

# GERM CELL TUMORS

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## 1. Overview

Pediatric germ cell tumors are a heterogeneous group of neoplasms that occur in both gonadal and extragonadal sites. The most frequently occurring germ cell tumor is the teratoma. Teratomas occurring in infants are usually extragonadal and in older children they occur most commonly in the testis or ovary. The most common malignant germ cell tumor in children is the yolk sac tumor. In neonates and young children, yolk sac tumors are primarily found in extragonadal sites or testes. In older children and adolescents, the ovary is the most common location. The current treatment for pediatric germ cell tumors consists of surgical resection and selective use of chemotherapy (cisplatin, etoposide, and bleomycin) based upon risk groups (Table 1). Unresectable tumors will often respond well to neoadjuvant chemotherapy making resection possible after treatment.

## 2. Surgical Management

In general, localized tumors that are amenable to surgical excision without loss of vital organs should be primarily excised. Prior to exploration, appropriate preoperative studies should be obtained including serum markers  $\alpha$ -fetoprotein and  $\beta$ -human chorionic gonadotropin. In addition, computed tomography (CT) of the chest and abdomen are helpful for the evaluation of metastatic disease. Finally, the use of metal clips during resection is discouraged. These clips may produce radiographic artifacts that could obscure findings or make the interpretation of imaging studies for evaluation of residual or recurrent disease more difficult. The recommendations for surgical treatment of specific sites of germ cell tumors follow.

### **Extragonadal Germ Cell Tumors – Sacrococcygeal, Mediastinum, Abdomen and Retroperitoneum, Vagina**

#### **Sacrococcygeal**

In neonates, these lesions are usually benign and amenable to resection via the posterior approach, including the coccyx with the specimen. In tumors with a large intraabdominal component, initial laparotomy with vascular control and tumor mobilization may be required. When the diagnosis is made later in infancy or childhood, these tumors are more often malignant, and up to half of the children will have metastatic disease, usually to the lung. For those children in whom the primary tumor is not resectable, biopsy followed by neoadjuvant chemotherapy and delayed resection is acceptable.

#### **Mediastinum**

The mediastinum is the second most common extragonadal site for germ cell tumors. Potential airway compromise makes anesthetic management paramount. These tumors may be approached either through a median sternotomy or thoracotomy. If initial resection is not possible, then a strategy utilizing biopsy, neoadjuvant chemotherapy and delayed resection does not appear to adversely affect outcome.

### **Abdomen or Retroperitoneum**

These tumors are often large at presentation and may require biopsy with neoadjuvant chemotherapy followed by delayed resection. Complete resection is required, as malignancy occurs in about fifteen percent of these tumors.

### **Vagina**

Germ cell tumors of the vagina are rare, but most present in the first year of life. Most of these tumors are yolk sac tumors. Surgical strategy is for preservation of function, therefore biopsy and neoadjuvant chemotherapy may allow for a vaginal preservation procedure.

### **Staging**

Table 2 delineates the current staging system for all germ cell tumors located in extragonadal sites.

## **Gonadal Germ Cell Tumors – Ovary and Testis**

### **Ovary**

The recommended treatment for ovarian germ cell tumors includes unilateral oophorectomy and inspection of the contralateral ovary with biopsy of suspicious lesions. In addition, ascitic fluid or peritoneal washings if no fluid is present are to be sent for cytological examination. The diaphragm, omentum, and lymph nodes are inspected and biopsies are performed only if there are any suspicious lesions. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is not advocated as an initial procedure, as most unresectable tumors will respond to neoadjuvant chemotherapy, making unilateral oophorectomy possible. In addition, if laparoscopy is utilized, care must be taken to avoid tumor spill, as this will upstage the patient and may result in a child requiring postoperative chemotherapy who would not have otherwise needed it.

### **Staging**

Table 3 outlines the current staging system for germ cell tumors located in the ovary.

### **Testis**

The surgical treatment of these tumors consists of an inguinal orchiectomy. An inguinal incision is performed and the spermatic cord structures isolated and controlled at the level of the internal ring. The testis is mobilized into the wound and removed with the cord structures. If the lesion is in question, a biopsy may be performed through the described inguinal approach. Retroperitoneal lymph nodes that are < 2 cm are considered benign and do not require biopsy. Nodes larger than 4 cm are considered to contain disease, and therefore are treated as Stage III. Retroperitoneal lymph nodes > 2 cm but < 4 cm should be biopsied.

## **Staging**

Table 4 outlines the current staging system for germ cell tumors of the testis.

### **3. Recent Literature**

Between 1990 and 1996, two organizations, the Children's Cancer Group and the Pediatric Oncology Group, conducted intergroup trials for children with malignant germ cell tumors. These studies are the source of our most recent surgical literature on this subject. Data from these studies demonstrated the success of surgical resection alone in the treatment of children with Stage I testis germ cell tumors. The studies reported an overall six year event free survival greater than 75% in these tumors. In addition, all of the boys that relapsed were salvaged with chemotherapy, resulting in a 6 year survival of 100% (1). Data addressing ovarian germ cell tumors were published in 2004. Billmire et al reported that platinum based therapy resulted in excellent survival in girls with malignant ovarian neoplasms and therefore revised the surgical management guidelines for these tumors (2). The data addressing the current recommended treatment of mediastinal, abdominal and retroperitoneal germ cell tumors was also provided by these intergroup studies. These studies showed that large mediastinal (3) and abdominal/retroperitoneal (4) germ cell tumors that were not amenable to primary surgical resection, could be treated with biopsy, neoadjuvant chemotherapy, and delayed surgical resection with outcomes similar to those tumors resected primarily.

### **4. COG Protocols for Malignant Germ Cell Tumors**

Currently, there are two COG protocols open for enrollment for patients with malignant germ cell tumors: AGCT0132 and AGCT0521. AGCT0132 is a Phase III study investigating whether treatment reduction is appropriate for low or intermediate risk tumors. In this study, low risk tumors were to be treated with surgery alone. However, a high rate of local relapse has resulted in the recommendation to treat these patients with chemotherapy. Children with intermediate risk tumors, or low risk patients whose tumors recur, receive standard chemotherapy consisting of cisplatin, etoposide, and bleomycin, but in a decreased cumulative dose. AGCT0521 is a Phase II study investigating the efficacy of treating recurrent or resistant malignant germ cell tumors with paclitaxel, ifosfamide, and caboplatin. To enter this study, patients must have measurable disease by imaging. If they have measurable disease by imaging and elevated tumor markers, they do not require repeat biopsy. However, if their imaging shows disease but their tumor markers are not elevated, they require a biopsy for confirmation of recurrence. After their treatment, they may undergo further medical therapy or surgical resection. There are currently no open COG protocols for high risk tumors. The AGCT01P1 study was the most recent open study, completing accrual in late 2007. The major finding in this study was that the addition of cyclophosphamide to the standard PEB (cisplatin, etoposide, and bleomycin) regime as a way to intensify therapy for high risk germ cell tumors is well tolerated and feasible.

**TABLE 1**

<u>Low Risk</u>	Stage I malignant gonadal germ cell tumors,
<u>Intermediate Risk</u>	Stage I-II extragonadal, stage II-III ovarian, Stage II-IV testicular germ cell tumors, stage I gonadal tumors that recur.
<u>High Risk</u>	Stage III-IV extragonadal and stage IV ovarian germ cell tumors

**TABLE 2: STAGING EXTRAGONADAL GERM CELL TUMORS**

<u>Stage</u>	<u>Disease Extent</u>
I	Complete resection with negative tumor margins and coccygectomy for sacrococcygeal location
II	Microscopic residual disease with negative lymph nodes
III	Lymph node involvement with metastatic disease. Gross residual or biopsy only; retroperitoneal nodes negative or positive
IV	Distant metastases

**TABLE 3: STAGING OVARIAN GERM CELL TUMORS**

<u>Stage</u>	<u>Disease Extent</u>
I	Confined to ovary with negative peritoneal evaluation
II	Microscopic residual disease with negative peritoneal evaluation. Tumor markers fail to normalize or decrease with appropriate half life.
III	Lymph node involvement; gross residual with biopsy only; contiguous visceral involvement (bladder, intestine, omentum); positive peritoneal evaluation for malignancy (benign gliomatosis peritonei does <u>not</u> upstage to stage III)
IV	Distant metastases

**TABLE 4: STAGING TESTICULAR GERM CELL TUMORS**

<u>Stage</u>	<u>Disease Extent</u>
I	Confined to testis with complete resection via high inguinal orchiectomy. Children with normal or unknown tumor markers must have negative ipsilateral retroperitoneal node sampling to confirm Stage I if radiographic studies demonstrate lymph nodes > 2 cm.
II	Transscrotal biopsy; microscopic disease in scrotum or high (< 5 cm from proximal end) in spermatic cord. Tumor markers fail to normalize or decrease with appropriate half life.
III	Retroperitoneal lymph nodes > 4 cm by CT, or lymph nodes > 2 cm and < 4 cm with biopsy proven involvement.
IV	Distant metastases including liver, visceral or extra-abdominal involvement

## **5. References**

1. Schlatter M, Rescorla F, Giller R, et al. Excellent outcome in patients with Stage I germ cell tumors of the testes: a study of the Children's Cancer Group/Pediatric Oncology Group. (2003) J Pediatr Surg 38:319-24.
2. Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. (2004) J Pediatr Surg 39:424-429.
3. Billmire D, Vinocur C, Rescorla F, et al. Malignant mediastinal germ cell tumors: an intergroup study. (2001) J Pediatr Surg 36:18-24.
4. Billmire D, Vinocur C, Rescorla F, et al. Malignant retroperitoneal and abdominal germ cell tumors: an intergroup study. (2003) J Pediatr Surg 38:315-318.