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## Primary Central Nervous System Germ Cell Tumors: A Review and Update

Kaleigh Fetcko, BS<sup>1</sup> and Mahua Dey, MD<sup>1,\*</sup><sup>1</sup>Department of Neurosurgery, Indiana University School of Medicine, IUPUI, Indiana, USA

### Abstract

**Importance**—Primary central nervous system (CNS) germ cell tumors (GCT) are a heterogeneous group of tumors that are still poorly understood. In North America, GCTs comprise approximately 1% of primary brain tumors in pediatric and young adult patients. GCTs can occur as pure or mixed subtypes; they are divided into germinomas, which are the most common subtype, and non-germinomatous germ cell tumors (NGGCTs), which consist of approximately one-third of GCTs and include teratomas, embryonal carcinomas, choriocarcinomas, and yolk sac tumors.

**Observations**—While the etiology of primary CNS GCT is not entirely clear, the various subtypes are lineage-related and may involve progenitor germ cells that fail to migrate and become trapped in midline locations. Primary CNS GCT most commonly arises in the pineal region but also occur in other areas. Presenting symptoms can include headache, Parinaud syndrome, diabetes insipidus, precocious puberty, ataxia, or hemiparesis. Diagnosis of primary CNS GCTs can be difficult and is often delayed. Various imaging studies and tumor markers can assist in specific diagnosis. Treatment plans differ depending on the subtype of GCT and may vary among physicians and institutions. Germinomas have a favorable prognosis with a greater than 90% overall survival, while NGGCTs only have survival rates ranging from 40–70%.

**Conclusions and Relevance**—Germinomas seem to be most effectively treated with chemotherapy and radiation, while NGGCT usually require surgical resection, chemotherapy, and radiation with the exception of mature teratomas frequently curable with surgery alone. Gamma knife radiosurgery is a promising treatment that may be an effective additional treatment option. Cytogenetic and molecular analyses are attempting to further specify the different GCT subtypes and are helping to direct the development of distinct therapeutic targets to improve treatment and prognosis.

### Keywords

CNS germ cell tumor; intracranial germ cell tumor; germinomas; nongerminomas

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\*Correspondence: Mahua Dey, MD, Indiana University Purdue University Indianapolis (IUPUI), Neuroscience Research Building, 320 W 15th Street, NB 400A, Indianapolis, IN 46202; Tel: 317-274-2601; mdey@iu.edu.

### Disclosure

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## INTRODUCTION

The second most common location for extragonadal germ cell tumors (GCT) is the central nervous system (CNS)<sup>1</sup>. Primary CNS GCT are a heterogeneous group of tumors that are still poorly understood in regards to etiology and molecular biology, which in turn can lead to difficulties in diagnosis and treatment. In North America, germ cell tumors (GCTs) comprise approximately 1% of primary brain tumors in pediatric and young adult patients with a median age of diagnosis of 16 years<sup>2</sup>. In the United States, the overall GCT incidence is 0.6 per million per year while 1.0 per million per year in Europe and 2.7 per million per year in Japan<sup>3</sup>. Primary CNS GCTs can occur as pure or mixed subtype tumors; in the United States and Europe, GCTs are commonly divided into germinomas, which are the most common subtype, and non-germinomatous germ cell tumors (NGGCTs), which consist of approximately one-third of GCTs and include teratomas, embryonal carcinomas, choriocarcinomas, and yolk sac tumors<sup>3-6</sup>. Teratomas can be classified further as mature, containing entirely fully differentiated tissues, or immature, containing mostly embryonic or fetal tissues<sup>7</sup>. Alternatively Japanese classification of GCT subtypes is separated into good, intermediate, and poor prognosis groups<sup>8</sup>. The good prognosis group includes pure germinoma and mature teratoma; the intermediate prognosis group contains mixed tumors with mainly germinoma or teratoma and immature teratomas; and the poor prognosis group consists of choriocarcinoma, yolk sac tumor, embryonal carcinoma, and mixed tumors with components from any of the subtypes of this group<sup>9,10</sup>.

CNS GCTs occur more frequently in the Asian population and are present more commonly in males with significantly higher rates in the pineal location; however, suprasellar germinomas were noted more frequently in females<sup>1,2,4,11</sup>. Goodwin and colleagues noted that among 700 cases of GCTs across 17 diverse regions, NGGCT specifically are not associated with a particular sex, location, race, or age with the exception of infant patients (Table 1)<sup>2</sup>. Timely diagnosis of primary central nervous system GCTs can be challenging due to nonspecific symptoms<sup>12,13</sup>. Additionally, treatment plans can differ depending on the subtype of GCT and can vary among different physicians and institutions. We reviewed the current literature to discuss the pathophysiology, clinical presentation, assessment and diagnosis, treatment, molecular biology, and prognosis of primary CNS GCTs.

## DISCUSSION

### Pathophysiology

While the etiology of primary CNS GCT is unclear, and there are several hypotheses that attempt to explain this disease process<sup>2</sup>. Germ cells are believed to be pluripotent and able to differentiate into any type of cell<sup>14</sup>. These cells originate in the yolk sac of the embryo around the third to fourth week of gestation, normally destined for the ovaries or testes but can aberrantly migrate to other locations for unknown reasons<sup>14</sup>. Some believe that progenitor germ cells wrongly migrate and become trapped in midline locations along the anteroposterior axis of the body as supported by extracranial GCTs in other midline sites, such as mediastinum and retroperitoneum, which share certain characteristics such as DNA methylation, gene expression, marker secretion, and chromosomal alterations<sup>9,11</sup>. Barkova and colleagues noted that CNS GCT had similar DNA damage response activation patterns

to that of gonadal GCT rather than that of CNS-originating tumors which share a common environment<sup>15</sup>.

Evidence shows that teratomas can arise from other non-progenitor germ cells, suggesting that other GCT subtypes may also have this capability of developing from non-germ cell lines<sup>9</sup>. Another theory posits that endogenous neural stem cells in the brain are the likely origin of primary CNS GCT since lack of methylation of the SNRPN gene previously linking GCT to progenitor germ cells has been found to be more similar in pattern to human neural stem cells<sup>16</sup>. Overexpression of a single particular gene, Oct4, was able to stimulate the development of normal progenitor cells in the brain from neural stem cells; the different GCT subtypes seem to be “lineage-related” as evidenced by their recurrence as a different subtype or mixed subtype following treatment<sup>9,17</sup>.

### Clinical Presentation

While CNS GCT usually arise in the pineal region, they can also occur in suprasellar areas, fourth ventricle, basal ganglia, and thalamus; about 5–10% of patients will have tumor present in both pineal and suprasellar regions, which happens more frequently in patients with germinomas<sup>6,18</sup>. In bifocal disease, it is unknown whether tumor spread occurred or simultaneous tumor development in two different sites took place<sup>6</sup>. Phi et al suggested that metastatic spread seemed more likely based on high ventricular seeding rates noted in patients with bifocal CNS GCTs<sup>13</sup>. Intracranial germinomas typically arise between 7 and 30 years of age, while NGGCT commonly occur from birth to 20 years<sup>17</sup>. Symptoms of primary CNS GCTs may include Parinaud syndrome due to hydrocephalus or compression of the tectal plate, ataxia and dysmetria if affecting the superior cerebellar peduncles, diabetes insipidus secondary to either hydrocephalus or additional tumor presence in the suprasellar area affecting the neurohypophysis, and precocious puberty from hormones secreted from certain GCT<sup>6,19</sup>. Patients may also experience headache, oculomotor paresis, facial paresis, or hemiparesis<sup>20,21</sup>.

### Assessment & Diagnosis

Diagnosis of CNS GCTs is delayed in approximately 54% of patients due to nonspecific symptoms that are usually present for greater than 6 months before any diagnostic imaging is obtained<sup>5,6,13</sup>. GCTs are typically found on computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain<sup>19</sup>. Additionally, certain tumor markers may be detected in the serum or cerebrospinal fluid (CSF) to aid in diagnosis<sup>19</sup>. In 2013, 117 multidisciplinary specialists from 25 countries developed Delphi consensus statements regarding the investigation and management of intracranial GCT, which required at least 70% of votes to support a statement and at least 60% participation of voters. In regards to statements biological work-up, they concluded that serum and CSF alpha-fetoprotein (AFP) and human chorionic gonadotrophic hormone (HCG) should be measured to aid in diagnosis<sup>3</sup>. Yolk sac tumors can secrete AFP; choriocarcinomas can release HCG<sup>6</sup>. Germinomas have been associated with mild increases in total HCG and may show elevated placental alkaline phosphatase (PLAP)<sup>6</sup>. Elevated AFP and HCG can sometimes occur with immature teratomas<sup>22</sup>. Pure embryonal carcinomas are not known to secrete any tumor markers; however, they tend to occur mixed with other GCT subtypes, especially yolk sac

tumors<sup>23</sup>. Immunohistochemical markers should also be determined<sup>3</sup>. Germinomas highly express c-kit/CD117, OCT3/4, and PLAP. Embryonal carcinomas stain strongly for CD30 and CK AE1/3. Yolk sac tumors are typically positive for AFP expression, while choriocarcinomas tend to express HCG<sup>3,24</sup>. However, normal tumor markers do not definitively rule out the presence of a GCT<sup>25</sup>.

CNS GCTs have a tendency to spread through the neuroaxis making extensive metastatic evaluation a necessity and should include MRI with gadolinium of the brain and spine<sup>6</sup>. Positive tumor markers can indicate malignant disease with AFP levels greater than 1000ng/ml considered high risk and may require intensified chemotherapy and radiation<sup>5,6</sup>. Even with negative or decreasing tumor marker levels, suspected metastatic disease should be explored and treated<sup>26</sup>. Without a positive tumor marker result, a biopsy is required for definitive diagnosis<sup>35,6</sup>. If tumor markers are detected in the blood or CSF, then a biopsy is not necessarily required for diagnosis<sup>3,11,27</sup>. However although bifocal intracranial tumors with elevated HCG and normal AFP was considered pathonomic for germinomas, Aizer et al found that 21% of their patients with bifocal disease and elevated HCG with normal to mildly elevated AFP were diagnosed with NGGCT, which is of importance to avoid undertreatment<sup>28</sup>. See Table 2 for a diagnostic summary of primary CNS GCT.

## Treatment

The management of primary CNS GCT can vary but typically includes a multimodal treatment plan. Chemotherapy alone without radiation has only proven ineffective resulting in increased relapse rates and worse outcomes<sup>6,25,29,30</sup>. Additionally, diabetes insipidus is a risk factor for complications when chemotherapy regimens include cisplatin or ifosfamide based protocols<sup>31</sup>. Survival significantly increases when patients receive radiation therapy<sup>4</sup>. Radiation alone has provided excellent survival for patients but can later result in secondary malignancies or neurocognitive and neuroendocrine sequelae, such as decreased processing speed, working memory, and visual memory<sup>6,25,32</sup>.

Germinomas are virtually curable with radiation therapy alone or more recently neoadjuvant chemotherapy plus radiation<sup>27,32,33</sup>. One study noted the outcomes of 24 patients with CNS germinomas treated with lowered radiation doses and a variety of chemotherapy agents, including carboplatin, etoposide, ifosfamide; they found that progression free survival at 5 years was 96% and overall survival was 100%<sup>25</sup>. Bouffet and colleagues also found that combining local radiation and chemotherapy for the treatment of non-metastatic germinomas achieved excellent survival rates<sup>34</sup>. Cyclophosphamide is another agent under investigation for treating GCTs and was noted as a feasible and well-tolerated additional treatment option<sup>35</sup>. In addition, pre-treatment and post-treatment neuropsychological and neurocognitive testing did not differ significantly at a mean follow-up of 38 months and then 189 months<sup>25</sup>. More specifically, treatment of germinomas has developed from high dose craniospinal irradiation (CSI) to now include platinum-based chemotherapy followed by boost radiation to the tumor bed and whole ventricular system<sup>3</sup> radiation therapy since most germinomas recur within the ventricular system<sup>36</sup>. Oral etoposide may also be used palliatively to treat CNS germinomas after conventional chemotherapy and radiation;

response to this treatment has been noted for other refractory or recurrent brain tumors in the pediatric population<sup>37</sup>.

Only 20–40% of NGGCT are effectively controlled with radiation alone and, therefore, require chemotherapy and radiation in addition to complete surgical resection when possible<sup>27,33,38</sup>. Chemotherapy prior to radiation therapy has significantly improved survival to 60–70% for patients with NGGCTs<sup>6,39</sup>. The most active agents for NGGCT include carboplatin, cisplatin, etoposide, gemcitabine, ifosfamide, taxanes, and vinblastine<sup>6</sup>. Masutani et al reports effective protocols using carboplatin or cisplatin with etoposide for treating germinomas or intermediated prognosis NGGCTs, but could not control poor prognosis NGGCT even with the use of ifosfamide-cisplatin-etoposide<sup>8</sup>. Surgical resection alone has not been shown to be sufficient treatment for NGGCTs with the exception of mature teratoma<sup>3,6,20,27</sup>. Although similar final outcomes in the United States and Japan, surgery is more frequently included in GCT treatment protocol in Japan than in the United States<sup>1</sup>. Yet surgical resection after completion of both chemotherapy and radiation occurs more commonly in Japan, while surgery after chemotherapy but followed by radiation typically occurs in the US and Europe<sup>3</sup>. Immature teratomas typically respond poorly to a cisplatin chemotherapy regimen but, for better outcomes, still require a combination of chemotherapy and radiation along with surgical resection when feasible<sup>22</sup>.

In the United States, CSI and boost radiation to tumor bed is typically used to treat NGGCT<sup>27,28</sup>; while Japanese protocols prefer the use of radiation at the tumor site and focal surrounding area for intermediate prognosis NGGCTs but recommends CSI for poor prognosis NGGCTs<sup>8,10</sup>. The European standard is to treat non-metastatic NGGCT with only local radiation therapy<sup>40</sup>. One study found that CSI was associated with significantly increased overall survival for poor prognosis NGGCT, suggesting the use of greater than 36 Gy for CSI and 54 Gy or greater radiation to the primary tumor site<sup>41</sup>. Additionally, Khafaga and colleagues reported that tumor radiation doses greater than 50Gy is preferred for improving outcomes<sup>41,42</sup>. Several studies have found increased survival with resection of residual tumor after chemotherapy and radiation, suggesting that surgery plays an important role in treating NGGCT particularly with failed radiologic response after initial chemotherapy and radiation<sup>36,43</sup>. Kochi et al treated 11 patients with NGGCT with chemotherapy and whole brain/ventricular radiation with boost radiation to tumor bed followed by complete excision of any residual tumor; this regimen resulted in a 91% 5-year overall survival<sup>43</sup>. Yet, Jinguji and colleagues found that an initial treatment strategy including gross total resection either before or after whole-brain radiation and chemotherapy provided effective therapeutic outcomes<sup>38</sup>. According to the Delphi consensus, treatment of NGGCT should include chemotherapy and radiation with CSI specially used in metastatic disease and resection of residual tumor<sup>3</sup>.

Endoscopic third ventriculostomy (ETV) should be considered since it has been shown to provide superior safety, diagnostic efficacy, and decreased morbidity and mortality at treating hydrocephalus and obtaining biopsies of tumors compared with open surgery or external ventricular drainage<sup>9,19</sup>. The Delphi consensus agreed that ETV is favored over other surgical interventions when feasible for the treatment of obstructive hydrocephalus<sup>3</sup>. ETV is ideal for non-emergent situations when intracranial blood pressure is well controlled;

however, risks to consider include lesion to the fornix and insufficient tissue sample for diagnosis of the tumor, especially for mixed GCT not diagnosed through elevated hormone markers<sup>9,19</sup>. The benefit of open surgical resection is still debated. While some report no significant differences in survival among any subtypes regardless of extent of surgical resection, others concluded that improved survival occurred for patients specifically with NGGCTs and advised radical removal over biopsy or subtotal resection<sup>4,6</sup>. However, germinomas are almost never treated with surgical resection unless residual tumor is persistent after other therapies are utilized<sup>27</sup>.

Gamma knife radiosurgery (GKRS) is another intervention under investigation and may provide benefit in the treatment for GCTs. Although no prospective study has taken place, one retrospective study found the average pineal tumor size decreased by roughly half 6 months after treatment with complete tumor disappearance in 39% of patients after 1 year<sup>44</sup>. Survival rates for GCTs specifically were 62.4% at 3 years and 54.4% at 5 years with local tumor control rates of 88% at 3 years and 77.27% at 5 years<sup>44</sup>. Huang et al observed that patients with NGGCT treated with GKRS experienced increased 5-year survival<sup>22</sup>. GKRS should be investigated further but appears to be relatively effective as an additional treatment option. See Table 3 for a treatment summary of primary CNS GCT.

A stem cell treatment is another area of research being explored for treating primary CNS GCT. The idea of using high dose chemotherapy with autologous stem cell rescue (ASCR) is meant to eliminate or at least reduce the radiation dose administered to young children with brain tumors to decrease the risk of long term adverse effects<sup>45</sup>. Tada and colleagues treated 6 patients with NGGCT with ASCR after chemotherapy, radiation therapy, and surgical excision. All patients survived one to seven years after diagnosis and lived with good performance status; however, mild liver dysfunction occurred in all patients along with hearing disturbance in half of patients<sup>46</sup>. The Delphi consensus agreed that relapsed malignant NGGCT should be treated with high dose chemotherapy followed by hematopoietic stem cell rescue along with surgery and radiation when possible<sup>3</sup>. Additionally, one case report mentioned the use of dendritic cell-based immunotherapy in which a 22-year old male with a germinoma was given five inoculations, resulting in rapid tumor shrinkage and decreased serum bHCG levels<sup>47</sup>.

### **Molecular Biology and Possible Therapeutic Targets**

Cytogenic and molecular analyses of pineal tumors have been increasingly pursued for further specification of the different GCT subtypes<sup>6</sup>. However, this scientific pursuit may be difficult as Schneider et al failed to observe any differences in the genetic profiles of germinomas and NGGCT in 19 patient samples, but the number of chromosomal imbalances was greater in the NGGCT samples<sup>48</sup>. One case report mentioned a patient who had a germinoma at age 5 but developed a yolk sac tumor 14 years later; it was unclear if or how the tumors were related but could not be distinctly separated since there was location overlap of the tumors<sup>37</sup>. Chromosomal analysis found that germinomas and mature teratomas revealed a mean number of 12.8 chromosomal changes (8 gains and 4.8 deletions)<sup>5</sup>. CNS GCT were also noted to have frequent aberrations of CCND2 (12p13), RB1 (13q14), and PRDM14 (8q13) genes, which play a role in the cyclin/CDK-RB-E2F pathway involved in



transcriptional regulation of primordial germ cell specification and development of CNS GCT<sup>9,49</sup>. Chromosome 4 and 5 losses were reported more commonly in primary CNS GCT than compared to extracranial GCT<sup>50</sup>. Interestingly, many pineal region GCT were found to have multiple copies of the X chromosomes, which may explain the high incidence of GCT in patients with Klinefelter's syndrome<sup>50</sup>. Additionally, Schulte and colleagues found global DNA demethylation in 49 germinoma samples compared to other tumors and normal tissues<sup>51</sup>.

Furthermore, decreased sensitivity to radiation therapy and chemotherapy along with poor prognosis were noted in 20% of CNS GCT that expressed p21 and 94% of CNS GCT that expressed p53<sup>9</sup>. Somatic alterations in the AKT/mTOR pathway have been noted in intracranial GCT; CNS GCT have also been linked to point mutations of the proto-oncogene KIT, especially among germinomas, which are associated with chromosomal instability<sup>6,9,51,52</sup>. One study found mutations in the KIT/RAS signaling pathway in over 50% of GCT patients, involving KIT, KRAS, NRAS and CBL, along with alterations in the AKT/mTOR pathway in 19% of GCT patients<sup>52</sup>. There are at least eight tyrosine kinase inhibitors targeting KIT that have been approved, which could potentially benefit patients with CNS GCT hopefully reducing or eliminating the use of radiation and/or chemotherapy; additionally, the therapeutic agent Selumetinib has shown great efficacy in preclinical trials targeting KRAS-mutated non-small cell lung cancer cells<sup>52</sup>. The use of Dasatinib has been suggested for patients with CNS GCT as it has been an effective tyrosine kinase inhibitor against myeloid leukemia cell lines with CBL mutations; however, one study investigating Dasatinib as a treatment for GCT was unclear of the benefits considering the multimodal treatment plans of the patients<sup>52,53</sup>.

## Prognosis

One study of 373 patients with pineal GCT reported having a 5-year overall survival of 80%, which carried the best survival rates compared to the other pineal tumor types<sup>4</sup>. Worse prognosis was significantly associated with female sex, age greater than 18 years, NGGCT, and lack of radiation therapy in treatment<sup>4</sup>. Prognosis is relatively favorable for germinomas showing a greater than 90% 5-year survival and overall survival even with metastasis compared to NGGCT with survival rates ranging from 30–70%<sup>6,25,36</sup>. Yet one study of 14 patients with NGGCT found that neoadjuvant combined chemotherapy and radiation therapy followed by complete resection of residual tumor resulted in a 5-year survival of 93%<sup>54</sup>. After analyzing 153 CNS GCT cases, Matsutani et al determined 10- and 20-year survival rates patients with pure germinomas as 93% and 81%, 10-year survival rates patients with mature teratomas and immature teratomas as 93% and 71% respectively, and 3-year survival rate of embryonal carcinoma, yolk sac tumor, and choriocarcinoma as 27%<sup>10</sup>. Another study evaluating the long-term outcomes of 455 germinomas and 94 NGGCT reported an 84.1% and 61.9% 20- and 30-year survival rates, respectively, for germinomas, and an 86.7% survival rate for both 20- and 30-year time points for NGGCTs<sup>55</sup>.

## CONCLUSIONS AND FUTURE DIRECTIONS

Primary CNS GCTs are rare and heterogeneous group of malignancies, primarily affecting pediatric population and young adults. The most effective treatment for germinomas seems to be radiation therapy with neoadjuvant chemotherapy<sup>9</sup>. On the other hand, NGGCT appear to be best treated with chemotherapy and radiation followed by gross total resection; complete tumor resection alone is the ideal treatment specifically for mature teratomas (Table 4)<sup>6,9</sup>. Cytogenetic and molecular analyses are attempting to further specify the different GCT subtypes and are helping to direct the development of distinct therapeutic targets to improve treatment and prognosis (Table 4)<sup>9</sup>.

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**Table 1**

Major epidemiologic facts about primary CNS GCT

Germinomas	Non-germinomatous germ cell tumors
Males	Not associated with a particular sex, location, race, or age with the exception of infant patients
Pineal location	
Asian	

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Table 2

Major diagnostic tools for primary CNS GCT

Germ Cell Tumors (GCT)	Serum/CSF tumor markers	Immunohistochemical tumor markers	Imaging Studies
Germinomas	HCG, PLAP	PLAP, c-kit and OCT3/4	CT brain, MRI brain, MRI spine
Non-germinomatous GCT			
<i>teratomas</i>			
	<i>mature</i>	-	
	<i>immature</i>	-	
<i>embryonal carcinomas</i>	HCG, AFP	CD30 and CK AE1/3	
<i>choriocarcinomas</i>	HCG	HCG	
<i>yolk sac tumors</i>	AFP	AFP	
<b>Germ Cell Tumors (GCT)</b>	<b>Serum/CSF tumor markers</b>	<b>Immunohistochemical tumor markers</b>	<b>Imaging Studies</b>
Germinomas	HCG, PLAP	PLAP, c-kit and OCT3/4	CT brain, MRI brain, MRI spine
Non-germinomatous GCT			
<i>teratomas</i>			
	<i>mature</i>	-	
	<i>immature</i>	-	
<i>embryonal carcinomas</i>	HCG, AFP	CD30 and CK AE1/3	
<i>choriocarcinomas</i>	HCG	HCG	
<i>yolk sac tumors</i>	AFP	AFP	

HCG=human chorionic gonadotrophic hormone, PLAP=placental alkaline phosphatase, AFP= alpha-fetoprotein

**Table 3**

Main treatments available for primary CNS GCT

<b>Germ Cell Tumors (GCT)</b>	<b>Treatment Options</b>
Germinomas	Chemotherapy, radiation therapy, GKRS
<hr/>	
Non-germinomatous GCT	
<i>teratomas</i>	
<i>mature</i>	Surgical resection
<i>immature</i>	Chemotherapy, radiation therapy, surgical resection, GKRS, hematopoietic stem cell rescue
<i>embryonal carcinomas</i>	
<i>choriocarcinomas</i>	
<i>yolk sac tumors</i>	

GKRS= Gamma knife radiosurgery

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**Table 4**

Current treatment recommendations for primary CNS GCT

<b>Germ Cell Tumors (GCT)</b>	<b>Recommendations</b>
Germinomas	<ul style="list-style-type: none"> <li>• 4 cycles of platinum based chemotherapy, usually including etoposide, ifosfamide, and either carboplatin or cisplatin<sup>8,36,56</sup></li> <li>• followed by whole ventricular radiotherapy (20-24Gy) and boost radiation (12-16) to tumor bed<sup>57,58</sup></li> <li>• if CSF metastasis detected, then craniospinal irradiation also administered<sup>36,59,60</sup></li> </ul>
<hr/>	
Non-germinomatous GCT	
<i>teratomas</i>	
<i>mature</i>	<ul style="list-style-type: none"> <li>• complete surgical resection<sup>6,22,27</sup></li> </ul>
<i>immature</i>	
<i>embryonal carcinomas</i>	<ul style="list-style-type: none"> <li>• 4–6 cycles of neoadjuvant chemotherapy, usually including carboplatin/cisplatin, etoposide, and ifosfamide, but may include gemcitabine, taxanes, or vinblastine<sup>6,27,56</sup>; however, immature teratomas do not respond well to cisplatin<sup>22</sup></li> </ul>
<i>choriocarcinomas</i>	
<i>yolk sac tumors</i>	<ul style="list-style-type: none"> <li>• more intensive chemotherapy regimens are recommended for worse prognosis NGGCT<sup>10</sup></li> <li>• craniospinal irradiation ( 36Gy) and boost radiation ( 54Gy) to tumor bed<sup>27,28,41</sup> or whole brain/ventricular radiation (24-40Gy) with boost radiation (15-30Gy) to tumor bed<sup>43</sup></li> <li>• complete surgical resection when possible<sup>3,6,28</sup></li> <li>• Some suggest best protocol for poor prognosis NGGCT should include simultaneous radiation and chemotherapy followed by resection of remaining tumor<sup>3,8</sup></li> </ul>