Imaging response assessment for Central Nervous System Germ Cell Tumours: consensus recommendations from the European Society for Paediatric Oncology Brain Tumour Group (SIOPE-BTG) and North American Children's Oncology Group (COG).

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ABSTRACT

Improving the ability to conduct international clinical trials for Central Nervous System (CNS) Germ Cell Tumours (GCT) requires use of homogeneous, common objective disease assessments and standardised response criteria. Currently, different criteria are employed between European and North American protocols for assessing radiological disease response. An international working group of the European Society for Paediatric Oncology (SIOPE) Brain Tumour Group (BTG) and North American Children's Oncology Group (COG) was therefore established to develop consensus recommendations for imaging response assessment for CNS GCT. The working group first reviewed existing literature and current practices and identified major challenges regarding imaging assessment. New clinical imaging standards were defined for the most common sites of intracranial GCT disease, as well as for definition of loco-regional extension. This will allow more consistent prospective neuroradiological evaluation of response to therapy for patients with CNS GCT and facilitate direct comparison of treatment outcomes across international studies.

INTRODUCTION

Central nervous system (CNS) germ cell tumours (GCT) comprise a heterogeneous and relatively rare group of neoplasms with variable geographic incidence, accounting for approximately 2-3% of paediatric brain tumours in Western countries and up to 10% in Far East Asian countries.[1-3] The peak incidence of CNS GCT is during adolescence, with the vast majority of cases occurring below 30 years of age,[4] and therefore CNS GCT are considered an 'adolescent and young adult' (AYA) cancer. Based on the histological components, response to treatment, and prognosis, malignant CNS GCT are classically categorised into germinomas (50-70% of cases) and nongerminomatous GCT (NGGCT).[5] The latter group include the subtypes endodermal sinus tumour (yolk sac tumour), embryonal carcinoma, choriocarcinoma, and more commonly mixed tumours, which may contain any of the above components, either alone or in combination, in addition to the potential presence of germinoma and/or teratoma. The management of pure CNS immature teratoma remains controversial and is beyond the scope of this review. CNS GCT arise predominantly in midline, supratentorial locations, particularly suprasellar (30-40% of cases) and pineal (50-60%) regions;[6] however, about 6-10% of these neoplasms arise in off-midline intracranial structures, usually comprising the thalamus and/or basal ganglia,[7,8] and much more rarely the cerebellum.[9,10] In addition, primary spinal cord GCT may very rarely occur.[11,12]

For most CNS tumours, histological confirmation represents the gold standard for accurate characterisation; however, current international consensus on the management of CNS GCT maintains that patients with consistent radiological imaging and 'secreting' tumours, [namely alpha-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG) elevation in the serum and/or cerebrospinal fluid (CSF) above defined thresholds], do not require surgical biopsy, and NGGCT treatment may be initiated without histological verification.[13,14] Therefore, at diagnosis, only AFP/HCG marker-negative tumours are usually biopsied.

Current treatment modalities for patients with germinoma and NGGCT in European and North American countries comprise a combination of chemotherapy and radiotherapy, with surgery playing a limited role. During treatment, surgery is recommended for germinoma when an associated substantial teratoma component is strongly suspected based on failure of the tumour to respond appropriately to induction chemotherapy – i.e., radiological Stable Disease (SD) or only a very modest Partial Response (PR);[14] surgery is also recommended for any residual NGGCT [i.e., those cases not in Complete Response (CR)] after induction chemotherapy and prior to radiotherapy, unless considered unsafe.[13,15,16] In addition, radiological progression of an NGGCT occurring during induction chemotherapy, while AFP/HCG markers are decreasing/have normalised, usually represents growing teratoma syndrome (GTS). This entity warrants surgical excision, given the known unresponsive nature of teratoma to chemoradiotherapy regimens.

Optimising comparisons between studies, and facilitating international clinical trials, involves the development of consistent, common objective disease assessments and standardised response criteria. Currently, different criteria are employed between European and North American protocols for assessing radiological disease response for CNS GCT. Given known difficulties in evaluating CR in this disease, better standardisation of the response definitions for CNS GCT is essential. Consequently, an international working group of the European Society for Paediatric Oncology (SIOPE) Brain Tumour Group (BTG) and North American Children's Oncology Group (COG) was established to develop consensus recommendations for imaging response assessment in CNS GCT. The committee consisted of international experts in the areas of paediatric neuroradiology, neuro-oncology, radiation oncology and neurosurgery. The working group first reviewed the published literature and current practices and identified existing major challenges with respect to neuroradiological assessment. This was the foundation for developing the method and recommendations to reach neuroradiological consensus. This approach will allow more consistent prospective neuroradiological evaluation of CNS GCT response to therapy and facilitate direct

comparison of treatment outcomes across international studies. Ultimately, it may allow international trials to be developed and undertaken across a larger group of collaborating nations, which will be essential to answer many of the remaining questions for this rare but diverse group of tumours.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this consensus paper were identified through searches of PubMed, including use of the search terms 'central nervous system', 'germ cell tumour', 'germinoma', 'intracranial', 'radiological assessment', 'response'; for articles published from January 1st 1980 until December 31st 2021. Articles were also identified through searches of authors' own files and databases. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the scope of this consensus paper.

SPECIFIC ISSUES AND CURRENT CHALLENGES WITH NEURORADIOLOGICAL RESPONSE ASSESSMENT IN CNS GCT

Normal Anatomy

<u>Sellar/suprasellar/pituitary region</u>

Pituitary gland size and shape change physiologically throughout life depending on age and sex, particularly in childhood. Furthermore, even amongst children of identical age and gender there is wide morphological and dimensional variability. Measurement of the pituitary gland height is still the most widely used method to obtain a rapid, indirect determination of gland size. Normal pituitary gland height values range from 3-6 mm in prepubertal children.[17] During puberty, the pituitary gland undergoes rapid and profound changes in size and shape, with marked enlargement. In females, the gland may swell symmetrically to a height of 10-11 mm, appearing nearly spherical, whereas in pubertal males it may reach 7-8 mm.[17-19] The posterior neural lobe (neurohypophysis) of the pituitary gland is recognisable next to the dorsum sellae as the 'bright spot' because of its marked hyperintensity on T1-weighted images. This finding has been demonstrated to specifically result from the storage of vasopressin [antidiuretic hormone (ADH)], a hormone synthesised by the

hypothalamus.[20,21] The bright spot serves as an important marker of neurohypophyseal function and, when present, documents integrity of the hypothalamic-neurohypophyseal tract/axis. The posterior pituitary lobe does not undergo physiological variations in either size or signal intensity during childhood.[17] Pituitary stalk (PS) evaluation is a crucial part of the assessment of a potential sellar/suprasellar GCT. Currently, in the paediatric population there are no studies demonstrating the physiological range for the size of the PS in healthy children. However, UK national guidelines for the investigation and management of children and young people aged less than 19 years of age, presenting with idiopathic thickened PS and/or central diabetes insipidus (CDI), have recently been proposed.[22] Based on literature search, Delphi consensus process, available scientific evidence and expert opinion, the PS (assessed by dedicated pituitary imaging) has been defined as pathologically thickened if there is uniform or focal thickening in the sagittal and/or coronal plane, measuring 3 mm or more in diameter at the pituitary insertion and/or 4 mm or more in diameter at the optic chiasm.[22] The PS should be measured in the sagittal and/or coronal plane, drawing a line perpendicular to the infundibular axis. Of note, intravenous contrast administration results in marked enhancement of the pituitary gland and of the infundibulo-tuberal region, due to the lack of the blood-brain barrier at this site and to the dense vascularisation of these regions, and is considered physiological.[17]

Pineal gland region

The normal pineal gland increases in weight and volume with age. A prior study established the average size of the normal pineal gland in infants, children, and adolescents (patient age range 2 weeks to 20 years old).[23] The maximum pineal gland length (L) and height (H) were measured on the T1-weighted sagittal images, and the width (W) was measured on the T1-weighted coronal or axial images. The volume was calculated according to the formula of a rotational ellipsoid (0.5 x L x H x W). A large variation in size among all age groups (minimum L = 3.5 mm, minimum H = 2 mm, minimum W = 2 mm, minimum volume = 10 mm^3; and maximum L = 8.5 mm, maximum H = 6 mm, maximum W = 7.5 mm, maximum volume = 138 mm^3) was demonstrated.[23] In a prior autopsy study

performed in adults, the pineal body measured on average 7.4 mm (5 to 10 mm) in length, 6.9 mm (5 to 9 mm) in width, and 2.5 mm (1.5 to 4 mm) in height.[24] The pineal gland may also appear cystic and may enhance heterogeneously after administration of intravenous contrast. The pineal gland enhances physiologically as it, too, is outside the blood-brain barrier, similar to the other circumventricular organs lining the third and fourth ventricles, including the pituitary gland and the infundibulo-tuberal region.[25] Of note, on delayed post-contrast images, cystic components fill in, demonstrating inhomogeneous enhancement at first, which becomes homogeneous on later scans, due to passive diffusion of contrast material from the surrounding pineal tissue. It is important to recognise benign pineal cysts on delayed images obtained after administration of the contrast medium and differentiate them from solid disease.[26] The pineal gland is typically not calcified in children younger than five years of age but may subsequently progressively calcify. Given the variability in size, appearance and enhancement pattern, a practical measurement to use is that the normal pineal gland should measure up to 10 mm in each dimension.[27,28] Thus, a solid enhancing pineal gland greater than 10 mm in any one dimension (L, H or W) should be considered pathological.[27]

Considerations for midline, off-midline and metastatic GCT

About 5-20% of GCT display synchronous involvement of the sellar/suprasellar and pineal regions; this occurs primarily, but not exclusively, in patients with pure germinoma; in the absence of disease elsewhere this is still considered localised disease.[29,30] Prior trials in North America (ACNS 1123) and Europe (SIOP CNS GCT II) included synchronous lesions occurring in both the sellar/suprasellar and pineal region with typical clinical presentation (i.e., patient age greater than 8-10 years and presence of CDI) and imaging characteristics, along with negative serum and CSF AFP and HCG markers, as consistent with a diagnosis of bifocal germinoma. In such cases, trial enrolment was possible without neurosurgical biopsy.[13] A recently published series of 89 such histologically verified cases highlighted that none were diagnosed with a non-GCT pathology and that only 3/89 (3.4%) had a more aggressive NGGCT diagnosis.[31] Given this data, whilst reasonable in such a scenario to

consider taking a small biopsy at the same time as neurosurgical management of acute hydrocephalus, in other cases without hydrocephalus, the relative merits/risks of neurosurgical biopsy need to be carefully evaluated and remain controversial. Of note, the presence of CDI with absence of the posterior pituitary MRI bright spot but with normal pituitary stalk/median eminence, in patients with pineal tumours, and with negative serum and CSF AFP and HCG markers, should be regarded as sufficient evidence of bifocal disease. In addition, patients diagnosed with sellar/suprasellar disease with an observed decrease in size of the pineal gland during therapy, should also be considered to have occult primary pineal disease.[28] Rarely, concomitant but not contiguous involvement of the sellar/suprasellar compartment and basal ganglia has been reported in prior studies.[10,32,33] Different from bifocal disease, this pattern has not been considered localised disease. Indeed, in the SIOP CNS GCT II trial the presence of more than one tumour site on MRI (head and spine, except bifocal) and/or positive CSF cytology, was considered metastatic disease. In the ACNS 1123 trial, GCT located in the sellar/suprasellar, pineal, bifocal (pineal + sellar/suprasellar) or within a ventricle with unifocal parenchymal extension, were considered localised disease. Patients with tumours located outside the ventricles (basal ganglia, thalamus) were not eligible since the trial excluded patients with metastatic disease. Of note, Duron *et al* described contiguous loco-regional extensions of CNS GCT and observed that these occurred in all patients in their cohort at diagnosis; the authors highlighted that these extensions need recognition and accurate reporting to ensure appropriate subsequent radiotherapy volumes.[34] In particular, the most common sites for such contiguous extension were the third ventricle (88% of cases, including contiguous extension to basal ganglia), thalamus (47%), midbrain (42%), and optic pathways (19%).[34] The working group specify that such contiguous loco-regional extension of a primary tumour is not considered disseminated disease, whereas non-contiguous and/or 'skip' spread of disease in the brain or ventricles is considered disseminated (metastatic) disease and should be treated as such with craniospinal irradiation (CSI). For example, in the Duron *et al* series, 19% of cases showed involvement of distant sub-ependymal locations.[34] The authors acknowledged that disease at this specific location represents a distinct pattern which

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might be considered skip (i.e., metastatic) lesions.[34] The working group concur that such involvement would represent metastatic spread. Accordingly, every patient presenting with a potential CNS GCT needs very careful neuroradiological evaluation at diagnosis and in follow-up. In some cases, second opinions may be helpful to ensure optimal staging to determine appropriate management and/or radiotherapy fields.

Furthermore, primary intracranial GCT disease may also arise very rarely at other anatomical sites, including the basal ganglia, thalamus, cerebellum, and spinal cord. We recommend that patients with such lesions/disease should be assessed by an experienced multidisciplinary team, but that the specific details and descriptions of response assessment at these sites is beyond the scope of this consensus.

Absence of consensus about tumour measurement and response criteria standards

There is no consensus among the SIOPE BTG and the COG on the most appropriate method to measure CNS GCT tumour on MRI and for response criteria. This lack of agreement has led to substantial challenges in comparing international and historical studies in which tumours were assessed and measured using different approaches. The most important differences among prior trials in North America (ACNS 1123) and Europe (SIOP CNS GCT II) are detailed as Supplementary Material.

RECOMMENDATION FOR ASSESSING CNS GCT RESPONSE

Imaging standards to facilitate studies and clinical trials for patients with GCT

Our goal was to establish a standardised protocol that is applied internationally and prospectively in order to facilitate potential risk-adapted radiotherapy concepts and comparison of international studies without substantial confounding factors. In keeping with the principles of maximising compliance of standards and imaging quality across imaging centres with varied capacity, image acquisition requires essential common sequences that are readily available at most centres, in order

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to successfully address future GCT trial endpoints. Complementary sequences that may be of additional benefit are also recommended, where feasible. As advised by the Brain Tumour Imaging Standardisation Steering Committee, clinical trials should have pre-specified imaging parameters, and ideally patients should be assessed using the same imaging method and magnet strength throughout the trial.[35] All patients must have a brain MRI with and without Gadolinium-Based Contrast Agent (GBCA) at diagnosis, and prior to trial/study enrolment. Macrocyclic agents (currently the safest available GBCA) should be used at a standard dose (0.1mmol/kg). If surgical resection is performed, patients must have pre-operative and post-operative brain MRI with and without GBCA. The post-operative brain MRI should be obtained within 72 hours of surgery and should be used as the new baseline scan for future comparisons of response assessment. If the patient has had a biopsy only, post-operative brain MRI is still recommended (to evaluate post-biopsy/haemorrhagic changes), but it is not mandated. All patients must have a spine MRI with GBCA obtained at diagnosis, and prior to trial/study enrolment. If the spine study is performed for the first time after diagnostic/staging lumbar puncture, or within 2-3 weeks of surgical resection or biopsy, it should be obtained with and without GBCA. Typically, it is best to acquire the baseline spine MRI before a surgical resection or biopsy; if unable to obtain pre-operatively, the baseline spine MRI should ideally be obtained concurrently with the brain MRI within 72 hours after surgical resection or biopsy. In cases where extensive post-operative enhancing subdural effusions are present, a repeat spine MRI, approximately 2-3 weeks post-surgery, is recommended.[36] Surveillance spinal MRI should be performed at the same intervals and concurrently with the brain MRI. Of note, since regression of CNS germinoma following cumulative X-ray based diagnostic irradiation (serial diagnostic brain Computed Tomography, with or without additional conventional angiography and Positron Emission Tomography) has been reported, the number and dose of such imaging exposures for patients with suspected intracranial GCT should be limited before diagnostic confirmation.[37-39]

Overall, the proposed brain and spine protocol, detailed below, is largely compatible with the recently

published Response Assessment in Pediatric Neuro-Oncology (RAPNO) guidelines for medulloblastoma,[36] low-grade gliomas,[40] high-grade gliomas [41] and the SIOPE CNS tumours imaging protocol.[42]

Standards for brain imaging

MRI is the primary imaging modality for evaluating GCT and should be performed as detailed in Table 1. The essential standard protocol for tumour assessment includes the following sequences: a) T1-weighted images before and after GBCA administration, b) T2-weighted images, c) fluid attenuation inversion recovery (FLAIR) images, and d) diffusion-weighted (DWI or DTI) images. Since contemporary MRI systems (both 1.5T and 3T) are capable of high-quality 3D T1-weighted imaging, it is ideal to acquire pre- and post-contrast T1-weighted images using isotropic volume (3D) MRI sequences, for improved resolution, better image reconstruction in any plane and the potential implementation of volumetric assessments, in accordance with previous recommendations.[36,41] A specific guidance is not provided for the type of 3D T1-weighted acquisition (gradient-based *versus* spin-echo-based technique) because no consensus regarding which technique is best exists.[41] However, it is important for the techniques to be identical in terms of the acquisition plane and acquisition type for both the pre- and post-contrast images. Depending on the MR scanner performance and capabilities at the specific sites, T1-weighted images can also be acquired as a 2D acquisition, as detailed in Table 1. Even though a 3D T1 acquisition is planned, a post-contrast 2D sagittal T1-weighted sequence, tailored for midline structures, with high in-plane resolution, 3 mm or less thick with minimal or no gap (0-10%), is also recommended (depending on the type and quality of 3D T1, contrast-enhancement may be less conspicuous compared to 2D spin-echo images and adding a 2D T1 may increase diagnostic confidence).[43,44]

3D FLAIR can be used instead of 2D FLAIR but should be consistent with that used for the same individual on previous occasions. The practice of acquiring FLAIR only post-contrast has been

recommended in prior RAPNO guidelines for medulloblastoma and in diffuse intrinsic pontine glioma (DIPG), since post-contrast FLAIR has been shown to be highly sensitive in identifying leptomeningeal metastasis.[36,45] However, for a more precise interpretation of post-contrast findings, similar to T1-weighted imaging, both pre- and post-contrast FLAIR should ideally be acquired (to avoid false-positive findings and to increase the accuracy). Considering the lack of uniformity regarding pre- or post-contrast FLAIR acquisition among different RAPNO guidelines [36-41,45] and the SIOPE CNS tumours imaging protocol,[42] a specific recommendation is not provided; however, pre- or post-contrast FLAIR acquisition should be consistent on serial imaging with that used for the same individual at baseline, as per agreed trial/management protocols. DWI is now used in nearly all centres as part of standard MRI protocols. Diffusion of water molecules is determined by the microstructure of any lesion and surrounding brain tissue, and decreases in densely packed cerebral tissue with high cellularity, small extracellular space, and high nuclear-to-cytoplasmic ratio. On DWI, pure germinomas usually demonstrate a predominant pattern of reduced diffusivity, though some germinomas can show diffusivity similar to normal brain parenchyma,[46-48] which might be related to the specific germinoma tumour microenvironment (variable amounts of lymphocytes, macrophages and histiocytes in addition to tumour cells).[49] NGGCTs usually show higher diffusivity when compared with pure germinomas.[48] In pure germinomas, DWI can therefore help to identify the hypercellular component of the tumour and metastatic lesions, which sometimes may show minimal GBCA enhancement. Furthermore, since differentiation between residual disease versus reactive changes following treatment remains challenging, complementary information offered by DWI should be explored in order to assess its potential in evaluating active disease.

Among additional complementary sequences, high-resolution anatomy visible with heavily T2-weighted sequences [driven equilibrium (DRIVE), constructive interference in steady state (CISS) or fast imaging employing steady-state acquisition (FIESTA) sequences] can be helpful to better define hypophyseal-suprasellar and pineal region involvement.[50,51] In particular, this 3D sequence, acquired

on the sagittal plane with sub-millimetric thickness, provides better evaluation of PS thickness when compared with conventional pre-contrast T1- and T2-weighted images and sensitivity is similar to that of post contrast T1-weighted images.[50] Furthermore, it allows a better and more reproducible evaluation of the PS on serial studies, as these images are of higher resolution and may be reformatted so as to obtain identical slice orientation when compared with prior studies. Additional midline structures, including the median eminence, tuber cinereum, mammillary bodies and the pineal gland are also extremely well depicted.[52] Finally, this sequence can be extremely helpful for surgical planning/biopsy, and may provide complementary information in the detection of residual CNS GCT following chemotherapy induction.[51]

A T2*-based MR sequence [conventional T2* gradient echo (GRE) or Susceptibility Weighted Imaging (SWI)] is also recommended as a complementary sequence. T2*-based MR imaging has been demonstrated to be very sensitive in the early detection of basal ganglia involvement, characterised by low signal intensity, compatible with the presence of blood products or tumour-related iron accumulation, which can occur at this site.[33,53] These sequences are also of particular relevance in patients presenting with CDI, non-specific lack of the posterior pituitary bright spot and absence of a sellar/ suprasellar mass lesion or pathological PS thickening. In such cases, careful evaluation of the basal ganglia is recommended and may potentially accelerate a correct aetiological diagnosis.[33]

Magnetic Resonance Spectroscopy (MRS), recommended as a complementary sequence at first admission/presentation, can provide additional information since GCT typically have a prominent lipid peak.[48] See Table 1 for single voxel MRS recommendations at intermediate versus long echo.[54]

Standards for spinal imaging

Imaging of the spine (Table 1) should be done immediately after brain MRI at the same examination,

and the essential sequence is a sagittal 2D T1 post-contrast of the whole spine including the entire dural sac, with a slice thickness ≤3 mm and minimal or no gap (0-10%). Axial 2D or 3D T1-weighted post-contrast sequences should always be performed over any region suspicious of metastasis or to confirm contrast enhancement over the surface of the cord as physiological vessels. As fat suppression sequences often lead to artefacts and are not specifically necessary for the delineation of meningeal disease, they should not be used routinely. Heavily T2-weighted sequences (CISS, DRIVE, FIESTA) are also extremely useful in detecting small drop metastasis (<3 mm diameter) and are recommended as complementary sequences. DWI is increasingly becoming part of the routine clinical spine MRI regimen. If available, a sagittal DWI sequence of the spine is also recommended as a complementary sequence.

Standards for determining tumour measurement and assessment

As outlined in Supplementary Material, SIOPE and COG have generated different response datasets for the assessment of intracranial GCT, using measurements in two or three perpendicular dimensions. Although prospective data comparing endpoints for measurements in two or three perpendicular dimensions are missing, there is wide experience of using both measurement systems for clinical trials internationally. In agreement with the recent RAPNO guidelines for low-grade gliomas,[40] the SIOPE-COG consensus committee proposes using both measurement systems in response assessment of patients with intracranial GCT, to allow comparison with available large historical datasets. The most reproducible way to measure two perpendicular planes consists of the longest measurement (width, W) of the tumour and the longest measurement perpendicular to the width (transverse, T). These same two measurements should be consistently used to compare subsequent imaging with previous imaging and accurately estimate response. The most reproducible way to determine measurements for three perpendicular planes consists of determining the maximum diameters in the standard antero-posterior (AP), transverse (T), and cranio-caudal (CC) dimensions obtained on multiplanar imaging.[40] Proposing that future clinical trials incorporate measurements in both two and

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three dimensions will also allow for these two strategies to be prospectively compared. Of note, to allow comparison between COG and SIOPE GCT studies, 3D (volume) dimensions should be calculated using the ellipsoid volume formula approximation, where tumour volume (V) = A x B x C x 0.5, and where A, B, and C are the maximum dimensions in the standard AP, T, and CC planes. The product of the perpendicular measurements should be used for 2D (area) measurements. Reports for follow-up exams should reiterate the measurements obtained at baseline for each target lesion. It is also desirable, if feasible, to save the measurements as annotated images. Newly occurring lesions should also be enumerated in these reports. In general, to determine tumour assessment, the size of a measurable (target) lesion at baseline should be at least twice the thickness of the slices showing the tumour. The sequence most representative of the tumour should be used to determine measurable disease, whether this sequence is T1-weighted for contrast-enhancing disease or T2-weighted in tumours with heterogeneous, minimal or no enhancement on baseline MRI. In some instances, therapy-related reduction of enhancement disproportionate to the change in tumour volume may be encountered. The best sequence cannot be predicted at the outset in these tumours. In these circumstances, it is useful to choose the initial sequence on which the tumour was assessed or change the sequence (e.g., due to a change in contrast behaviour) and compare the tumour characteristics with the same sequence on the previous staging MRI to assess response.

Pure germinoma are typically solid lesions, but can be predominantly cystic if they arise as a primary in the basal ganglia (note: basal ganglia disease is outside the formal scope of this consensus). Furthermore, cystic components of NGGCT may be prominent and may persist following treatment with chemotherapy and radiotherapy. In addition, epidermoid cystic (teratoma) components may be present in either malignant NGGCT or pure teratomas. From a radiological perspective, cystic components should not be considered in tumour measurements (i.e., are excluded from target lesion assessment). Thus, only the solid component(s) of cystic tumours should therefore be measured. If cysts comprise the majority of the lesion, the lesion may not be 'measurable' for response assessment

but monitored qualitatively. In addition, similar to cystic components, calcific components should not be considered in the treatment response evaluation.

For most GCT cases, only one lesion/mass is present and therefore is considered a 'target' for measurement/follow up to assess for tumour progression/response. In the case of bifocal disease, both sellar/suprasellar and pineal lesions should be selected as 'target' lesions. Leptomeningeal and/or subependymal secondary lesions are typically non-measurable (measurable nodular areas are rare). If multiple measurable lesions are present, up to four target lesions should be selected to follow for response assessment.

DWI is of limited use for quantitative measures because of its susceptibility to the effects of post-surgical change or haemorrhage, or both, in the tumour, and differences in field strength acquisition parameters.[41] Similar to RAPNO high-grade glioma guidelines,[41] we recommend DWI as a qualitative measure for response assessment of target lesion/s. Furthermore, since DWI has not previously been used alone to determine progressive disease, it must be used in conjunction with other radiographical determinants. If DWI is not obtained at baseline, determination of tumour response or progression is acceptable with the omission of this criterion moving forward.

Regarding T2*-GRE or SWI imaging, even though their potential role in the early recognition of basal ganglia germinoma has been demonstrated,[33,53] little is known about their role in evaluating treatment response. Of note, persistence of basal ganglia T2* hypo-intensity on follow-up studies has been reported, despite disappearance of visible disease on structural sequences, probably related to persistence of hemosiderin or iron deposition rather than active disease.[33] Since larger studies are needed to elucidate the pathological mechanism of such changes in basal ganglia GCT evaluated with T2*-based imaging, their acquisition is recommended to better define their role on prospective studies, but currently are not included among response criteria. Further data are needed before

incorporating these sequences into response assessment.

Definitions of response criteria

Response criteria need to include radiological assessments alongside biochemical (marker), and cytological assessments where necessary, and be evaluated with the current neurological status of the patient at that time. Serum and CSF AFP/HCG markers and CSF cytology should be reassessed as per agreed guidance/trial protocols.

The agreed radiological response criteria for assessment of intracranial GCT enrolled on clinical trials, based on the available literature, existing clinical practice, and SIOPE-COG working group clinical experience, are shown in Table 2. An 'overall' disease assessment should first be performed. For most CNS GCT cases, which have only a single site of disease, this is entirely sufficient (at diagnosis only ~20% of cases are metastatic and only ~5-20% bifocal). However, for bifocal disease, or in cases of multiple measurable lesions (up to four target lesions), the sum of 2D (area) or 3D (ellipsoid volume) measurements of target lesions should demonstrate ≥50% decrease to be considered PR. This PR definition is entirely consistent with prior RAPNO[36,40,41] guidelines. However, it is also noted by the SIOPE-COG working group that for bifocal or multiple sites of disease, very rarely discrepant/different responses may be observed at different sites. Accordingly, we advocate that in addition to the 'overall' assessment, a specific target lesion assessment should next be undertaken in all such cases. For PR, we have now specified that the degree of response of each target lesion should also be evaluated, and, if a different degree of response of bifocal or multiple lesions is present (e.g., if one lesion does not reach the cut-off for PR, despite the sum of 2D or 3D measurements of target lesions showing a ≥50% decrease), then any such lesion(s) and their individual responses should be described separately in the report, and all sites of disease assessed by the relevant multidisciplinary team (MDT) to determine appropriate management (which may include consideration of second-look surgery and/or determination of optimal radiotherapy fields/doses).

For NGGCT cases where Progressive Disease (PD) might be considered, if a growing lesion is visualised radiologically during chemotherapy induction and/or early follow-up, but tumour markers are normalising/normalised, growing teratoma syndrome (GTS) is suspected and a surgical resection should be attempted with neuropathological correlation. Cases may also display apparent SD. This applies even in cases of bifocal or multiple lesions in NGGCT demonstrating a divergent response pattern with decrease in one or more lesion(s) and growth in another. GTS was first described in extracranial tumours[55] and occurs in only ~5% of intracranial NGGCT.[56] Pineal region is a more frequent location for GTS and for patients with an initial tissue diagnosis of CNS GCT, immature teratoma is present in 50%.[56] In such suspected GTS cases, surgical resection should be attempted. If such a growing lesion is later found to represent GTS, or only necrosis/fibrosis with no viable elements present, then the patient will not be considered to have PD. It is not possible therefore to assign a standard CR/PR/SD/PD assessment to such cases at the time of neuroradiological imaging - this is a retrospective definition following surgical and pathological correlation. Following surgery therefore, all patients should be carefully discussed at an MDT and resume adjuvant therapy or post-treatment follow-up for CNS GCT, and outcomes remain good.[56]

In addition to the radiological criteria, re-assessment of biochemical serum and CSF GCT (AFP/HCG) markers and CSF cytology is included, where indicated. For tumour markers, any rise should also exclude any another obvious cause (e.g., for AFP, any concomitant liver function test derangement secondary to chemotherapy)[57] prior to attributing to PD. Often, a number of frequent serial measurements are helpful in establishing whether marker rises are truly increasing or due to low level fluctuation.[58] In the future, quantification of specific non-coding RNAs termed microRNAs in the serum and CSF may assist the diagnosis and follow-up of patients with intracranial GCTs.[59,60]

Representative images of CNS GCTs in patients at presentation and following treatment are

highlighted in Figures 1 and 2.

CONCLUSION

Patients with intracranial GCT are relatively rare and this disease is a heterogeneous CNS malignancy. The variation of response assessment criteria used across European and North American trials support the need for standardised response criteria. These recommendations represent an initial consensus to uniformly assess response at common intracranial GCT sites; we recognise that continual reassessment and refinement of these criteria will be necessary as more prospective and retrospective comparisons become available, including possible future studies on true tumour volumetric assessment in comparison with current linear methods. This consensus approach will allow more consistent prospective neuroradiological evaluation of response to therapy for patients with CNS GCT and facilitate direct comparison of treatment outcomes across international studies.

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FIGURE LEGENDS

Figure 1. Pineal germinoma in a 12-year-old male patient. A-E. Brain MRI at presentation: Contrast-enhancing mass lesion involving the pineal region with contiguous thalamic extension and aqueductal stenosis, causing supratentorial hydrocephalus. DWI and corresponding ADC images show reduced diffusivity, in keeping with increased cellularity. There is no evidence of pathologic involvement of the sellar-suprasellar region. **F-J.** Brain MRI performed following treatment: T2-weighted image shows small cystic/cavitating areas in the pineal region and along the medial surface of the thalami (arrows, F), with resolution of reduced diffusivity on DWI and ADC images, and lack of CE, in keeping with post-treatment/post-biopsy sequelae. CE-T1-weighted images reveal a small enhancing solid component in the pineal region, less than 1 cm in all dimensions (arrows, I, J), located above a small hypointense calcification (arrowhead, J). Overall findings are compatible with Complete Response (CR). [Axial T2-weighted images (A, F); Axial Diffusion-Weighted Imaging (DWI) (B, G); Axial Apparent Diffusion Coefficient (ADC) maps (C, H); Axial contrast-enhanced (CE) T1-weighted images (D, I); Sagittal contrast-enhanced (CE) T1-weighted images (E, J)].

Figure 2. Complete response (CR) in patients with pineal and sellar/suprasellar germinoma. A-D. Pineal germinoma in a 14-year-old male patient. Brain MRI performed at presentation (A, B) shows a contrast-enhancing solid and cystic lesion involving the pineal region. Following treatment (C, D) the contrast-enhancing pineal gland is smaller than 1 cm in all dimensions. **E-H.** Sellar-suprasellar germinoma in a 5-year-old female patient with central diabetes insipidus (DI). Brain MRI performed at presentation (E, F) demonstrates a sellar/suprasellar mass lesions with heterogeneous contrast-enhancement. Following treatment (G, H) the thickness of the contrast-enhancing pituitary stalk is less than 0.4 cm near the optic chiasm and less than 0.3 cm at pituitary insertion. There is concomitant reduction in size of the pituitary gland which shows normal dimensions. [Sagittal contrast-enhanced (CE) T1-weighted images (A, C, E, G); Coronal contrast-enhanced (CE) T1-weighted images (B, D, F, H)].

Table 1. Brain and spine MRI protocol

Sequence	Slice thickness (mm)	Gap (mm)	Comment
Essential MRI study			
Pre-contrast brain sequences			
Axial DWI (b = 0,1000) with ADC	≤4	0-0.4	Or axial DTI
Axial T2 TSE/FSE	≤4	0-0.4	
Sagittal 3D T1 [a] (axial and coronal reformats)	1	0	Or Axial T1 SE/TSE/FSE [b] (≤4 mm slice thickness - gap: 0-0.4 mm) and Sagittal T1 SE/TSE/FSE [c] (≤3 mm slice thickness - gap: 0-0.3 mm)
Axial 2D FLAIR [d]	≤4	0-0.4	Or 3D FLAIR [c] (gap: 0 mm)
Post-contrast brain sequences			
Sagittal 3D T1 [a] (axial and coronal reformats)	1	0	If a pre-contrast Axial T1 SE/TSE/FSE [b] is performed, the same sequence should be acquired post-contrast (in addition to 3D T1)
Sagittal T1 SE/TSE/FSE [c]	≤3	0-0.3	
Axial 2D FLAIR [d]	≤4	0-0.4	Or 3D FLAIR [d] (gap: 0 mm)
Spine sequences			
Post-contrast sagittal T1 SE/TSE (whole thecal sac)	3	0-0.3	Use anterior saturation band
Post-contrast axial T1 SE [e]	4	0-0.4	Or axial 3D T1 GRE [e] (3 mm thickness - gap: 0-0.3 mm)
Complementary brain/spine sequences			
Axial SWI			Or Axial T2* GRE (≤4 mm slice thickness - gap: 0-0.4 mm) - Brain
Sagittal CISS, FIESTA or DRIVE	≤1	0	Midline brain structures / lower spinal cord
Single voxel MRS			TE = 135-144ms at 1.5T; TE = 288 ms at 3T (due to j-coupling at 135-144 ms)
Sagittal DWI	3	0-0.3	Midline brain structures
	2-3	0-1	Spine - b = 500-1000

Abbreviations: DWI= Diffusion Weighted Imaging; ADC= Apparent Diffusion Coefficient; DTI= Diffusion Tensor Imaging, TSE= Turbo Spin Echo; FSE= Fast Spin Echo; SE= Spin Echo, FLAIR= Fluid Attenuated Inversion recovery; SWI= Susceptibility Weighted Imaging; GRE= Gradient Echo; CISS= Constructive Interference in Steady State; FIESTA= Fast Imaging Employing Steady-state Acquisition; DRIVE= Driven Equilibrium, MRS= Magnetic Resonance Spectroscopy, TE= Echo Time, ms= milliseconds, mm= millimetres

[a] 3D isotropic GRE-based or SE-based techniques. Techniques need to be identical in terms of acquisition plane and acquisition type for both the pre- and post-contrast images.

[b] 2D GRE T1 or FLAIR T1 are recommended as an alternative if TSE/FSE present vascular or CSF pulsation artifacts. Recommended field of view: 230 mm (range 220-250 mm depending on patient head size).

[c] Recommended field of view: 160 mm (range 150-180 mm depending on patient head size).

[d] FLAIR images can be performed post-contrast, pre-contrast, or both, as per agreed trial protocols.

[e] To be performed if there are findings within the spine suspicious of metastasis. Field of view smallest possible.

	Criterion	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)
A	**Radiological: target lesion/s**	Complete disappearance of target lesion/s allowing for pituitary stalk thickness <0.3 cm on maximal dimension at pituitary insertion and <0.4 cm near the optic chiasm, or a solid enhancing pineal gland ≤1 cm in all dimensions	**Overall Assessment** Pituitary stalk thickness ≥0.3 cm on maximal dimension at pituitary insertion and ≥0.4 cm near the optic chiasm, or a solid enhancing pineal gland >1 cm in one dimension after completion of chemotherapy, but ≥50% decrease in the sum of 2D (area) or 3D (ellipsoid volume) measurements of target lesion(s) (up to 4 target lesions) **Specific Target Lesion Assessment (if >1 target lesion)** Degree of response of each target lesion evaluated, and, if a different degree of response of bifocal or multiple lesions is present (e.g., if one lesion does not reach the cut-off for PR, despite the overall assessment showing a ≥50% decrease), then any such lesion(s) and their individual responses should be described separately	Does not meet criteria for CR, PR, or PD	≥25% increase in 2D (area) or 3D (ellipsoid volume) measurements of any target lesion[*]
B	**Radiological: Diffusion-Weighted Imaging [a]**	Complete resolution of previously seen reduced diffusion [b]	Decreased size of previously noted reduced diffusion	Does not meet criteria for CR, PR, or PD	Clear increased extension of previously noted reduced diffusion or any new focus of reduced diffusion not attributable to complications of therapy [b, c]
C	**Radiological: non-measurable metastatic disease [d] / new lesion**	Complete disappearance of all areas of metastatic disease / No new lesion	No evidence of progression of metastatic disease (if negative at baseline, must remain negative) / No new lesion	Does not meet criteria for CR, PR, or PD	Clear progression of metastatic disease / any new lesion
D	**Biochemical: AFP/HCG tumour markers**	Normalised tumour markers[**]	No rise in tumour markers[**]	No rise in tumour markers[**]	Increase in tumour markers[**] (except during first cycle of chemotherapy, when an initial 'flare' in AFP/HCG can be observed due to treatment response, prior to decline)
E	**Cytological: cerebrospinal fluid (CSF) cytology**	If positive at baseline, must become negative	If positive at baseline, must become negative	If negative at baseline, must remain negative. If positive at baseline, can remain positive or be negative	Previously absent tumour cells in CSF now present (positive)
F	**Neurological status**	Stable or improved	Stable or improved	Stable or improved	Deterioration not attributable to other causes [***]

Requirement for response	C-F,	All CR criteria (A-F) must be met [e]	All PR criteria (A-F) must be met [e]	All SD criteria (A-F) must be met [e]	If any of the criteria for A or C-F, occur alone or in conjunction with other criteria, this is considered progressive disease.

Table 2. Radiological, biochemical and cytological response criteria for assessment of intracranial GCT

[a]: DWI is estimated qualitatively for response assessment of target lesion/s.

[b]: Decreased diffusivity corresponding to haemorrhagic components should not be considered because of DWI susceptibility to blood products.

[c]: DWI has not previously been used to determine progressive disease alone, and it is required to be used in conjunction with other radiographical determinants: either T1-weighted contrast-enhancing disease or T2-FLAIR.

[d]: The extent of non-measurable metastatic disease can only be estimated qualitatively.

[e]: if diffusion-weighted imaging is not obtained at baseline, determination of tumour response or progression is acceptable with the omission of this criterion moving forward .

[*] It is essential before ascribing Progressive Disease (PD) to any intracranial nongerminomatous GCT (NGGCT) case, that growing teratoma syndrome (GTS) is considered first. See text for more details.

[**] For tumour markers, any rise should also exclude any another obvious cause (e.g., for AFP, any concomitant liver function test derangement secondary to chemotherapy) prior to attributing to PD. Often, a number of frequent serial measurements are helpful in establishing whether marker rises are truly increasing or due to low level fluctuation

[***] If it is unclear that the patient has disease progression, it may be a reasonable option to keep the patient on the same study/treatment until subsequent assessments (e.g., radiological, tumour marker, CSF cytology) confirm progression. If subsequent testing confirms progression, the date of progression should be backdated to the original onset of neurological deterioration.

SUPPLEMENTARY MATERIAL

Absence of consensus regarding tumour measurement and response criteria standards

Tumour measurements
According to the SIOP CNS GCT II trial, tumour measurement was performed by 3-dimensional (3D) measurement of the longest tumour diameters and the approximation to the volume according to the formula of a rotational ellipsoid (A x B x C x 0.5), where A, B and C are the maximum dimensions (diameters) in the standard planes: antero-posterior (AP), transverse (T), and cranio-caudal (CC). In the COG ACNS1123 trial, both 2-dimensional (2D; area) or 3-dimensional (3D; volume) tumour dimensions were allowed. 2D dimensions were determined by measurement of the longest tumour dimension and its perpendicular for each target lesion, whereas 3D (volume) tumour dimensions were determined by measurement of the longest tumour dimension and its perpendicular, and the length (perpendicular to the plane of the 2D measurement) for each target lesion. However, unlike the SIOP CNS GCT II trial, volume calculation was not performed using the formula of a rotational ellipsoid (A x B x C x 0.5) but instead with the formula of a rectangular solid (A x B x C). This latter approach will overestimate true tumour volume, but as long as the same methodology is utilised subsequently as at diagnosis, the same percentage tumour volume reduction would be obtained as using the SIOP CNS GCT II method. However, as different percentage reductions were used between the two trials to describe response assessments, direct comparison is challenging. This led to the development of the European - North American neuroradiology consensus criteria.

Regarding tumour estimation, in the COG ACNS1123 trial, whatever sequence best highlighted the tumour (T1-enhanced or T2-weighted or FLAIR images) was used for serial measurements. This information was not specified in the SIOP CNS GCT II trial, where contrast-enhancing components were mainly considered. Of note, the SIOP CNS GCT II protocol did not provide specific information regarding the evaluation of cystic components, whereas according to the COG ACNS1123 trial, cystic or necrotic components were typically not considered in tumour measurements.

Response criteria
According to the SIOP CNS GCT II trial, complete response (CR) was defined on imaging as no evidence of disease. The protocol specified that as the PS is a structure that physiologically shows contrast enhancement, any kind of abnormal thickening or enhancement had to be categorised as questionable and therefore as partial response (PR). Similarly, the protocol reported that if anything more than physiological enhancement due to the internal cerebral veins was seen at the pineal gland, the response had been to be classified as PR. In some PR cases, there was almost complete radiological resolution of disease except for minimal residual thickening/enhancement, of uncertain significance. In such borderline (PR *vs.* CR) cases, a proportion of patients had a further follow-up MRI whilst still undergoing treatment, although this was not specifically specified in the SIOP CNS GCT II trial protocol. If this additional assessment MRI displayed a further tumour volume reduction compared with previous, then the case was considered a PR in retrospect. If the tumour volume remained stable, the previous MRI counted as first CR. However, normal reference values for the pituitary stalk or pineal gland region were not provided.

A recent retrospective evaluation of neuroradiological response to induction chemotherapy for patients with localised germinoma in the SIOP CNS GCT II trial demonstrated a significant number of discrepant CR rates among central reviewers, mainly regarding pineal gland tumour evaluation, with CR rates ~80% for German patients, compared with ~30-40% for UK and France.[1] Several critical points emerged, given the variability in normal pineal gland dimensions, frequency of incidental cysts, and physiological lack of blood-brain barrier with variable degree of contrast enhancement among healthy children, resulting in equivocal evaluation of treatment response and increased frequency of PR.[1] Of note, germinomas, in addition to tumour cells, comprise variable numbers of lymphocytes, macrophages and histiocytes.[2] These components may show contrast enhancement following treatment and may be interpreted as residual disease. Interestingly, a prior subanalysis of the SIOP CNS GCT 96 trial evaluated the impact on outcome of residual lesions in germinoma patients after treatment. A residual lesion was defined as any contrast enhancement >1 mm (>0.1 cm) at the primary tumour site. Thirty patients (28% of the whole trial cohort described) with residual tumour after radiotherapy were identified; residual lesions were noted to be between 0.2 cm and 2.0 cm in diameter. No patient underwent surgery or any other treatment for this residual disease and in follow-up, 13/30 tumours resolved spontaneously (43%), 16/30 remained stable and only one out of 30 patients (3%) developed progression/relapse. The study concluded that residual lesions after therapy were not a risk for early relapse, nor an adverse prognostic factor.[3,4] Considering this biological behaviour of germinomas, spontaneous resolution or stability of residual lesions termed PR in almost the totality of patients (29/30; 97%) raises the question as to whether residual radiological appearances classified as disease (PR) might have instead been expression of reactive changes/inflammatory cell infiltration/fibrosis rather than active disease, and highlights the potential utility of a pragmatic approach to PR cases in the future. An additional early follow-up MRI, may help to facilitate our understanding of the natural history of such cases, and whether such residuum represents necrosis/fibrosis/scar (stable MRI findings over a short timeframe) or residual active disease, responding to treatment (improved appearances).

Different and less restrictive criteria were included in the COG ACNS1123 trial. CR was defined as disappearance of visible disease on imaging allowing for minimal residual disease/enhancement ≤0.5 cm maximal dimension in suprasellar and/or ≤1 cm in pineal locations. Therefore, different from the SIOP CNS GCT II protocol, the COG ACNS1123 trial CR criteria took the physiological size and enhancement pattern of the hypophyseal and pineal gland into account, and permitted a minimal residual disease description. Of note, it should be observed that the permissive ≤0.5 cm maximal dimension for suprasellar disease defined in the COG ACNS1123 trial is greater than the <0.3 cm and <0.4 cm cut-off for physiological PS size described in the UK national guidelines.[5]

An additional substantial difference, which limits comparability among trials, is the PR and Progressive Disease (PD) criteria. According to the SIOP CNS GCT II trial, PR was defined as >50% decrease in the sum of the volume of all measurable lesions (calculated from the maximum diameters on MRI in three dimensions). The COG ACNS1123 trial considered instead different response criteria on the basis of 2D or 3D measurements. In detail, PR was defined as a ≥50% decrease in 2D (area) measurement or ≥65% decrease in the sum of the products of the three perpendicular diameters (volume). Different criteria were also used for defining PD, where according to SIOP CNS GCT II trial, which used 3D criteria, PD was considered in cases of >25% increase in the size of any measurable lesion. The COG ACNS1123 trial defined PD as ≥ 25% increase in 2D (area) or ≥ 40% increase in 3D (volume) measurements of any target lesion.

One prior study compared 2D *vs.* 3D measurements using the current SIOP-Europe and COG cut-offs described above.[6] In this study, frequency of agreement and concordance of best response categorisation was slightly higher between 2D and 3D measurements using the same cut-offs.[6] An additional study also reported that 'further research regarding the range of deviation of tumours from the idealised spherical shape will be necessary to determine the best values for most accurate response rate comparisons, and validation of each approach will be important'.[7] This is therefore an area that warrants further investigation.

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