



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

Version: GermCell 3.1.0.1

Protocol Posting Date: August 2016

Includes the Children’s Oncology Group staging system

This protocol is NOT required for accreditation purposes

*This protocol applies to pediatric and adult patients with germ cell tumors located in the mediastinum, sacrococcygeal area, retroperitoneum, neck, and intracranial sites.

The following should NOT be reported using this protocol:

Tumor Type
Testicular germ cell tumors (consider the Testis protocol)
Ovarian germ cell tumors (consider the Ovary, Fallopian Tube, Peritoneum protocol)

Authors

Erin Rudzinski, MD*; Megan Dishop, MD*; M. John Hicks, MD

With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

** Denotes primary author. All other contributing authors are listed alphabetically.*

Accreditation Requirements

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

CAP Laboratory Accreditation Program Protocol Required Use Date: Not applicable

Surgical Pathology Cancer Case Summary

Protocol posting date: August 2016

EXTRAGONADAL GERM CELL TUMOR: Biopsy, Resection**Note: This case summary is recommended for reporting Extragonadal Germ Cell tumors, but is not required for accreditation purposes.****Select a single response unless otherwise indicated.****Procedure**Biopsy

- Core needle biopsy
 Incisional biopsy
 Excisional biopsy

Resection

- Marginal resection
 Wide resection
 Other (specify): _____
 Not specified

Patient Age (Note A)

- Congenital/neonatal (birth - 6 mo)
 Childhood/prepubertal (7 mo - 11 y)
 Postpubertal/adult (≥ 12 y)

Tumor Site (Note B)

- Intracranial
 Head and neck region (including thyroid; excluding intracranial)
 Mediastinum (pericardium, heart, thymus, and lung)
 Retroperitoneum/abdomen
 Sacrococcygeal
 Other (specify): _____
 Not specified

Tumor Size (Note C)

- Greatest dimension: ____ cm
 + Additional dimensions: ____ x ____ cm
 Cannot be determined (explain): _____

Histologic Type (Note D)Teratoma

- Mature teratoma
 Immature teratoma
 Mature or immature teratoma with additional malignant somatic component
 (specify type, eg, 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 Grade (applicable to immature teratomas only) (Note E)

- + Grade 1
- + Grade 2
- + Grade 3
 - + Percent of teratoma composed of immature elements (if applicable): ____%
- + Cannot be determined (explain): _____

+Treatment History

- + No known preoperative therapy
- + Preoperative therapy given
- + Not specified

+ Treatment Effect (Note F)

- + No known preoperative therapy (not applicable)
- + Not identified
- + Present
 - + Percent tumor necrosis: ____%
- + Percent tumor necrosis cannot be determined

Microscopic Tumor Extension (applicable to sacrococcygeal resections only)

- Tumor involving coccyx identified
- Coccyx uninvolved
- Cannot be determined (explain): _____

Margins (Note G)

- Cannot be assessed
- Uninvolved by tumor
 - Distance of tumor from closest margin: ____ cm
 - Specify margin: _____
- Involved by tumor
 - Specify margin: _____

+ Lymph-Vascular Invasion (Note G)

- + Not identified
- + Present
- + Cannot be determined

+ Perineural Invasion

- + Not identified
- + Present
- + Cannot be determined

Regional Lymph Nodes

- No nodes submitted or found

Number of Lymph Nodes Examined

- Specify: ____
- Number cannot be determined (explain): _____

Number of Lymph Nodes Involved

Specify: _____

Specify site(s), if known: _____

+ Histologic type present (specify): _____

___ Number cannot be determined (explain): _____

Distant Metastasis (required only if confirmed pathologically for this case)

___ Present

Specify site(s), if known: _____

+ Size of largest metastasis (specify): _____

+ Metastases to other organs (specify): _____

+ Histologic type present (specify): _____

+ Pathologic Staging (select all that apply) (Note H)**+ Children's Oncology Group Staging for any Malignant Extragenital Germ Cell Tumors**

(see also specific staging systems for mediastinal germ cell tumors)

Note: COG Staging is based on pretreatment tumor characteristics. Clinical information required to definitively assign stage (eg, 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[#]

+ ___ 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 (ie, 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

[#] Applies to adult (postpubertal) extragenital germ cell tumors.**+ Additional Clinical or Laboratory Findings (select all that apply)**

+ ___ None identified

+ ___ Cytogenetics (Note I)

+ ___ Not performed

+ ___ Not available

+ ___ Normal karyotype

+ ___ Abnormal karyotype

+ ___ Isochromosome 12p abnormality [i(12p)]

+ ___ Other [eg, del(5q), trisomy 8, 11q23 abnormality] (specify): _____

+ ___ Serologic markers (Note J)

+ ___ Not available

+ ___ Serum α -fetoprotein (AFP) (specify level): _____

+ ___ Serum human chorionic gonadotropin (HCG) (specify level): _____

+ ___ Associated syndromes (Note K)

+ ___ Not known

+ ___ Klinefelter

+ ___ Down

+ ___ Other (eg, intersex, Li Fraumeni) (specify): _____

+ ___ Associated malignancy (not part of the extragenital germ cell tumor)

+ ___ Leukemia (specify): _____

+ Data elements preceded by this symbol may be clinically important but are not yet validated or regularly used in patient management.

- + ___ Myelodysplastic syndrome (specify): _____
- + ___ Other (specify): _____
- + ___ Other findings (specify): _____

+ 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.¹⁻⁵ A recent study⁶ 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

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.^{6,9} Sacrococcygeal teratomas are the most common GCT of the neonate, occurring more frequently in girls.¹⁰ 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.^{6,7,9,11,12} 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.

In one published study¹³ of 535 fetal and neonatal GCTs, they were enumerated as follows: sacrococcygeal teratoma was the leading teratoma (214; 40%). Next were intracranial (71; 13.3%) and cervical teratomas (70; 13.1%), followed by palatal and nasopharyngeal (41; 8%), cardiac (40; 7.5%), gastric (14; 2.6%), mediastinal (13; 2.6%), orbital (13; 2.4%), facial (8; 1.5%), and placental (8; 1.5%) teratomas. There were 17 miscellaneous teratomas (3%) variously located in the tongue, tonsil, liver, retroperitoneum, eye, mesentery, ileum, testis, vulva, and anorectal area. In addition, 25 examples of fetus in fetu were identified.

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.¹⁴ 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).¹⁵ Rarely, sarcomatous elements are reported in pediatric mediastinal GCTs.¹⁶

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.^{12,17} 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.^{12,18}

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. Other sites include intraventricular, basal ganglionic, thalamic, cerebral hemispheric, bulbar, intramedullary, and intrasellar. Most occur in the second decade of life, with approximately one-quarter of all central nervous system germ cell tumors arising in the prepubertal years.¹⁹ The most common subtype is germinoma, followed by teratoma.²⁰

Postpubertal/Adult

The mediastinum is the most common anatomic site for extragenital GCTs in adults. These tumors are overwhelmingly restricted to males, but well-documented cases in women do exist.²¹⁻²² 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.²³

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.

Intracranial germ cell tumors are more common in the postpubertal child and younger adult, with the anatomic location as described above.

C. 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.²⁴

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.¹¹ 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.

Some *epignathi* and *nasopharyngeal teratomas* are so large and extensive that they are incompatible with life and therefore inoperable, which explains the high mortality rate.²⁵ The most common presenting findings in these cases are a mass, respiratory distress, polyhydramnios, and dysphagia.¹³

Because of the size of some intracranial teratomas, identifiable anatomic landmarks are lost, making it practically impossible to determine the exact site of origin.¹³ The anatomic location of the teratoma cannot be determined in about a third of the patients because the brain is replaced by tumor. When a point of origin can be found, the cerebral hemisphere is the most common primary site, followed by the third ventricle and the pineal region. Large tumors erode through the skull and extend into the orbit, oral cavity, or the neck. Spontaneous rupture during delivery of a fetal head enlarged by tumor has been reported.²⁶

D. 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.²⁷ 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.²⁷ 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).²⁸

Congenital/Neonatal

Most germ cell tumors of the fetus and neonate are histologically benign and are classified as either mature or immature teratomas.¹³ *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% to 25%.^{13,29} The presence of immature neuroglial elements in a neonatal teratoma has no bearing on prognosis, and generally these patients have a favorable outcome. It is well known that an important relationship exists between the age at diagnosis of a patient with a sacrococcygeal teratoma and outcome. The incidence of malignancy in the neonate is approximately 10%, approaching almost 100% by 3 years.^{13,29-31}

Congenital teratomas are commonly immature and often contain admixed yolk sac tumor and rarely, embryonal carcinoma. In the neonate, the diagnosis of an immature tumor is routinely based on the presence of immature neuroepithelium. Choriocarcinoma may be seen as a metastasis from the placenta in the infant but is not reported

as a component of primary extracranial EGCTs of childhood.³² Similarly, the presence of germinoma in a congenital teratoma would be very unusual.

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.¹⁴ 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 study⁶ 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%).²⁸ Because histologically mature mediastinal 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.³³ 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.³⁴ All nonteratomatous elements should be regarded as malignant in adults.

In most SGCTs in adults with adequate descriptions or illustrations, the histology of the germ cell component is that of a mature teratoma, which is benign if it is pure. Several cases are reported as “malignant teratoma” without further description or illustration. Specific diagnoses and clear descriptions or illustrations do reveal the existence of rare cases of nonteratomatous GCTs including dysgerminoma, yolk sac tumor, and embryonal carcinoma.^{35,36} When follow-up is provided, these tumors exhibit the expected malignant behavior.

Cervical GCTs are quite rare in adults but have been described with a variety of histologic patterns. Mature teratomas may occur at this site and, when pure, have a uniformly benign behavior.³⁶⁻⁴⁰ Nonteratomatous GCTs, including embryonal carcinoma and yolk sac tumor, have been described.^{41,42} The few reports of non-germ cell neoplasms arising in CGCT include carcinomas^{43,44} and, possibly, chondrosarcoma.⁴¹ Too few of such cases have been described to make generalizations about their behavior, but they would be expected to be aggressive, based on reports from other sites (see Note J).

E. 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.⁴⁵

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.

Congenital/Neonatal

The presence or grade of immaturity, as defined by Norris et al⁴⁵ 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.^{8,24,46,47} In some cases with recurrence, foci of the yolk sac tumor could not be identified in the original resected teratoma.^{8,24} 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.⁴⁶

Postpubertal/Adult

Mediastinal 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.

In SGCTs, the existence of an immature teratoma in the absence of a nonteratomatous component seems to be quite infrequent, because it is only rarely described.⁴⁸ The significance of immature tissues is not clear, but we are not aware of a documented case of aggressive behavior.

Immature cervical teratomas demonstrate malignant behavior,⁴⁹⁻⁵² similar to those arising in the mediastinum, but unlike those of other extragonadal sites. In some cases, the immature component is described as predominantly neural.

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 posttherapy 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.⁵³ Less than 10% viable tumor cells is a good prognostic factor as defined by the International Germ Cell Consensus Classification Group (IGCCCG).⁵⁴ Residual viable tumor may be relatively focal; therefore, areas of scarring, necrosis, or hemorrhage should be carefully examined.

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.

Incomplete resection of a neonatal mature teratoma has been reported to recur in adulthood as adenocarcinoma.^{55,56} The presence of a non-germ cell malignancy in a SGCT is a poor prognostic feature and requires complete surgical excision and consideration of chemotherapy or radiation therapy.

Vascular invasion can involve blood vessels or lymphatics. In suspicious cases, blood vessels can be highlighted 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.¹² 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.⁵⁷ Moran and Suster²⁸ 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,⁴⁶ 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.⁴⁶

A rare finding in extragonadal teratomas of very young children is the occurrence of nodal gliomatosis in regional lymph nodes draining the teratoma.⁵⁸ 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.⁵⁸ Studies suggest that gliomatosis peritonei is a metaplastic phenomenon of pluripotent Müllerian stem cells because it appears to be genetically unrelated to the teratoma.^{59,60} It is unclear whether the finding in lymph nodes is clonally related to the teratoma.

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.⁶¹⁻⁶⁴ 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.⁵⁴

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.^{61,62,65} Poor prognostic features of pure seminoma include liver or other nonpulmonary visceral metastases and metastases to 2 or more sites.⁶¹ 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.⁶⁶ At least some studies that include choriocarcinomas suggest an improved prognosis under current chemotherapeutic regimens.⁶⁷ 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.

I. 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.⁶⁸ Although some yolk sac tumors have shown aberrations of the short arm of chromosome 12 by interphase fluorescence in situ hybridization,^{69,70} 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.^{68,71} In a Children's Oncology Group study of 81 pediatric GCTs (gonadal and extragonadal), the 12p isochromosome was only found in adolescent boys. It remains to be investigated whether isochromosome 12p might be a better prognostic factor than age in the peripubertal period.

There is an unusual association between mediastinal GCTs, hematologic malignancies, and cytogenetics.⁷²⁻⁷⁹ 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.^{72,75} The germ cell component is typically yolk sac tumor, but immature teratomas and other nonseminomatous GCTs are also described. The most commonly associated hematopoietic malignancy is acute myeloid leukemia of megakaryocytic or monocytic differentiation (ie, M7, M4, and M5), which comprises approximately half of all cases.^{65,80,81} Other reported malignancies include the spectrum of acute myeloid leukemia subtypes,^{78,79} acute undifferentiated leukemia,⁸⁰ myelodysplastic syndrome,^{82,83} myeloproliferative disorder,^{80,84,85} “malignant histiocytosis,”⁷⁵ mastocytosis,⁸⁶ and acute lymphoblastic leukemia.^{76,80} These hematopoietic tumors may involve the mediastinal GCT or be completely extramediastinal.⁸¹ The hematopoietic component frequently shows an isochromosome 12 [i(12p)],⁷² 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 following etoposide administration.⁷³ 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 11q23.⁸⁷⁻⁸⁹

J. Tissue and Serologic Markers

Tissue Immunohistochemistry

Extragonadal GCTs typically show immunoreactivity patterns identical to their gonadal counterparts.⁹⁰ In general, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and the epithelial elements of teratoma all show cytokeratin AE1/AE3 reactivity. Although cytokeratin AE1/AE3 expression in testicular seminomas has been proposed as a potential marker of early carcinomatous progression,⁹¹ this concept has not been addressed in extragonadal sites. A dotlike paranuclear reactivity pattern to low-molecular-weight cytokeratin (ie, CAM 5.2) is seen in up to 80% of mediastinal seminomas.^{90,92}

Although placental-like alkaline phosphatase has traditionally been the marker of choice to objectively verify germ cell origin (mostly seminoma) in the setting of an “undifferentiated” neoplasm,⁹³⁻⁹⁵ its lack of sensitivity, generally high background staining, and the development of newer antibodies have rendered placental-like alkaline phosphatase less useful in current diagnostic practice. Strong membranous CD117 (c-kit) immunoreactivity has been reported in 75% to 100% of seminomas,⁹⁴ but it is not specific because it marks other non-germ cell carcinomas in the differential diagnosis, such as lung⁹⁶ and thymic carcinomas.⁹⁶⁻⁹⁸ In addition, embryonal carcinoma, yolk sac tumor, and choriocarcinoma may show some degree of weak CD117 reactivity. CD30 is also used in the workup of a poorly differentiated malignant neoplasm because it is positive in more than 80% of embryonal carcinomas, but careful morphologic and clinical correlation is required because it also marks a spectrum of hematopoietic malignancies in the differential diagnosis as well.⁹⁹

Newer markers show better specificity for germ cells tumors. Nearly 100% of seminomas and embryonal carcinomas show nuclear reactivity for OCT4, and the specificity within this morphologic differential seems better than other available markers.¹⁰⁰⁻¹⁰² 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.^{103,104} 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.^{105,106} The mononuclear trophoblast cells of choriocarcinoma are also reactive for SALL4.

α-Fetoprotein

Serum AFP is not a reliable marker for yolk sac tumor because of its low sensitivity.¹⁰⁷ Serum evaluation of AFP and HCG is frequently more useful than immunohistochemistry.

The presence of minute, occult, yolk sac tumor elements in large sacrococcygeal teratomas can be overlooked. Hawkins et al²⁴ described 6 children with mature or immature sacrococcygeal teratomas initially diagnosed in the newborn period, who had the appropriate operation and subsequently had yolk sac tumor recurrences 7 to 33 months later. 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.²⁴ 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.^{7,17}

Human Chorionic Gonadotropin

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

K. Associated Syndromes and Malignancies

Some constitutional syndromes are thought to have an increased incidence of EGCTs, including Klinefelter^{68,108-113} and Down syndrome.^{68,114,115} The association of hematopoietic malignancies with mediastinal EGCTs was described in note H (Cytogenetics). Sarcomatous differentiation, which is most frequent in the mediastinum, may occur in association with teratomas or, less commonly, with other malignant GCTs.^{82,116-120} As in the gonads, secondary squamous cell carcinoma, adenosquamous carcinoma, and colonic-type adenocarcinoma may rarely complicate extragonadal teratomas.¹²⁰ The presence of sarcomatous or carcinomatous elements portend a very poor prognosis.

References

- Bethel CA, Mutabagani K, Hammond S, Besner GE, Caniano DA, Cooney DR. Nonteratomatous germ cell tumors in children. *J Pediatr Surg.* 1998;33(7):1122-1126; discussion 1126-1127.
- Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049 and Children's Cancer Group 8882. *J Clin Oncol.* 2004;22(13):2691-2700.
- De Giorgi U, Demirer T, Wandt H, et al. Second-line high-dose chemotherapy in patients with mediastinal and retroperitoneal primary non-seminomatous germ cell tumors: the EBMT experience. *Ann Oncol.* 2005;16(1):146-151.
- De Giorgi U, Rosti G, Slavin S, et al. Salvage high-dose chemotherapy for children with extragonadal germ-cell tumours. *Br J Cancer.* 2005;93(4):412-417.
- Lo Curto M, Lumia F, Alaggio R, et al. Malignant germ cell tumors in childhood: results of the first Italian cooperative study "TCG 91". *Med Pediatr Oncol.* 2003;41(5):417-425.
- 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.
- Heerema-McKenney A, Harrison MR, Bratton B, Farrell J, Zaloudek C. Congenital teratoma: a clinicopathologic study of 22 fetal and neonatal tumors. *Am J Surg Pathol.* 2005;29(1):29-38.
- Huddart SN, Mann JR, Robinson K, et al. Sacrococcygeal teratomas: the UK Children's Cancer Study Group's experience. I. Neonatal. *Pediatr Surg Int.* 2003;19(1-2):47-51.
- Marina N, Fontanesi J, Kun L, et al. Treatment of childhood germ cell tumors: review of the St. Jude experience from 1979 to 1988. *Cancer.* 1992;70(10):2568-2575.
- Harms D, Schmidt D, Leuschner I. Abdominal, retroperitoneal and sacrococcygeal tumours of the newborn and the very young infant: report from the Kiel Paediatric Tumour Registry. *Eur J Pediatr.* 1989;148(8):720-728.
- Dehner LP. Gonadal and extragonadal germ cell neoplasia of childhood. *Hum Pathol.* 1983;14(6):493-511.
- Rescorla FJ. Pediatric germ cell tumors. *Semin Surg Oncol.* 1999;16(2):144-158.
- Isaacs H Jr. Perinatal (fetal and neonatal) germ cell tumors. *J Pediatr Surg.* 2004;39(7):1003-1013.

14. 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.
15. 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.
16. Cushing B, Bhanot PK, Watts FB Jr, Hertzler JH, Brough AJ. Rhabdomyosarcoma and benign teratoma. *Pediatr Pathol*. 1983;1(3):345-348.
17. 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.
18. Gobel U, Schneider DT, Calaminus G, Haas RJ, Schmidt P, Harms D. Germ-cell tumors in childhood and adolescence. GPOH MAKEI and the MAHO study groups. *Ann Oncol*. 2000;11(3):263-271.
19. Rosenblum MD, Matsutani M, Va Meir EG. CNS germ cell tumors. In: Kleihues P, Cavenee WK, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumors of the Nervous System*. Lyon, France: IARC Press; 2000:208.
20. Bjornsson J, Scheithauer BW, Okazaki H, Leech RW. Intracranial germ cell tumors: pathobiological and immunohistochemical aspects of 70 cases. *J Neuropathol Exp Neurol*. 1985;44(1):32-46.
21. Coskun U, Gunel N, Yildirim Y, Memis L, Boyacioglu ZM. Primary mediastinal yolk sac tumor in a 66-year-old woman. *Med Princ Pract*. 2002;11(4):218-220.
22. Shimizu J, Yazaki U, Kinoshita T, Tatsuzawa Y, Kawaura Y, Nonomura A. Primary mediastinal germ cell tumor in a middle-aged woman: case report and literature review. *Tumori*. 2001;87(4):269-271.
23. Ng EW, Porcu P, Loehrer PJ Sr. Sacrococcygeal teratoma in adults: case reports and a review of the literature. *Cancer*. 1999;86(7):1198-1202.
24. Hawkins E, Issacs H, Cushing B, Rogers P. Occult malignancy in neonatal sacrococcygeal teratomas: a report from a Combined Pediatric Oncology Group and Children's Cancer Group study. *Am J Pediatr Hematol Oncol*. 1993;15(4):406-409.
25. Isaacs H Jr. Tumors. In: Gilbert-Barness E, ed. *Potter's Pathology of the Fetus and Infant*. Vol 2. St. Louis, MO: Mosby; 1997:1242-1339.
26. Isaacs H Jr. I. Perinatal brain tumors: a review of 250 cases. *Pediatr Neurol*. 2002;27(4):249-261.
27. Nogales F, Talerman A, Kubik-Huch RA, Tavassoli FA, Devouassoux-Shisheboran M. Germ cell tumors. In: Tavassoli FA, Devilee P, eds. *Pathology and Genetics of Tumours of the Breast and Female Genital Organs*. Lyon, France: IARC Press; 2003. *World Health Organization Classification of Tumours*.
28. 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.
29. Isaacs H Jr. *Germ Cell Tumors: Tumors of the Fetus and Newborn*. Vol 35. Philadelphia, PA: Saunders; 1997.
30. 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.
31. Dehner LP. Neoplasms of the fetus and neonate. In: Naeye RL, Kissane JM, N Kaufman N, eds. *Perinatal Diseases, International Academy of Pathology*. Vol. 22. Baltimore, MD: Williams and Wilkins; 1981:286-345.
32. Sebire NJ, Lindsay I, Fisher RA, Seckl MJ. Intraplental choriocarcinoma: experience from a tertiary referral center and relationship with infantile choriocarcinoma. *Fetal Pediatr Pathol*. 2005;24(1):21-29.
33. 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.
34. Ulbright TM, Amin MB, Young RH. *Tumors of the Testis, Adnexa, Spermatic Cord, and Scrotum*. Washington, DC: Armed Forces Institute of Pathology; 1999.
35. Ahmed HA, Pollock DJ. Malignant sacrococcygeal teratoma in the adult. *Histopathology*. 1985;9(3):359-363.
36. Conklin J, Abell MR. Germ cell neoplasms of sacrococcygeal region. *Cancer*. 1967;20(12):2105-2117.
37. Kuhel WI. Adherence of benign cervical teratomas to surrounding soft tissue. *Arch Otolaryngol Head Neck Surg*. 1999;125(2):236-237.
38. Kuhel WI, Yagoda M, Peterson P. Benign cervical teratoma in the adult: report of a rare case with dense fibrosis involving adjacent vital structures. *Otolaryngol Head Neck Surg*. 1996;115(1):152-155.
39. Mochizuki Y, Noguchi S, Yokoyama S, et al. Cervical teratoma in a fetus and an adult: two case reports and review of literature. *Acta Pathol Jpn*. 1986;36(6):935-943.

40. Sawafuji M, Kakizaki T, Yamamoto T, Kikuchi K, Kobayashi K, Ito K. A case of cervical teratoma in adult [in Japanese]. *Nippon Kyobu Geka Gakkai Zasshi*. 1993;41(11):2220-2223.
41. Als C, Laeng H, Cerny T, Kinser JA, Rosler H, Hausler R. Primary cervical malignant teratoma with a rib metastasis in an adult: five-year survival after surgery and chemotherapy. A case report with a review of the literature. *Ann Oncol*. 1998;9(9):1015-1022.
42. Tobey DN, Mangham C. Malignant cervical teratomas. *Otolaryngol Head Neck Surg*. 1980;88(3):215-217.
43. Colton JJ, Batsakis JG, Work WP. Teratomas of the neck in adults. *Arch Otolaryngol*. 1978;104(5):271-272.
44. Muraio T, Nakanishi M, Toda K, Konishi H. Malignant teratoma of the thyroid gland in an adolescent female. *Acta Pathol Jpn*. 1979;29(1):109-117.
45. Norris HJ, Zirkin HJ, Benson WL. Immature (malignant) teratoma of the ovary: a clinical and pathologic study of 58 cases. *Cancer*. 1976;37(5):2359-2372.
46. Marina NM, Cushing B, Giller R, et al. Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: a Pediatric Oncology Group/Children's Cancer Group Intergroup Study. *J Clin Oncol*. 1999;17(7):2137-2143.
47. Tapper D, Lack EE. Teratomas in infancy and childhood: a 54-year experience at the Children's Hospital Medical Center. *Ann Surg*. 1983;198(3):398-410.
48. Lopes A, Pearson SE, Roberts JT, Monaghan JM. Immature presacral teratoma in an adult female. *Gynecol Oncol*. 1990;38(1):135-137.
49. Bowker CM, Whittaker RS. Malignant teratoma of the thyroid: case report and literature review of thyroid teratoma in adults. *Histopathology*. 1992;21(1):81-83.
50. Buckley NJ, Burch WM, Leight GS. Malignant teratoma in the thyroid gland of an adult: a case report and a review of the literature. *Surgery*. 1986;100(5):932-937.
51. Hajdu SI, Hajdu EO. Malignant teratoma of the neck. *Arch Pathol*. 1967;83(6):567-570.
52. Jayaram G, Cheah PL, Yip CH. Malignant teratoma of the thyroid with predominantly neuroepithelial differentiation: fine needle aspiration cytologic, histologic and immunocytochemical features of a case. *Acta Cytol*. 2000;44(3):375-379.
53. Ulbright TM, Roth LM. A pathologic analysis of lesions following modern chemotherapy for metastatic germ-cell tumors. *Pathol Annu*. 1990;25 Pt 1:313-340.
54. International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol*. 1997;15(2):594-603.
55. Lack EE, Glaun RS, Hefter LG, Seneca RP, Steigman C, Athari F. Late occurrence of malignancy following resection of a histologically mature sacrococcygeal teratoma: report of a case and literature review. *Arch Pathol Lab Med*. 1993;117(7):724-728.
56. Lahdenne P, Heikinheimo M, Perkkio M, Rapola J, Miettinen M. Cell differentiation in sacrococcygeal teratomas: an immunohistochemical and follow-up study. *Pathol Res Pract*. 1990;186(3):336-343.
57. Wick MR, Perlman EJ, Orazi A, et al. Germ cell tumors of the mediastinum. In: Travis WD, Brambilla E, Muller-Hermelink HK, et al, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus, and Heart*. Lyon, France: IARC press; 2004:198-201.
58. Perrone T, Steiner M, Dehner LP. Nodal gliomatosis and alpha-fetoprotein production: two unusual facets of grade I ovarian teratoma. *Arch Pathol Lab Med*. 1986;110(10):975-977.
59. Robboy SJ, Scully RE. Ovarian teratoma with glial implants on the peritoneum: an analysis of 12 cases. *Hum Pathol*. 1970;1(4):643-653.
60. Ferguson AW, Katabuchi H, Ronnett BM, Cho KR. Glial implants in gliomatosis peritonei arise from normal tissue, not from the associated teratoma. *Am J Pathol*. 2001;159(1):51-55.
61. Bokemeyer C, Droz JP, Horwich A, et al. Extragenital seminoma: an international multicenter analysis of prognostic factors and long term treatment outcome. *Cancer*. 2001;91(7):1394-1401.
62. Bokemeyer C, Hartmann JT, Fossa SD, et al. Extragenital germ cell tumors: relation to testicular neoplasia and management options. *APMIS*. 2003;111(1):49-59; discussion 59-63.
63. Fizazi K, Tjulandin S, Salvioni R, et al. Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy--results from an international study group. *J Clin Oncol*. 2001;19(10):2647-2657.
64. Hartmann JT, Nichols CR, Droz JP, et al. Prognostic variables for response and outcome in patients with extragenital germ-cell tumors. *Ann Oncol*. 2002;13(7):1017-1028.
65. Bokemeyer C, Nichols CR, Droz JP, et al. Extragenital germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol*. 2002;20(7):1864-1873.

66. Moran CA, Suster S. Primary mediastinal choriocarcinomas: a clinicopathologic and immunohistochemical study of eight cases. *Am J Surg Pathol*. 1997;21(9):1007-1012.
67. Takeda S, Miyoshi S, Ohta M, Minami M, Masaoka A, Matsuda H. Primary germ cell tumors in the mediastinum: a 50-year experience at a single Japanese institution. *Cancer*. 2003;97(2):367-376.
68. Bussey KJ, Lawce HJ, Olson SB, et al. Chromosome abnormalities of eighty-one pediatric germ cell tumors: sex-, age-, site-, and histopathology-related differences: a Children's Cancer Group study. *Genes Chromosomes Cancer*. 1999;25(2):134-146.
69. Jenderny J, Koster E, Borchers O, et al. Interphase cytogenetics on paraffin sections of paediatric extragonadal yolk sac tumours. *Virchows Arch*. 1996;428(1):53-57.
70. Stock C, Ambros IM, Lion T, et al. Detection of numerical and structural chromosome abnormalities in pediatric germ cell tumors by means of interphase cytogenetics. *Genes Chromosomes Cancer*. 1994;11(1):40-50.
71. Perlman EJ, Cushing B, Hawkins E, Griffin CA. Cytogenetic analysis of childhood endodermal sinus tumors: a Pediatric Oncology Group study. *Pediatr Pathol*. 1994;14(4):695-708.
72. Downie PA, Vogelzang NJ, Moldwin RL, et al. Establishment of a leukemia cell line with i(12p) from a patient with a mediastinal germ cell tumor and acute lymphoblastic leukemia. *Cancer Res*. 1994;54(18):4999-5004.
73. Hartmann JT, Nichols CR, Droz JP, et al. Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. *J Natl Cancer Inst*. 2000;92(1):54-61.
74. Keung YK, Liang R, Chiu EK. Acute leukemia associated with mediastinal germ cell tumor: de novo versus therapy-related leukemia. *West J Med*. 1993;158(4):409-412.
75. Ladanyi M, Samaniego F, Reuter VE, et al. Cytogenetic and immunohistochemical evidence for the germ cell origin of a subset of acute leukemias associated with mediastinal germ cell tumors. *J Natl Cancer Inst*. 1990;82(3):221-227.
76. Larsen M, Evans WK, Shepherd FA, Phillips MJ, Bailey D, Messner H. Acute lymphoblastic leukemia: possible origin from a mediastinal germ cell tumor. *Cancer*. 1984;53(3):441-444.
77. Lee KC. Hematopoietic precursor cells within the yolk sac tumor component are the source of secondary hematopoietic malignancies in patients with mediastinal germ cell tumors. *Cancer*. 1994;73(5):1535-1536.
78. Vasey PA, Dunlop DJ, Kaye SB. Primary mediastinal germ cell tumour and acute monocytic leukaemia occurring concurrently in a 15-year-old boy. *Ann Oncol*. 1994;5(7):649-652.
79. Vlasveld LT, Splinter TA, Hagemeyer A, Van Lom K, Lowenberg B. Acute myeloid leukaemia with +i(12p) shortly after treatment of mediastinal germ cell tumour. *Br J Haematol*. 1994;88(1):196-198.
80. Nichols CR, Roth BJ, Heerema N, Griep J, Tricot G. Hematologic neoplasia associated with primary mediastinal germ-cell tumors. *N Engl J Med*. 1990;322(20):1425-1429.
81. Orazi A, Neiman RS, Ulbright TM, Heerema NA, John K, Nichols CR. Hematopoietic precursor cells within the yolk sac tumor component are the source of secondary hematopoietic malignancies in patients with mediastinal germ cell tumors. *Cancer*. 1993;71(12):3873-3881.
82. Motzer RJ, Amsterdam A, Prieto V, et al. Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. *J Urol*. 1998;159(1):133-138.
83. Sole F, Bosch F, Woessner S, et al. Refractory anemia with excess of blasts and isochromosome 12p in a patient with primary mediastinal germ-cell tumor. *Cancer Genet Cytogenet*. 1994;77(2):111-113.
84. Garnick MB, Griffin JD. Idiopathic thrombocytopenia in association with extragonadal germ cell cancer. *Ann Intern Med*. 1983;98(6):926-927.
85. Helman LJ, Ozols RF, Longo DL. Thrombocytopenia and extragonadal germ-cell neoplasm. *Ann Intern Med*. 1984;101(2):280.
86. Chariot P, Monnet I, Gaulard P, Abd-Alsamad I, Ruffie P, De Cremoux H. Systemic mastocytosis following mediastinal germ cell tumor: an association confirmed. *Hum Pathol*. 1993;24(1):111-112.
87. Felix CA. Leukemias related to treatment with DNA topoisomerase II inhibitors. *Med Pediatr Oncol*. 2001;36(5):525-535.
88. Ohshima A, Miura I, Chubachi A, et al. 11q23 aberration is an additional chromosomal change in de novo acute leukemia after treatment with etoposide and mitoxantrone. *Am J Hematol*. 1996;53(4):264-266.
89. Stanulla M, Wang J, Chervinsky DS, Aplan PD. Topoisomerase II inhibitors induce DNA double-strand breaks at a specific site within the AML1 locus. *Leukemia*. 1997;11(4):490-496.
90. Suster S, Moran CA, Dominguez-Malagon H, Quevedo-Blanco P. Germ cell tumors of the mediastinum and testis: a comparative immunohistochemical study of 120 cases. *Hum Pathol*. 1998;29(7):737-742.

91. Tickoo SK, Hutchinson B, Bacik J, et al. Testicular seminoma: a clinicopathologic and immunohistochemical study of 105 cases with special reference to seminomas with atypical features. *Int J Surg Pathol.* 2002;10(1):23-32.
92. Moran CA, Suster S, Przygodzki RM, Koss MN. Primary germ cell tumors of the mediastinum, II: mediastinal seminomas--a clinicopathologic and immunohistochemical study of 120 cases. *Cancer.* 1997;80(4):691-698.
93. Cheville JC, Rao S, Iczkowski KA, Lohse CM, Pankratz VS. Cytokeratin expression in seminoma of the human testis. *Am J Clin Pathol.* 2000;113(4):583-588.
94. Leroy X, Augusto D, Leteurtre E, Gosselin B. CD30 and CD117 (c-kit) used in combination are useful for distinguishing embryonal carcinoma from seminoma. *J Histochem Cytochem.* 2002;50(2):283-285.
95. Niehans GA, Manivel JC, Copland GT, Scheithauer BW, Wick MR. Immunohistochemistry of germ cell and trophoblastic neoplasms. *Cancer.* 1988;62(6):1113-1123.
96. Butnor KJ, Burchette JL, Sporn TA, Hammar SP, Roggli VL. The spectrum of Kit (CD117) immunoreactivity in lung and pleural tumors: a study of 96 cases using a single-source antibody with a review of the literature. *Arch Pathol Lab Med.* 2004;128(5):538-543.
97. Nakagawa K, Matsuno Y, Kunitoh H, Maeshima A, Asamura H, Tsuchiya R. Immunohistochemical KIT (CD117) expression in thymic epithelial tumors. *Chest.* 2005;128(1):140-144.
98. Pan CC, Chen PC, Chiang H. KIT (CD117) is frequently overexpressed in thymic carcinomas but is absent in thymomas. *J Pathol.* 2004;202(3):375-381.
99. Ferreira JA. Ber-H2 expression in testicular germ cell tumors. *Hum Pathol.* 1994;25(5):522-524.
100. Emerson RE, Ulbright TM. The use of immunohistochemistry in the differential diagnosis of tumors of the testis and paratestis. *Semin Diagn Pathol.* 2005;22(1):33-50.
101. Hattab EM, Tu PH, Wilson JD, Cheng L. OCT4 immunohistochemistry is superior to placental alkaline phosphatase (PLAP) in the diagnosis of central nervous system germinoma. *Am J Surg Pathol.* 2005;29(3):368-371.
102. Jones TD, Ulbright TM, Eble JN, Baldrige LA, Cheng L. OCT4 staining in testicular tumors: a sensitive and specific marker for seminoma and embryonal carcinoma. *Am J Surg Pathol.* 2004;28(7):935-940.
103. Zynger DL, Dimov ND, Luan C, Teh BT, Yang XJ. Glypican 3: a novel marker in testicular germ cell tumors. *Am J Surg Pathol.* 2006;30(12):1570-1575.
104. Zynger DL, Everton MJ, Dimov ND, Chou PM, Yang XJ. Expression of glypican 3 in ovarian and extragonadal germ cell tumors. *Am J Clin Pathol.* 2008;130(2):224-230.
105. Cao D, Li J, Guo CC, Allan RW, Humphrey PA. SALL4 is a novel diagnostic marker for testicular germ cell tumors. *Am J Surg Pathol.* 2009;33(7):1065-1077.
106. Cao D, Guo S, Allan RW, Molberg KH, Peng Y. SALL4 is a novel sensitive and specific marker of ovarian primitive germ cell tumors and is particularly useful in distinguishing yolk sac tumor from clear cell carcinoma. *Am J Surg Pathol.* 2009;33(6):894-904.
107. Ramalingam P, Malpica A, Silva EG, Gershenson DM, Liu JL, Deavers MT. The use of cytokeratin 7 and EMA in differentiating ovarian yolk sac tumors from endometrioid and clear cell carcinomas. *Am J Surg Pathol.* 2004;28(11):1499-1505.
108. Hasle H, Mellempgaard A, Nielsen J, Hansen J. Cancer incidence in men with Klinefelter syndrome. *Br J Cancer.* 1995;71(2):416-420.
109. Aguirre D, Nieto K, Lazos M, et al. Extragonadal germ cell tumors are often associated with Klinefelter syndrome. *Hum Pathol.* 2006;37(4):477-480.
110. Beresford L, Fernandez CV, Cummings E, Sanderson S, Ming-Yu W, Giacomantonio M. Mediastinal polyembryoma associated with Klinefelter syndrome. *J Pediatr Hematol Oncol.* 2003;25(4):321-323.
111. Nichols CR, Heerema NA, Palmer C, Loehrer PJ Sr, Williams SD, Einhorn LH. Klinefelter's syndrome associated with mediastinal germ cell neoplasms. *J Clin Oncol.* 1987;5(8):1290-1294.
112. Turner AR, MacDonald RN, Gilbert JA, Petursson S. Mediastinal germ cell cancers in Klinefelter's syndrome. *Ann Intern Med.* 1981;94(2):279.
113. Volkl TM, Langer T, Aigner T, et al. Klinefelter syndrome and mediastinal germ cell tumors. *Am J Med Genet A.* 2006;140(5):471-481.
114. Dexeus FH, Logothetis CJ, Chong C, Sella A, Ogden S. Genetic abnormalities in men with germ cell tumors. *J Urol.* 1988;140(1):80-84.
115. Satge D, Sommelet D, Geneix A, Nishi M, Malet P, Vekemans M. A tumor profile in Down syndrome. *Am J Med Genet.* 1998;78(3):207-216.
116. Caballero C, Gomez S, Matias-Guiu X, Prat J. Rhabdomyosarcomas developing in association with mediastinal germ cell tumours. *Virchows Arch A Pathol Anat Histopathol.* 1992;420(6):539-543.

117. Gonzalez-Vela JL, Savage PD, Manivel JC, Torkelson JL, Kennedy BJ. Poor prognosis of mediastinal germ cell cancers containing sarcomatous components. *Cancer*. 1990;66(6):1114-1116.
118. Manivel C, Wick MR, Abenzoza P, Rosai J. The occurrence of sarcomatous components in primary mediastinal germ cell tumors. *Am J Surg Pathol*. 1986;10(10):711-717.
119. Ulbright TM, Clark SA, Einhorn LH. Angiosarcoma associated with germ cell tumors. *Hum Pathol*. 1985;16(3):268-272.
120. Ulbright TM, Loehrer PJ, Roth LM, Einhorn LH, Williams SD, Clark SA. The development of non-germ cell malignancies within germ cell tumors: a clinicopathologic study of 11 cases. *Cancer*. 1984;54(9):1824-1833.