OPEN ACCESS

Clinical and Translational Oncology GUIDELINE



# Management of CNS nongerminomatous germ cell tumors: Consensus recommendations bridging global trials and clinical practice

**Zhen Chen,[1,2,6] Bing-xin Cheng,[1,3,6] Feng-yi Duan,[4,6] Jun Zhang,[5,6] and Hua You[4,6,*]**

[1]Department of Emergency, the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430000, China

[2]Key Laboratory for Molecular Diagnosis of Hubei Province, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China

[3]Clinical medicine, School of Medicine, Jiang han University, Wuhan 430000, China

[4]Department of Pediatric Oncology, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu 610041, China

[5]Department of Surgical Oncology of Children's Hospital of Chongqing Medical University, National Clinical Research Center for Children and Adolescents' Health and Diseases, Chongqing 400000, China

[6]These authors contributed equally to this work

*Correspondence: youhua307@163.com

Received: August 14, 2026; Accepted: October 23, 2026; Published Online: October 23, 2026; https://doi.org/10.59717/j.xinn-oncol.2026.100038

© 2026 The Author(s). This is an open access article under the CC BY license (https://creativecommons.org/licenses/by/4.0/).

Citation: Chen Z., Cheng B.-x., Duan F.-y., et al. (2026). Management of CNS nongerminomatous germ cell tumors: Consensus recommendations bridging global trials and clinical practice. *The Innovation Oncology* **1**:100038.

Central nervous system germ cell tumors (CNS GCTs) represent malignant intracranial neoplasms predominantly affecting children and adolescents. Histologically, they are categorized as germinomas or nongerminomatous germ cell tumors (NGGCTs). Distinct from pure germinomas, which are highly sensitive to radiation and chemotherapy, NGGCTs are characterized by poor response to conventional radiochemotherapy and inferior prognostic outcomes. The clinical manifestations of CNS NGGCTs are primarily determined by tumor location, with the pineal region, suprasellar region, and basal ganglia serving as the most prevalent lesion sites. The standard diagnostic workflow integrates neuroaxis magnetic resonance imaging (MRI) and measurement of serum and cerebrospinal fluid (CSF) tumor markers, including alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-hCG), while pathological biopsy is performed for definitive diagnosis when necessary.[1] Consequently, we strongly recommend individualized therapeutic regimens for patients with CNS NGGCTs. This guideline is developed based on the prospective clinical trial data from the Children's Oncology Group (COG ACNS0122/1123), the International Society of Paediatric Oncology (SIOP CNS GCT 96/II), and the 2026 Chinese guidelines, as well as authoritative expert consensus, with the ultimate goal of optimizing therapeutic efficacy and improving long-term prognosis in patients with CNS NGGCTs.

## DIAGNOSIS AND ASSESSMENT

We recommend that the diagnostic process start with recognition of suspicious clinical features, including intracranial hypertension, diabetes insipidus, limb weakness, and visual disturbances (Figure 1). When MRI identifies a lesion in the pineal, suprasellar, or basal ganglia, serum and/or CSF AFP and β-hCG should be measured (GRADE: high; strong). Diagnostic thresholds vary across international protocols, with SIOP CNS GCT 96/II using AFP >25 ng/mL or β-hCG ≥50 IU/L, COG ACNS0122 using AFP >10 ng/mL or β-hCG >50 IU/L, and COG ACNS1123 uses AFP >10 ng/mL or β-hCG >100 IU/L.[1] The 2026 Chinese guidelines adopt AFP >10 ng/mL and/or β-hCG >50 IU/L as positive criteria. Patients meeting these thresholds can be clinically diagnosed without biopsy; these thresholds also guide risk stratification and treatment decisions (GRADE: moderate; strong).

When tumor markers in both serum and CSF remain negative and MRI identifies a suspicious lesion, a neurosurgical biopsy is required to establish a histological diagnosis (GRADE: moderate; strong). Although PET/CT with tracers such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) is not routinely mandated, it serves as a valuable adjunct for differential diagnosis, staging, and radiotherapy target delineation in selected challenging cases (GRADE: low; conditional).

## TREATMENT

### Initial treatment

When clinical features and radiological findings strongly suggest a mature teratoma, we strongly advise upfront complete surgical resection, as clinicians generally do not need to administer adjuvant chemotherapy or radiotherapy postoperatively (GRADE: high; strong). However, for immature teratomas, physicians must prioritize postoperative chemotherapy (GRADE: high; strong). The cisplatin, etoposide, and ifosfamide (PEI) regimen is the preferred platinum-based choice, while bleomycin, etoposide, and cisplatin (BEP) is no longer recommended for intracranial disease, primarily due to significant cumulative pulmonary toxicity and the availability of superior regimens like PEI.[1] For both localized and metastatic NGGCTs, the PEI regimen is used, with 4 cycles under the SIOP 96/II protocol and 4–6 cycles under the 2026 Chinese guidelines. The COG ACNS0122/1123 studies use an alternating regimen, with carboplatin/etoposide (CE) followed by ifosfamide/etoposide (IE) over 6 cycles.

Growing teratoma syndrome (GTS) is paradoxical tumor enlargement during or after chemotherapy, despite normalization or decline of serum and CSF tumor markers. Histologically, the enlarging mass contains only mature teratoma or necrotic/fibrotic tissue without viable malignant components. When we suspect GTS based on imaging and marker discordance, we should perform surgical resection before proceeding with radiotherapy, as we must avoid misinterpreting GTS as disease progression (GRADE: high; strong).[2]

The radiotherapy regimens after chemotherapy for localized or metastatic NGGCTs differ among SIOP, COG, and the 2026 Chinese guidelines. In the SIOP protocol, patients with localized disease receive focal radiation (FR, 54 Gy), whereas those with metastatic disease receive craniospinal irradiation (CSI, 36 Gy) plus a boost (18 Gy) to the primary tumor and metastases. The COG protocols differ: ACNS0122 treats all localized patients with CSI (36 Gy) plus a boost (total 54 Gy), while ACNS1123 uses whole ventricular irradiation (WVI, 30.6 Gy) with a local boost (total 54 Gy).[3] For metastatic disease, COG follows the same regimen as SIOP. The 2026 Chinese guidelines recommend WVI (30.6 Gy) with a boost (23.4 Gy, total 54 Gy) for localized NGGCTs, and CSI (30–36 Gy) with a boost (total 54 Gy) for metastatic disease.[4]

However, the optimal radiation volume remains debated. In COG ACNS1123, reduced radiotherapy (WVI without spinal coverage) achieved promising survival, but all recurrences involved the spine, suggesting that spinal irradiation may be necessary even for localized disease. These findings have prompted the next COG trial (ACNS2021), which reintroduces spinal canal irradiation (30.6 Gy) while maintaining WVI for the brain volume.[5]

The choice between CSI-based and WVI-based radiotherapy should be guided by disease stage and response to chemotherapy: CSI is preferred for metastatic disease, whereas WVI with tumor-bed boost is preferred for localized NGGCTs achieving complete response (CR) or partial response (PR) after chemotherapy to reduce late toxicity.

### Relapse treatment

Salvage surgery is indicated for recurrent tumors causing significant mass effect, post-chemotherapy residual disease (second-look resection), or equivocal lesions requiring histological verification (GRADE: moderate; strong).[2] We must emphasize the stark reality that recurrent NGGCTs face a dismal prognosis. For relapses with elevated tumor markers, high-dose

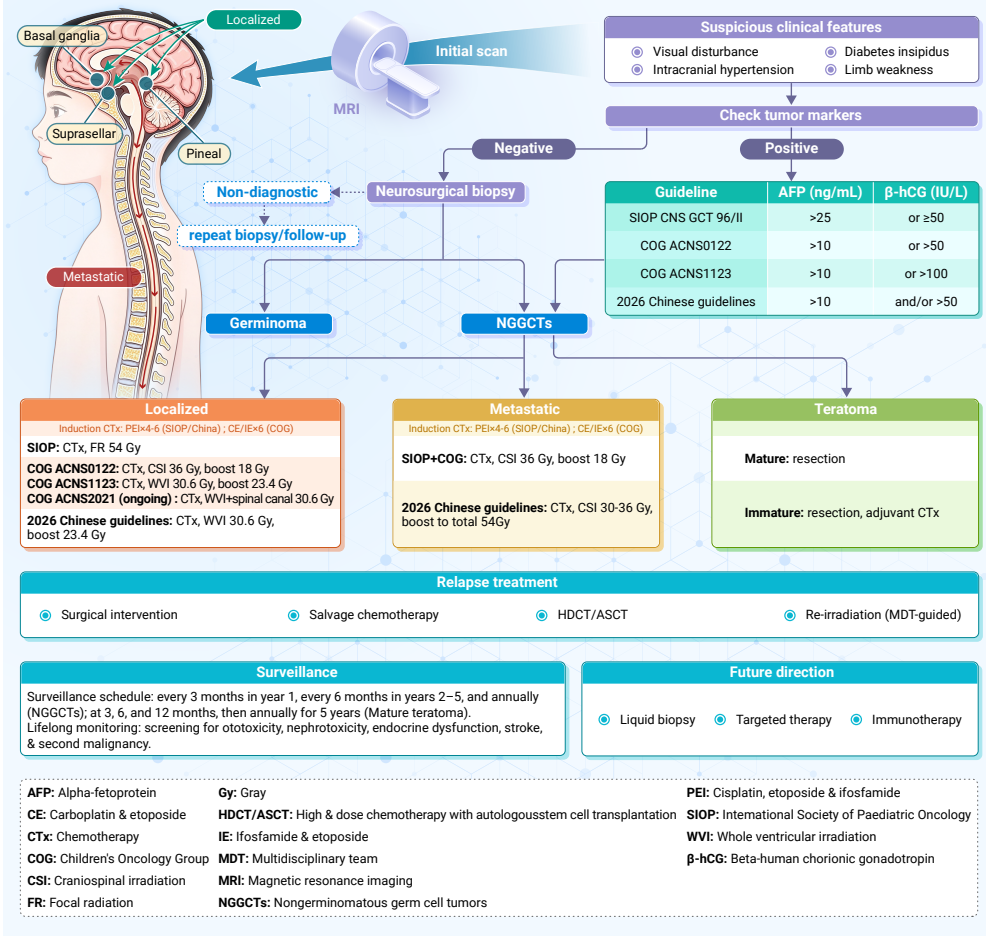



**Figure 1. Management of CNS NGGCTs** Induction chemotherapy (CTx) regimens consist of 4–6 cycles of PEI according to the SIOP CNS GCT 96/II protocol and the 2026 Chinese guidelines, or 6 alternating cycles of CE/IE following Children's Oncology Group (COG) protocols.

chemotherapy paired with autologous stem cell transplantation (HDCT/ASCT) yields limited efficacy in small cohorts, with specific trial settings showing a 3-year overall survival of 36.4% for NGGCTs compared to 88.9% for germinomas. Nevertheless, clinical outcomes can vary significantly; recent evidence indicates that patients receiving comprehensive salvage modalities, especially re-irradiation, can achieve substantially higher survival rates. Re-irradiation serves as a critical salvage option but requires mandatory multidisciplinary team (MDT) evaluation. Precision focal techniques such as stereotactic radiosurgery (SRS) are indicated for localized recurrences, whereas repeat CSI is reserved for cerebrospinal fluid dissemination. Cumulative radiation doses must strictly remain within normal tissue tolerance limits to mitigate severe late neurotoxicity (GRADE: moderate; strong).

## MONITORING

For NGGCTs other than completely resected mature teratoma, we recommend long-term surveillance consisting of contrast-enhanced whole-neuraxis MRI and serum AFP/β-hCG evaluations every 3 months in year 1, every 6 months in years 2–5, and then annually in years 6–10 (GRADE: moderate; strong). For completely resected mature teratoma, imaging and markers are recommended at 3, 6, and 12 months, then annually for 5 years (GRADE: moderate; strong). Once relapse is suspected, complete restaging is mandatory regardless of marker status (GRADE: moderate; strong). Because most patients survive for decades, lifelong monitoring for platinum-related ototoxicity, nephrotoxicity, neuropathy, endocrine dysfunction, stroke risk, and second malignancy is advised (GRADE: Consensus-based; strong).[4]

## FUTURE DIRECTION

### Liquid biopsy

Given the constraints imposed by the blood-brain barrier on plasma biomarkers, cerebrospinal fluid (CSF) serves as a primary source for liquid biopsy in iGCTs. Quantitative tracking of CSF circulating tumor DNA (ctDNA) enables real-time residual disease monitoring and molecular characterization. Additionally, specific embryonic microRNAs, notably the miR-371a-3p and miR-302/367 clusters, offer high sensitivity for non-invasive diagnosis and early relapse monitoring.[1] Standardizing CSF collection procedures and validating detection assays are necessary steps toward leveraging these biomarkers in risk-adapted treatment protocols.

### Targeted therapies and immunotherapy

Genomic profiling has identified recurrent driver alterations in the RTK/RAS/MAPK and PI3K/mTOR pathways, including KIT and KRAS mutations, as well as PD-L1 overexpression. Early-phase clinical trials are investigating targeted agents, including MEK, KIT, and mTOR inhibitors, alongside immune checkpoint inhibitors. Incorporating these targeted approaches into frontline management aims to preserve high survival outcomes while mitigating the adverse effects associated with conventional chemoradiotherapy.[1]

## REFERENCES

1. Frappaz D., Dhall G., Murray M.J., et al. (2022). EANO, SNO and Euracan consensus review on the current management and future development of intracranial germ cell tumors in adolescents and young adults. *Neuro-Oncology* **24**:516–527. DOI:10.1093/neuonc/noab252
2. Calaminus G., Frappaz D., Kortmann R.D., et al. (2017). Outcome of patients with intracranial non-germinomatous germ cell tumors—lessons from the SIOP-CNS-GCT-96 trial. *Neuro-Oncology* **19**:1661–1672. DOI:10.1093/neuonc/nox122
3. Fangusaro J., Wu S., MacDonald S., et al. (2019). 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.* **37**:3283–3290. DOI:10.1200/JCO.19.00701
4. Subspecialty Group of Pediatric Neurosurgery, Neurosurgical Society of Chinese Medical Association, Ma J., Chen Z.P., et al. (2026). Chinese guidelines for the diagnosis and treatment of pediatric and adolescent central nervous system nongerminomatous germ cell tumors (2026 edition). *Chin. J. Neurosurg. Dis. Res.* **20**:8–15. DOI:10.3969/j.issn.1671-2897.2026.02.002
5. Goldman S., Bouffet E., Fisher P.G., et al. (2015). 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.* **33**:2464–2471. DOI:10.1200/JCO.2014.59.5132

## FUNDING AND ACKNOWLEDGMENTS

Not Applicable.

## AUTHOR CONTRIBUTIONS

Conceptualization, H.Y; data curation and writing, Z.C., BC; Clinical Insights: F.D., J.Z., H.Y. All authors contributed to the manuscript and approved the final version.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## ETHICAL STATEMENT AND PATIENT CONSENT

Not Applicable.

## DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.