

### Pediatric Central Nervous System Germ Cell Tumors: A Review

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#### LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the basic epidemiology of pediatric CNS GCTs.
2. Perform the diagnostic workup and full evaluation that is necessary when evaluating a patient with a suspected CNS GCT.
3. Select among the different therapeutic alternatives employed in treating children with a CNS GCT.

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#### ABSTRACT

Central nervous system (CNS) germ cell tumors (GCTs) represent approximately 3% of primary pediatric brain tumors and encompass a wide pathologic spectrum. CNS GCTs are most commonly located in the pineal and suprasellar regions of the brain and can be divided into major groups including germinomas and nongerminomatous GCTs (NGGCTs), with teratomas often considered a separate category. The clinical presentation varies by location and size, and it frequently includes endocrine abnormalities, visual changes, and signs of increased intracranial pressure. Neuroimaging studies cannot differentiate GCTs from other tumors, and therefore, the diagnosis usually requires histologic confirmation. The rare exceptions are the cases where characteristic elevations of tumor markers, including alpha-fetoprotein and/or  $\beta$ -human chorionic gonadotropin are documented in the serum and/or cerebrospinal

fluid. In these cases, the imaging findings along with the tumor marker elevation may be diagnostic in themselves without the need for tissue confirmation.

Treatment and prognosis differ greatly between groups. Germinomas have a superior prognosis than NGGCTs. Five-year overall survival rates >90% were reported initially with the use of craniospinal irradiation. More recently, the use of chemotherapy in addition to radiation therapy has afforded the ability to decrease the dose and volume of radiation therapy without affecting survival rates. NGGCTs are less radiosensitive than germinomas, but the use of adjuvant chemotherapy has improved survival rates in this group as well. The standard management for CNS GCTs remains controversial. Treatment regimens aimed to improve progression-free and overall survival times are ongoing. *The Oncologist* 2008;13:690–699

## INTRODUCTION

Malignant germ cell tumors (GCTs) represent approximately 3% of neoplasms reported in children's cancer registries [1]. The distribution of GCTs with regard to tumor site and histology varies with age. Mature and immature teratomas predominate in the neonatal period followed by an increased proportion of malignant tumors with the onset of puberty. Primary central nervous system (CNS) GCTs share histologic, genetic, and therapeutic similarities to extracranial GCTs. Based on the histologic components and the variable degree of differentiation, the classification of GCTs has classically been divided into germinomas and nongerminomatous germ cell tumors (NGGCTs). Germinomas account for approximately 50%–70% of cases and NGGCTs make up the remaining third [2, 3]. NGGCTs include choriocarcinomas, endodermal sinus tumors (yolk sac tumors), embryonal carcinomas, and mixed tumors. Mixed tumors are a common variant that have areas of more than one type of histology.

Patients with intracranial GCTs often present with clinical features related to the tumor's location and size. These findings most frequently include endocrine abnormalities, signs of increased intracranial pressure, and visual changes. Adequate staging and deciphering the histology of CNS GCTs are important factors used to properly stratify patients into appropriate treatment groups [4]. Historically, surgical management has been limited by tumor location, and standard treatment consisted of craniospinal irradiation (CSI). Over the last two decades, however, advances in diagnostic imaging, surgical techniques, radiation techniques, and chemotherapy have led to drastic improvements in the prognosis of malignant GCTs, especially pure germinomas.

For the purposes of this review, we focus on the epidemiology, pathology diagnosis, classification, molecular features, current management, and new therapeutic approaches for CNS GCTs.

## EPIDEMIOLOGY

CNS GCTs represent a rare heterogeneous group of lesions that commonly arise from the pineal and/or suprasellar regions in patients of all ages. The incidence of intracranial GCTs varies significantly according to geography. In Western countries, they account for 0.4%–3.4% of all pediatric CNS tumors [2], while series from Japan and other Asian countries have reported that CNS GCTs account for up to 11% of all pediatric brain tumors [2, 5–7]. CNS GCTs occur most commonly in the young population, with approximately 90% of cases occurring in patients before the age of 20 years old. The peak incidence for CNS GCTs is 10–12 years of age. This peak in incidence can be separated by his-

tology, with most NGGCTs occurring in younger children whereas pure germinomas are more commonly seen in older patients [2]. Incidences by location also have specific trends based on gender. In males, 70% of tumors occur in the pineal region, and in females, 75% of tumors are suprasellar [2]. There is an overall male predominance in CNS GCTs. In patients with NGGCTs there is an estimated male-to-female ratio of 3:1, whereas in germinomas the trend is less striking with an estimated ratio of 1.8:1 [2, 8].

CNS GCTs can arise as a solitary nodule or multiple lesions. The pineal region to suprasellar ratio is approximately 2:1, but about 5%–10% of patients have both suprasellar and pineal gland involvement at the time of diagnosis. These so-called “doublet lesions” are most commonly pure germinomas [2, 9]. Other areas that may be involved less commonly include the basal ganglia, ventricles, thalamus, cerebral hemispheres, and medulla oblongata [10]. In Asian countries, however, where the overall incidence of CNS GCTs is greater than in the U.S., tumors are more frequently seen in these locations [10–12].

## PATHOLOGY

### Etiology

The multiple histologic subtypes of GCTs are presumed to share a common cell of origin, and several theories have been proposed to explain this. Teilum's “germ cell theory” proposes that extragonadal GCTs arise from primordial germ cells that have migrated aberrantly during embryonic development and then undergo malignant transformation [13–15]. An alternative theory is the “embryonic cell theory,” which suggests that a mismigrational pluripotent embryonic cell gives rise to GCTs [13]. Sano and colleagues suggested that pure germinomas are the only tumors that truly arise from germ cells, and other GCTs develop secondary to misfolding and misplacement of embryonic cells into the lateral mesoderm causing these cells to become entrapped in different brain regions [13, 14, 16].

### Molecular Biology

The data obtained from conventional cytogenetic analysis thus far do not allow decisive conclusions to be drawn concerning the meaning of molecular and cytogenetic changes associated with GCTs. Most of the available data are extrapolated from extracranial GCTs, but data do support the idea that GCTs may arise from germinal elements at differing stages of development. Isochrome 12 p (i (12p)) is found in about 80% of malignant testicular GCTs in young adults, and the duplication of the short arm of chromosome 12 (i12p) is the most common anomaly described in adult-onset extragonadal germinomas [17–19].

There are only limited data regarding cytogenetic patterns of CNS GCTs. Analyses of CNS teratoma, for example, have shown a high frequency of sex chromosome abnormalities, most commonly increased copies of the X chromosome. In the pediatric population, a gain of chromosomal material at 12p has been described in a small percentage of pineal region tumors as well [8, 20]. Recently, chromosomal comparative genomic hybridization analysis of CNS GCTs was used to compare those GCTs from gonadal and non-CNS extragonadal sites, and the results suggested that the genomic alterations in CNS GCTs are almost indistinguishable from their extracranial counterparts [21].

In children <4 years old, CNS GCTs that arise from gonadal and extragonadal sites are histologically, clinically, and genetically very similar. Recurring cytogenetic abnormalities commonly seen involve loss of 1p and 6q, alterations in the sex chromosomes, and, rarely, abnormalities of 12p [22, 23]. In situ hybridization studies have demonstrated a deletion of 1p36 in 80%–100% of infantile malignant GCTs arising from testicular and extragonadal sites. A minority of tumors also show evidence for C-myc or N-myc amplification. The clinical significance for these findings is not yet entirely known [23].

### Classification

Most commonly, CNS GCTs have been classified using the World Health Organization classification system (Table 1) [24]. This system is based on histology, the presence or absence of tumor markers on the tumor cells, and the associated protein markers secreted by the tumor cells. These secreted markers can be measured in both serum and cerebrospinal fluid (CSF), though CSF levels are a more sensitive and reliable measure for diagnosis. The most common markers are alpha-fetoprotein (AFP) and  $\beta$ -human chorionic gonadotropin ( $\beta$ -HCG), but placental alkaline phosphatase and the soluble isoform of c-Kit may become clinically relevant in the future [25, 26]. Variations in tumor markers help define CNS GCT subtypes as shown in Table 2 [24].

Histologically, germinomas are composed of undifferentiated large cells that resemble primordial germinal elements with abundant cytoplasm arranged in nests separated by bands of connective tissue. The histologic characteristics of NGGCTs vary by primary diagnosis. Embryonal carcinomas are composed of large cells with a high mitotic index that proliferate in cohesive nests and sheets demonstrating zones of coagulative necrosis. Choriocarcinomas are characterized by extraembryonic differentiation along trophoblastic lines with  $\beta$ -HCG-secreting syncytiotrophoblasts. Finally, endodermal sinus tumors are composed of primitive-appearing epithelial cells linked to extraembry-

**Table 1.** World Health Organization classification of intracranial germ cell tumors

Germ cell tumors	
Germinomas	
Nongerminomatous germ cell tumors	
Embryonal carcinoma	
Yolk sac tumor	
Choriocarcinoma	
Teratoma	
Bening teratomas	
Immature <sup>a</sup>	
Mature	
Teratoma with malignant transformation	
Mixed germ cell tumors	

<sup>a</sup>May contain rare malignant germ cell elements.  
From: Louis DN, Ohgaki H, Wiestler O et al., eds. WHO Classification of Tumours of the Central Nervous System, Third Edition. Albany, NY: WHO Publication Center, 2007:197–204.

**Table 2.** Classification of GCTs according to tumor markers

Tumor type	Marker			
	$\beta$ -HCG	AFP	PLAP	c-Kit
Pure germinoma	–	–	+/-	+
Germinoma (syncytiotrophoblastic)	+	–	+/-	+
Endodermal sinus tumor	–	+	+/-	–
Choriocarcinoma	+	–	+/-	–
Embryonal carcinoma	–	–	+	–
Mixed GCT	+/-	+/-	+/-	+/-
Mature teratoma	–	–	–	–
Immature teratoma	+/-	+/-	–	+/-

Abbreviations: AFP, alpha-fetoprotein;  $\beta$ -HCG,  $\beta$ -human chorionic gonadotropin; GCT, germ cell tumor; PLAP, placental alkaline phosphatase.

From: Louis DN, Ohgaki H, Wiestler O et al., eds. WHO Classification of Tumours of the Central Nervous System, Third Edition. Albany, NY: WHO Publication Center, 2007:203.

onic mesoblast [8, 13]. Interestingly, about 25% of all pediatric CNS GCTs present with more than one histologic component and are known as mixed GCTs [27].

Although sometimes classified under the NGGCT category, teratomas are often considered a separate entity and are classically divided into mature and immature teratomas [24]. Mature teratomas are composed of fully differentiated “adult-like” tissue elements from ectoderm, mesoderm, and

endoderm. Immature teratomas contain incompletely differentiated tissue elements, like neuroepithelium, that resemble fetal tissue [28, 29]. Lesions are classified as immature teratomas even if only a minor component of the tumor is composed of these less differentiated tissues, and frequently, the mitotic activity is higher than in mature teratomas [24]. Most commonly, mature teratomas are treated with surgical excision alone, but some immature teratomas may need further treatment [28–31].

A new classification system was recently adopted in some European studies. CNS GCTs are separated into “secreting” or “nonsecreting” tumors. Secreting tumors are defined as presenting with an elevated CSF AFP  $\geq 10$  ng/ml or above the local laboratory’s normal range and/or a CSF  $\beta$ -HCG level  $>50$  IU/l or greater than the accepted laboratory normal range. These elevations in the CSF may or may not be associated with serum  $\beta$ -HCG or AFP elevations. This differs from pure germinomas, which usually do not secrete appreciable tumor markers [32, 33].

Other proposed classification systems separate histologic variants into differing therapeutic groups based on their prognosis (Table 3) [31, 34].

### Clinical Presentation

The initial clinical presentation in CNS GCTs is dependent upon the patient’s age, tumor location, and tumor size. Pineal region tumors usually present with signs of increased intracranial pressure (ICP) resulting from obstructive hydrocephalus, often requiring shunt placement or ventriculostomy. Ophthalmologic abnormalities and somnolence are seen in approximately 25%–50% of patients and ataxia, seizures, and behavioral changes are seen in another 25% of patients. Parinaud’s syndrome, caused by involvement of adjacent midbrain structures, is also seen at presentation in up to 50% of pineal GCTs. Endocrinopathies and disturbances in sexual development in patients with isolated pineal region tumors are less common. The presence of diabetes insipidus (DI) has been suggested to indicate the likely presence of germinomatous tissue on the floor of the fourth ventricle, even in those cases without radiographic evidence of gross tumor involvement [14, 35].

Patients with suprasellar GCTs frequently present with hypothalamic/pituitary axis dysfunction such as DI, delayed sexual development, hypopituitarism, isolated growth hormone deficiency, and precocious puberty. Patients may also present with ophthalmic abnormalities such as bilateral temporal hemianopsia. These patients rarely present with signs of increased ICP. Often, patients may be asymptomatic for  $>6$  months prior to a diagnosis of a CNS GCT. This is more commonly observed in patients with undiagnosed isolated endocrinopathies [13, 14].

**Table 3.** Therapeutic classification of intracranial GCTs

A. Good prognosis
a. Pure germinoma
b. Mature teratoma
B. Intermediate prognosis
a. Germinoma with elevated levels of $\beta$ -HCG
b. Extensive/multifocal/germinoma
c. Immature teratoma
d. Teratoma with malignant transformation
e. Mixed tumors composed mainly of germinoma or teratoma
C. Poor prognosis
a. Choriocarcinoma
b. Yolk sac tumor
c. Embryonal carcinoma
d. Mixed tumors composed mainly of choriocarcinoma, yolk sac tumor, or embryonal carcinoma

Abbreviations:  $\beta$ -HCG,  $\beta$ -human chorionic gonadotropin; GCT germ cell tumor.

From: Matsutani M, Sano K, Takakura K et al. Primary intracranial germ cell tumors: A clinical analysis of 153 histologically verified cases. *J Neurosurg* 1997;86:446–455 and Sawamura Y, Ikeda J, Shirato H et al. Germ cell tumours of the central nervous system: Treatment consideration based on 111 cases and their long-term clinical outcomes. *Eur J Cancer* 1998;34:104–110.

On a retrospective analysis over a 16-year period, Crawford and colleagues found a relationship between the presenting symptoms and time of diagnosis [36]. Nausea, vomiting, and visual complaints led to an earlier diagnosis. Nine of 30 patients had symptoms for  $>6$  months. Symptoms associated with a delayed diagnosis were prolonged history of enuresis, insidious development of endocrine dysfunction, motor and movement disorders, and psychiatric complaints such as anorexia or abrupt changes in school performance. In this study, the event-free survival (EFS) duration, at a mean of 35 months, was unaffected by time of diagnosis, but further studies are necessary to determine whether delayed diagnosis adversely affects morbidity and mortality [36].

### Diagnosis

The diagnosis of CNS GCTs is based on clinical symptoms and signs, tumor markers, neuroimaging characteristics, and cytological (CSF) and/or histological assessments. Confirmation of the diagnosis requires measurement of serum and CSF tumor markers and/or biopsy. The accuracy of both the initial histologic diagnosis and staging are crucial in establishing the appropriate treatment regimen. In mixed GCTs, the prognosis and treatment recommendations are dictated by the most malignant component.

Radiographic characteristics of CNS GCTs alone are unable to reliably differentiate germinoma from NGGCTs or from other tumors. Historically, the high risk for operative morbidity and mortality led to the use of alternative diagnostic measures, such as therapeutic trials of irradiation. If the patient's tumor exhibited a "good" response to irradiation as seen on imaging studies, a diagnosis of germinoma was made and radiation therapy proceeded to completion. For patients whose tumor exhibited a "poor" response to a trial of irradiation, a diagnosis of NGGCT, glioma, or other was established [37]. Advances in surgical approaches and a better understanding of CNS GCTs have allowed for more accurate diagnostic techniques.

Both computed tomography and magnetic resonance imaging (MRI) are very sensitive in detecting suprasellar and pineal region masses, but the radiographic characteristics are very similar in all GCTs, therefore limiting their usefulness in determining the exact histology of these tumors. Germinomas can enhance diffusely and NGGCTs commonly may have associated hemorrhage, causing a more heterogeneous pattern of enhancement. Lesions involving both the suprasellar and pineal regions are usually bifocal germinomas [2, 38, 39]. A tumor biopsy is required for diagnosis, except in cases where characteristic serum and/or CSF tumor marker elevations exist. CNS GCTs have a propensity to disseminate throughout the neuroaxis, even at early disease stages, and thus, complete CNS staging is mandatory in all CNS GCTs.

All patients with a suspected CNS GCT require an extensive metastatic evaluation including an MRI of the brain and spine with gadolinium, measurement of AFP and  $\beta$ -HCG levels in both serum and CSF, CSF cytology, and evaluation of pituitary/hypothalamic function. Visual field examinations for suprasellar or hypothalamic tumors and baseline neuropsychologic examinations are also recommended.

Pure germinomas and teratomas usually present with negative markers, whereas NGGCTs often present with tumor marker elevation. Interestingly, however, very low levels of  $\beta$ -HCG can be detected in pure germinomas with leptomeningeal spread or among those that contain syncytiotrophoblastic giant cells. Elevated levels of AFP can also sometimes be seen in teratomas. The laboratory tests used to detect tumor markers have become more reliable during the last decade, but the exact interpretation and meaning of specific values often varies within study groups. Many of the European and U.S. groups have traditionally classified tumors as "secreting" if the serum and/or CSF AFP is  $\geq 10$  ng/dl (or higher than the laboratory normal values) and when the  $\beta$ -HCG is  $\geq 50$  IU/l (or higher than the laboratory normal values). Some Asian groups, however, use higher

levels of  $\beta$ -HCG to categorize a patient into differing risk groups. Also, different study groups place more or less significance upon the importance of an isolated elevation in  $\beta$ -HCG.

### Surgery

As suggested above, many patients with pineal masses present with signs and symptoms of obstructive hydrocephalus, and this often necessitates either a ventriculoperitoneal shunt (VPS) or an endoscopic third ventriculostomy (ETV). Although many neurosurgeons are increasingly using ETV instead of VPS as the initial management for obstructive hydrocephalus, this still remains controversial. In a recent retrospective review of 43 patients and at a mean of 2 years follow-up, there was nearly a 70% success rate using ETV instead of VPS [40]. Other studies have shown similar encouraging results, especially in patients whose hydrocephalus is caused by aqueductal stenosis and space-occupying lesions such as tumors [41].

Most often, the diagnosis of CNS GCTs requires a tumor biopsy, except in those cases with characteristic elevations of tumor markers. When the tumor markers are slightly elevated but remain in the normal range, or if there are any noncharacteristic findings, a tumor biopsy should be strongly considered. Surgical biopsies for CNS GCTs usually are limited, secondary to location and associated morbidity. It is possible, however, to have a misdiagnosis from a small biopsy because of sampling error. Recent advances in surgical techniques have allowed for open procedures without major complications, even in the pineal region. Gross total resections, however, are not currently recommended because of the risk for postsurgical morbidity. The value of partial or gross total resections in germinomas has not been proven, and the role of radical resection in NGGCTs is still unclear. Few definitive studies have been conducted to evaluate the importance of resection in CNS GCTs [14, 32, 42–46]. For patients with mature teratomas, however, gross total resection of the tumor is usually curative.

For patients with NGGCTs that do not obtain a complete radiographic response after chemotherapy, especially if there is normalization of tumor markers, a second-look surgery should be considered. In these cases, the residual lesion may be necrosis and fibrosis devoid of tumor or even a mature teratoma, a phenomenon known as "growing teratoma syndrome." Growing teratoma syndrome is a distinctive pathophysiologic process characterized by enlarging tumor masses during or after chemotherapy and in the presence of normal or declining tumor markers [47]. Typically, only residual mature teratoma remains upon surgical exploration. Often, in these cases, surgery is the most curative

treatment. Most importantly, this process should not be misdiagnosed as progressive disease, as treatments vary significantly. Second-look surgery should also be considered in those patients with persistent positive markers, because residual malignant elements can be better assessed by histologic evaluation and confirmation. Second-look surgery is increasingly being studied in many U.S. and international trials, especially in the aforementioned situations, in order to better define its role in the treatment of CNS GCTs.

## TREATMENT

### Germinomas

Germinomas are highly responsive to radiation therapy. In most cases, a complete response (CR) can be achieved with radiotherapy alone. Five-year survival rates >90% have been reported using irradiation alone; however, the optimal doses and fields of radiation remain controversial. These excellent survival rates have allowed investigators to focus on the reduction of treatment intensity in an effort to minimize late effects [31, 34].

Traditionally, patients with germinomas have received at least 50 Gy to the primary site with additional prophylactic therapy to the craniospinal axis. The late effects of these relatively large volumes and high doses, however, are not insignificant. Multiple studies have used dose reductions to the primary site and have maintained cure rates >90% [48–50]. Patterns of relapse following CSI versus reduced-volume radiation, either with whole-brain or whole-ventricular radiation therapy are not significantly different. These studies have concluded that CSI is not necessary for localized germinomas, and most experts no longer advocate CSI in localized pure germinoma [51].

It is not yet completely clear what the optimal volume and dose of radiation should be for patients with pure germinomas, especially those patients with localized disease. In a recent study by Haas-Kogan and colleagues, 21 of 49 patients with pure CNS germinomas were treated with local irradiation alone, including whole-ventricular irradiation. The results again suggest that treatment with whole-ventricular irradiation does not result in a greater number of relapses than with CSI [52]. The optimal radiation dose to the whole ventricular field and the boost to the primary site are also controversial, but most experts agree that a boost to the primary tumor bed is essential in preventing local recurrences. Some data suggest that 45 Gy may be the optimal upper dose limit [53]. Many ongoing U.S. and international studies are evaluating differing volumes and doses of radiation therapy in an effort to better define the optimal radiation strategy in CNS germinomas.

Ongoing trials treating CNS pure germinomas are evaluating the use of irradiation alone versus neoadjuvant chemotherapy plus radiotherapy. Another objective is to evaluate the importance and efficacy of response-based radiotherapy. Current trials in the U.S. will compare the EFS and overall survival (OS) times following conventional radiotherapy-alone versus a cohort randomized to receive chemotherapy followed by response-based radiotherapy. In the radiotherapy-alone arm, patients with localized or multifocal disease will receive 24 Gy to the whole ventricular system and a 21-Gy boost to the tumor bed, and patients with disseminated disease will receive 24 Gy of CSI with a 21-Gy boost to all measurable disease. In the chemotherapy–radiotherapy arm, patients will receive decreased doses and/or volumes if a CR or minimal residual disease is achieved after two to four cycles of chemotherapy. Patients with initial localized disease will receive 30 Gy to the primary tumor bed without whole-ventricular radiation. Patients with multifocal disease will receive reduced 21-Gy whole-ventricular radiation and 9-Gy boost to areas of pretreatment measurable disease. Finally, patients with disseminated disease will receive reduced doses of 21 Gy to the craniospinal axis and a 9-Gy boost.

Treatment regimens consisting solely of chemotherapy without irradiation have also been investigated. Chemotherapy agents such as cyclophosphamide, ifosfamide, etoposide, cisplatin, and carboplatin are highly active in patients with CNS germinomas [54]. The First International Central Nervous System Germ Cell Cooperative trial enrolled 45 patients with pure germinomas. Eighty-four percent of these patients achieved a CR with chemotherapy alone, with or without second-look surgery. Twenty patients had recurrence, but most recurrences were salvaged with radiation therapy. They reported a 2-year overall probability of survival of 84% [45].

Chemotherapy has also been explored in an effort to reduce radiation therapy doses. Several studies have confirmed the feasibility of this approach while maintaining excellent survival rates, but the number of treated patients has been small [33, 48, 55–57]. Fouladi et al. [58] and Sawamura et al. [59] examined the use of platinum-based chemotherapy with lower local irradiation doses with comparable survival rates. Aomaya et al. [60] treated 27 patients with CNS germinoma using three or four cycles of platinum-based chemotherapy, depending upon the extent of resection, followed by 24 Gy of involved-field radiation therapy. The 5-year OS and EFS rates for pure germinomas were 100% and 86%, respectively. For patients with  $\beta$ -HCG-secreting germinomas, the OS and EFS rates were 100% and 44%, respectively. The overall relapse rate was higher in the  $\beta$ -HCG-secreting group [60]. The exact clin-

ical behavior of the  $\beta$ -HCG–secreting germinomas remains unclear, and in several reports, patients with these  $\beta$ -HCG–secreting tumors appear to have inferior outcomes with the use of irradiation alone [31, 61]. The Japanese Pediatric Brain Tumor Study Group conducted a study in which patients with a low-risk germinoma were treated with three courses of chemotherapy followed by 24 Gy of focal irradiation. The overall initial response rate to this regimen was 92%, but within 2.5 years, 12% of the patients recurred. Seven of nine patients relapsed outside the radiation field [62]. Single-institution experiences suggest that the cure rates for localized germinomas are excellent with the addition of whole ventricular field irradiation [52, 63].

### NGGCTs

NGGCTs are less radiosensitive than pure germinomas and their prognosis following standard CSI alone has been poor, with 5-year OS rates in the range of 30%–50%, and with many tumors relapsing within 18 months of diagnosis [2, 5, 31, 64]. Matsutani and colleagues reviewed 153 histologically verified intracranial GCTs treated uniformly with surgical resection followed by radiation therapy with or without chemotherapy. OS rates could be stratified by histologic subtypes. Patients with pure malignant choriocarcinoma, endodermal sinus tumor, or embryonal carcinoma had a 5-year OS rate of 9.3%. This greatly contrasted with a 70% 5-year OS rate in patients with mixed germinoma, teratoma, immature teratoma with malignant elements or mixed tumors that predominantly consisted of germinomas or teratomas. This suggests that histological confirmation of the elements comprising the mixed tumors is important for determining the most effective treatment strategy [31]. The optimal dose, timing, and volume of radiation therapy still remain controversial.

The addition of chemotherapy has improved OS rates in patients with CNS NGGCTs. Robertson and colleagues treated 18 patients with four cycles of platinum-based chemotherapy followed by radiation therapy and further adjuvant chemotherapy. Of the 12 patients assessable for response, nine had objective responses (four CRs and five partial responses) to the adjuvant chemotherapy. The 4-year EFS and OS rates were 67% and 74%, respectively [65]. In 1999, the French Society of Pediatric Oncology (SFOP) reported their results using chemotherapy followed by local irradiation. Twenty seven patients with NGGCTs were treated with six to eight courses of chemotherapy and focal radiation therapy for patients with localized disease and CSI for patients with dissemination. All patients had normalization of tumor markers and 14 of 27 underwent a second-look surgery for residual abnormalities. Results of the second-look surgery revealed only mature and imma-

ture teratomas or fibrosis. At a median follow-up of 53 months, 74% of the patients were alive [66]. Calaminus et al. [67, 68] reported the work of the German Group, showing a 67% 5-year survival rate for patients treated with two cycles of chemotherapy followed by surgical resection, 36 Gy of CSI, and 14 Gy to the tumor bed followed by two further courses of chemotherapy.

High-dose chemotherapy with autologous hematopoietic cell rescue (AuHCR) has traditionally been reserved for patients with refractory or recurrent GCTs; however, this approach has also shown promise as consolidation therapy for some high-risk gonadal GCTs at diagnosis [69]. Ongoing trials in CNS NGGCTs are evaluating the efficacy of response-based therapy. Second-look surgery has been recommended for patients with responses to chemotherapy who exhibit residual tumor with or without tumor marker elevation. Finally, some ongoing trials will use AuHCR in newly diagnosed patients with residual active disease after induction chemotherapy in an effort to improve disease control. Radiation therapy remains a vital accepted treatment strategy in CNS NGGCTs; however, controversy still exists over the necessity of CSI versus focal or whole-ventricular radiotherapy, especially in patients with localized disease.

### Relapsed GCTs

CNS GCT relapses most commonly occur at the primary tumor site, but in up to 30% of cases, there is concomitant leptomeningeal spread. The outcome of relapsed patients, especially those with NGGCTs, continues to be very poor [70, 71]. Salvage therapies include additional surgery, focal or craniospinal irradiation, and myeloablative chemotherapy with AuHCR. Patients with pure germinomas who have been treated with chemotherapy alone often benefit from further chemotherapy followed by radiation therapy [70, 72]. For pure germinoma patients that have previously received radiation therapy, myeloablative chemotherapy with AuHCR is often recommended. High-dose chemotherapy and AuHCR has also shown curative potential for some relapsed systemic NGGCTs, especially in those patients who can achieve a CR to chemotherapy. Outcomes for NGGCTs, however, are more discouraging [73–75].

### SUMMARY

Pediatric CNS GCTs, just like their extracranial counterparts, represent a wide array of diseases. These tumors can be seen from birth and throughout childhood, with varying incidences depending upon the patient's age and gender. In general, these tumors are diagnosed based on a biopsy sample; however, they are one of a small group of tumors that can secrete tumor markers that often assist in the diagnosis.

Although significant controversy still exists over how to define the different types of CNS GCTs, the majority of experts would agree that there is a distinction between pure germinomas and NGGCTs. Another manner of dividing these tumors is by classifying them as “secreting” and “non-secreting” tumors. The exact characteristics that dictate these divisions remain controversial and are currently still under investigation. There is a clear division based on prognosis, however. The pure germinomas or “nonsecreting” tumors are much more responsive to irradiation and chemotherapy than NGGCTs and “secreting” tumors.

These tumors have a tendency to spread throughout the CNS, and therefore, a complete CNS disease evaluation, including brain and spine MRI, measurement of CSF and serum tumor markers, and CSF cytology, is an essential part of the diagnostic evaluation. Because many of the patients with these tumors present with endocrinopathies and visual impairment depending upon location, a through endocrinologic and ophthalmologic evaluation are also highly recommended.

Treatment strategies are highly dependent upon histology, but in general, a combination of chemotherapy and radiation therapy is often used. Efforts are currently being employed to decrease radiation exposure when possible by using chemotherapy and basing continued treatment on tu-

mor response to previous therapies. The hope is that less exposure to radiation therapy will decrease the patient’s risk for late effects, including neurocognitive dysfunction, endocrinopathies, and secondary malignancies.

Germinomas are both radiosensitive and chemosensitive. In pure germinomas, treatment with CSI has led to 5-year OS rates >90%. The addition of chemotherapy has allowed for a decrease in the field and dose of irradiation, and subsequently, a decrease in the associated long-term morbidities. Using a combined approach, EFS rates >95% have been reported in pure germinomas [38]. NGGCTs are less radiosensitive than pure germinomas and their prognosis following standard radiotherapy has been poor, with 5-year OS rates of 30%–50% [2, 5, 64]. The standard treatment regimens for NGGCTs remain controversial, and treatment regimens aimed to improve progression-free survival and OS times are ongoing.

Advances in our understanding of this unique group of CNS tumors are currently ongoing. Further prospective trials offer the hope for a clearer division among differing prognostic groups based on biologic markers, cytogenetic abnormalities, and responses to therapy.

#### AUTHOR CONTRIBUTIONS

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