**Protocol for the Examination of Resection Specimens From Patients With Extragonadal Germ Cell Tumors**

**Version:** 4.1.0.0

**Protocol Posting Date:** June 2021

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

**This protocol should be used for the following procedures AND tumor types:**

|  |  |
| --- | --- |
| **Procedure** | **Description** |
| Resection | Includes specimens designated marginal and wide resections |
| **Tumor Type** | **Description** |
| Germ cell tumors | Includes pediatric and adult patients with germ cell tumors located in the mediastinum, sacrococcygeal area, retroperitoneum, and neck |

**The following should NOT be reported using this protocol:**

|  |
| --- |
| **Procedure** |
| Biopsy (consider Extragonadal Germ Cell Biopsy protocol) |
| **Tumor Type** |
| Testicular germ cell tumors (consider the Testis protocol) |
| Ovarian germ cell tumors (consider the Ovary, Fallopian Tube, Peritoneum protocol) |
| CNS (intracranial only) germ cell tumors (consider the CNS protocol) |

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**Accreditation Requirements**

The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

**Summary of Changes**

**v 4.1.0.0**

* General Reformatting
* Revised Margins Section
* Revised Lymph Nodes Section
* Added Distant Metastasis Section
* New Microscopic Coccyx Involvement Question
* New Tumor Extent Question
* New Immunohistochemistry Markers Added
* Elements that are recommended for clinical care purposes are designated as Core and Conditional (indicated by bolded text), while Non-core elements are now indicated with a plus (+) sign

**Reporting Template**

**Protocol Posting Date: June 2021**

**Select a single response unless otherwise indicated.**

**CASE SUMMARY: (EXTRAGONADAL GERM CELL TUMOR: Resection)**

**CLINICAL**

**+Treatment History**

\_\_\_ No known preoperative therapy

\_\_\_ Preoperative therapy given

\_\_\_ Not specified

**Patient Age (Note** [**A**](#1924)**)**

\_\_\_ Congenital / neonatal (birth - 6 months)

\_\_\_ Childhood / prepubertal (7 months - 11 years)

\_\_\_ Postpubertal / adult (greater than or equal to 12 years)

**SPECIMEN**

**Procedure**

\_\_\_ Marginal resection

\_\_\_ Wide resection

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**TUMOR**

**Tumor Site (Note** [**B**](#1925)**)**

\_\_\_ Intracranial: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Head and neck region (including thyroid; excluding intracranial): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Mediastinum (pericardium, heart, thymus, and lung): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Retroperitoneum / abdomen: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Sacrococcygeal: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

**Histologic Type (Note** [**C**](#1926)**)**

*Teratoma*

\_\_\_ Mature teratoma

\_\_\_ Immature teratoma

**Percentage of Teratoma Composed of Immature Elements**

\_\_\_ Specify percentage: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ %

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined

\_\_\_ Mature or immature teratoma with additional malignant somatic component (specify type, e.g., epithelial malignancy, sarcoma): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*Malignant Germ Cell*

\_\_\_ Germinoma

\_\_\_ Yolk sac tumor

\_\_\_ Embryonal carcinoma

\_\_\_ Choriocarcinoma

\_\_\_ Mixed germ cell tumor (any combination of the above, with or without teratoma) (specify components): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Histologic Type Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**+Histologic Grade (applicable to immature teratomas only) (Note** [**D**](#1927)**)**

\_\_\_ 1

\_\_\_ 2

\_\_\_ 3

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Tumor Size (Note** [**E**](#1931)**)**

\_\_\_ Greatest dimension in Centimeters (cm): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

**+Additional Dimension in Centimeters (cm): \_\_\_\_ x \_\_\_\_ cm**

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Microscopic Coccyx Involvement (applicable to sacrococcygeal resections only)**

\_\_\_ Not applicable

\_\_\_ Not identified

\_\_\_ Present

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Tumor Extent (applicable to adult [post-pubertal] extragonadal germ cell tumors)**

\_\_\_ Well-circumscribed without focal adhesions to pleura or pericardium

\_\_\_ Well-circumscribed with focal adhesions to pleura or pericardium

\_\_\_ Confined to the mediastinum with macroscopic and / or microscopic invasion into adjacent structures (i.e., pleura, pericardium, and great vessels) (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not applicable

**+Lymphovascular Invasion**

\_\_\_ Not identified

\_\_\_ Present

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Perineural Invasion**

\_\_\_ Not identified

\_\_\_ Present

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Treatment Effect (Note** [**F**](#1932)**)**

\_\_\_ Not identified

\_\_\_ Present

**+Percentage of Tumor Necrosis**

\_\_\_ Specify percentage: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ %

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not applicable

**+Tumor Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**MARGINS (Note** [**G**](#1933)**)**

**Margin Status**

\_\_\_ All margins negative for tumor

**+Closest Margin(s) to Tumor**

\_\_\_ Specify closest margin(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Distance from Tumor to Closest Margin**

*Specify in Centimeters (cm)*

\_\_\_ Exact distance: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

\_\_\_ Greater than: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

\_\_\_ At least: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

\_\_\_ Less than: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

\_\_\_ Less than 0.1 cm

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Tumor present at margin

**+Margin(s) Involved by Tumor**

\_\_\_ Specify involved margin(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not applicable

**+Margin Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**REGIONAL LYMPH NODES**

**Regional Lymph Node Status**

\_\_\_ Not applicable (no regional lymph nodes submitted or found)

\_\_\_ Regional lymph nodes present

\_\_\_ All regional lymph nodes negative for tumor

\_\_\_ Tumor present in regional lymph node(s)

**Number of Lymph Nodes with Tumor**

\_\_\_ Exact number (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ At least (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Nodal Site(s) with Tumor, if known**

\_\_\_ Not known

\_\_\_ Specify nodal site(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Histologic Type Present in Involved Node(s)**

\_\_\_ Specify type(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Number of Lymph Nodes Examined**

\_\_\_ Exact number (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ At least (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Regional Lymph Node Comment: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**DISTANT METASTASIS**

**Distant Site(s) Involved, if applicable (select all that apply)**

\_\_\_ Not applicable

\_\_\_ Intrathoracic organ(s) or site(s) (i.e., lymph nodes, lung, etc.) (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Liver: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other extrathoracic organ(s) or site(s) (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Size of Largest Distant Metastasis**

\_\_\_ Specify in Centimeters (cm): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ cm

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Histologic Type Present in Distant Metastasis**

\_\_\_ Specify type(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**PATHOLOGIC STAGE (Note** [**H**](#1934)**)**

**+Children’s Oncology Group Staging for any Malignant Extragonadal Germ Cell Tumor (see also specific staging systems for mediastinal germ cell tumors)**

*COG Staging is based on pretreatment tumor characteristics. Clinical information required to definitively assign stage (e.g., gross residual disease or presence of metastatic disease) may not be available to the pathologist. If applicable, the appropriate stage group may be assigned by the pathologist.*

\_\_\_ Stage I: Complete resection at any site; coccygectomy for sacrococcygeal site; negative tumor margins

\_\_\_ Stage II: Microscopic residual; lymph nodes negative

\_\_\_ Stage III: Lymph nodes involved by metastatic disease. Gross residual or biopsy only, retroperitoneal nodes negative or positive

\_\_\_ Stage IV: Distant metastases, including liver

**+Moran and Suster Proposed Clinical Staging for Mediastinal Germ Cell Tumors#**

*# Applies to adult (postpubertal) extragonadal germ cell tumors.*

\_\_\_ Stage I: Well-circumscribed tumor with or without focal adhesions to the pleura or pericardium but without microscopic evidence of invasion into adjacent structures

\_\_\_ Stage II: Tumor confined to the mediastinum with macroscopic and / or microscopic evidence of infiltration into adjacent structures (i.e., pleura, pericardium, and great vessels)

\_\_\_ Stage III: Tumor with metastases

\_\_\_ Stage IIIA: With metastases to intrathoracic organs (lymph nodes, lung, etc)

\_\_\_ Stage IIIB: With extrathoracic metastases

**ADDITIONAL FINDINGS (Note** [**I**](#1928)**)**

**+Associated Syndrome(s) (select all that apply)**

\_\_\_ Not known

\_\_\_ Klinefelter

\_\_\_ Down

\_\_\_ Other (e.g., intersex, Li Fraumeni) (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Associated Malignancy (not part of the extragonadal germ cell tumor) (select all that apply)**

\_\_\_ Leukemia (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Myelodysplastic syndrome (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+Other Clinical Findings (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**SPECIAL STUDIES (Notes** [**J**](#1929)**,**[**K**](#1930)**)**

*Immunohistochemistry*

**+SALL4 IHC**

\_\_\_ Not performed

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

**+OCT3/4 IHC**

\_\_\_ Not performed

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

**+CD30 IHC**

\_\_\_ Not performed

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

**+AFP IHC**

\_\_\_ Not performed

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

**+Glypican-3 IHC**

\_\_\_ Not performed

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

**+Beta-HCG IHC**

\_\_\_ Not performed

\_\_\_ Positive

\_\_\_ Negative

\_\_\_ Pending

**+Other Immunohistochemistry (IHC) Studies (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

*Cytogenetic Studies*

**+Results of Cytogenetic Studies (select all that apply)**

\_\_\_ Not specified

\_\_\_ Not performed

\_\_\_ Pending

\_\_\_ Normal karyotype

\_\_\_ Isochromosome 12p abnormality [i(12p)]

\_\_\_ Other [e.g., del(5q), trisomy 8, 11q23 abnormality] (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*Serologic Markers*

**+Serologic Marker Testing (select all that apply)**

\_\_\_ Not specified

\_\_\_ Not performed

\_\_\_ Serum alpha-fetoprotein (AFP) (specify level): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Serum human chorionic gonadotropin (hCG) (specify level): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**COMMENTS**

**Comment(s): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Explanatory Notes**

**A. Patient Age**

The behavior of pediatric and adult extragonadal germ cell tumors (EGCTs) is quite distinct. As outlined below, within the pediatric age range, prognosis is worse with increasing age. Most studies of pediatric EGCTs include both neonates and older children, making it difficult to discern the precise pathology and clinical course of EGCTs in the older child. A recent study[1](#7148) has suggested that age 12 years or older is a significantly adverse prognostic factor, especially for thoracic tumors, and therefore may represent the transition point to adult type tumors.

The notes that follow are divided into congenital/neonatal EGCTs (birth to 6 months) and childhood/prepubertal GCTs (7 months to approximately 12 years) because of the well-documented differences in their pathology and prognosis. Postpubertal/adult EGCTs are defined as occurring in patients 12 years and older.

These notes describe important differences in the pathologic diagnosis and prognosis of EGCTs in different age groups: congenital/neonatal, children (prepubertal), and adult (postpubertal). They are summarized in the Table. Within each age group, the significance of anatomic site and morphologic subtyping is emphasized. Other issues discussed include postchemotherapy evaluation, unique associated malignancies, and associated syndromes. Finally, discussion of differential diagnoses is presented based on anatomic location and patient age.

|  |
| --- |
| **Key Features of Extragonadal Germ Cell Tumors (GCTs)** |
| Congenital/neonatal (birth - 6 mo) |
| Sacrococcygeal site most common |
| All sites appear to behave similarly |
| Most are teratoma with or without yolk sac tumor |
| Immaturity and histologic type of GCT may not be critical |
| Conservative approach with follow-up after surgical excision may be indicated |
| Childhood (7 mo - puberty) |
| Rare |
| More frequently yolk sac tumor |
| More frequent aggressive behavior and worse prognosis than neonatal |
| Adult (postpubertal) |
| All may be associated with the development of non-germ cell neoplasms |
| Generally poor prognosis at any site if present |
| Mediastinal (including thymus) |
| Mature teratoma is benign |
| Immature teratoma and other nonteratomatous GCTs are potentially aggressive |
| Unique association with hematopoietic neoplasms |
| Sacrococcygeal |
| Most are mature teratoma, with benign behavior |
| Immaturity not shown to be an adverse feature |
| Rarely associated with nonteratomatous GCTs, which behave aggressively |
| Cervical (including thyroid) |
| Mature teratoma is benign |
| Immature teratoma and other nonteratomatous GCTs are potentially aggressive |
| Retroperitoneal |
| Most are derived from occult gonadal primary |

References

1. Marina N, London WB, Frazier AL, et al. Prognostic factors in children with extragonadal malignant germ cell tumors: a pediatric intergroup study. J Clin Oncol. 2006;24(16):2544-2548.

**B. Site**

Congenital/Neonatal

Other than direct effects on local vital organs, the behavior of congenital and neonatal extragonadal GCTs seems to be independent of anatomic location.[1](#7149) Sacrococcygeal teratomas are the most common GCT of the neonate, occurring more frequently in girls. After intracranial teratomas, other more common sites of neonatal teratoma include the mediastinum (pericardium, heart, thymus, and lung), head and neck region (including thyroid), and the retroperitoneum. Neonatal teratomas may occur anywhere along the body midline, following the course of the embryonic germ cell ridge. These tumors have a similar morphology at each site.

Prepubertal/Child

Mediastinal GCTs occur more commonly in older adolescence and the postpubertal child. Mixed malignant GCTs comprised of teratoma, yolk sac tumor, embryonal carcinoma, and rarely choriocarcinoma are more frequent with increasing age. Germinoma is generally not seen in children less than 10 years of age.[2](#7150) As in congenital teratoma, the prognosis of mediastinal GCTs in children is significantly affected by tumor stage and completeness of surgical excision (see Notes F and G).[3](#7151) Rarely, sarcomatous elements are reported in pediatric mediastinal GCTs.

Sacrococcygeal tumors in the older infant and child are predominantly presacral and pelvic, with no externalized mass noted at birth. Malignancy rates are reportedly very high in these children, most commonly due to yolk sac tumor.[4](#7152) It is thought that many of these tumors represent congenital sacrococcygeal GCTs (SGCTs) with an overgrowth of yolk sac tumor, analogous to the malignant recurrences of yolk sac tumors in children with incompletely excised congenital SGCT.[5](#7153)

Although pelvic and/or retroperitoneal extension of a sacrococcygeal tumor is not unusual, an exclusively retroperitoneal or abdominal location is uncommon, comprising less than 5% of all EGCTs.

The majority of intracranial germ cell tumors arise in structures around the third ventricle, most commonly in the pineal gland or suprasellar region. The CAP protocol for reporting CNS tumors can be used for tumors arising from a primary intracranial site.

Postpubertal/Adult

The mediastinum is the most common anatomic site for extragonadal GCTs in adults. These tumors are overwhelmingly restricted to males, but well-documented cases in women do exist. The histologic classification of GCTs at this site is identical to that used in the gonads: seminomatous (pure), nonseminomatous (yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed GCTs), and teratomas. One important difference is that, unlike the situation in the adult testis or in congenital/pediatric GCT, the distinction between mature and immature teratoma is important in the adult mediastinum.

Sacrococcygeal GCTs in this age group are generally considered to have been present since birth. In some cases, there is a history of a partially resected neonatal lesion to support this interpretation. The location is similar to that seen in pediatric cases except that most are intrapelvic because tumors with an external component would be expected to have been discovered in childhood. Adenocarcinoma may arise in the SGCT of adults.

The distribution of cervical GCTs (CGCTs) in adults is similar to that seen in children, with frequent involvement of the thyroid. Some cases have presented in continuity with a mediastinal GCT. Most purely retroperitoneal GCTs in adults represent metastases from an undiscovered or occult primary in the testicle or, rarely, in the ovary. In general, a testicular primary must be excluded clinically.

References

1. Marina N, London WB, Frazier AL, et al. Prognostic factors in children with extragonadal malignant germ cell tumors: a pediatric intergroup study. J Clin Oncol. 2006;24(16):2544-2548.
2. Schneider DT, Calaminus G, Koch S, et al. Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer. 2004;42(2):169-175.
3. Schneider DT, Calaminus G, Reinhard H, et al. Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. J Clin Oncol. 2000;18(4):832-839.
4. Rescorla FJ, Sawin RS, Coran AG, Dillon PW, Azizkhan RG. Long-term outcome for infants and children with sacrococcygeal teratoma: a report from the Childrens Cancer Group. J Pediatr Surg. 1998;33(2):171-176.
5. Gobel U, Schneider DT, Calaminus G, et al. Germ-cell tumors in childhood and adolescence. GPOH MAKEI and the MAHO study groups. Ann Oncol. 2000;11(3):263-271.

**C. Histologic Type**

The World Health Organization (WHO) classification of germ cell tumors is the basis for most contemporary classifications and is the one generally used for EGCTs. According to this classification, germ cell neoplasms are divided roughly into 7 histologic categories: dysgerminoma, yolk sac tumor, embryonal carcinoma, polyembryoma, choriocarcinoma, teratoma, and gonadoblastoma.[1](#7154) Gonadoblastoma, a neoplasm typically found in dysgenetic gonads, is included in the category of germ cell tumors (mixed germ cell, sex cord-stromal tumors). According to this classification, fetus in fetu is regarded as a form of mature teratoma. The most common germ cell tumors occurring in the perinatal period in order of rank are teratoma, yolk sac tumor, choriocarcinoma, and gonadoblastoma.

Extragonadal germ cell neoplasms can be classified for histopathology using mediastinal nomenclature (ie, teratomatous and nonteratomatous lesions).[2](#7155)

Congenital/Neonatal

Most germ cell tumors of the fetus and neonate are histologically benign and are classified as either mature or immature teratomas.[3](#7156) Yolk sac tumor (endodermal sinus tumor) is the leading malignant germ cell tumor of the perinatal period and throughout childhood. In the fetus and neonate, it occurs most often with a teratoma and adversely affects the prognosis.

The sacrococcygeal area is the location associated with the highest incidence of malignancy, in the form of yolk sac tumor. The overall frequency of neonatal sacrococcygeal teratomas with a yolk sac tumor is approximately 10%. The values cited in the literature range from 2.5%-25%.[3,](#7156)[4](#7157) The incidence of malignancy in the neonate is approximately 10%, approaching almost 100% by 3 years.[3,](#7156)[4,](#7157)[5,](#7158)[6](#7159)

Prepubertal/Child

The occurrence of admixed yolk sac tumor or recurrence as yolk sac tumor is more common with the presentation of teratoma in patients older than 6 months. Similarly, in older infants (after 7 months), the incidence of teratoma falls, whereas the incidence of pure yolk sac tumor increases. Most yolk sac tumors are diagnosed between 7 months and the third year of life. Pure embryonal carcinomas are rare before 5 years old.[7](#7160) As noted, prognosis worsens with increasing age, and the prognosis (ie, recurrence rate) of completely resected EGCTs worsens at approximately 7 months. The designation of a child as prepubertal is sometimes difficult, but at least 1 study[8](#7161) suggests 12 years or older is a significant age boundary.

Postpubertal/Adult

Approximately 43% of all mediastinal GCTs contain teratoma and include mature teratoma (63%), immature teratoma (4%), and teratoma with other malignant components (ie, sarcoma, other malignant germ cell element, or carcinoma; 33%).[2](#7155) Because histologically mature teratomas behave in a clinically benign fashion regardless of patient age, and immature teratomas have the potential for aggressive behavior, the distinction is critical to patient management in adults. Mature teratomas are histologically similar to those occurring in the ovary. Despite their similarity to ovarian GCTs, monodermal teratomas such as struma ovarii have not been described in the mediastinum.

In adults, the most common nonteratomatous component is germinoma/seminoma, but yolk sac tumor, embryonal carcinoma, and choriocarcinoma may also occur. Mediastinal germinoma frequently involves the thymus, with resultant cyst formation and thymic epithelial cell hyperplasia.[9](#7162) This may make the recognition of the germinomatous component difficult. A high level of suspicion is necessary in the case of cystic lesions of the thymus, especially if associated with a granulomatous response. The morphology of nonteratomatous components is otherwise identical to those in the gonads and will not be repeated here because it has been reviewed in detail elsewhere.[10](#7163) All nonteratomatous elements should be regarded as malignant in adults.

References

1. Nogales F, Talerman A, Kubik-Huch RA, Tavassoli FA, Devouassoux-Shisheboran M. Germ cell tumors. In: Tavassoli FA, Devilee P, eds. World Health Organization (WHO) Classification of Tumours: Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon, France: IARC Press; 2003.
2. Moran CA, Suster S. Primary germ cell tumors of the mediastinum, I: analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. Cancer. 1997;80(4):681-690.
3. Isaacs Jr. H. Perinatal (fetal and neonatal) germ cell tumors. J Pediatr Surg. 2004;39(7):1003-1013.
4. Isaacs Jr. H. Germ Cell Tumors: Tumors of the Fetus and Newborn. Vol 35. Philadelphia, PA: Saunders; 1997.
5. Noseworthy J, Lack EE, Kozakewich HP, Vawter GF, Welch KJ. Sacrococcygeal germ cell tumors in childhood: an updated experience with 118 patients. J Pediatr Surg. 1981;16(3):358-364.
6. Dehner LP. Neoplasms of the fetus and neonate. In: Naeye RL, Kissane JM, Kaufman N, eds. Perinatal Diseases, International Academy of Pathology. Vol. 22. Baltimore, MD: Williams and Wilkins; 1981:286-345.
7. Schneider DT, Calaminus G, Koch S, et al. Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer. 2004;42(2):169-175.
8. Marina N, London WB, Frazier AL, et al. Prognostic factors in children with extragonadal malignant germ cell tumors: a pediatric intergroup study. J Clin Oncol. 2006;24(16):2544-2548.
9. Moran CA, Suster S. Mediastinal seminomas with prominent cystic changes: a clinicopathologic study of 10 cases. Am J Surg Pathol. 1995;19(9):1047-53.
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**D. Grade (Immature Teratomas)**

The histologic grade of the tumor is based on 3 factors: degree of immaturity, presence of a neuroepithelial component, and the quantity of the latter.[1](#7164)

Grade 1 is given to neoplasms with some immaturity but with neuroepithelium absent or limited to a rare low-power magnification (X40) field within the tumor, and not more than 1 such focus in any slide.

Grade 2 is given when immaturity and neuroepithelium were present to a greater degree than grade 1. Neuroepithelium is common but does not exceed 3 low-power microscopic fields in any 1 slide.

Grade 3 is given when immaturity and neuroepithelium were prominent, the latter occupying 4 or more low-magnification microscopic fields within individual sections.

Care should be taken in establishing a grade on biopsy specimens, and limitations of sampling should be noted.

Congenital/Neonatal

The presence or grade of immaturity, as defined by Norris et al.[1](#7164) for ovarian teratomas, is not predictive of malignant behavior in congenital EGCTs, although immature teratomas are more likely to have admixed yolk sac tumor. It is well recognized that incomplete surgical resection of neonatal teratomas is associated with recurrences of a pure yolk sac tumor, as seen in cases of sacrococcygeal teratoma for which coccygectomy was not performed.[2](#7165) In some cases with recurrence, foci of the yolk sac tumor could not be identified in the original resected teratoma. It is unclear whether that is due to incomplete sampling of the original lesion or whether elements of a residual immature teratoma can give rise to a yolk sac tumor.

Prepubertal/Child

Increased patient age, sacrococcygeal location, and grade 2 to 3 immaturity are more frequently associated with admixed yolk sac tumor.[2](#7165)

Postpubertal/Adult

Immature teratomas, like their testicular counterparts, are most commonly identified by cellular spindled stroma (ie, immature mesenchyme) surrounding glandular epithelium. Immature neuroepithelial elements similar to those seen in immature teratomas of the ovary may also be identified. Immature neuroepithelium should be distinguished from mature ependyma, a relatively common finding in mature teratomas. Other admixed immature elements frequently include cartilage and glandular epithelium, but the diagnosis of immaturity does not typically depend on these elements. At present, there is no grading schema for extragonadal immature teratomas; however, it is reasonable to report the percentage of immature elements.

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**E. Tumor Size**

The number of sections submitted varies with the size and character of the specimen and the nature of the underlying neoplastic process. At least 1 section per centimeter of the tumor’s greatest diameter is recommended if the tumor is a germ cell neoplasm because diverse elements may only be found in this way and might affect the tumor classification.[1](#7184)

Congenital/Neonatal

Large SGCTs may be associated with fetal hydrops because of increased demands on the heart to supply the tumor vasculature and may be associated with fatal intratumoral hemorrhage with delivery. Survival with cervical teratoma depends on the size of the tumor and extent of tissue involvement, with respiratory compromise being the main cause of subsequent morbidity and mortality.[2](#7185) Neonates with cervical teratomas generally have a good outcome when the tumor is resectable. Fetuses have a much lower survival rate than neonates (23% versus 85%). Ten percent of the fetuses are stillborn.

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**F. Postchemotherapy Evaluation**

Patients with malignant EGCTs (especially adults) often receive cisplatin-based chemotherapy before surgical resection. This clinical practice places an extreme importance on the initial biopsy interpretation and also creates challenges in the evaluation of the resection specimen. The post-therapy tissue usually shows necrosis, fibrosis, mixed inflammatory infiltrates, and xanthogranulomatous inflammation. Because response to therapy is one of the main prognostic variables, the percentage of viable nonteratomatous GCT should be reported, a finding present in up to 50% of resection specimens, even after normalization of serum markers.[1](#7186) Less than 10% viable tumor cells is a good prognostic factor as defined by the International Germ Cell Consensus Classification Group (IGCCCG).[2](#7187) Residual viable tumor may be relatively focal; therefore, areas of scarring, necrosis, or hemorrhage should be carefully examined.

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**G. Margins/Vascular Invasion**

Because completeness of excision is also an important prognostic factor, the excision specimens should be inked and the margin status should be reported. Any adherence of the mass to other structures should be carefully described. If there is question about adherence, consultation with the surgeon is strongly recommended.

Vascular invasion can involve blood vessels or lymphatics. In suspicious cases, blood vessels can behighlighted with immunoperoxidase staining for factor VIII, CD31, and CD34. Lymphatic markers such as D2-40 (podoplanin) or LYVE1 may confirm lymphatic invasion.

**H. Staging**

Clinical and pathologic staging is very important in the prognosis of EGCTs. Unfortunately, there is not an officially recognized American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM staging protocol for EGCTs. The Children’s Oncology Group utilizes a 4-tiered staging system for all EGCTs.[1](#7188) Surgeons also carefully define anatomic resections specifically of sacrococcygeal EGCTs. The WHO recommends using a modification of the AJCC TNM staging of soft tissue tumors.[2](#7189) Moran and Suster[3](#7190) have also proposed a novel staging system specifically for mediastinal GCTs based on an outcome study of 322 cases.

In the Pediatric Oncology Group/Children’s Cancer Group Intergroup study,[4](#7191) there were 22 children with completely resected, extragonadal, immature teratomas, including 6 (27%) with admixed yolk sac tumor. None of the patients received adjuvant chemotherapy. Three of the 22 children (14%) developed recurrent yolk sac tumors, including 1 child with no admixed yolk sac tumor at diagnosis. Each of these children was treated for their recurrence with surgery and platinum-based chemotherapy (cisplatin, etoposide, and bleomycin). The conclusion of the study was that complete surgical excision is effective treatment for children with immature teratomas, with or without admixed yolk sac tumor. The authors noted that patients with extragonadal tumors are a higher risk group and require very careful follow-up. Although adjuvant chemotherapy could be considered in these patients, it is not recommended because of the toxicity of unnecessary chemotherapy and the success of salvage therapy for those children who do relapse.[4](#7191)

A rare finding in extragonadal teratomas of very young children is the occurrence of nodal gliomatosis in regional lymph nodes draining the teratoma.[5](#7192) The authors have had personal experience with such cases in which the finding had no effect on the patient’s clinical course and did not seem to warrant a designation of a “metastasis” upstaging the patient. It is thought that the phenomenon is similar to peritoneal gliomatosis in ovarian teratomas.[5](#7192)

Mediastinal Germ Cell Tumors

The overall clinical outcome for primary mediastinal immature teratoma and nonteratomatous GCTs is reportedly worse than gonadal GCTs, but outcomes are improving with preoperative cisplatin-based combination chemotherapy strategies.[6,](#7193)[7](#7194) With neoadjuvant chemotherapy, good prognostic factors include completeness of resection, less than 10% viable tumor cells, and low-risk group as defined by the IGCCCG’s Moran and Suster Proposed Clinical Staging System for Mediastinal GCTs.[8](#7195)

In the IGCCCG groupings, there are prognostic differences among histologic subtypes of GCT. Pure mediastinal seminoma has a better outcome than tumors with a nonseminomatous component. The reported 5-year survival of 90% with cisplatin-based combination chemotherapy rivals the outcome of testicular seminomas.[9](#7196) Poor prognostic features of pure seminoma include liver or other nonpulmonary visceral metastases and metastases to 2 or more sites.[9](#7196) Primary mediastinal choriocarcinoma is rare but reportedly has a much worse prognosis than other histologic subtypes owing to the hematogenous dissemination at the time of diagnosis.[10](#7197) At least some studies that include choriocarcinomas suggest an improved prognosis under current chemotherapeutic regimens.[11](#7198) Embryonal carcinoma and yolk sac tumor, whether pure or in association with any other components (seminoma or teratoma), have a similar outcome and are generally regarded as poor prognostic findings. As discussed above, mature teratoma is benign, but immature teratoma has some potential for malignant behavior. In stage I pure immature teratomas (ie, no infiltration of adjacent structures and no mixed germ cell elements or secondary malignancy), the risk for aggressive behavior may be fairly low, but clinical outcome data are limited.

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**I. Associated Syndromes and Malignancies**

Some constitutional syndromes are thought to have an increased incidence of EGCTs, including Klinefelter[1](#7166) and Down syndrome.[2](#7167) The association of hematopoietic malignancies with mediastinal EGCTs was described in the Cytogenetics Note. Sarcomatous differentiation, which is most frequent in the mediastinum, may occur in association with teratomas or, less commonly, with other malignant GCTs. As in the gonads, secondary squamous cell carcinoma, adenosquamous carcinoma, and colonic-type adenocarcinoma may rarely complicate extragonadal teratomas.[3](#7168) The presence of sarcomatous or carcinomatous elements portend a very poor prognosis.

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**J. Cytogenetics**

It is well documented that pediatric GCTs are distinct from adult GCTs cytogenetically. Although the majority of adult malignant GCTs have the isochromosome 12p abnormality, this aberration is very rare in children younger than 10 years.[1](#7169) Although some yolk sac tumors have shown aberrations of the short arm of chromosome 12 by interphase fluorescence in situ hybridization,[2,](#7170)[3](#7171) no cytogenetic abnormality has been found to specifically correlate with histology or primary tumor site in children. Aberrations of 1p, 1q, 6q, chromosome and the sex chromosomes are also frequently encountered.[1,](#7169)[4](#7172) In a Children’s Oncology Group study of 81 pediatric GCTs (gonadal and extragonadal), the 12p isochromosome was only found in adolescent boys.

There is an unusual association between mediastinal GCTs, hematologic malignancies, and cytogenetics.[5](#7173) Although it is unknown why they are associated with only mediastinal tumors, genetic studies have demonstrated that both the GCT and hematopoietic components are clonally related.[5](#7173) The germ cell component is typically yolk sac tumor, but immature teratomas and other nonseminomatous GCTs are also described. The hematopoietic component frequently shows an isochromosome 12 [i(12p)], the most common genetic alteration in GCTs, but may additionally harbor translocations more typical of the specific morphologic phenotype [eg, del (5q), trisomy 8]. This finding suggests that the non-i(12p) aberration determines the tumor phenotype.

Germ cell tumor-associated acute leukemias are an ominous finding because they are typically refractory to current treatment modalities, with a reported survival of less than 2 years in all reported patients. The main differential diagnostic consideration in this setting is a therapy-related myelodysplastic syndrome or acute leukemia. Therapy-related diseases can be distinguished by their occurrence later in the course (25 to 60 months), the absence of i(12p), and the possible presence of an etoposide-related translocation such as 11q23.[6](#7174)

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**K. Tissue and Serologic Markers**

Tissue Immunohistochemistry

Extragonadal GCTs typically show immunoreactivity patterns identical to their gonadal counterparts.[1](#7175) In general, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and the epithelial elements of teratoma all show cytokeratin AE1/AE3 reactivity. A dotlike paranuclear reactivity pattern to low-molecular-weight cytokeratin (ie, CAM 5.2) is seen in up to 80% of mediastinal seminomas.

Strong membranous CD117 (c-KIT) immunoreactivity has been reported in 75%-100% of seminomas,[2](#7176) but it is not specific. CD30 is also used in the workup of a poorly differentiated malignant neoplasm because it is positive in more than 80% of embryonal carcinomas, and it also marks a spectrum of hematopoietic malignancies.[3](#7177)

Newer markers show better specificity for germ cells tumors. Nearly 100% of seminomas and embryonal carcinomas show nuclear reactivity for OCT4.[4](#7178) OCT4 is rapidly becoming the marker of choice for documenting germ cell origin (ie, seminoma or embryonal carcinoma) in the workup of an undifferentiated neoplasm. Yolk sac tumors and choriocarcinoma show cytoplasmic and membranous reactivity for the oncofetal protein glypican-3, with no significant reactivity in embryonal carcinoma or germinoma.[5](#7179) Most recently, SALL4 has been shown to demonstrate strong nuclear staining in germinoma, embryonal carcinoma, and yolk sac tumors. SALL4 appears more sensitive than either glypican-3 or AFP for the diagnosis of yolk sac tumor.[6](#7180) The mononuclear trophoblast cells of choriocarcinoma are also reactive for SALL4.

α-Fetoprotein

The presence of minute, occult, yolk sac tumor elements in large sacrococcygeal teratomas can be overlooked. Histologic detection of foci of yolk sac tumor in sacrococcygeal teratomas is very important because serum AFP levels are not always helpful as a marker, being normally high in the newborn period as a result of fetal production.[7](#7181) Moreover, primitive gut and liver tissues in preterm teratomas also react with the AFP antibody, which makes establishing the histologic diagnosis of this sometimes subtle malignancy difficult.

Most of the tumor recurrences after congenital teratoma are yolk sac tumor, and AFP is useful in following these patients. Neonatal levels are normally elevated, and the initial AFP level does not seem to correlate with the presence or absence of yolk sac tumor in neonatal teratomas. Postoperative monitoring can be useful, because the AFP level should fall after tumor excision, as it normally would in the neonate.[8,](#7182)[9](#7183)

Human Chorionic Gonadotropin

Serum ß-HCG immunohistochemistry can be used to identify choriocarcinoma. Isolated syncytial trophoblasts can stain positively in seminomas. Evaluation of serum ß-HCG is also helpful in establishing the presence of occult choriocarcinoma.

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