	x	x	x	x	x	x
MRI spine	x	Based on symptoms or clinician discretion, but at least with alternate MRI head/brain in patients with CNS involvement at diagnosis, assuming clear spinal MRI at the EOT								
Serum AFP + HCG (Germinoma)	x	x	x	x	x	x	x	x	x	x
Serum AFP + HCG (NGGCT)	x	Monthly				q2 months		q3 months	x	x
Endocrine	Timing according to local practice									
Ophthalmological	Timing according to local practice									
Hearing assessment	Timing according to local practice									
GFR/Creat clearance	Timing according to local practice									
Neuropsychological	Timing according to local practice									

Appendix K: European-wide clinical advice structure

A key theme for this Standard Clinical Practice Document is the need for support/advice – from all specialties throughout the patient journey. The SIOPE CNS GCT Working Group (WG), within the Brain Tumour Group (BTG), has an existing effective and timely provision of support/advice to European colleagues via email. We will continue to encourage email contact/discussion with members of the CNS GCT WG for challenging cases. We propose to continue this as part of this document.

Email advice/support

Key professionals and their email addresses are listed below alphabetically by specialty. We recommend including a wide distribution of email recipients rather than just restricting requests for advice to a specific group or individual.

Neuroradiologists

Brigitte Bison, Germany (brigitte.bison@uk-augsburg.de)

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

Hervé Brisse, France (herve.brisse@curie.fr)

Neurosurgeons

Thomas Czech, Austria (thomas.czech@meduniwien.ac.at)

Conor Mallucci, UK (conor.mallucci@alderhey.nhs.uk)

Neuropathologists

Torsten Pietsch, Germany (t.pietsch@uni-bonn.de)

Colin Smith, UK (col.smith@ed.ac.uk)

Paediatric Oncologists

Matthew Murray, UK (mjm16@cam.ac.uk)

James Nicholson, UK (james.nicholson4@nhs.net)

Gabriele Calaminus, Germany (gabriele.calaminus@ukbonn.de)

Cecile Faure-Conter, France (cecile.conter@ihope.fr)

Didier Frappaz, France (didier.frappaz@ihope.fr)

Maria Luisa Garrè, Italy (mluisagarre@gaslini.org)

Radiation Oncologists

Thankamma Ajithkumar, UK (thankamma.ajithkumar@nhs.net)

Claire Alapetite, France (claire.alapetite@curie.fr)

Beate Timmermann, Germany (beate.timmermann@uk-essen.de)

Yasmin Lassen, Danemark (yasmin.lassen@auh.rm.dk)

References

1. Diezi, M., B. Pizer, and M.J. Murray, *Overview of current European practice for the management of patients with intracranial germ cell tumours.* EJC Paediatric Oncology, 2024. **3**.
2. Murray, M.J. and J.C. Nicholson, *alpha-Fetoprotein.* Arch Dis Child Educ Pract Ed, 2011. **96**(4): p. 141-7.
3. Calaminus, G., et al., *Outcome of patients with intracranial non-germinomatous germ cell tumors-lessons from the SIOP-CNS-GCT-96 trial.* Neuro Oncol, 2017. **19**(12): p. 1661-1672.
4. Louis, D.N., H. Ohgaki, and O.D. Wiestler, *WHO Classification of Tumours of the Central Nervous System*. Medicine Series. 2016: International Agency for Research on Cancer.
5. Murray, M.J., et al., *Consensus on the management of intracranial germ-cell tumours.* Lancet Oncol, 2015. **16**(9): p. e470-e477.
6. Palmer, R.D., et al., *Malignant germ cell tumors display common microRNA profiles resulting in global changes in expression of messenger RNA targets.* Cancer Res, 2010. **70**(7): p. 2911-23.
7. Murray, M.J., et al., *A pipeline to quantify serum and cerebrospinal fluid microRNAs for diagnosis and detection of relapse in paediatric malignant germ-cell tumours.* Br J Cancer, 2016. **114**(2): p. 151-62.
8. Murray, M.J., et al., *Clinical utility of circulating miR-371a-3p for the management of patients with intracranial malignant germ cell tumors.* Neurooncol Adv, 2020. **2**(1): p. vdaa048.
9. Wang, L., et al., *Novel somatic and germline mutations in intracranial germ cell tumours.* Nature, 2014. **511**(7508): p. 241-5.
10. Fukushima, S., et al., *Mutually exclusive mutations of KIT and RAS are associated with KIT mRNA expression and chromosomal instability in primary intracranial pure germinomas.* Acta Neuropathol, 2014. **127**(6): p. 911-25.
11. Ichimura, K., et al., *Recurrent neomorphic mutations of MTOR in central nervous system and testicular germ cell tumors may be targeted for therapy.* Acta Neuropathol, 2016. **131**(6): p. 889-901.
12. Takami, H., et al., *Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium.* Neuro Oncol, 2019. **21**(12): p. 1565-1577.
13. Schulte, S.L., et al., *CNS germinomas are characterized by global demethylation, chromosomal instability and mutational activation of the Kit-, Ras/Raf/Erk- and Akt-pathways.* Oncotarget, 2016. **7**(34): p. 55026-55042.
14. Galvez-Carvajal, L., et al., *Targeted treatment approaches in refractory germ cell tumors.* Critical Reviews in Oncology/Hematology, 2019. **143**: p. 130-138.
15. Rutkowski, S., et al., *Biological material collection to advance translational research and treatment of children with CNS tumours: position paper from the SIOPE Brain Tumour Group.* Lancet Oncol, 2018. **19**(8): p. e419-e428.
16. Calaminus, G., et al., *SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease.* Neuro Oncol, 2013. **15**(6): p. 788-96.
17. Kanamori, M., et al., *So-called bifocal tumors with diabetes insipidus and negative tumor markers: are they all germinoma?* Neuro Oncol, 2021. **23**(2): p. 295-303.
18. Duron, L., et al., *Loco-regional extensions of central nervous system germ cell tumors: a retrospective radiological analysis of 100 patients.* Neuroradiology, 2018. **60**(1): p. 27-34.
19. Fujisawa, I., et al., *Magnetic resonance imaging of neurohypophyseal germinomas.* Cancer, 1991. **68**(5): p. 1009-14.
20. Kanagaki, M., et al., *MRI and CT findings of neurohypophyseal germinoma.* European Journal of Radiology, 2004. **49**(3): p. 204-211.

21. Avula, S., et al., *European Society for Paediatric Oncology (SIOPE) MRI guidelines for imaging patients with central nervous system tumours.* Childs Nerv Syst, 2021.
22. Afzal, S., et al., *Challenges in management of patients with intracranial germ cell tumor and diabetes insipidus treated with cisplatin and/or ifosfamide based chemotherapy.* J Neurooncol, 2010. **97**(3): p. 393-9.
23. Kellie, S.J., et al., *Intensive cisplatin and cyclophosphamide-based chemotherapy without radiotherapy for intracranial germinomas: Failure of a primary chemotherapy approach.* Pediatric Blood & Cancer, 2004. **43**(2): p. 126-133.
24. Kretschmar, C., et al., *Pre-radiation chemotherapy with response-based radiation therapy in children with central nervous system germ cell tumors: a report from the Children's Oncology Group.* Pediatr Blood Cancer, 2007. **48**(3): p. 285-91.
25. Matsutani, M. and G. Japanese Pediatric Brain Tumor Study, *Combined chemotherapy and radiation therapy for CNS germ cell tumors--the Japanese experience.* J Neurooncol, 2001. **54**(3): p. 311-6.
26. Alapetite, C., et al., *Pattern of relapse and outcome of non-metastatic germinoma patients treated with chemotherapy and limited field radiation: the SFOP experience.* Neuro Oncol, 2010. **12**(12): p. 1318-25.
27. Calaminus, G., et al., *GCT-11. 24 Gy whole ventricular radiotherapy alone is sufficient for disease control in localised germinoma in CR after initial chemotherapy – final of the SIOP CNS GCT II study.* Neuro-Oncology, 2022. **24**(Supplement_1): p. i56-i56.
28. Calaminus, G., et al., *GCT-20. PRESENTATION AND OUTCOME OF BIFOCAL GERMINOMA TREATED ACCORDING TO SIOP CNS GCT II.* Neuro-Oncology, 2024. **26**(Supplement_4): p. 0-0.
29. Murray, M.J., et al., *Treatment and outcomes of UK and German patients with relapsed intracranial germ cell tumors following uniform first-line therapy.* Int J Cancer, 2017. **141**(3): p. 621-635.
30. Kubota, H., et al., *High-dose chemotherapy with autologous stem cell transplantation spares re-irradiation for recurrent intracranial germinoma.* Pediatr Blood Cancer, 2018. **65**(8): p. e27104.
31. Callec, L., et al., *Relapsing intracranial germ cell tumours warrant retreatment.* European Journal of Cancer, 2020. **136**: p. 186-194.
32. Calaminus, G., et al., *Impact of surgery, chemotherapy and irradiation on long term outcome of intracranial malignant non-germinomatous germ cell tumors: results of the German Cooperative Trial MAKEI 89.* Klin Padiatr, 2004. **216**(3): p. 141-9.
33. Goldman, S., et al., *Phase II Trial Assessing the Ability of Neoadjuvant Chemotherapy With or Without Second-Look Surgery to Eliminate Measurable Disease for Nongerminomatous Germ Cell Tumors: A Children's Oncology Group Study.* J Clin Oncol, 2015. **33**(22): p. 2464-71.
34. Fangusaro, J., et al., *Phase II Trial of Response-Based Radiation Therapy for Patients With Localized CNS Nongerminomatous Germ Cell Tumors: A Children's Oncology Group Study.* J Clin Oncol, 2019. **37**(34): p. 3283-3290.
35. Garre, M.L., et al., *Is chemotherapy effective therapy for intracranial immature teratoma? A case report.* Cancer, 1996. **77**(5): p. 977-82.
36. Michaiel, G., et al., *Intracranial growing teratoma syndrome (iGTS): an international case series and review of the literature.* J Neurooncol, 2020. **147**(3): p. 721-730.
37. Tsuyuguchi, S., et al., *Primary and Recurrent Growing Teratoma Syndrome in Central Nervous System Nongerminomatous Germ Cell Tumors: Case Series and Review of the Literature.* World Neurosurg, 2020. **134**: p. e360-e371.
38. Schultz, K.A.P., et al., *PD0332991 (Palbociclib) for treatment of pediatric intracranial growing teratoma syndrome.* Pediatric Blood & Cancer, 2015. **62**(6): p. 1072-1074.
39. Vaughn, D.J., et al., *Phase 2 trial of the cyclin-dependent kinase 4/6 inhibitor palbociclib in patients with retinoblastoma protein-expressing germ cell tumors.* Cancer, 2015. **121**(9): p. 1463-1468.
40. Phi, J.H., et al., *Immature teratomas of the central nervous system: is adjuvant therapy mandatory?* Journal of Neurosurgery: Pediatrics, 2005. **103**(6): p. 524-530.

41. Murray, M.J., et al., *Vinblastine monotherapy induction prior to radiotherapy for patients with intracranial germinoma during the COVID-19 pandemic.* Pediatric Blood & Cancer, 2021.
42. Schwartz, G.J., L.P. Brion, and A. Spitzer, *The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents.* Pediatr Clin North Am, 1987. **34**(3): p. 571-90.
43. Brock, P.R., et al., *Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale.* Journal of Clinical Oncology, 2012. **30**(19): p. 2408-2417.