CHAPTER NINE

Non-germinomatous germ cell tumors of the CNS: Classification, diagnosis, and treatment

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Abstract

Non-germinomatous germ cell tumors (NGGCTs) are rare, histologically diverse malignancies that primarily affect children and adolescents. Unlike germinomas, NGGCTs are less

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responsive to chemotherapy and radiation, resulting in a less favorable prognosis and necessitating intensified multimodal therapy. This chapter provides a comprehensive overview of NGGCTs, including histological subtypes, clinical presentation, diagnostic strategies, and established as well as emerging treatment paradigms. We discuss current classification systems, the roles of tumor markers and neuroimaging, and challenges in histopathologic diagnosis. Treatment approaches vary globally but typically include intensive chemotherapy combined with craniospinal or whole-ventricular irradiation. Long-term outcomes remain suboptimal for high-risk subtypes, especially those with yolk sac tumor, choriocarcinoma or embryonal carcinoma components. Recent genomic and epigenomic studies have revealed recurrent alterations in the RTK/MAPK and PI3K/mTOR pathways, along with distinctive methylation signatures and copy number aberrations, offering insights into tumorigenesis and potential therapeutic targets. Ongoing trials continue to focus on refining risk stratification and minimizing treatment-related toxicities. These efforts, along with advances in molecular characterization, may ultimately improve survival and long-term quality of life in patients with CNS NGGCTs.

1. Introduction

Non-germinomatous germ cell tumors (NGGCTs) include mature teratoma, immature teratoma, teratoma with somatic-type malignancy, yolk sac tumor, choriocarcinoma, and embryonal carcinoma, according to the latest WHO 2021 classification (Louis et al., 2021). The pineal region is the most common site of tumor occurrence, even more so than germinoma (Takami et al., 2019). NGGCTs rarely present as a single histological subtype. Instead, they are commonly found as mixed GCTs, often coexisting with other components, such as germinoma and teratoma, with "pure" NGGCTs accounting for only 10–20 % of cases. Among NGGCTs, immature teratoma and yolk sac tumor are more common, whereas choriocarcinoma and embryonal carcinoma are exceedingly rare as solitary histologies. Compared to germinomas, NGGCTs are more resistant to chemotherapy and radiation therapy, leading to a less favorable prognosis. GCTs have a peak incidence in early adolescence, making the long-term complications associated with standard treatment—primarily chemotherapy and radiation therapy—a major concern later in life. From this perspective, key challenges include optimizing treatment efficacy while minimizing treatment-related burdens, identifying genomic abnormalities that could serve as targets for precision therapies, and exploring the incorporation of immunotherapy into treatment strategies.

This chapter provides an overview of the essential histological classification of NGGCTs, the standardized treatment approaches established through past clinical trials, and the therapeutic strategies currently being

investigated in ongoing clinical trials. Additionally, it discusses the potential therapeutic targets and stratification strategies that have emerged from genomic and pathological analyses conducted over the past decades.

2. Clinical presentations

CNS GCTs most commonly arise in the pineal region, followed by the neurohypophyseal region, with less frequent occurrences in other locations such as the basal ganglia, thalamus, cerebral and cerebellar hemispheres, and spinal cord. GCTs in the pineal region predominantly affect males, accounting for approximately 90 % of cases, whereas their occurrence in females is rare. In contrast, tumors in the neurohypophyseal region show no apparent sex predilection. The neurohypophyseal region, traditionally referred to as the suprasellar region, is so named because tumors in this area typically involve the posterior pituitary, pituitary stalk, and hypothalamus.

Lesions occurring in the pineal region often present with obstruction of the cerebral aqueduct, resulting in obstructive hydrocephalus with associated symptoms such as nausea, vomiting and headache and/or symptoms due to compression of the midbrain tectum, leading to ocular movement disorders such as upward gaze palsy (Parinaud's sign) and Argyll-Robertson pupils (light reflex is lost, but pupillary constriction in response to accommodation is preserved) (Hankinson et al., 2016; Hart et al., 2013; Takami et al., 2021).

Lesions in the neurohypophyseal region frequently manifest as endocrine dysfunction, particularly diabetes insipidus, and anterior pituitary dysfunction. These lesions may also cause visual impairment due to compression of the optic chiasm.

Lesions in the cerebral or cerebellar hemispheres, brainstem, or basal ganglia present with symptoms corresponding to the affected area. In particular, basal ganglia lesions may be associated with unilateral cerebral hemisphere atrophy, leading to hemiparesis and cognitive-behavioral changes (Graham et al., 2021).

Furthermore, it is well known that precocious puberty can result from tumor-derived human chorionic gonadotropin (HCG) production. In addition, HCG-producing tumors—particularly choriocarcinomas—frequently present with intratumoral hemorrhage.

2.1 Diagnosis

Diagnosis is based on an integrated assessment of clinical presentation, imaging findings, tumor marker analysis in blood and cerebrospinal fluid (CSF), and histopathological examination of tumor tissue obtained through surgery. The necessity of pathological diagnosis is evaluated on a case-by-case basis, taking into account the results of other diagnostic tests.

2.2 Tumor marker

Currently, two tumor markers in blood serum and CSF are used in the diagnosis of GCTs: HCG and alpha-fetoprotein (AFP) (Kim et al., 2008). HCG is markedly elevated in choriocarcinoma, while AFP is typically elevated in yolk sac tumors. However, germinomas can also produce HCG, and mild to moderate HCG elevation is often observed in germinoma patients (Takami et al. 2022a). In the previous WHO classification, germinoma with syncytiotrophoblastic giant cells (STGCs) was recognized, and cases with HCG elevation are sometimes referred to as HCG-producing germinoma, which has a prognosis similar to pure germinoma (Takami et al., 2024). Given that choriocarcinoma is extremely rare, HCG elevation up to a certain level more commonly indicates germinoma rather than choriocarcinoma, which is typically in the thousands. Similarly, AFP elevation can be observed in teratomas, particularly immature teratomas (Takami et al., 2023a).

HCG tends to be higher in CSF, while AFP tends to be higher in serum (Legault & Allen, 2013). As GCTs often consist of mixed histological components, tumor marker elevation alone is insufficient to distinguish between germinomas and NGGCTs (Takami et al., 2023a). NGGCTs are frequently diagnosed as per a biopsy in the setting of negative tumor markers, or based on elevated tumor markers only (Calaminus et al., 2017; Fangusaro et al., 2019; Frappaz et al., 2022; Goldman et al., 2015; Takami et al., 2022a). However, the cutoff values for tumor markers differ by organization. Specifically, SIOP defines NGGCTs as HCG ≥ 50 IU/L or AFP ≥ 25 ng/mL, while COG sets the cutoff at HCG ≥ 100 IU/L or AFP ≥ 10 ng/mL. The current Japanese clinical trial adopts even higher thresholds of HCG ≥ 500 IU/L and AFP ≥ 250 ng/mL. When lower cutoffs are used, some HCG-elevated germinomas—which could be managed with less intensive therapy—may undergo unnecessarily aggressive treatment. Conversely, a pathological diagnosis based on biopsy specimens may underestimate malignancy, particularly in the presence of

tumor heterogeneity. If AFP is elevated beyond a certain level, the tumor should be treated as an NGGCT, even if biopsy suggests germinoma. Therefore, when appropriate, integrating tumor marker profiles and histopathological findings is essential for accurate diagnosis and appropriate treatment selection (Takami et al., 2023a).

2.3 Imaging

At presentation, brain and whole-spine MRI with and without contrast enhancement are necessary (Murray et al., 2015). A head CT scan, with or without contrast enhancement, can reveal the presence of abnormal calcification within the tumor. Spinal cord MRI provides information on tumor dissemination, helping to determine whether extensive spinal canal irradiation is necessary. Most tumors exhibit contrast enhancement. Mature teratomas typically appear as well-circumscribed, heterogeneous masses containing fat, calcifications, and cystic components, with minimal or no enhancement after contrast administration. In contrast, immature teratomas present as heterogeneous lesions with mixed solid and cystic areas and demonstrate more prominent contrast enhancement; they may also show restricted diffusion on diffusion-weighted image (DWI). Embryonal carcinomas often appear as large, irregular, solid masses with strong and heterogeneous enhancement, commonly accompanied by hemorrhage, necrosis, and marked diffusion restriction. Choriocarcinomas are highly vascular and frequently exhibit prominent intratumoral hemorrhage and intense contrast enhancement, sometimes with flow voids indicative of high blood flow. Yolk sac tumors tend to show heterogeneous enhancement with necrotic areas. Finally, mixed GCTs display variable imaging characteristics depending on the predominant histological component, often appearing as large, heterogeneous, and strongly enhancing masses (Morana et al., 2018; Wu et al., 2017; Yamasaki et al., 2018). However, the correlation between imaging findings and histological subtype is generally limited—except in select cases—and it is widely recognized that accurate histological classification cannot be reliably determined based on imaging alone.

2.4 Cerebrospinal fluid cytology

CSF should be obtained via lumbar puncture. CSF can also be obtained via ventricular drainage, or during endoscopic surgery through the ventricles. Lumbar puncture is contraindicated when intracranial pressure is suspected to be significantly elevated. CSF should typically be examined for cytology and tumor markers. The presence of tumor cells in the CSF indicates

tumor dissemination within the CSF cavity, regardless of MRI findings. However, there is a scarcity of studies investigating the relationship between CSF cytology results and MRI findings for NGGCTs.

2.5 Histopathological features

Approximately 20–30 % of GCTs are of mixed type, containing various histological components in differing proportions (Fig. 1A). The most common combination is germinoma (Fig. 1B) with immature teratoma, although other histological types may also be present, albeit less frequently.

Mature Teratoma: Mature teratomas are composed entirely of well-differentiated somatic tissues derived from all three germ layers. These tumors minimal mitotic activity. Ectodermal derivatives include epidermis and neuroectoderm; mesodermal elements consist of muscle, bone, and adipose tissue; and endodermal components often form respiratory or enteric-type glandular structures. Rarely, fetiform organization or "fetus in fitu" may be observed. Expansion during therapy may reflect "growing teratoma syndrome," in which lesions consist solely of mature elements despite apparent clinical progression (Fig. 1C).

Immature Teratoma: Immature teratomas are characterized by the presence of incompletely differentiated, fetal-like tissues. Hallmark features include hypercellular, mitotically active stroma resembling embryonic mesenchyme, primitive neuroepithelial structures forming multilayered rosettes or canalicular arrays, and glands resembling fetal gut or respiratory epithelium. Retinal differentiation may be suggested by clefts lined with melanotic neuroepithelium. Immunohistochemically, these tumors reflect the profiles of their somatic counterparts. Retained SMARCB1 (INI1) expression helps distinguish immature teratomas from atypical teratoid/rhabdoid tumors, and the absence of C19MC amplification differentiates them from embryonal tumor with multilayered rosettes (Fig. 1D).

Teratoma with Somatic-Type Malignancy: Malignant transformation wuthin teratomas most frequently results in rhabdomyosarcoma or undifferentiated sarcoma, with less common occurrences of enteric-type adenocarcinoma and squamous cell carcinoma. Rare secondary malignancies include erythroleukemia, leiomyosarcoma, and carcinoid tumor. Primitive neuroepithelial neoplasms arising in CNS GCT-predilection sites may originate from teratomatous elements. Notably, yolk sac tumor components have been proposed as precursors in some cases of enteric-type

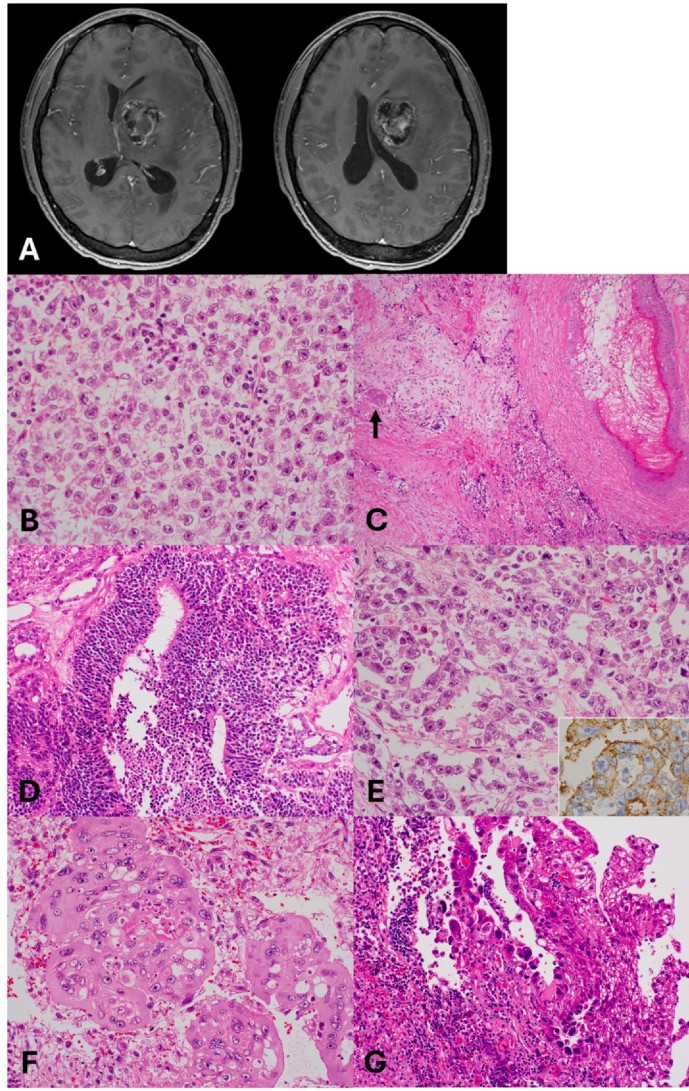

Fig. 1 T1-weighted contrast-enhanced MRI reveals a heterogeneous lesion with areas of strong enhancement in a case of mixed germ cell tumor [A]. The germinoma component exhibits large, round nuclei with rectangular, prominent nucleoli and clear cytoplasm, accompanied by interspersed lymphocytic infiltrates ("two-cell pattern") [B]. In addition to germinoma with syncytiotrophoblastic giant cells (arrow), mature teratoma elements are present, including a cyst lined by squamous epithelium [C]. Immature teratoma components contain undifferentiated neuroepithelium forming multilayered, neural tube–like structures [D]. The tumor also includes embryonal carcinoma cells showing pleomorphic epithelioid cells with large nuclei

(Continued)

adenocarcinomas. Importantly, cytological atypia alone is insufficient for the diagnosis of somatic-type malignancy, as atypia may also be observed in mature teratomas, particularly following therapy.

Embryonal Carcinoma: Embryonal carcinomas are composed of large epithelioid cells with vesicular nuclei, prominent nucleoli, and clear to violaceous cytoplasm, arranged in nests, sheets, or gland-like formations. Mitotic activity is high, and necrosis is common. Rarely, embryoid bodies may be present. Immunohistochemically, these tumors demonstrate strong membranous CD30 positivity and express cytokeratin, OCT4, and SALL4, with frequent positivity for PLAP, LIN28A, and SOX2. KIT expression may be focal and non-membranous. AFP and β-hCG are typically negative (Fig. 1E).

Choriocarcinoma: Choriocarcinomas are composed of syncytiotrophoblasts and cytotrophoblasts, typically wihtin a background of hemorrhage and necrosis. Syncytiotrophoblasts demonstrate diffuse β-hCG positivity, while both cell types express cytokeratin. PLAP expression is variabe; KIT and OCT4 are negative. The biphasic trophoblastic architecture and immunoprofile are key diagnostic feaures (Fig. 1F).

Yolk Sac Tumor: Yolk sac tumors consist of primitive epithelial cells within a myxoid stroma. Architectural patterns include reticular, solid, papillary, and polyvesicular vitelline forms. Schiller–Duval bodies and PAS-positive hyaline globules are diagnostically helpful when present. Tumor cells express AFP, SALL4, GPC3, cytokeratins, and LIN28A, while OCT4 and KIT are typically absent or only focally positive without Golgi accentuation (Fig. 1G).

Mixed Germ Cell Tumor (MGCT): Mixed GCTs comprise combinations of the above subtypes. Accurate diagnosis requires identification and quantification of each histological component, as their immunophenotypes remain unchanged in mixed forms.

Immunohistochemistry SALL4 serves as a sensitive marker of cellular immaturity and is broadly positive across GCTs, including germinomas. It is typically negative in mature teratomas but shows limited positivity in immature components, such as primitive neuroepithelial structures within

Fig. 1—Cont'd and prominent nucleoli that are immunopositive for membranous CD30 (inset) [E]. Choriocarcinoma areas are characterized by extensive hemorrhage and a biphasic population of multinucleated syncytiotrophoblastic giant cells and mononuclear cytotrophoblasts [F]. Yolk sac tumor components consist of epithelioid cells with marked nuclear atypia and a characteristic loosely organized histoarchitecture [G].

Table 1 Summary of immunohistochemical marker expression across histological subtypes*.

	KIT	Beta HCG	AFP	PLAP	OCT4	CD30	SALL4
Germinoma	+	+*	−	+	+	−	+
Mature teratoma	−	−	−	±	−	−	−
Immature teratoma	±	±	±	−	−	−	±
Yolk sac tumor	±	−	+	±	−	−	+
Choriocarcinoma	−	+	−	±	−	−	−
Embryonal carcinoma	±	−	±	±	+	+	+

*Positive in intermingled syncytiotrophoblasts.

immature teratomas. KIT expression is generally restricted to germinomas, though focal or weak expression can occasionally be seen in NGGCTs. Accurate diagnosis requires the integration of multiple immunohistochemical markers. OCT4, podoplanin (D2-40), and Nanog are also markers of cellular immaturity and are positive in both germinomas and embryonal carcinomas. While these entities often have distinctive morphologies, use of these markers is especially valuable in diagnostically challenging cases. CD30 is a highly reliable and indispensable marker for embryonal carcinoma. With respect to β-hCG, germinoma cells are typically negative, with staining restricted to syncytiotrophoblastic giant cells (STGCs). Therefore, the diagnosis of choriocarcinoma necessitates integration with histomorphological assessment, identifying both syncytiotrophoblastic and cytotrophoblastic components reflective of extraembryonic chorionic differentiation. PLAP has traditionally been employed in GCT diagnostics; however, due to its limited specificity, its use in routine diagnostic practice has been less frequent (Table 1).

3. Treatment strategy

3.1 Initial management and biopsy strategy

Pineal region tumors often cause obstructive hydrocephalus and therefore require prompt management (see Surgery section for details). If endocrine dysfunction is present, appropriate treatment should also be initiated.

Tumor markers should be evaluated in both serum and CSF. The need for surgical tissue sampling should be considered on a case-by-case basis, as a diagnosis can often be made clinically when tumor markers are markedly elevated.

3.2 Chemotherapy and radiation therapy

NGGCTs are known to be less sensitive to radiation and chemotherapy compared to germinomas, and treatment with either modality alone is generally insufficient (Balmaceda et al., 1996; Baranzelli et al., 1998; Fuller et al., 1994). Therefore, a combined approach using both radiation and chemotherapy is required. The standard strategy is to initiate treatment with chemotherapy to achieve complete remission (CR), followed by radiation therapy. The intensity of chemotherapy and the dose and field of radiation therapy vary significantly depending on whether the tumor is a germinoma or an NGGCT, as well as on whether the disease is localized or disseminated. Furthermore, the management of NGGCTs remains highly diverse worldwide (Table 2) (Abu Arja et al., 2019; Breen et al., 2017; Hong et al., 2022; Nakamura et al., 2022). In contrast, mature teratomas can be completely cured through surgical resection or, potentially, stereotactic radiosurgery (Franzini et al., 2021; Noudel et al., 2008). Residual tumor, however, almost invariably leads to regrowth.

In North America, the COG ACNS0122 trial was a single-arm phase 2 study evaluating the response to alternating cycles of carboplatin + etoposide and ifosfamide + etoposide chemotherapy. Patients who achieved a complete response CR proceeded to craniospinal irradiation (CSI) to 36 Gy and a focal boost to the tumor bed of 54 Gy, while those who did not achieve CR underwent second-look surgery. After chemotherapy, 69 % of patients achieved either CR or partial response (PR). With a median follow-up of 5.1 years, the 5-year event-free survival (EFS) and overall survival (OS) were 84 ± 4 % and 93 ± 3 %, respectively (Goldman et al., 2015). This chemotherapy backbone was carried forward into subsequent trials. The COG ACNS1123 (Stratum 1) trial employed the same chemotherapy regimen, followed by whole-ventricular irradiation (30.6 Gy) and local irradiation (23.4 Gy) for cases in CR or PR, including those undergoing second-look surgery. The three-year progression-free survival (PFS) rate was 88 ± 4 %, and the three-year OS rate was 92 ± 3 % (Fangusaro et al., 2019). However, due to a high incidence of spinal relapse, the trial was prematurely terminated. Based on these findings, the subsequent COG ACNS2021 trial adopted a revised strategy: patients

Table 2 Summary of past and ongoing interventional trial for patients with non-germinomatous germ cell tumors.

Study	Year	N	Chemotherapy	RT	Outcome
Japanese trial	95–03	66	3 Cycles: Carboplatin + Etoposide (intermediate prognosis group) 3 Cycles: Ifosfamide + Cisplatin + Etoposide (poor prognosis group)	WVI 30 Gy + boost 20 Gy (intermediate prognosis group) CSI 30 Gy + boost 30 Gy (poor prognosis group)	5y-EFS 84 %; 5y-OS 92 % (intermediate prognosis group) 5y-EFS 61 %; 5y-OS 61 % (poor prognosis group)
SIOP CNS GCT−96	96−05	149	4 Cycles: Cisplatin + Etoposide + Ifosfamide	Focal 54 Gy (localized) CSI 30 Gy + boost 24 Gy (disseminated)	5y-PFS 72 %; 5y-OS 82 % (localized) 5y-PFS 68 %; 5y-OS 75 % (disseminated)
COG ACNS0122	04−08	102	3 Cycles: Carboplatin + Etoposide with Ifosfamide + Etoposide	CSI 36 Gy + boost 18 Gy (CR/PR to chemotherapy w/or w/o second-look surgery)	5y-EFS 84 %; 5y-OS 93 %
SIOP CNS GCTII	12−18	89	4 Cycles: Cisplatin + Etoposide + Ifosfamide (standard risk) 4 Cycles: Cisplatin + Etoposide + Ifosfamide (higher dose) (high risk)	Focal 54 Gy (localized) CSI 30 Gy + boost 24 Gy (disseminated)	Results pending
COG ACNS1123 (stratum 1)	12−16	107 (Localized)	3 Cycles: Carboplatin + Etoposide with Ifosfamide + Etoposide	WVI 30.6 Gy + boost 23.4 Gy (CR/PR to chemotherapy w/or w/o second-look surgery)	3y-EFS 88 %; 3y-OS 92 %

achieving tumor marker normalization and CR or PR following chemotherapy receive whole-ventricular irradiation (30.6 Gy), plus whole-spinal irradiation (30.6 Gy), and a focal tumor boost (23.4 Gy). For cases that do not meet these criteria but are not classified as progressive disease (PD), high-dose chemotherapy (HDC) with thiotepa and etoposide is administered. Patient enrollment began in 2021 and is expected to continue until 2029.

In Europe, in the SIOP CNS GCT-96 trial, 149 patients with NGGCT were treated with a chemotherapy regimen consisting of cisplatin, etoposide, and ifosfamide ("PEI" chemotherapy regimen). Patients with localized disease received local irradiation of 54 Gy, while those with disseminated disease received CSI of 30 Gy with a local boost of 24 Gy. The 5-year PFS and OS rates were 72 ± 4 % and 82 ± 4 %, respectively, for localized disease, and 68 ± 9 % and 75 ± 8 %, respectively, for disseminated disease. Among the 41 relapses in the local irradiation group, 24 were local recurrences, 5 were distant, and 8 involved both local and distant recurrence (Calaminus et al., 2017). The following study, SIOP CNS GCTII trial, utilized the same chemotherapy regimen. For localized tumors, local irradiation (54 Gy) was applied, whereas disseminated disease was treated with CSI (30 Gy) and focal tumor boost (24 Gy). High-risk patients, defined as those under six years of age or with AFP > 1000 ng/mL, receive an intensified "HyperPEI" regimen incorporating peripheral blood stem cell transplantation alongside dose-intensified cisplatin, etoposide, and ifosfamide. The trial is currently in the follow-up phase. As a preliminary report, the 3-year EFS was 63 % for localized disease and 94 % for metastatic disease. While investigating the relapse pattern in localized disease is important, a wider radiation field may be necessary for localized NGGCTs.

In Japan, treatment had been stratified by classifying tumors into two categories: intermediate-prognosis group and poor prognosis group. Intermediate prognosis group included immature teratomas, as well as mixed GCTs with predominant components of germinomas and teratomas. Poor prognosis group included yolk sac tumors, embryonal carcinomas, choriocarcinomas, and mixed germ cell tumors in which these components predominate. For the intermediate prognosis group, treatment consisted of carboplatin and etoposide ("CARE" chemotherapy regimen) combined with whole-ventricular irradiation (23.4 Gy) and focal tumor boost (27 Gy). The poor prognosis group underwent a chemotherapy regimen of ifosfamide, cisplatin and etoposide ("ICE" chemotherapy

regimen) in combination with CSI (30.6 Gy) and focal tumor boost (30.6 Gy). The 10-year EFS rates for intermediate and poor prognosis group were 76 % and 49 %, respectively, while the 20-year EFS rates were 66 % and 49 %. Similarly, the 10-year OS rates for these groups were 87 % and 61 %, respectively, and the 20-year OS rates were 70 % and 53 % (Takami et al., 2024). The ongoing CNSGCT2021 phase II trial is evaluating a chemotherapy regimen consisting of cyclophosphamide, cisplatin and etoposide("PEC" chemotherapy regimen), which compares two randomized treatment arms: one with CSI (23.4 Gy) and focal tumor boost (30.6 Gy), and another with focal tumor boost (54 Gy) combined with intrathecal methotrexate therapy. In cases of residual tumors that are not completely resected, HDC using thiotepa and melphalan is administered for the latter arm patients. Tumor marker for this group is set at AFP levels ≥ 250 ng/mL or HCG levels ≥ 500 IU/L. The enrollment period is scheduled to continue until the end of June 2027, and the observation period is planned until the end of June 2032.

Approaches to treating immature teratomas are not standardized globally. In many countries, a consensus on optimal treatment is lacking. As these tumors often present with elevated AFP levels, they are frequently managed as NGGCTs. In Japan, they have traditionally classified as part of the intermediate prognosis group and treated with intermediate intensity chemoradiotherapy (Matsutani et al., 1997). It is important to note that immature teratomas are unlikely to be cured by surgery alone, as they have been shown to carry a prognosis comparable to NGGCTs with malignant components. Additionally, some studies have reported the efficacy of stereotactic radiotherapy in treating these tumors (Huang et al., 2009).

3.3 Surgery

In principle, surgical resection at the initial presentation is rarely performed unless histopathological diagnosis confirms a mature teratoma or there are debilitating symptoms or a life-threatening risk due to mass effect or intratumoral hemorrhage such as in choriocarcinoma. The primary goal of surgery is usually to achieve a definitive histopathological diagnosis in selected cases (Murray et al., 2015; Nakamura et al., 2022).

NGGCTs often occur in the pineal region. Patients frequently present with obstructive hydrocephalus and require external ventricular drainage or endoscopic third ventriculostomy. Ventriculoperitoneal shunt placement is not recommended, as it can lead to peritoneal dissemination (Back et al., 1997; Kurokawa et al., 2024). Using an endoscope, especially a flexible

endoscope, is often more feasible; third ventriculostomy and tumor biopsy in the pineal region can be achieved (Nakamura et al., 2022; Souweidane et al., 2010). When examining the ventricular cavity with an endoscope, disseminated nodules may sometimes be detected. During surgery, CSF should be collected for tumor marker analysis and cytological examination. However, CSF via lumbar puncture is still necessary, except if contra-indicated. For tumors in the neurohypophyseal region that extend into the third ventricle, an endoscopic biopsy may be feasible; however, a transnasal endoscopic biopsy should also be considered. In cases where tumors originate in the basal ganglia, cerebrum, or cerebellum, a stereotactic needle biopsy via burr hole should be considered. For brainstem lesions, an open biopsy is typically performed.

For NGGCTs, residual lesions following treatment have been identified as independent prognostic factors for both recurrence and survival (Calaminus et al., 2017). It is well known that residual disease significantly increases the risk of recurrence, highlighting the importance of achieving complete resection through "second-look surgery" whenever possible and safe.

3.4 Management of growing teratoma syndrome during NGGCT treatment

Growing teratoma syndrome (GTS) is characterized by tumor enlargement despite the normalization of tumor markers during or after chemotherapy and radiation therapy (Michaiel et al., 2020; Oya et al., 2014). This is not a recurrence but rather a phenomenon caused by the enlargement of the teratomatous component within a mixed GCT. Complete resection and pathological evaluation are necessary to confirm the diagnosis (Kim et al., 2011; Michaiel et al., 2020). GTS occurs in approximately 20 % of NGGCT cases, emphasizing the need for vigilant monitoring and timely surgical intervention.

3.5 Follow-up

GCTs require long-term follow-up. The Japanese clinical practice guidelines state that "long-term follow-up is strongly recommended whenever possible" (Nakamura et al., 2022). GCTs are known to recur even more than 20 years after initial treatment, and annual brain MRI follow-up and, if feasible, tumor marker monitoring, necessary (Takami et al., 2024). There is no clear evidence regarding the necessity of spinal MRI follow-up for cases with intracranial primary tumors. Additionally, long-term adverse

effects—such as vascular disorders, secondary malignancies, meningiomas, and cavernous hemangiomas—increase over time following chemotherapy and radiotherapy (Choudhary et al., 2006; Doyle & Einhorn, 2008; Pettorini et al., 2008; Sawamura et al., 1998). The incidence of these late complications is reported to be approximately 6 % at 15 years and 11 % at 20 years (Takami et al., 2024). When GCTs develop in the neurohypophyseal region, they almost invariably cause endocrine dysfunction, necessitating lifelong hormone replacement therapy. Furthermore, the potential for radiation-induced cognitive impairment must be carefully considered in treatment planning.

3.6 Relapse

Germinomas predominantly recur as germinomas, but in rare cases, they may recur as NGGCTs. Tumor marker testing is essential for detecting recurrence and estimating the histological subtype upon relapse (Fonseca et al., 2019). In cases of recurrent germinoma with elevated tumor markers, recurrence as an NGGCT should be suspected. During recurrence with tumor marker elevation, histopathological diagnosis via tissue sampling does not necessarily influence treatment decisions. The difference in pathological findings between initial and recurrent tumors likely reflects the histological diversity of GCTs and the pluripotency of their originating cells.

The prognosis after recurrence varies significantly depending on the initial diagnostic classification. In NGGCTs, a Japanese group study reported that two-year survival rates were markedly low, at 50 % in the intermediate prognosis group and 9 % in the poor prognosis group (Takami et al., 2024). Similarly, a European study showed dismal outcomes: the 5-year OS was 0 % for patients treated with standard dose chemotherapy and only 14 % for patients treated with HDC with autologous stem cell rescue (Murray et al., 2017).

The treatment of relapsed NGGCTs involves either curative-intent therapy or palliative care, depending on the clinical context. In a study from the United States, a combination of HDC with thiotepa and radiotherapy resulted in disease-free survival in 4 out of 12 patients, with a median survival of 35 months (Modak et al., 2004). Similarly, in the KSPNO S-530 trial conducted in South Korea, 4 out of 11 patients achieved a CR following HDC (Baek et al., 2013). In Europe, the SIOP CNS GCT-96 trial reported that among 32 patients, 3 out of 22 who received HDC survived for more than five years, whereas none of the 10 patients who received conventional chemotherapy survived beyond

five years (Murray et al., 2017). Additionally, a study from France analyzing 25 patients showed a five-year OS rate of 72 % in those who received HDC, compared to 29 % in those who did not (Callec et al., 2020). A systematic literature review analyzing 101 cases found that 48 % of patients who underwent HDC survived, whereas only 12 % of those who did not receive HDC survived. Furthermore, surgical resection and radiotherapy were not found to be significantly associated with survival outcomes (Abu-Arja et al., 2022).

These findings suggest that HDC offers a clear prognostic advantage over standard chemotherapy in the treatment of relapsed NGGCTs, making it an essential component of therapy (Bouffet, 2010). However, the role of additional radiation therapy remains controversial, as it depends on the initial treatment strategy, including the radiation field and dose, and the typically short interval to recurrence. To reduce the risk of relapse, more intensive initial treatment strategies should be considered. Furthermore, the development of effective therapeutic approaches for recurrent disease remains an urgent priority.

4. Tumor-specific biology

Currently, no advanced therapies targeting genetic mutations or genomic abnormalities, tumor immunotherapy, or Chimeric Antigen Receptor (CAR) T-cell therapy have been developed for CNS GCTs. Over the past decade, however, significant advancements have been made in understanding the pathogenesis of CNS GCTs through genomic and epigenomic analyses. The following sections provide an overview of the characteristic pathological features of CNS GCTs that have been elucidated in recent years.

4.1 Genomic abnormalities

Whole-exome and targeted sequencing studies have identified genetic mutations and copy number alterations in CNS GCTs. A 2014 U.S. study reported RTK/MAPK and MTOR/PI3K pathway alterations in 53 % of cases (Wang et al., 2014), while the iGCT Genome Analysis Consortium in Japan (2016) found RTK/MAPK mutations in 48 % and MTOR/PI3K mutations in 13 %, with mutual exclusivity (Ichimura et al., 2016).

Genetic alterations vary between germinomas and NGGCTs, with germinomas exhibiting higher RTK/MAPK pathway mutation rates

(70 % vs. 33 % in NGGCTs) (Ichimura et al., 2016). *KIT* mutations were the most frequent (~40 %), prompting investigations into targeted therapies. CNS GCTs also display frequent copy number alterations, notably gains in 1q, 12p, 21q, and X and loss of 13q (Fukushima et al., 2014; Schulte et al., 2016). Copy number alteration is more obvious in NGGCTs compared with germinomas. Especially 12p gain, the most common copy number alteration in GCTs, which contains *KRAS*, is more commonly found in NGGCT, up to 50 % of the cases. Especially this copy number alteration is more commonly found in NGGCT with malignant components, such as yolk sac tumor, choriocarcinoma and embryonal carcinoma, and the presence of this copy number alteration showed more unfavorable prognosis than those without, which shows that 12p gain can be a poor prognosis factor (Satomi et al., 2022).

A study on testicular GCTs reported that 3p25.3 gain is associated with cisplatin resistance and serves as a prognostic factor for poor outcomes (Timmerman et al., 2022). Following this finding, an analysis was conducted on CNS GCTs, where 3p25.3 gain was detected in 6.2 % of cases, exclusively in NGGCTs. It was mutually exclusive with *KIT* mutations, and in NGGCTs, cases with 3p25.3 gain had significantly shorter progression-free survival (Takami et al., 2023b). When considered alongside 12p gain, the presence of either aberration strongly suggested the presence of malignant components in GCTs, highlighting their potential value as prognostic markers.

Structural variant analyses using RNA sequencing have not identified recurrent fusion genes. However, ongoing studies employing whole-genome sequencing, non-coding region variant analysis, long-read sequencing, and transposon analysis aim to uncover additional genomic abnormalities and novel therapeutic targets. As pediatric brain tumors are often driven by a single genetic alteration, identifying mutations in cases without known abnormalities remains a key research focus.

4.2 Cellular origins and differentiation

Transcriptome analysis has revealed distinct gene expression profiles between germinomas and NGGCTs. Germinomas exhibit high expression of genes related to meiosis and mitosis, —such as *POU5F1*, *KLF4*, and *DAZL*—resembling immature embryonic cells. In contrast, NGGCTs show enriched expression of genes involved in tissue differentiation, organogenesis and somitogenesis, as well as Wnt/β-catenin signaling, invasiveness and epithelial-mesenchymal transition (Takami et al., 2022b;

Wang et al., 2010). Comparisons with embryonic cells indicate that germinomas share similarities with primordial germ cells (PGCs), including spermatogonia and oogonia. NGGCTs exhibit gene expression patterns akin to differentiated embryonic stem cells, suggesting that both tumor types originate from a common, fully pluripotent early developmental cell.

4.3 Epigenetic features and tumorigenesis

DNA methylation clearly distinguishes germinomas from NGGCTs. While germinomas exhibit global hypomethylation, NGGCTs display a somatic-type methylation pattern. Global hypomethylation in germinomas is thought to reflect a hallmark of PGCs during early fetal development. This supports the hypothesis that germinomas arise from mis-migrated PGCs that fail to undergo apoptosis. PGCs arise from epiblast-derived cells in the yolk sac during the third week of embryogenesis, migrating via the hindgut to the gonadal ridges. Failure to reach the gonads or to undergo apoptosis may contribute to the formation of CNS GCTs (Oosterhuis & Looijenga, 2019). While PGCs differentiate upon reaching the gonads, they retain their pluripotency during migration, which explains the histological heterogeneity of CNS GCTs. The higher methylation profile in NGGCTs is thought to reflect their differentiation into various tissues and organs. Approximately 30 % of CNS GCTs are mixed GCTs, comprising both germinoma and NGGCT components. Microdissection studies reveal that these components share genetic mutations and copy number alterations, yet they exhibit distinct methylation patterns: germinomas are hypomethylated, whereas NGGCTs are hypermethylated (Fukushima et al., 2017). These findings suggest that all components originate from a common precursor—a fully pluripotent early PGC—and undergo tumorigenesis through genetic alterations. Subsequent epigenetic divergence drives differentiation into distinct histological subtypes.

MicroRNAs from the miR-371a-373p and miR-302/367 clusters are characteristic of GCTs and have the potential to serve as alternative tumor markers for early detection, as well as indicators of disease status during and after treatment (Murray et al., 2020).

4.4 Comparison with testicular germ cell tumors

CNS GCTs and testicular GCTs are thought to arise from a common cell of origin—PGCs. Testicular GCTs are classified as gonadal GCTs, whereas CNS GCTs are considered a type of extragonadal GCT. Comparative genomic analyses have shown that germinomas and seminomas share similar global hypomethylation, reinforcing their common origin from

PGC. In contrast, NGGCTs and non-seminomatous testicular tumors ehibit distinct set of molecular features, including differential methylation profiles, indicating shared biological characteristics. Furthermore, both CNS and testicular GCTs display recurrent mutations in the RTK/MAPK and MTOR/PI3K pathways, and they share similar patterns of copy number alterations. These findings suggest that GCTs represent a single molecular tumor entity across anatomical locations, raising the possibility of site-agnostic treatment strategies.

Despite these molecular similarities, testicular GCTs show more prominent copy number alterations, present at a later age (typically in the 20 s to 30 s), are more common in Nordic populations, and more frequently display non-seminomatous histology—features that contrast with those of CNS GCTs (Bosl & Motzer, 1997). These phenotypic differences underscore the need to further investigate the biological distinctions between GCTs at different sites, which may offer insights into disease mechanisms and inform tailored therapeutic approaches.

4.5 Genetic factors underlying ethnic differences in CNS GCT incidence

Genome-wide association studies (GWAS) have identified 44 risk-associated single nucleotide polymorphisms (SNPs) for testicular GCTs (Litchfield et al., 2017). In 2022, a study identified a four-nucleotide deletion in the enhancer region of the *BAK1* (BCL-2-antagonist/killer 1) as a significant risk factor for CNS GCTs, with an odds ratio of 2.46. This risk variant attenuates *BAK1* expression, a pro-apoptotic gene that is negatively regulated by the *KIT* pathway in GCTs. *BAK1* functions through *KITLG* (the ligand for *KIT*) to inhibit apoptosis in PGCs. A decrease in *BAK1* expression may impair the natural apoptotic elimination of ectopically migrated PGCs, thereby contributing to the development of CNS GCTs. Notably, this genetic variant is more prevalent in East Asian populations (49 %) than in European populations (20 %), potentially explaining the higher incidence of CNS GCTs in East Asia (Sonehara et al., 2022). Moreover, additional SNPs contributing to the risk of CNS GCTs are continuously being identified, and further discoveries are anticipated with increasing case numbers.

4.6 Future perspectives

With further advancements in GWAS, a deeper understanding of why GCTs are more prevalent in East Asia is expected. To achieve this,

broad international collaboration within East Asia, as well as with Western countries, is essential to facilitate analyses using larger and more diverse cohorts.

Several biological questions remain unanswered. The higher incidence in males raises the possibility of genomic abnormalities related to sex chromosomes, while the susceptibility during adolescence suggests that hormonal influences may act as a trigger. The predilection for the neurohypophyseal and pineal regions could be linked to the local microenvironment, or it may simply result from the mis-migration of PGCs. Additionally, the abundant presence of immune cells in germinomas raises the question of whether this reflects anti-tumor immunity or if these immune cells are merely coexisting with the tumor.

From a translational research perspective, further efforts are needed to identify genomic abnormalities that could serve as potential therapeutic targets. RNA in situ hybridization (RNA Scope) and immunohistochemical analyses have demonstrated PD-L1 expression in tumor cells and PD-1 expression in stromal immune cells in the majority of GCT cases (Takami et al., 2020). Additionally, gene expression analyses suggest a high infiltration of M2 macrophages in the stroma of non-germinomatous GCTs (Takami et al., 2022b). Based on these findings, immune checkpoint inhibitors (ICIs) may have therapeutic potential in these tumors. However, evidence supporting the efficacy of ICIs in brain tumors remains limited. Furthermore, clinical trials of ICIs in testicular GCTs have shown minimal treatment response in most cases. Thus, the effectiveness of ICIs may be restricted to specific tumor subtypes, such as choriocarcinoma, which exhibits particularly high PD-L1 expression.

GCTs primarily affect young individuals, and their management relies more on radiation therapy and chemotherapy than on surgical resection. With the exception of certain non-germinomatous subtypes, long-term survival is generally achievable. However, long-term treatment-related complications can pose significant challenges. Globally, current clinical trials are focused on reducing the burden of radiation therapy and chemotherapy while maintaining therapeutic efficacy. At the same time, there is growing momentum for the integration of targeted therapies, alongside ongoing genomic analyses aimed at identifying novel therapeutic targets. Significant advancements in both basic and clinical research over the next decade are highly anticipated.

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