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Cancer Diagnosis GUIDELINE

The Innovation Oncology

Practical guideline for the diagnosis and management of central nervous system germ cell tumors

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Central nervous system germ cell tumors (CNS GCTs) represent a rare, heterogeneous group of malignancies requiring intricate, risk-stratified management.[1] While modern protocols have improved survival, universal consensus on optimal management is lacking. To address this, this guideline synthesizes prospective trial data from the Children's Oncology Group (COG ACNS0122/1123) and International Society of Paediatric Oncology (SIOP CNS GCT 96/II) and the China Anti-Cancer Association (CACA) expert consensus, offering a systematic, evidence-based framework to balance treatment efficacy with neurocognitive function preservation. We emphasize a "diagnosis-first" approach, integrating neuraxis magnetic resonance imaging (MRI) with serum/cerebrospinal fluid (CSF) tumor marker (alpha-fetoprotein [AFP]/beta-human chorionic gonadotropin [β-hCG]) thresholds, while mandating biopsy for marker-negative or equivocal cases. Furthermore, we define standardized salvage strategies for relapsed disease and highlight the transformative potential of molecular profiling and CSF-derived cell-free DNA for minimal residual disease monitoring.[2] This integrative framework aims to reconcile international evidence-based practices with the evolving landscape of precision oncology to optimize long-term outcomes and surveillance for pediatric and adolescent patients.

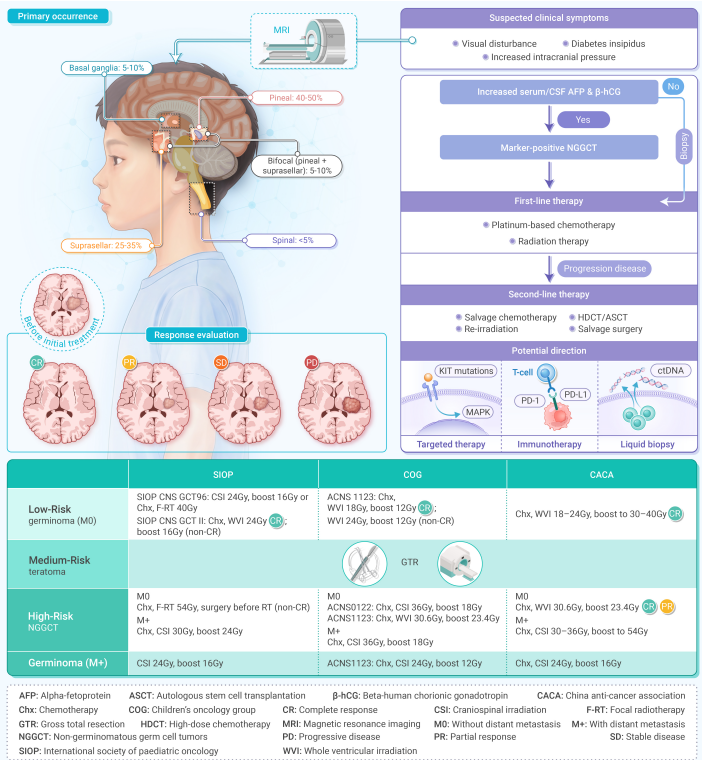

Figure 1. Management of CNS GCTs.

DIAGNOSIS AND ASSESSMENT

When pediatric or adolescent patients present with visual disturbances, diabetes insipidus, or increased intracranial pressure, CNS GCTs should be strongly suspected, especially if imaging reveals a lesion in the pineal(40%-50%), suprasellar (25%-35%), basal ganglia (5%-10%), bifocal pineal and suprasellar (5%-10%), or spinal (<5%) regions (Figure 1). To confirm the diagnosis and assess spinal metastasis, the evaluation must immediately include a contrast-enhanced MRI of the entire neuraxis, along with tumor marker and histopathologic verification.

Global thresholds vary. In serum or CSF, SIOP defines NGGCTs by AFP >10 ng/mL or β-hCG >100 IU/L;[3] COG tightens CSF β-hCG to >50 mIU/mL.[4] Comparatively, the CACA guidelines require AFP >10 ng/mL or β-hCG >50 IU/L in either compartment.[5]

Endoscopic biopsy is mandatory for marker-negative bifocal tumors, atypical imaging, or cases where markers remain below diagnostic thresholds.

TREATMENT

Risk-stratified initial (first-line) treatment

Low-risk (localized pure germinoma). The low-risk group is strictly defined as non-disseminated localized pure germinoma, characterized by completely negative tumor markers or extremely low serum β-hCG levels, together with a favorable response to induction chemotherapy.

For localized intracranial pure germinomas, the SIOP CNS GCT 96 trial evaluated two strategies: reduced-dose craniospinal irradiation (CSI) alone with 24 Gy CSI plus a 16 Gy primary tumor boost, or alternating CE (carboplatin/etoposide) and IE (ifosfamide/etoposide) cycles followed by 40 Gy focal radiotherapy.[3] Subsequently, the SIOP CNS GCT II protocol utilized four cycles of cisplatin/etoposide (EP). Following EP, patients achieving complete radiological remission received 24 Gy whole ventricular irradiation (WVI) without a boost, whereas those with incomplete remission received an additional 16 Gy boost to the primary site, for a total dose of 40 Gy. The COG ACNS1123 protocol mandates four cycles of induction carboplatin/etoposide, followed by response-stratified radiotherapy: complete responders (CR) receive 18 Gy WVI plus a 12 Gy focal boost to the primary lesion for a total radiation dose of 30 Gy, whereas partial responders (PR) undergo escalated 24 Gy WVI plus a 12 Gy primary tumor boost, for a total dose of 36 Gy.[1] Similarly, the CACA protocol utilizes four induction cycles of either EP or CE. Radiotherapy is then tailored to chemotherapy response, delivering 18–24 Gy WVI followed by a focal boost to reach a total dose of 30–40 Gy (Figure 1).

Bifocal involvement of the pineal and suprasellar regions represents a unique yet highly characteristic presentation. Without tumor markers, and after neuraxis dissemination has been ruled out by negative CSF cytology and spinal MRI, these cases are stratified as localized pure germinomas. Although nearly pathognomonic, biopsy confirmation is recommended to avert therapeutic bias.

Medium-risk (teratomas, marginal/gray-zone cases). The intermediate-risk group includes histologically confirmed mature or immature teratomas, marker-gray-zone cases, and patients with significant residual disease following chemotherapy. Consistent with the global consensus that radical surgical resection is the cornerstone of teratoma management, achieving gross total resection (GTR) remains the primary determinant of long-term survival for these patients.

High-risk (malignant NGGCTs and disseminated germinomas). The high-risk group includes all secreting NGGCTs that meet established diagnostic thresholds. It also includes non-secreting NGGCTs confirmed by histology, along with any disseminated disease (M1–M4).

Management of NGGCTs varies significantly among SIOP, COG, and CACA protocols. Upfront cisplatin/etoposide/ifosfamide (PEI) is given for both localized and metastatic diseases: 4 cycles under SIOP 96/II, 4–6 cycles under CACA. COG ACNS0122/1123 instead alternates carboplatin/etoposide (CE) with ifosfamide/etoposide (IE) for 6 cycles. Post-chemotherapy radiotherapy (RT) strategies are highly risk- and response-adapted. For localized NGGCTs, SIOP mandates 54 Gy focal RT with mandatory residual tumor resection for incomplete responders, whereas COG ACNS0122 requires 36 Gy CSI plus an 18 Gy boost. To mitigate toxicity, COG ACNS1123 limits RT to 30.6 Gy WVI plus a 23.4 Gy boost for complete or partial responders. CACA permits omitting CSI in localized complete responders by adopting WVI with a focal boost, while reserving CSI for incomplete responders. For metastatic NGGCTs, all three organizations mandate CSI (30 Gy for SIOP; 36 Gy for COG; 30–36 Gy for CACA) combined with focal boosts to the primary and metastatic lesions to achieve a total dose of 54 Gy (Figure 1).

For metastatic pure germinomas, 24 Gy CSI represents the consensus lower limit for dose reduction across all protocols. The SIOP 96 trial established the efficacy of definitive radiotherapy alone using 24 Gy CSI plus a focal boost. In contrast, subsequent protocols adopt combined chemoradiotherapy strategies: COG ACNS1123 mandates platinum/etoposide chemotherapy, SIOP CNS GCT II delivers PEI, and CACA guidelines prescribe 2–4 cycles of EP. Post-chemotherapy radiotherapy remains identical across these three modern protocols, administering 24 Gy CSI supplemented by focal boosts to primary and metastatic lesions to a total dose of 40–45 Gy (Figure 1).

Relapsed/refractory CNS GCTs

Pure germinomas exhibit high salvageability upon recurrence. Management is stratified by prior RT exposure and by whether relapse is localized or disseminated. Under SIOP and COG frameworks, patients who are RT-naive, having received only upfront chemotherapy or those who missed initial CSI are optimally salvaged with conventional-dose chemotherapy plus CSI at a routine dose of 24 Gy, yielding excellent long-term survival. Conversely, for in-field recurrences after initial RT, high-dose chemotherapy paired with autologous stem cell transplantation (HDCT/ASCT) is the standard of care, occasionally supplemented by a second focal RT boost.

Recurrent NGGCTs carry a dismal prognosis. We consider HDCT/ASCT the therapeutic cornerstone, not merely an option-for marker-elevated relapses, endorsed across SIOP, COG, and CACA. COG protocols specify thiotepa/carboplatin/etoposide-based conditioning regimens. For re-induction, CACA recommends ifosfamide-containing PEI or teniposide-based regimens to achieve secondary remission.[5]

Across all protocols, salvage surgery and re-irradiation follow stringent, response-adapted criteria. CACA guidelines preferentially advocate second-look bioptic resection to clarify pathological transformation, such as growing teratoma syndrome.[5] Otherwise, surgery aims for maximal safe resection under three specific scenarios: suspected mature teratoma components, symptomatic solitary lesions, or necessary tissue acquisition. Regarding re-irradiation, CSI-naive patients receive complementary CSI, whereas those with prior adequate CSI require cautious evaluation for focal re-irradiation, proton beam therapy, or stereotactic boosts.

RESPONSE ASSESSMENT AND MONITORING

Therapeutic response is assessed via contrast-enhanced MRI and serial serum/CSF AFP/β-hCG, adopting volume- and marker-based criteria adapted from the SIOP CNS GCT II and COG ACNS1123 protocols:

(1) Complete Response (CR): Disappearance of all lesions and normalized markers; (2) Partial Response (PR): ≥65% reduction in tumor volume and no new lesions; (3) Progressive Disease (PD): ≥40% increase in tumor volume, or appearance of new lesions, or sustained elevation of tumor markers;[4] (4) Stable Disease (SD): Disease failing to meet CR/PR/PD criteria withoutnew lesions (Figure1).

For patients with atypical imaging, borderline markers, or equivocal biopsy results, close monitoring is mandated at 3–6 months. For confirmed cases, surveillance is scheduled every 3–4 months during years 1–2 post-treatment, every 6 months during years 3–5, and annually thereafter. Surveillance intervals can be individualized for patients maintaining stable disease (> PR/SD). Suspicious imaging or marker elevation warrants immediate positron emission tomography - computed tomography (PET-CT) and pathological biopsy to guide prompt salvage therapy. Crucially, long-term toxicity surveillance must be integrated into the survivorship management framework.

CONCLUSION AND FUTURE DIRECTIONS

We integrate risk-stratified, platinum-based chemotherapy with tailored radiotherapy to optimize cure rates and reduce neurotoxicity. Looking ahead, this framework is poised for refinement through emerging modalities. Molecular profiling has identified recurrent, actionable alterations, including MAPK/KIT pathway mutations in germinomas and chromatin remodeling gene defects in NGGCTs, thereby paving the way for targeted therapeutics. Concurrently, cerebrospinal fluid-derived cell-free tumor DNA (ctDNA) analysis offers a transformative liquid biopsy tool for high-sensitivity genomic profiling and minimal residual disease monitoring, facilitating dynamic treatment adaptation. Furthermore, immune checkpoint inhibitors targeting PD-1/PD-L1 show therapeutic promise (Figure1).[2] For progressive disease, active enrollment in clinical trials investigating these novel agents remains imperative to advance the therapeutic landscape.

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AUTHOR CONTRIBUTIONS

All authors contributed to the original idea, study design, data interpretation, and manuscript writing. C.Z. & Y.H. also contributed to the scientific literature search, data collection, and data analysis. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.