CHAPTER EIGHT

# Germinoma: Presentation, Management, and Recent Advances

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## Abstract

Central Nervous System (CNS) germinomas are rare, malignant germ cell tumors that predominantly affect children, adolescents and young adults (AYA). These tumors are

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highly sensitive to irradiation and chemotherapy, making them one of the most curable intracranial malignancies. This review provides a comprehensive overview of germinoma, covering epidemiology, pathogenesis, clinical presentation, diagnostic approaches, treatment strategies, and long-term outcomes. We also discuss recent advances in molecular biology and their implications on future therapeutic developments.

## 1. Introduction

Germ cell tumors (GCTs) are a heterogeneous group of neoplasms that are hypothesized to arise from primordial germ cells (Göbel et al., 2000; Jennings et al., 1985). While they most commonly occur in the gonads, they can also develop in extragonadal sites, including the central nervous system (CNS). CNS GCTs are broadly classified into two categories: germinomas and non-germinomatous germ cell tumors (NGGCTs) (Louis et al., 2021). Germinomas account for approximately 60–70 % of all CNS GCTs, and will be the focus for this review.

Earlier studies on CNS germinomas classified these tumors as "atypical teratomas" due to their histological resemblance to gonadal GCTs (Russell, 1954, 1944; Friedman, 1947). Over time, advances in diagnostics and accumulation of clinical experience led to the recognition of germinomas as a distinct entity. Commonly arising from midline structures including the pineal gland and suprasellar region, and less commonly from the thalamus and basal ganglia, they are most frequently diagnosed in AYA (Jennings et al., 1985). Despite their malignant nature and propensity for dissemination, CNS germinomas are highly radio- and chemo-sensitive, with long-term survival rates exceeding 90 % when treated with appropriate therapy. Ongoing research aims to elucidate the mechanisms of oncogenesis, nature of the enriched immune responses, determine the lowest dose of radiation therapy (RT) that is essential for cure and refine treatment stratification in order to preserve survivors' quality of life.

## 2. Epidemiology and genetic predisposition

CNS GCTs are relatively uncommon in the Western hemisphere, with an estimated annual incidence of 0.08 cases per 100,000 population (Price et al., 2024). The median age at diagnosis of CNS GCT is 18 years, with majority of cases occurring in individuals aged 10–24 years (Fig. 1) (Gittleman et al., 2019). CNS germinomas can also occur in older adults, albeit less frequently. The pineal and suprasellar regions are the most

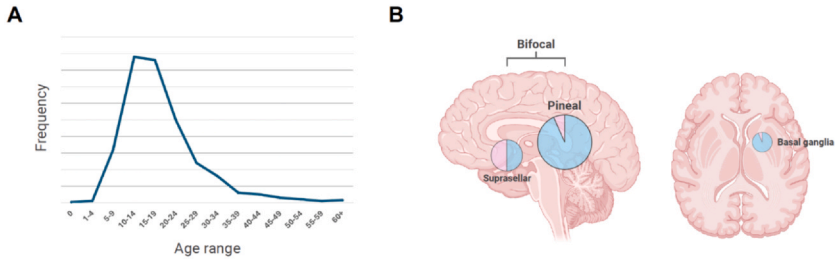


**Fig. 1** Distribution by (A) age of diagnosis, (B) tumor location and sex predilection (blue: male, pink: female; size of pie-charts proportionate to frequency) for patients with CNS germinomas. Overall male preponderance is observed in tumors from the pineal region and basal ganglia, with the latter being enriched in patients of East Asian descent.

common sites of origin, accounting for approximately 80–90 % of cases. Occasionally, germinomas can arise in the basal ganglia, thalamus, or other CNS locations. They exhibit a strong predilection for males, with a male-to-female ratio of around 3:1, with such preponderance restricted largely to tumors of pineal and basal ganglial origins.

The incidence of CNS GCTs varies geographically, with higher rates reported in East Asia compared to Western countries. Reports from Japan, Korea, Mainland China, Taiwan, and Hong Kong have described that CNS GCTs account for 8–15 % of all pediatric CNS tumors, with non-midline tumors being disproportionately high (~20 %) (Takami et al., 2020a; Makino et al., 2014; Lee et al., 2017; Zhou et al., 2008; Wong et al., 2005; Liu et al., 2020). Within the CBTRUS dataset of the United States, incidence of CNS GCT remained to be the highest in Asians and Pacific Islanders among all ethnic groups (Price et al., 2024). This disparity may be attributed to genetic factors, such as polymorphisms in genes involved in germ cell development, or environmental factors.

Indeed, germline variants involving *JMJD1C*, which codes for a histone demethylase and is a coactivator of the androgen receptor, and polymorphism altering the expression of *BAK1*, have been demonstrated to be enriched in Japanese cohorts of CNS GCT (Wang et al., 2014; Sonehara et al., 2022). Interestingly, CNS germinoma is the one of the most common solid tumors in patients with Down syndrome, where treatment toxicity represents a major concern, (Matsumura et al., 1998; Harris et al., 2022) it has also been reported in Klinefelter syndrome, (Bonouvrie et al., 2020) and anecdotally, Noonan, and Cornelia de Lange syndrome (Murray, 2024; Sato et al., 1986).

## 3. Clinical presentation

Presentation of CNS germinomas vary according to their anatomical locations and may mimic other neoplastic or non-neoplastic conditions. Patients with pineal region tumors present more acutely with features of increased intracranial pressure (ICP) due to obstruction of the aqueduct. Common symptoms include headache, nausea, vomiting, and papilledema. Patients may experience Parinaud's syndrome, characterized by upward gaze palsy, convergence-retraction nystagmus, and light-near dissociation of the pupils. Suprasellar germinomas typically present with endocrine dysfunction, including diabetes insipidus, growth hormone deficiency, and hypogonadism. Visual disturbance may also occur as these lesions become sizable leading to compression of the optic chiasm. Bifocal tumors refer to the co-existence of both pineal and suprasellar components, although the suprasellar lesion can be subtle or radiographically occult and may therefore be inferred by the presence of diabetes insipidus. Germinomas arising in the basal ganglia often present with hemiparesis, spasticity, cognitive impairment, and behavioral changes. Radiographically, hemiatrophy of the ipsilateral cerebral hemisphere and brainstem may be seen (Ozelame et al., 2006). Precocious puberty can occur due to pituitary stalk disruption, or as a result of human chorionic gonadotropin (HCG) secretion from the syncytiotrophoblastic component of the tumor (pseudo-precocious puberty). In non-pineal tumors, diagnostic delays are frequent, with symptoms that can predate the oncologic diagnosis for years (Bennett et al., 2024; Li et al., 2023). A high index of suspicion and early consideration of corresponding work-up to diagnose or exclude CNS GCT is warranted.

## 4. Pathogenesis

The pathogenesis of CNS germinomas remains incompletely understood. The germ cell theory hypothesizes that these tumors arise from primordial germ cells migrating from the yolk sac wall to the genital ridges during embryogenesis, when they become ectopically arrested in the CNS (Oosterhuis & Looijenga, 2019). Such postulation is supported by the commonly midline location for these tumors, their expression of primordial germ cell (PGC) antigens, phenotypic and molecular similarities to gonadal GCTs, as well as the global hypomethylation signature aligning with the pattern for migrating PGCs (Fukushima et al., 2017; Hoei-Hansen et al., 2006).

Alternative theories include the proposal of neural stem cells transforming into germinomas after cellular pluripotency maintained by OCT4 activation (Tan & Scotting, 2013).

Recent advances in molecular biology have shed light on the genetic drivers associated with CNS GCTs (Wang et al., 2014; Schulte et al., 2016; Li et al., 2024; Ichimura et al., 2016; Fukushima et al., 2014). Genome-wide sequencing studies have identified recurrent alterations in genes activating the MAPK/ERK and PI3K/AKT/mTOR signaling pathways, accompanied by chromosomal instability and frequent chromosomal copy-number aberrations (Fig. 2). Germinomas exhibit a particularly high frequency (60 %) of activating mutations in *KIT*, *KRAS*, and *NRAS*, as well as frequent coactivation of the PI3K/AKT/mTOR pathway members (*AKT1*, *AKT3*, *mTOR*), and/or loss of function mutation of the negative regulator *CBL* (Wang et al., 2014; Fukushima et al., 2014). In addition to mutations, *KIT* and *KRAS* are also activated *via* high level copy-number amplifications (Schulte et al., 2016; Li et al., 2024; Fukushima et al., 2014).

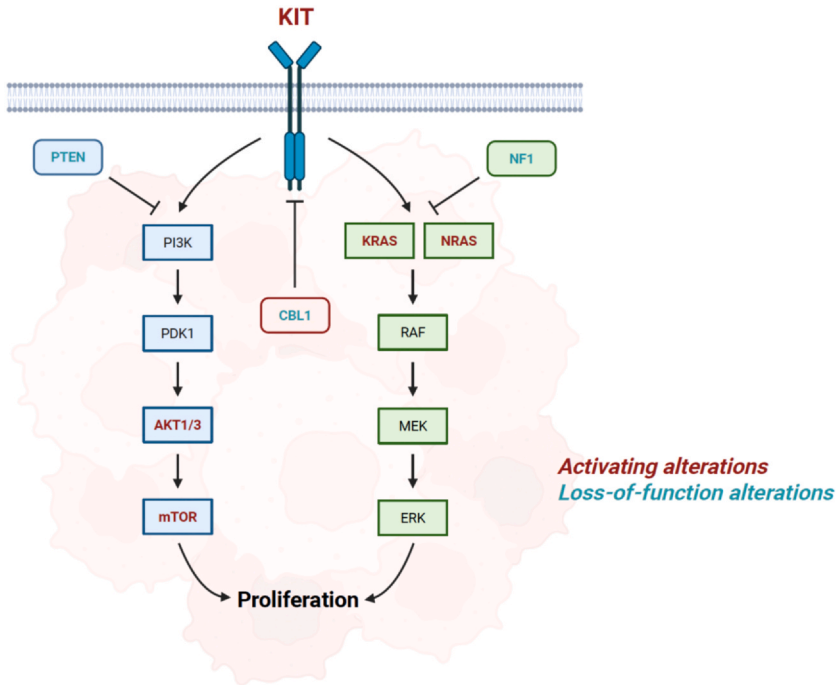


**Fig. 2** Molecular alteration driving tumorigenesis in patients with CNS germ cell tumors converges on the RAS/MAPK and PI3K/mTOR pathways.

Further to the resulting proliferative effects of pathway upregulation, persistent *KIT* expression may play a key role in enabling PGCs to evade apoptosis during embryogenesis (Runyan et al., 2006).

## 5. Histopathology

Macroscopically, germinomas are solid, tan-white, and friable tumors, with occasional focal cystic changes, and are usually infiltrative. Under the microscope, germinoma cells resemble seminomas or dysgerminomas from gonads, and are characterized by large, undifferentiated-looking cells that have round, vesicular, and centrally positioned nuclei with prominent nucleoli, and clear, wispy cytoplasm (Fig. 3). Tumor cells are disposed in sheets, lobules, or regimented cords and trabeculae, with variable mitosis. Germinomas are noted for their high immune infiltrates, with nests of lymphoplasmacytic, histiocytic, or even granulomatous reactions potentially obscuring neoplastic cells, sometime referred to as a "two-cell pattern"

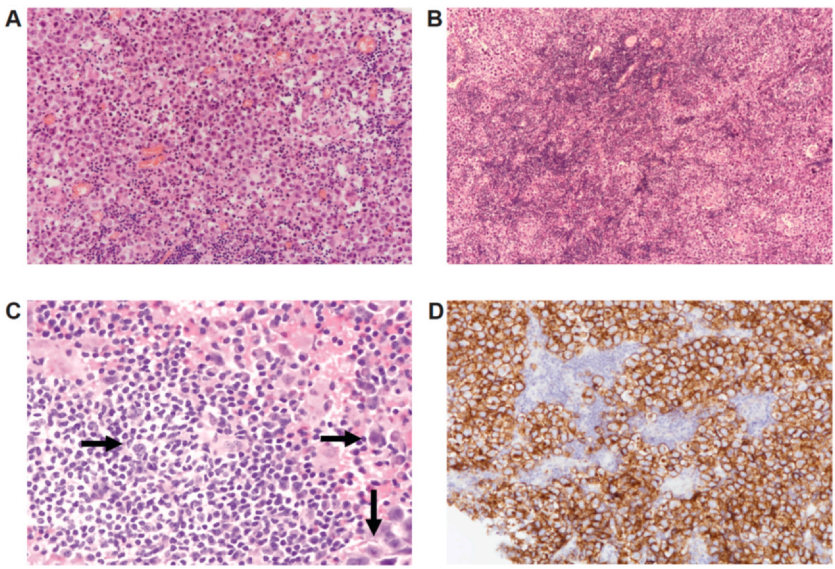


**Fig. 3** Typical histopathologic characteristics of germinoma. (A) H&E stained slides showing large germinomatous cells with clear cytoplasm. (B) Low-power field depicted the mix between tumor and immune cells. (C) Occasionally excessive immune infiltrates may obscure germinomatous cells (arrows). (D) c-Kit immunohistochemical staining highlighting tumor but not immune cells.

(Moon et al., 2005; Zapka et al., 2018). It is imperative that germinomatous cells be scoured for in specimens that would otherwise be considered as hypophysitis (Ghorbani et al., 2018; Pal et al., 2020). Moreover, studies have reported that extensive lymphocytic infiltration correlates with favorable prognosis (Takami et al., 2020b). Around one-fifth of germinomas harbor syncytiotrophoblastic giant cells (STGCs), (Takami et al., 2024) which are multinucleated syncytial atypical giant cells and account for the elevated HCG levels in these patients. Such cases are collectively termed HCG-producing germinomas. Germinoma can also present as part of a mixed GCT.

Immunophenotypically, germinomatous cells are immunoreactive to KIT/CD117 (membranous and golgian), OCT4 (nuclear), and PLAP, while negative for CD30 (embryonal carcinoma) and AFP (yolk sac tumor) (Gao et al., 2014). STGCs are stained positive for HCG (versus diffuse positivity in choriocarcinoma). The repertoire of immune infiltrates within germinomas include CD4+ and CD8+ T cells, B cells, plasma cells, histiocytes, and macrophages (Zapka et al., 2018; Takami et al., 2020b).

## 6. Diagnostic and staging evaluations

The diagnosis of CNS germinomas requires coordination of clinical evaluation, imaging studies, tumor marker analysis, and histopathological examination. Delineation from the non-germinomatous counterparts is key for treatment stratification and prognostication.

### 6.1 Neuroimaging

Majority of diagnoses are initially suspected based on abnormalities on neuroimaging. Patients who present with acute symptoms such as those attributed to raised ICP are often imaged with non-contrast computed tomography (CT). Sizable tumorous lesion with accompanying ventriculomegaly may be evident. Pineal germinomas can be associated with calcification in an engulfed pattern, in contrast to the exploded pattern in patients with pineal parenchymal tumors (Liu et al., 2024). Heavily calcified suprasellar lesions on the other hand are more commonly observed in craniopharyngiomas.

Contrast-enhanced magnetic resonance imaging (MRI) is the imaging modality of choice for evaluating and staging CNS lesions including germinomas (Osorio & Allen, 2015). Diffusion-weighted imaging are useful in assessing cellularity, while CISS or FIESTA sequences are particularly

relevant for the imaging of midline structures. On MRI, germinomas from the midline typically appear as well-defined, homogeneously enhancing masses, which may be associated with calcification (pineal) and/or cystic formation (Fig. 4). Loss of the posterior pituitary bright spot on T1-weighted images is associated with diabetes insipidus and can be an indicator of bifocality for patients with obvious pineal lesions, even without evident pituitary lesion. Basal ganglia and thalamic germinomas may present as more infiltrative lesions, that are possibly subtle, and with variable enhancement (Fig. 5). Cerebral atrophy of the ipsilateral side with prominence of sulci, as well as Wallerian degeneration resulting in asymmetry

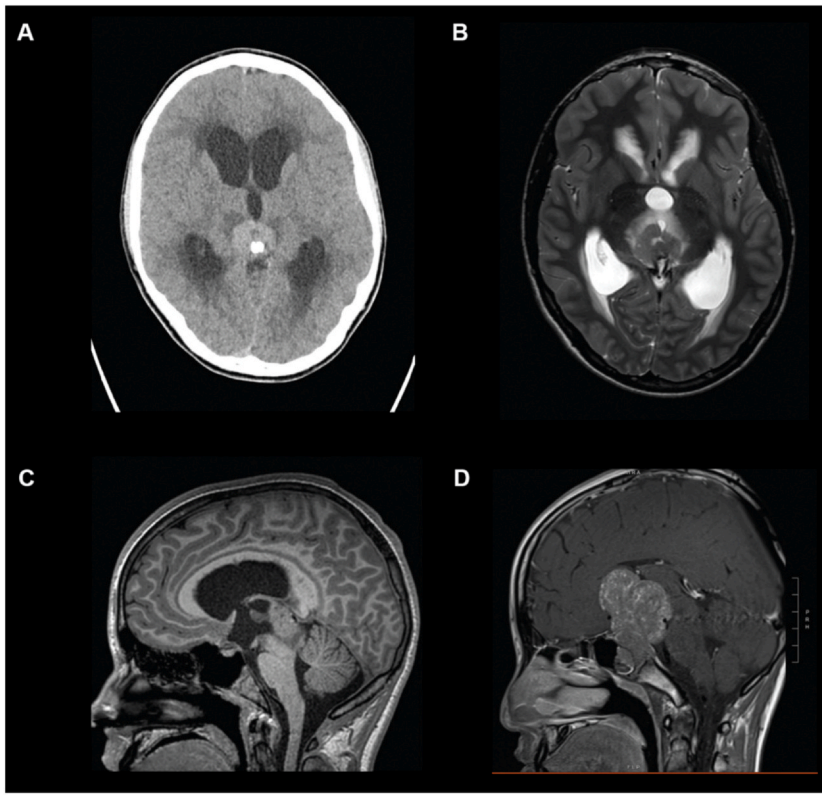


**Fig. 4** Radiographic features of midline CNS germinomas. (A) Plain CT scan for a patient with pineal germinoma showing typical "engulfed" pattern of calcification. (B) Axial section of MRI for the same patient depicted the pineal lesion and hydrocephalus. (C) Sagittal section in a patient with pineal germinoma after endoscopic third ventrculostomy. (D) Sagittal imaging for a patient with sizable suprasellar germinoma.

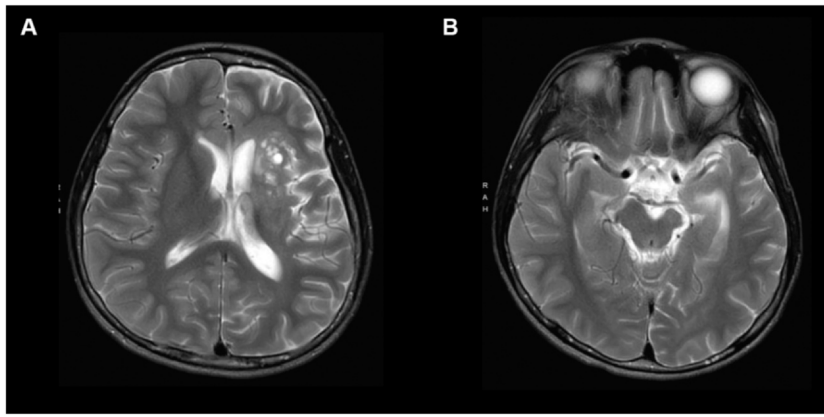


**Fig. 5** Magnetic resonance imaging of (A) left basal ganglia germinoma associated with ipsilateral cerebral hemiatrophy and (B) Wallerian degeneration of brainstem depicted by asymmetry at the midbrain level.

of the brainstem are supportive evidence of such atypically-located germinomas. Ventriculomegaly with transependymal edema can be observed in obstructive hydrocephalus or ventricular entrapment. The propensity of CNS germinomas to spread to the ventricular linings and leptomeninges mandates imaging of the whole brain and spinal cord as part of disease staging in all patients. Bifocal tumors without additional foci are not considered to be evidence of dissemination. Moreover, contiguous ventricular lesions with the primary lesion are not considered to be metastatic.

## 6.2 Tumor markers

Measurement of tumor markers in serum and cerebrospinal fluid (CSF), namely alpha-fetoprotein (AFP) and HCG, are integral to the diagnosis and surveillance for CNS GCTs. Pure germinomas are associated with normal AFP, and normal to mildly elevated HCG. CNS germinomas can be diagnosed without histology based on typical radiographic appearance and compatible HCG levels. Nonetheless, normal reference range for tumor markers varies among laboratories or sensitivity of assay, (Takami et al., 2015) and thresholds for calling germinoma *versus* NGGCT remain controversial. Proposed HCG cut-offs for the latter range from <50 IU/L (International Society of Paediatric Oncology [SIOP], Europe), to <100 IU/L (Children's Oncology Group [COG], North America and Australasia); (Calaminus et al., 2013; Bartels et al., 2022) and to <200 IU/L (Korean SMC-G13 trial and Brazil); whereas the multi-institutional Japanese study did not incorporate

HCG level as part of the diagnostic criteria (Takami et al., 2024; Lee et al., 2020; Cappellano et al., 2023). Raised AFP, which is seen in some patients with NGGCT, is defined as levels >10 ng/mL by COG, and >25 ng/mL by SIOP. Serum and CSF placental alkaline phosphatase (PLAP) levels are also elevated in patients with CNS germinomas, although the marker has not been widely utilized (Shinoda et al., 1988; Aihara et al., 2019).

### 6.3 Histopathologic and cytologic examination

Histopathologic examination is essential for confirming the diagnosis of CNS germinoma that are non-secreting. Typically, biopsy or limited resection is advocated due to the anticipated sensitivity of CNS germinoma to adjuvant therapy. Wider resections that may impact the patient's quality of life are discouraged. Tissue sampling can often be performed endoscopically, in conjunction with CSF diversion procedures if necessary. Microscopic features of germinoma have been described in the previous section. As part of tumor staging, CSF cytologic examination may reveal scattered fragments or individual large, pleomorphic and polygonal cells, featuring cytoplasm filled with vacuoles, enlarged oval-shaped nuclei, and noticeable nucleoli. The implications of positive CSF cytology will be discussed in the Treatment section. It is worth noting that a biopsy diagnostic of germinoma in the presence of elevated tumor markers beyond the HCG and AFP cutoffs can occur, given that a biopsy does not reflect the whole tumor, these patients should therefore be treated as NGGCT.

## 7. Treatment strategies

### 7.1 Emergency management

The objectives of initial management are to stabilize the patient while organizing relevant diagnostic investigations. When possible, patients should be transferred to a tertiary referral center for further treatment. As pineal region primaries often present with increased ICP, precautions to avoid transtentorial herniation, and prompt consultation with the Neurosurgical and Critical Care teams for CSF diversion procedures are important first steps. Although patients with suprasellar germinomas have more indolent symptomatology, adrenal insufficiency due to hypopituitarism, hypernatremia caused by adipsic diabetes insipidus or inadvertent fluid restriction, and refeeding syndrome related to extreme emaciation are examples of medical emergencies that may arise during the early phase of care. Hence, input from Endocrinology upfront is essential.

## 7.2 Surgery

Potential roles for neurosurgical intervention in patients with CNS germinomas include CSF diversion, diagnostic tissue acquisition, and resection of growing teratomas in those with mixed pathology (germinoma + mature teratoma). For the unstable patient, insertion of external ventricular drain (EVD) would allow rapid ICP stabilization. Definitive CSF diversion can be achieved *via* endoscopic third ventriculostomy (ETV), or insertion of ventriculoperitoneal shunt (VPS). If deemed feasible based on tumor anatomy, ETV is favored as it allows tumor biopsy to be performed during the same procedure, has possibly lower procedural complication rate than VPS, and does not carry the risk of peritoneal dissemination (Dewan et al., 2017). While surgery is indicated – even during or at the end of therapy – for growing teratoma syndrome from known or unsuspected teratomatous components, (Michaiel et al., 2020) second-look surgery for radiographic residual in a responding germinoma is not of prognostic relevance, and thus not recommended (Calaminus et al., 2013; Bartels et al., 2022). Second-look surgery is not indicated in germinoma except in the setting of increasing tumor size (indicative of growing teratoma syndrome) or rising tumor markers (indicative of a NGGCT component).

## 7.3 Adjuvant therapy

Up till the 1970s, post-operative radiotherapy has been the only adjuvant modality for the management of patients with CNS germinomas (Sung et al., 1978; Jenkin et al., 1978; Sano & Matsutani, 1981). With distant failures following focal radiation to patients with localized disease, craniospinal irradiation (CSI) has consequentially become standard therapy that resulted in cure for >90 % of patients with CNS germinoma (Calaminus et al., 2013; Maity et al., 2004; Bamberg et al., 1999). Despite the radiosensitivity of these tumors, use of CSI predisposes these young individuals to debilitating, long-term adverse effects, and aggravation of pre-treatment tumor-related morbidities. Neurocognitive impairments, endocrinopathies, vasculopathy, metabolic syndrome, and subsequent neoplasms are among the chronic health deficits that are more prevalent in this cohort of survivors. Analysis of the US SEER database indicated that survivors of germinoma treated between 1973 and 2005 experienced a 10-fold increase in mortality risk compared to their peers, in addition to a 59-fold increase in risk of stroke-related death, and a 25-year cumulative incidence of death due to subsequent malignancy of 6 % (Acharya et al., 2015). Similarly, long-term follow-up data from 111 CNS GCT

patients, including 74 with germinomas, treated in Japan between 1970 and 1995 indicate frequent late effects, and one-third of patient with performance score of less than 80. Sixty-eight percent of patients required hormone replacement therapy, and only one male patient was able to father children. More than one-fifth of patients demonstrated generalized or focal encephalomalacia, among which one-third had learning difficulties with IQ ranging from 65–83 (Sawamura et al., 1998).

In view of the morbidities and impact on quality of life after a radiation-only strategy, neoadjuvant chemotherapy was introduced during the 1980s in attempt to reduce the radiation dose and volume (Allen et al., 1987, 1994). CNS germinomas were proven to be exquisitely sensitive to cytotoxic agents, including monotherapy of carboplatin and cyclophosphamide. This inspired a multi-national clinical trial to evaluate the efficacy of a chemotherapy-only regimen, where patients with CNS GCTs were treated with six cycles of carboplatin, etoposide, bleomycin, with or without cyclophosphamide, and complete omission of radiotherapy (Balmaceda et al., 1996). While the complete response (CR) rate for patients with germinoma was 84 %, half of the patients eventually progressed. Such experience established chemotherapy and radiotherapy as indispensable components for germinoma therapy. Clinical studies over the subsequent quarter of century represented a global effort in attempt to determine the optimal intensity of therapy required for these patients (Table 1).

## 7.4 The European experience

While the German cooperative group-led study series GPOH-MAKEI83/86/89 adopted a CSI only approach for patients with CNS germinomas, it is of relevance that 4 out of 60 patients developed extra-CNS metastatic relapse, suggesting the role of chemotherapy in eradicating microscopic spread as such pattern of failure is rarely seen in current cohorts treated with chemo-irradiation (Bamberg et al., 1999). In 1990, the French cooperative group Société Française d'Oncologie Pédiatrique (SFOP) initiated a study where patients were treated with four induction cycles of chemotherapy (alternating between carboplatin+etoposide, and ifosfamide+etoposide), followed by focal RT (40 Gy) or CSI (25–30 Gy + 10 Gy boost) for patients with localized or metastatic disease respectively. While the overall outcome is encouraging with 3-year EFS of 96 %, all 10 patients with localized disease who relapsed failed with a periventricular (n = 8) or distant component (n = 2) (Bouffet et al., 1999; Alapetite et al., 2010). Such evidence for the inadequacy of focal RT for patients with localized

**Table 1** Summary of published interventional trial for patients with CNS germinoma.

| Study | Year | N | Chemotherapy | RT | Outcome |
|---|---|---|---|---|---|
| **GPOH MAKEI 83/86/89** | 83–93 | 60 | Nil | CSI + boost 83/86 (36 +14 Gy); 89 (30 +15 Gy) | 5y-RFS 91 %; 5y-OS 94 % *(4 patients with extra-CNS failure)* |
| **SFOP TGM-90** | 90–96 | 57 | 4 Cycles: carboplatin+etoposide alt ifosfamide + etoposide | Focal RT (40 Gy) for localized disease CSI 24 Gy + boost 16 Gy for metastatic disease | 3y-EFS 96 % 3y-OS 98 % *(All relapses for patients with localized disease with periventricular/ distant component)* |
| **Japanese phase II study** | 95–03 | 161 | 3 Cycles: carboplatin, etoposide | WVI 24 Gy | 5y-EFS 87 %, 10 y-EFS 82 %, 20y-EFS 73 % 5y-OS 98 %, 10 y-OS 97 %, 20y-OS 90 % |
| **POG 9530** | 97–99 | 12 | 4 Cycles: cisplatin, etoposide, cyclophosphamide, vincristine | Focal RT | 3y-EFS 92 % |

*(continued)*

**Table 1** Summary of published interventional trial for patients with CNS germinoma. (*cont'd*)

| Study | Year | N | Chemotherapy | RT | Outcome |
|---|---|---|---|---|---|
| **SIOP CNS-GCT 96 (2 arms, non-randomized)** | 96–05 | 125 | Nil | CSI | 5y-PFS: 97 % |
| | | 65 | 4 Cycles: carboplatin+etoposide alt ifosfamide + etoposide | Focal RT | 5y- PFS 88 % (p = 0.04) *(6/7 relapses in ventricles outside RT field)* |
| **COG ACNS0232 (2 arms, randomized)** | 07–09 | 10 | Nil | CSI 24 Gy + boost 21 Gy | 5y-EFS 89 % |
| | | 12 | 2 Cycles: carboplatin+etoposide, if not in CR, 2 additional cycles of cisplatin+cyclophosphamide | CSI 21 Gy + boost of 9 Gy | 5y-EFS 92 % |
| **COG ACNS1123 (B)** | 12–18 | 137 | 4 Cycles: carboplatin+etoposide response-adapted RT | WVI + boost (response adapted dosing) | 4y-EFS ~ 94 % |
| **SIOP CNS-GCT II** | 12–18 | 167 | 4 Cycles: carboplatin+etoposide *alt* ifosfamide+etoposide | WVI only (CR), + boost (< CR) (response adapted) | 4y-EFS 95–97 % |
| **Toronto protocol** | 00–21 | 46 | 4 Cycles: carboplatin+etoposide response-adapted RT | WVI/WBI/CSI, 24 Gy, no boost | 5y-PFS 91 %<br>5y-OS 100 % |

germinoma is supported by a similar observation from the first multinational European study, the SIOP CNS-GCT-96 protocol, where the GPOH and SFOP strategies were compared in a non-randomized fashion, with the CSI dose reduced to 24 Gy plus 16 Gy of boost in the RT-only arm for patients with localized disease (Calaminus et al., 2013). Inferior 5-year PFS was observed in the combined therapy arm (88 % vs 97 %), again, with most relapses after chemotherapy and focal RT occurring in the ventricles, confirming the necessity of whole ventricular irradiation (WVI). Patients with metastatic germinoma on this trial had a 5-year PFS of 98 % after 24 Gy of CSI and 16 Gy of boost, with or without induction chemotherapy (Calaminus et al., 2013).

These results informed the design of the succeeding SIOP CNS-GCT-II study, which recruited 194 patients between 2012 and 2018 (Calaminus et al., 2022). Patients with localized germinoma were treated with the same 4 cycle induction, followed by WVI of 24 Gy, with additional RT boost (16–30 Gy) reserved for patients who were not in CR after chemotherapy. Interim analysis suggested that 65 of 167 protocol patients achieved CR with chemotherapy, while the remaining patients had partial remission (n = 91), stable disease (n = 8), or progressive disease (n = 3). Four-year EFS rates for patients in CR and non-CR were 97 % and 95 % respectively, with 6/7 relapses representing local failures. Such results suggest 24 Gy of WVI suffice as consolidation for patients with localized germinoma achieving CR after induction chemotherapy.

## 7.5 The North American and Australian experience

The first national CNS GCT study in the United States was the then Pediatric Oncology Group (POG) 9530 trial, where patients with germinomas received alternating cisplatin+etoposide and vincristine+cyclophosphamide, consolidation was focal RT of 50.4 Gy for patients with localized disease, which was decreased to 30.6 Gy for patients who achieved CR (Kretschmar et al., 2007). Those with dissemination received added 23.4 Gy CSI if in CR, or 45 Gy to spine + 36 Gy neuraxis not in CR. For low-risk patients with pure germinoma, 11 of 12 children were progression-free at median 66 months (range, 61–73 months). One patient in CR after chemotherapy, whose parents refused RT, recurred at 10 months, then received craniospinal RT and was progression-free at 56 months.

The subsequent North American study, COG ACNS0232, which tested CSI alone versus chemotherapy followed by response-based CSI for newly-diagnosed primary CNS germinoma, closed early in 2009 due to

poor accrual (Shatara et al., 2024a). Between 2012 and 2018, the ensuing COG ACNS1123 study (Stratum 2) recruited 151 patients with germinoma from the US, Canada, and Australia (Bartels et al., 2022). Patients were treated with four cycles of carboplatin and etoposide, and were then assessed for response to receive either a reduced dose of WVI (18 Gy) + RT boost (12 Gy) in those in CR or had second-look surgery confirming absence of viable tumor, or a standard WVI (24 Gy) + RT boost (12 Gy) in those with a PR but no second-look surgery. Patients with less than a PR and no second-look surgery were removed from the study. Respective 3-year PFS were 94.5 % and 93.8 % the 18 Gy and 24 Gy WVI cohorts (two of four failures at biopsy/shunt track). While encouraging, this fell short of the pre-defined criteria for non-inferiority of 95 %, although such analysis could have been undermined by the conservative approach to define patients non-evaluable at 3 years as failures (6 patients were considered as failures despite being lost to follow up or withdrew consent). Besides, potentially toxicities from cisplatin or ifosfamide were effectively avoided by the ACNS1123 induction regimen.

In parallel, the Toronto group approached RT de-escalation by omitting primary tumor boost, akin to the European CNS-GCT-II strategy for localized germinoma in CR after induction (Foo et al., 2023). Notably, similar strategies have been employed in Japanese clinical trials since as early as 1995. Five-year PFS was 91 % and OS 100 %; 24 patients with midline tumors received WVI only and the two patients who failed relapsed outside of the RT field.

## 7.6 The East Asian experience

Key insights in the management of CNS germinoma could be garnered by the Japanese collaborative group experience, where more comprehensive tissue sampling upfront was historically favored (Takami et al., 2024). Based on histology and tumor-markers, CNS GCTs have been classified into three risk categories in an inaugural, Consortium-wide Phase II study that ran between 1995 and 2003. Patients with germinoma received three cycles of carboplatin+etoposide followed by extended local RT of 24 Gy (equivalent coverage to WVI other than the lower part of fourth ventricle), while germinomas with STGC received the same three cycles of induction, followed by 30 Gy extended local RT plus tumor bed boost 20 Gy, and five cycles of carboplatin+etoposide as maintenance. The 10- and 20-year EFS rates for patients with germinoma (with or without STGC) were 82 % and 73 %, respectively, while the corresponding OS rates were 97 % and

92 % - such mature data indicated that more than one-quarter of relapses occurred beyond 10 years from diagnosis, cautioning the need for continued surveillance for these salvageable events beyond the conventional five-year mark. No difference in survival was observed between patients with germinoma and those with germinoma and STGC, leading to the current strategy to include patients with germinoma and STGC as favorable-risk patients.

The prospective Korean trial SMC-G13 has also demonstrated excellent results when attempting to reduce RT dose. The induction regimen comprised four cycles of chemotherapy (carboplatin+etoposide alternating with cyclophosphamide+etoposide), whereas 18 Gy WVI and 12.6 Gy primary site boost was used regardless of response to induction. Among the 30 patients with localized disease, all remained event-free during a median follow-up of 3.4 (range, 0.3–7.0) years. In the SMC G-18 trial that is currently accruing, efficacy of further de-intensified RT prescription (10.8 Gy WVI + 10.8 Gy tumor bed boost for localized disease) will be evaluated after an induction regimen that is prolonged to six cycles.

## 7.7 Basal ganglia and metastatic germinoma

The strategy for treatment de-escalation is less studied for patients with basal ganglia, or metastatic germinoma (including patients with positive CSF cytology from lumbar puncture). Basal ganglia primaries were for example excluded from the COG ACNS1123 and SIOP CNS-GCT-II studies. The approach of radiation therapy for patients with basal ganglia primaries have been variable, ranging from focal, whole-ventricular, whole-brain, and to craniospinal irradiation. No statistical difference in outcome was observed based on RT prescription in an international multi-institutional study of 43 patients with localized, basal ganglia germinoma, describing 5-year EFS and OS of 86 % and 100 % respectively (Graham et al., 2021). From the aforementioned Japanese consortium study that included 20 patients with basal ganglia tumors, relapses occurred in patients with more restricted RT field (5/5 with focal RT, 4/12 with extended local RT, 0/3 with whole brain irradiation [WBI] failed), with 7/9 failures occurring outside of the RT field (Takami et al., 2024). The largest cohort of patients with basal ganglia tumors to date have been reported by Capital Medical University in China, where retrospective analysis of 161 patients with localized disease indicated superiority of WBI with tumor boost over focal RT (5-year disease free survival of 97 % vs 74 %), and similarly, failures after focal RT was documented either in the periventricular area or

frontal lobes (Li et al., 2021). Currently enrolling trials by the COG (ACNS2321) and Japanese consortium (CNSGCT2021) adopt WBI with or without boost for patients with basal ganglia primaries.

For patients with metastatic germinoma, CSI of 24 Gy with boost to metastatic deposits alone has been shown to be highly effective in the SIOP CNS-GCT-96 study (no relapse among 45 patients with metastatic disease), and represent the current standard of care (Calaminus et al., 2013). The Korean SMC-G13 trial included 11 patients with metastatic disease were treated with 18 Gy CSI and 12.6 Gy boost following chemotherapy, reporting one failure (Lee et al., 2020). Further approaches for safe dose-reduction with the use of induction regimen are being assessed prospectively in patients with metastatic germinoma. In the COG ACNS2321 study, patients are treated with response-adapted CSI (18–24 Gy) and 12 Gy boost following four cycles of carboplatin and etoposide.

### 7.8 Relapsed germinoma

Recurrent germinomas are treatable entities. Salvage regimens commonly include re-irradiation, with potential role of high-dose chemotherapy and stem cell rescue (Kanamori et al., 2023; Callec et al., 2020; Shatara et al., 2024b; Hu et al., 2012). Based on the SFOP and French National Registry experience, the 5-year EFS and OS for patients with histologically proven germinoma who relapsed were 79 % and 86 % respectively, with only one out of 11 patients relapsing after second RT (Callec et al., 2020). An earlier meta-analysis including 88 patients with recurrent germinomas from 13 studies demonstrated that 5-year survival rates after recurrence was 92.9 % for all patients receiving salvage CSI (Hu et al., 2012). While CSI is known to be an effective salvage strategy, it remains unclear whether WVI is an alternative, or whether high-dose chemotherapy can serve as a substitute for RT.

## 8. Recent advances and future directions

Current and planned clinical trials build on results from the past decades in formulating treatment protocols that are more encompassing and refined. The ongoing COG ACNS2321 study is currently enrolling patients with localized midline, basal ganglia/thalamic and metastatic germinoma, with response-adapted radiation prescription after four induction cycles of carboplatin and etoposide – where the best responders with

midline primaries will receive merely 12 Gy of WVI and 12 Gy of primary site boost. The Japanese CNSGCT-2021 trial randomizes patients with localized midline or basal ganglia tumors to receive 23.4 Gy *versus* 18 Gy of WVI or WBI respectively. In the United Kingdom, MonoGerm is a Phase II trial that investigates the feasibility of decreasing the intensity of chemotherapy, using vinblastine or carboplatin monotherapy (Kirton et al., 2024). Further studies may unveil novel therapeutic avenues that target the MAPK/ERK and PI3K/AKT/mTOR signaling pathways, or in leveraging the rich immune milieu of the tumor microenvironment. Development of CSF-based biomarkers, starting with microRNAs (miRNA) and then circulating tumor DNA (ctDNA), will enable a non-invasive approach for tumor classification, monitoring of tumor response, and detection of minimal residual disease (Nakano et al., 2024; Schönberger et al., 2023). Expression of serum and CSF miRNAs, namely miR-371a (−3p), miR-372–3p, miR367(−3p), and miR-302d-3p, were discriminatory between patients with CNS GCT and control (Schönberger et al., 2023). Furthermore, the analysis of CSF-derived cell-free DNA using low-pass whole genome sequencing has revealed a high detection rate of ctDNA (~90 %) in patients with CNS GCT, indicating its potential for non-invasive diagnosis and disease monitoring by tracking treatment responses and clarifying ambiguous imaging results (Nakano et al., 2024). The availability of such complementary markers can enhance the objectiveness in treatment stratification, allowing patients with good-risk disease to be managed with minimal risk of short and long-term toxicities.

## 9. Conclusion

CNS germinomas are highly curable malignancies that predominantly affect children and young adults. International efforts in conducting prospective multi-center studies have resulted in major progress in reducing long-term side effects surrounding the use of chemotherapy and RT. The minimum dose of WVI and the necessity of a tumor bed boost remain areas of active investigation. Similarly, the optimal RT dose following neoadjuvant chemotherapy for patients with metastatic and basal ganglia germinoma is still being studied. Ongoing research into the molecular biology of CNS germinomas, as well as development of novel biomarkers, are paving the way for development of more personalized approach for patient management.

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