Neonatal Malignant Disorders: Germ Cell Tumors

Rachana Shah, MD, MS[a,*], Brent R. Weil, MD, MPH[b,c], Christopher B. Weldon, MD, PhD[b,c], James F. Amatruda, MD, PhD[a], A. Lindsay Frazier, MD, ScM[c]

KEYWORDS

• Germ cell tumor • Fetal • Neonatal • Molecular genetics • Teratoma
• Yolk sac tumor • Choriocarcinoma • Fetus-in-fetu

KEY POINTS

- Teratomas (mature or immature) account for a vast majority of the neonatal germ cell tumors, approximately 5% of which contain a malignant component that is predominantly yolk sac tumor.
- Most neonatal germ cell tumors are curable with surgery alone.
- In the rare instance of a neonate with metastatic malignant disease or malignant disease for which upfront surgical resection is not feasible without significant morbidity, an initial biopsy followed by neoadjuvant chemotherapy and delayed surgical resection is recommended.
- If chemotherapy is indicated, a carboplatin-based regimen should be considered to minimize treatment-related toxicity.

INTRODUCTION

Germ cell tumors (GCTs) are a wide spectrum of biologically diverse and histologically heterogenous tumors that can arise in gonadal or extragonadal sites. In the neonatal period, GCTs rank as the fifth most frequent malignant neoplasm, after neuroblastoma, leukemia, sarcoma, Wilms tumor, and retinoblastoma.[1] Benign mature or immature teratomas account for a vast majority of the neonatal GCTs, roughly 5% to 10% of which contain a malignant component that is predominantly yolk sac tumor (YST).[1,2]

[a] Division of Oncology, Department of Pediatrics, Cancer and Blood Disease Institute, Children's Hospital Los Angeles, University of Southern California, Keck School of Medicine, 4650 Sunset Boulevard, MS#54, Los Angeles, CA 90027, USA; [b] Department of Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; [c] Department of Pediatric Oncology, Children's Cancer and Blood Disorders Center, Children's Hospital Dana-Farber Cancer Center, Harvard Medical School, 450 Brookline Avenue, Boston, MA 02215, USA
* Corresponding author.
E-mail address: rshah@chla.usc.edu

Clin Perinatol 48 (2021) 147–165
https://doi.org/10.1016/j.clp.2020.11.010
perinatology.theclinics.com

PATHOGENESIS

Germ cells are set aside from somatic cells very early in the fetal period, and germline development proceeds in a programmatic series of steps. Defects in this developmental program can give rise to GCTs in the fetus and neonate (Fig. 1).

Specification and Migration of Primordial Germ Cells

At the time of blastocyst implantation, the extraembryonic ectoderm and the visceral endoderm send signals to the embryonic ectoderm, resulting in expression of the transcriptional repressor *BLIMP1/PRDM14* in a few cells in the epiblast.[3] These cells, in which expression of somatic genes, such as *Hoxb1*, *T/brachyury*, and *Snail*, is repressed, will become the primordial germ cells (PGCs). Unlike other epiblast-derived cells, PGCs regain or maintain expression of pluripotency associated genes, such as *LIN28A*, *SOX2*, *OCT3/4 (POU5F1)*, and *NANOG*.[4,5] Certain pluripotency genes can be reactivated in GCTs and may contribute to malignant potential.[6] In humans, PGCs can be identified in the wall of the yolk sac beginning around day 24.[7] The PGCs begin to proliferate as they migrate out of the yolk sac into the embryo.[8] Proper PGC migration is critical to survival of the germ cells and formation of the gonad. Failure of this migration can result in ectopic germ cells, persistence of which is one possible mechanism by which extragonadal GCTs are thought to arise. Toward the end of gastrulation, morphogenetic movements in the developing embryo bring the PGCs in proximity to the hindgut. Invading the endoderm, the PGCs colonize the hindgut and begin migration, a process dependent on the receptor tyrosine kinase *c-KIT*, expressed in PGCs, and its ligand, *KITL*, expressed in somatic cells.[9] Knockdown of *CXCR4* and its ligand *CXCL12* results in PGC mismigration and failure to reach the gonadal ridge after PGCs reach the dorsal wall.[10] At 5 to 6 weeks' after fertilization, the PGCs exit the hindgut to colonize the gonadal ridge primordia; PGCs failing to reach the gonadal ridge are eliminated by *BAX*-dependent apoptosis.[11] Once they have entered the gonadal ridges, PGCs become much less motile but

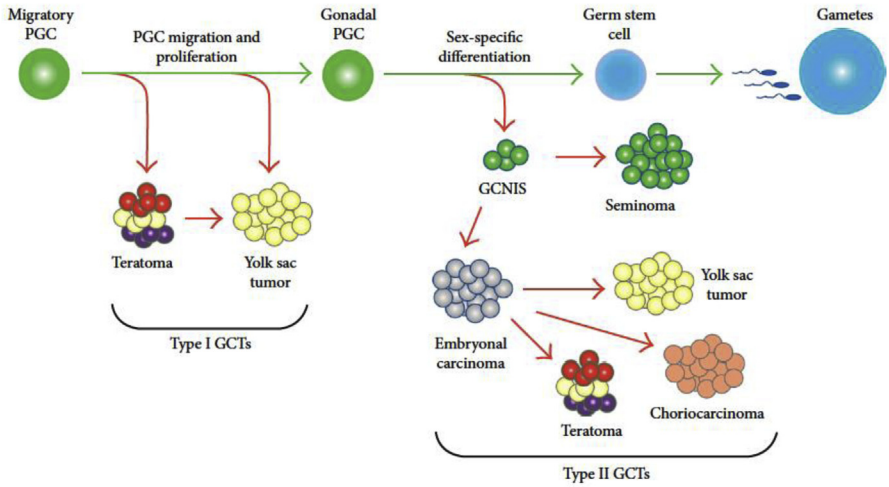

Fig. 1. Germline development and histologic subtypes of GCTs. GCNIS, germ cell neoplasia in situ. (*From* Pierce, J. L., Frazier, A. L. & Amatruda, J. F. Pediatric Germ Cell Tumors: A Developmental Perspective. Adv Urol 2018, (2018); with permission).

continue several more rounds of division. This proliferation depends on continued *KITL/c-KIT* signaling.

Erasure of Imprinting

"Imprinting" refers to the epigenetic modification of certain genes (typically by cytosine methylation) such that only the maternal or paternal allele of the gene is expressed. Lineage-specific patterns of imprinting are established in different tissues, including the germline, around the time of gastrulation. Upon entering the gonadal ridges, PGCs actively erase these genomic methylation patterns. This erasure is necessary in order to allow the maternal and paternal imprinting patterns to be established in the oocytes and sperm, respectively. Prepubertal (type I) GCTs show only partial erasure of parental imprinting, indicating that prepubertal tumors likely arise from an earlier stage of embryonic germ cell development than do the postpubertal (type II) tumors.[12] A similar pattern of imprinting is seen in gonadal and extragonadal pediatric GCTs, suggesting that gonadal and nongonadal tumors share a common pathogenesis and cell of origin.

Gonadogenesis

Beginning shortly before the arrival of the PGCs in the gonadal ridges, the coelomic epithelium begins to proliferate and invade the underlying mesenchyme, forming the primitive sex cords. Migrating PGCs entering the gonad are surrounded by the cords. Subsequently, changes occur in both the germ cells and the gonadal somatic cells, according to the genetic sex of the embryo.

In summary, the complex process of gonadal organogenesis is subject to both genetic and environmental influences. Abnormal development of the gonads during the embryonic and fetal periods leads to defects, such as cryptorchidism and gonadal dysgenesis, which are strongly associated with the risk of developing GCTs.[13,14]

MOLECULAR GENETICS

The most common chromosomal aberration seen in adolescent/adult malignant GCTs is chromosome 12p gain, typically because of isochromosome 12p,[15] regardless of histologic subtype and primary site. The genomic aberrations seen in malignant GCTs of infants and children (prepubertal) are generally distinct from those occurring in postpubertal tumors. In the prepubertal period, pure teratomas of the testis or extragonadal sites almost always exhibit a normal profile in genomic analyses, including cytogenetics, fluorescence in situ hybridization, loss of heterozygosity (LOH) analysis, and array comparative genomic hybridization. These data contrast sharply with the universally abnormal cytogenetic profile of postpubertal teratomas arising as a component of a mixed malignant GCT. Unlike teratomas, cytogenetic and other genomic aberrations are consistently reported in analyses of YSTs in infants and children. The most common imbalances reported are gains at chromosomes 1p, 3p, and 20q, and losses at chromosome 1p and chromosome 6q.[16–18] Loss of chromosomes 1p and 6q correlates with LOH analysis, indicating true allelic loss in these regions in pediatric GCTs.

MicroRNAs are short, non-protein-coding RNAs that regulate the stability and translation of target messenger RNAs. Individual microRNAs from 2 clusters, miR-371-373 and miR-302-367, are overexpressed in all malignant GCTs, regardless of patient age, tumor site, and subtype ($P \leq .00005$).[19] A panel of 4 circulating microRNAs (miR-371a-3p, miR-372-3p, miR-373-3p, miR-367-3p) is highly sensitive and specific for the diagnosis of malignant GCT, including seminoma. In contrast, microRNAs are not

overexpressed in teratomas. Clinically, this may be valuable in distinguishing a recurrent teratoma from a malignant recurrence. The current Children's Oncology Group (COG) trial, AGCT1531, aims at prospective validation of serum microRNA as a candidate biomarker for early detection of relapse in malignant GCTs, especially in tumor marker negative disease.

EPIDEMIOLOGY

In the United States, GCTs occur at a rate of 5.4 per million children, representing approximately 3.5% of cancer diagnoses for children under 15 years of age.[20] The age-adjusted incidence of GCT is characterized by a bimodal pattern: there is an initial peak between birth and 4 years of age, followed by a second peak coinciding with the onset of puberty that continues into the third and fourth decades of young adult life. In male children, the incidence of testicular and extracranial extragonadal GCTs is similar between birth and 4 years of age, followed by a dramatic increase in incidence of testicular GCTs between ages 15 and 19 years (**Fig. 2**). In female children, the incidence of extracranial extragonadal GCTs accounts for a vast majority of the cases between birth and 4 years of age with a trend toward an increase in the incidence of ovarian GCTs at 8 to 9 years of age, peaking at 18 years of age (**Fig. 3**).

In newborns, the vast majority of GCTs are extragonadal as compared with gonadal predominance in children and adolescents. Neonatal GCTs are more frequent in female than male newborns (female:male, 3:1) at sacrococcygeal, gastric, orbital, and facial sites. Intracranial, head, and neck (ie, cervical and oro-nasopharyngeal), cardiac, mediastinal teratomas, and fetus-in-fetu (FIF) are equally distributed between female and male newborns.[2]

Overall, black children have a lower incidence of GCTs than white children (7.0 vs 10.7 per million).[20] Analysis of the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) data from 18 registries (2000–2015) demonstrated that there were no significant racial/ethnic survival differences among female children, whereas male survival differed by race/ethnicity ($P<.0001$), with non-Hispanic white male children having the best survival.[21] When adjusted for age and year at diagnosis, tumor histology, location, and stage, Asian, Pacific Islander, and Hispanic male children had significantly higher risks of death compared with non-Hispanic white male children. This association was not influenced by stage of disease, except for gonadal tumors in Hispanic male children. The investigators concluded that unidentified factors, such as differences in exposures, tumor biology, or treatment received, may be driving the observed disparity.

RISK FACTORS

Family History

In a population-based Childhood Cancer Research Network (CCRN) study evaluating the family history of GCTs and other cancers in relatives of pediatric GCT, probands demonstrated familial aggregation of GCTs, suggesting an underlying genetic cause. Male and female relatives of probands had a higher number of GCTs than expected when compared with incidence data from the SEER program, although this reached statistical significance only among male relatives. Notably, most reported GCTs occurred in relatives of probands with an intracranial tumor. The investigators observed an elevated risk of melanoma in male relatives of probands and an elevated, but nonsignificant risk of melanoma in female relatives of probands.[22]

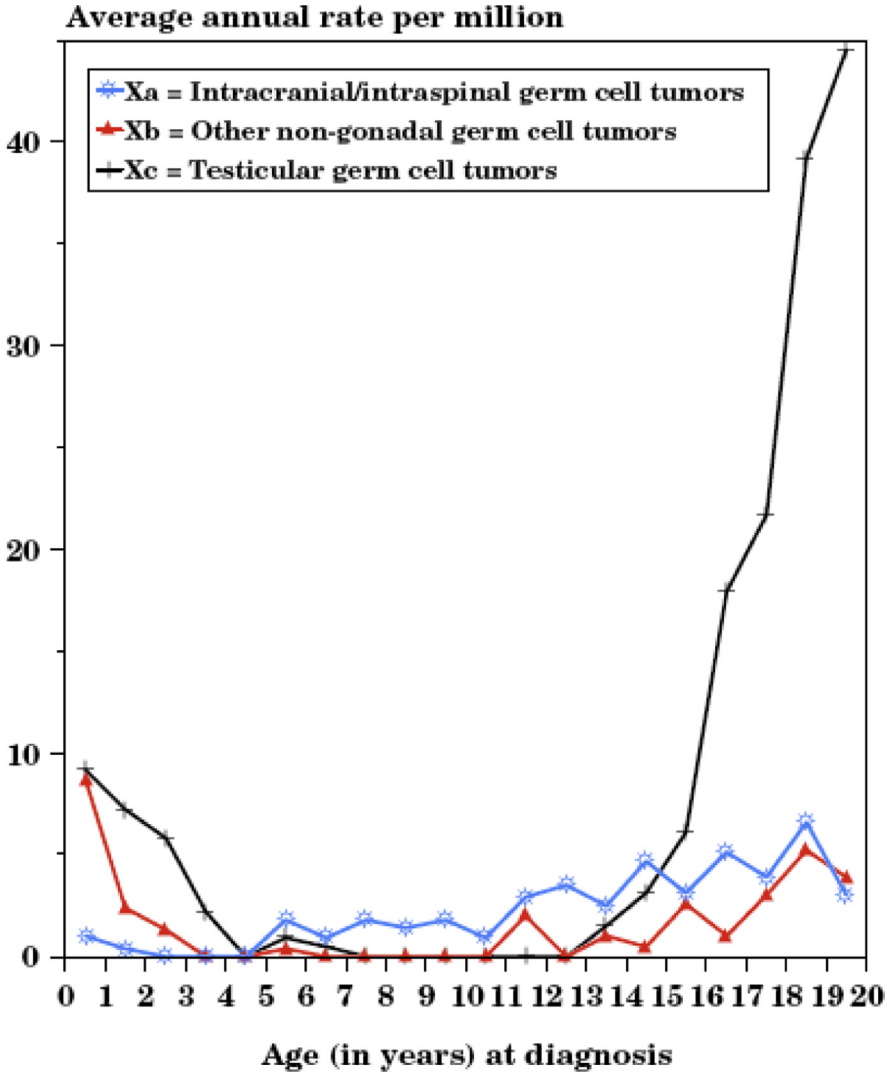

Fig. 2. Age-specific incidence rates by selected International Classification of Childhood Cancer subgroups, male children all races, SEER, 1986 to 1994. GCTOG, germ cell, trophoblastic and other gonadal. (*From* Figure X.2: GCTOG age-specific incidence rates by sex, all races, SEER, 1986-94. Page: 130. SEER monograph: Bernstein L, Smith MA, Liu L, Deapen D, and Friedman DL, *Germ Cell Trophoblastic and other Gonadal Neoplasms ICCC X*, in *SEER Cancer Statistics Review, 1975-2004*, Ries L, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, Reichman M, and Edwards BK, Editors. 2007, National Cancer Institute: Bethesda, MD p. 125-137; with permission.)

Congenital Abnormalities

Maternally reported congenital abnormalities were examined in a case-control study of 278 pediatric patients with GCTs and 423 controls. GCTs were significantly associated with cryptorchidism in male pediatric patients (odds ratio = 10.8, 95% confidence interval [CI] = 2.1 to 55.1), but not with any other specific congenital abnormality in either sex.[14]

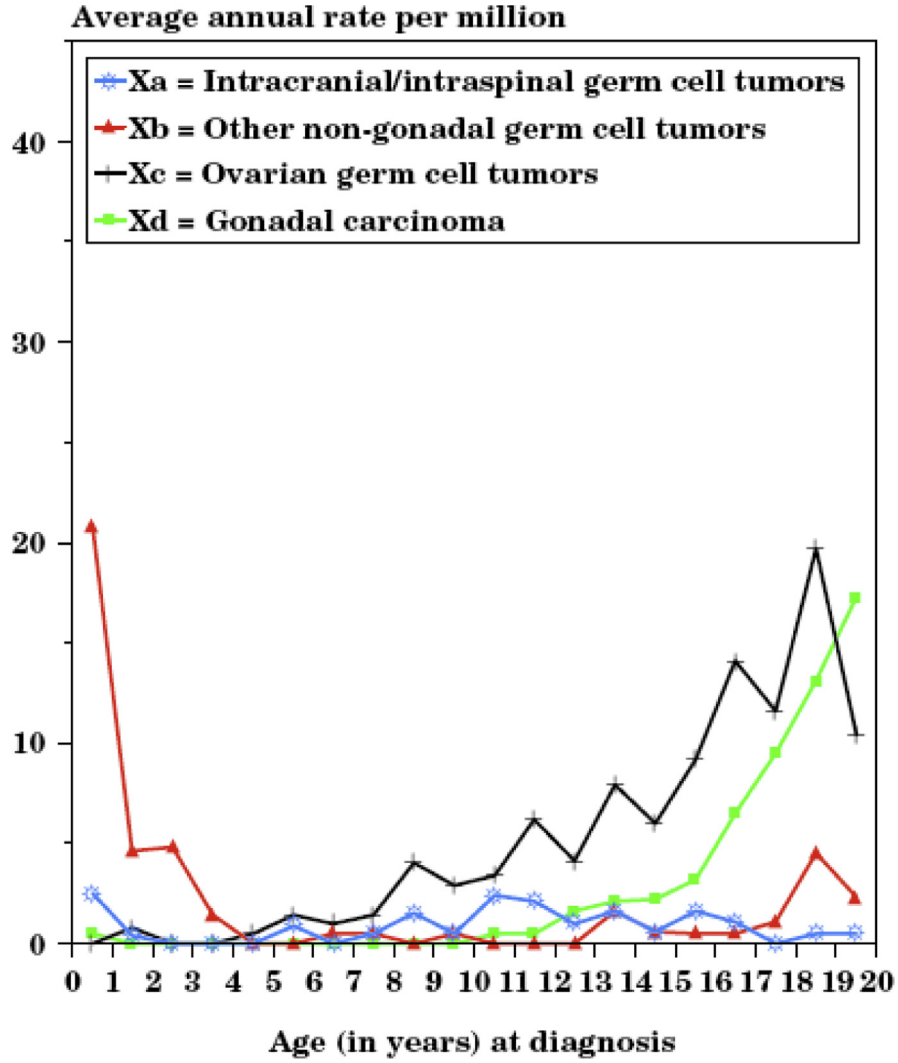

Fig. 3. Age-specific incidence rates by selected International Classification of Childhood Cancer subgroups, female children all races, SEER, 1986 to 1994. GCTOG, germ cell, trophoblastic and other gonadal. (*From* Figure X.3: GCTOG age-specific incidence rates by selected ICCC subgroups females, all races, SEER, 1986-94. Page 130: SEER monograph: Bernstein L, Smith MA, Liu L, Deapen D, and Friedman DL, *Germ Cell Trophoblastic and other Gonadal Neoplasms ICCC X*, in *SEER Cancer Statistics Review, 1975-2004*, Ries L, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, Reichman M, and Edwards BK, Editors. 2007, National Cancer Institute: Bethesda, MD p. 125-137; with permission.)

Virilization Syndrome

Patients with hypervirilization syndromes are not at an increased risk for development of GCTs. In contrast, patients with undervirilization syndromes, such as androgen insensitivity syndrome, have a 5.5% calculated prevalence of GCTs, which

dramatically increases after puberty to reach 33% at the age of 50 years. Although the data are limited, the risk seems to be markedly higher in the partial than in the complete variant.[13] In patients with androgen biosynthetic defects, gonadectomy should be performed before puberty.[23]

Disorders of Sex Development

Disorders of sex development or intersex disorders, including patients with Y chromosome or Y-derived sequence, exhibit a significant risk of gonadal GCTs. Ovarian dysgerminoma and testicular seminoma are the most prevalent GCTs arising in dysgenetic gonads and are almost always preceded by the presence of an in situ neoplastic lesion—either germ cell neoplasia in situ or gonadoblastoma. Patients with 46,XY pure gonadal dysgenesis have the highest tumor incidence and malignancy risk.[13,24] In contrast to patients with undervirilization syndromes, GCTs in patients with gonadal dysgenesis are frequently found at a very young age (eg, in the first year of life or may even be present at birth).[13]

Analysis of pediatric patients with malignant ovarian (MO)GCT in the COG trial AGCT0132 highlighted that patients with nonseminomatous MOGCT in the context of dysgenetic gonads had higher rates of event and death (estimated 3-year event-free survival [EFS_3] and overall survival [OS_3] were 66.7% and 87.5%, respectively) compared with patients with normal gonadal development (EFS_3 = 88.8%, OS_3 = 97.6%).[25] These results emphasize the importance of noting a contralateral streak ovary or gonadoblastoma at histology for any ovarian GCT and support the recommendation for early bilateral gonadectomy in patients known to have gonadal dysgenesis with Y-chromosome material.[23]

Klinefelter Syndrome

Based on analysis of array genotyping data from a COG CCRN epidemiology study of 433 male children aged birth to 19 years, male childrenwith Klinefelter syndrome (47,XXY) were significantly more likely to be diagnosed with a mediastinal GCT compared with male children without chromosomal abnormalities (risk ratio = 18.8, 95% CI = 11.7–30, $P<.01$). Therefore, screening of male children with mediastinal GCTs for Klinefelter syndrome is warranted.[26]

CLINICAL PRESENTATION

The most common initial presentation of neonatal GCTs is a mass, detected by antenatal imaging and/or postnatally by physical examination. Signs and symptoms typically correspond to the site of origin. The sacrococcygeal region (40%) is the most common site of neonatal GCTs; other sites include intracranial (13%), cardiac (7.5%), FIF (5%), mediastinal (3%), gastric (3%), and head and neck, including cervical (13%), oropharynx and nasopharynx (8%), orbital (3%), and facial (1.5%).[2] Additional miscellaneous sites (3%) reported include tongue, tonsil, liver, retroperitoneum, mesentery, ileum, testis, vulva, and the anorectal region.

Polyhydramnios, respiratory distress, and still birth are more common findings than hydrops fetalis, prematurity, malpresentations, and dystocia.[2] Most patients with intracerebral teratoma present with macrocephaly and hydrocephalus, whereas most patients with cardiac teratoma have pericardial effusion and tamponade. Patients with sacrococcygeal teratomas (SCT, 15%) have the largest number of congenital anomalies followed by those with oronasopharyngeal (12%) and cervical teratomas (6%).[2] Common associated congenital anomalies reported include hydrocephalus, absence of septum pellucidum, congenital heart defects, Potter sequence,

genitourinary malformations, shoulder dystocia, and congenital hip dislocation. Screening and/or consideration of these conditions should be a part of the initial diagnostic workup for patients with these particular teratomas.

HISTOLOGY

Histologic subtypes of GCTs include teratoma (mature or immature), YST (also known as endodermal sinus tumor), choriocarcinoma, embryonal carcinoma, and germinoma (dysgerminoma or seminoma).[6] The predominant histology in neonates is either mature (51%) or immature (49%) teratoma, with YST being the second most common. An extremely rare entity in the newborn period is FIF (see later discussion).[2]

Teratoma

The most common histologic subtype of neonatal GCTs is typically composed of tissues derived from all 3 embryonic layers, that is, ectoderm, endoderm, and mesoderm. Occasionally, teratomas may be monodermal or bidermal. The histologic composition of mature teratomas includes well-differentiated tissues, such as cartilage, bone, skin, and skin appendages. In contrast, immature teratomas contain varying degrees of immature fetal tissue, usually neuroectodermal. Teratomas are histologically graded according to the proportion of tissue containing immature neuroepithelial elements.[27] Mature teratomas containing only mature tissue are considered grade 0. Immature teratomas may be grade 1 (presence of <10% immature neuroepithelium) to grade 3 (presence of >50% immature neuroepithelium).

The Malignant Germ Cell International Consortium (MaGIC) merged data from the GCT clinical trials, conducted between 1983 to 2009, by the COG (US), which used cisplatin-based regimens, and by Children's Cancer and Leukaemia Group (CCLG, UK), which used carboplatin-based regimens. A pooled MaGIC analysis of ovarian immature teratomas in children, adolescents, and young adults demonstrated that histologic grade was the most important risk factor for relapse. Among histologic grade 3 tumors, the stage (see later discussion) was significantly associated with relapse. However, adjuvant chemotherapy did not decrease the risk of relapse in the pediatric cohort regardless of the grade or stage of the immature teratoma.[28] Surgical resection remains the mainstay of treatment in teratomas, either mature or immature.[29] A Pediatric Oncology Group (POG) study in children demonstrated that surgery alone is curative for most children and adolescents with completely resected stage I immature teratomas of any grade, even when associated with elevated levels of serum alpha-fetoprotein (AFP) or microscopic foci of YST.[30,31]

Yolk Sac Tumor

Prepubertal children predominantly present with a pure YST. In contrast, only 5% of all neonatal teratomas have a yolk sac component; the incidence is higher in neonatal SCT (10%).[2] The differentiation of tumor cells in YSTs is predominantly endodermal and can take the form of both intraembryonic (primitive gut and liver) and extraembryonic (allantois and yolk sac) derivatives. Serum AFP is generally elevated in patients with YST; however, low levels of AFP can be detected in the setting of an immature teratoma with microscopic foci of YST.

Macroscopically, YSTs are generally well-circumscribed and nonencapsulated and consist of friable, yellow, mucoid tissue with frequent areas of hemorrhage, necrosis, and liquefaction. Microscopically, they display a loose, myxoid stroma containing a reticulated pattern of microcystic spaces that are lined by a flattened, periodic

acid–Schiff stain–positive, diastase-resistant epithelium. Approximately 20% of YSTs exhibit characteristic Schiller-Duval bodies, which are a clustering of cells around a small central blood vessel. In addition to the microcystic/reticular pattern, several variant histologies of YST have been described, including the solid, polyvesicular, and parietal types (corresponding to primitive endoderm and extraembryonic structures) and the glandular and hepatic types (corresponding to the intraembryonic endodermal derivatives). Chemotherapy is reserved for YSTs presenting with advanced stage or relapse.

Infantile Choriocarcinoma

Infantile choriocarcinoma was first described as a distinct clinicopathologic syndrome in 1968.[32] Choriocarcinoma is composed of cytotrophoblast, syncytiotrophoblast, and extravillous trophoblast, often mixed in random fashion, surrounding areas of hemorrhage and necrosis. Vascular invasion is a common feature.

The median age at presentation is typically 1 month (range, 0 days to 5 months).[33] Classic symptoms at diagnosis include severe anemia, failure to thrive, and hepatomegaly. Infrequently, infants can also present with hemoptysis, respiratory failure, seizures, or signs of precocious puberty.[33,34] Multiorgan involvement is fairly common, with liver (77%), lung (67%), brain (27%), or skin (10%) being the most common involved sites.[33] Beta-human chorionic gonadotropin (βhCG) is typically markedly elevated at the time of diagnosis. The natural progression of choriocarcinoma can be rapidly progressive and fatal without prompt and appropriate treatment.[33] Treatment should not be delayed for definitive histologic confirmation in an infant who presents with a markedly elevated β-hCG and a clinical presentation consistent with infantile choriocarcinoma.[33] Optimal treatment of infantile choriocarcinoma is multiagent chemotherapy with either carboplatin- or cisplatin-based regimens.[33–37] Upfront surgical resection of tumor is not recommended in these patients because of tumor friability, risk of uncontrolled bleeding, as well as clinical fragility of the infant at diagnosis.[33–37] Surgical resection of residual masses may not be necessary in a patient in whom the β-hCG has normalized.

Infantile choriocarcinoma is thought to represent a metastatic focus from primary maternal or placental gestational trophoblastic tumor; hence, maternal screening with β-hCG is recommended.[33] A history of maternal choriocarcinoma or hydatidiform molar pregnancy is associated with a higher risk of infantile choriocarcinoma in subsequent pregnancies.[37]

Fetus-In-Fetu

The term “FIF” was coined by Meckel in the eighteenth century to describe a rare congenital fetiform anomaly. The embryogenesis remains controversial, and it is unclear if FIF is a monochorionic, monozygotic, diamniotic twin of the host, or a well-differentiated teratoma (fetiform teratoma).[38,39] FIF is typically diagnosed antenatally or in infancy as a slow-growing asymptomatic mass. It occurs predominantly in the upper retroperitoneum (80%), but other reported sites of FIF include intracranial, oropharynx, neck, mediastinum, liver, kidney, sacrococcygeal, pelvis, ovary, and scrotum or undescended testicle.[40] Karyotype of the FIF is identical to that of the host.[41] The recommended treatment of FIF is complete surgical resection. Incomplete surgical resection merits postoperative surveillance for early detection of recurrences. Only 2 malignant recurrences have been reported to date.[42,43]

SERUM TUMOR MARKERS

Serum tumor markers, such as AFP and β-hCG, aid in the diagnosis, risk stratification, or prognostication, assessing response to therapy and detection of relapse of GCTs. AFP is the predominant serum-binding glycoprotein in the fetus, with peak concentration at 12 to 14 weeks of gestation. In early embryogenesis, AFP is produced in the yolk sac and subsequently in hepatocytes and the gastrointestinal tract. Over the course of the first 2 years of life, AFP gradually declines to a normal adult level as synthesis in the liver ceases, corresponding with albumin becoming the principal serum-binding protein. The interpretation of AFP levels is complex because of this age-related variability in the reference range.[44,45] Values of AFP obtained in children less than 2 years of age can be plotted on the nomogram developed by Blohm and colleagues[44] or Wu and colleagues[45] to determine whether the value falls within the normal range (**Table 1**).

AFP is generally elevated in patients with YST; however, low levels can be detected in the setting of an immature teratoma with microscopic foci of YST. Differential diagnoses for an elevated AFP may include benign liver conditions, including hepatic dysfunction, viral hepatitis (hepatitis B or C and human immunodeficiency virus-associated hepatitis) and cirrhosis, hepatoblastoma, hepatocellular carcinoma, pancreatic and gastrointestinal malignancies, cystic fibrosis, lung cancer, congenital heart defects, hypothyroidism, folate deficiencies, or platelet aggregation disorders. It is important to note that AFP is elevated in all infants at birth.

β-hCG, a peptide hormone normally elevated in pregnancy, is produced by the embryo soon after conception and later by the syncytiotrophoblast in the placenta to prevent disintegration of the corpus luteum of the ovary and thereby maintain progesterone production. β-hCG is generally significantly elevated in tumors that originate from extraembryonic tissue, such as choriocarcinoma. The serum half-life ($t_{1/2}$) of AFP and β-hCG is 5 to 7 days and 24 to 36 hours, respectively.

Table 1
Normal range of serum alpha-fetoprotein (ng/mL) in infants

Wu et al,[45] 1981		Blohm et al,[44] 1998	
Age	Mean ± Standard Deviation	Age	Mean (95% CI)
Premature	134,734 ± 41,444	Premature	158,125 (31,261–799,834)
Newborn	48,406 ± 34,718	Newborn	41,687 (9120–190,546)
0–2 wk	33,113 ± 32,503	Day 8–14	9333 (1480–58,887)
2 wk to 1 mo	9452 ± 12,610	Day 22–28	1396 (316–6310)
2 mo	323 ± 278	Day 46–60	178 (16–1045)
3 mo	88 ± 87	Day 61–90	80 (6–1045)
4 mo	74 + 56	Day 91–120	36 (3–417)
5 mo	47 ± 19	Day 121–150	20 (2–216)
6 mo	13 ± 10	Day 151–180	13 (1–129)
7 mo	10 ± 7	Day 181–720	8 (1–87)

Adapted from, Wu, J.T., Book, L., Sudar, K., 1981. Serum Alpha Fetoprotein (AFP) Levels in Normal Infants. Pediatric Research 15, 50 to 52. Blohm MEG, Vesterling-Horner D, Calaminus G, Gobel U. Alpha$_1$-Fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatric Hematology & Oncology Journal 1998 15:135 to 142; with permission.

STAGING AND REVISED RISK STRATIFICATION

The POG and Children's Cancer Group devised a pediatric staging system for the intergroup studies that was subsequently adapted in the COG trials (**Table 2**). A recent MaGIC analysis of data merged from 7 GCT trials conducted by the COG (US) or the CCLG (UK) established an evidence-based clinical risk stratification for malignant extracranial pediatric GCTs.[46]

SURGICAL MANAGEMENT

General Principles

In the neonatal period, surgical resection is the mainstay of GCT treatment, regardless of site. Despite the presence of microscopic residual disease owing to positive margins, recurrence rates and mortality are low, even in tumors with malignant elements.[47] Hence, morbid procedures in order to achieve negative margins are not justified in a fetus or neonate. A fetus with a large, rapidly growing and highly vascular teratoma is at risk for developing hydrops fetalis because of high-output cardiac failure and anemia. Fetal interventions, such as laser vessel ablation, alcohol sclerosis, cyst drainage, amniodrainage, vesicoamniotic shunt insertion, or preoperative embolization, are advocated in the setting of impending hydrops in a fetus who cannot yet be delivered. Detailed cross-sectional imaging is necessary in order to delineate critical neurovascular structures in relation to these often large and vascular tumors before operative intervention. Site-specific considerations in the surgical management of extracranial GCTs are discussed herein.

Sacrococcygeal Germ Cell Tumors

The principles of resection for SCT are largely unchanged since the early description.[48] The anatomic classification of SCT, developed by Altman and colleagues,[49] relies on the amount of the tumor that is exophytic versus endophytic (**Fig. 4**). Preoperative cross-sectional imaging is critical to determine the internal extent of the tumor, and hence, the operative approach. Most presacral lesions are initially approached through a posterior, transsacral incision. If the peritoneal cavity is entered, a sample of fluid or washings should be obtained for cytology. Appropriate surgical intervention involves complete tumor resection, removal of the coccyx, and preservation of muscle and neurovascular structures. In neonates with malignant GCT, if complete excision cannot be accomplished without significant risk to adjacent structures, biopsy followed by neoadjuvant chemotherapy should be pursued. Prior studies have demonstrated no difference in survival in patients treated with initial biopsy, neoadjuvant chemotherapy, and a delayed resection compared with upfront resection.[50,51] Gastrointestinal and genitourinary dysfunction are common following neonatal SCT resection.[52] Long-term follow-up is mandatory in these children to ensure that normal bowel, bladder, and sensory-motor function is preserved.[53] Recurrence is more likely among patients with immature teratoma than mature teratoma; approximately 50% recur with a malignant component.[47]

Cervicofacial Germ Cell Tumors

Cervicofacial GCTs most commonly present during the prenatal or perinatal period. Lesions can encompass, compress, or emanate from the nasopharynx, oropharynx, hypopharynx, larynx, anterior mediastinum, or other areas. Involvement of the thyroid gland is common, and preoperative and postoperative monitoring is mandatory to assess for normal thyroid function and the need for thyroid hormone replacement. The lesions often cause esophageal and tracheal obstruction leading to

Table 2
The Children's Oncology Group pediatric staging system for germ cell tumors

		Gonadal	
Stage	**Extragonadal**	**Ovarian**	**Testicular**
I	Complete resection at any site, including coccygectomy for sacrococcygeal site Tumor capsule intact Negative margins and lymph nodes	Complete resection Tumor limited to ovary Tumor capsule intact Negative margins, cytology, and lymph nodes	Complete resection by high inguinal orchiectomy Tumor limited to testis Tumor capsule intact Negative margins and lymph nodes
II	Microscopic residual Tumor capsule intact or disrupted Negative lymph nodes	Microscopic residual Tumor capsule intact or disrupted Negative cytology and lymph nodes Failure of tumor markers to normalize or decrease with an appropriate half-life	Microscopic residual Transcrotal orchiectomy Tumor capsule intact or disrupted Negative lymph nodes Failure of tumor markers to normalize or decrease with an appropriate half-life
III	Gross residual or biopsy only Regional lymph nodes negative or positive	Gross residual or biopsy only Positive cytology Contiguous visceral involvement (omentum, intestine, bladder) Regional lymph nodes negative or positive	Gross residual or biopsy only No visceral or extraabdominal involvement Regional lymph node negative or positive
IV	Distant metastases, including liver, lung, bone, brain	Distant metastases, including liver, lung, bone, brain	Distant metastases, including liver, lung, bone, brain

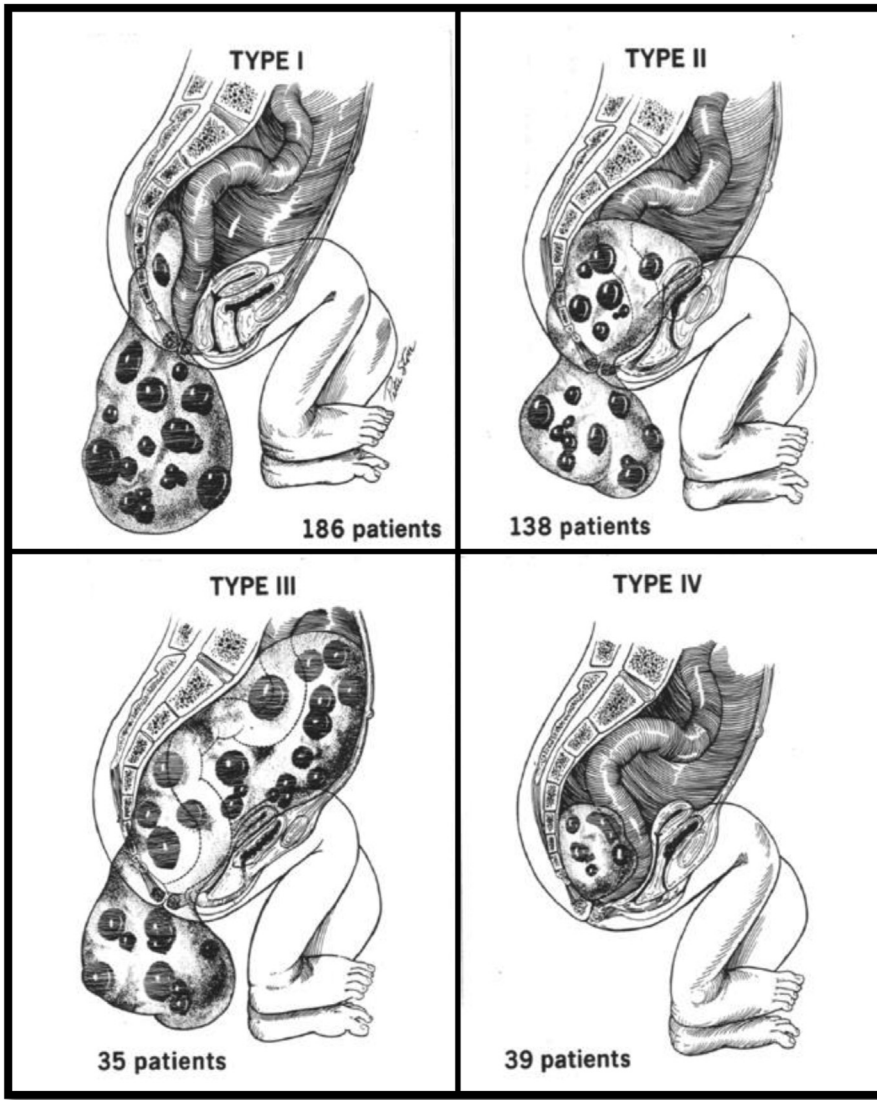

Fig. 4. Altman classification of sacrococcygeal GCTs. (*From* Peter Altman, R., Randolph, J. G. & Lilly, J. R. Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section survey—1973. Journal of Pediatric Surgery 9, 389–398 (1974); with permission).

polyhydramnios on antenatal imaging. Appropriate prenatal imaging (fetal MRI) is critical to assess the degree of involvement of surrounding structures and the possible need for emergent perinatal intervention to secure adequate airway access for oxygenation and ventilation. These interventions may entail ex utero intrapartum treatment whereby the fetus remains on the placental circulation while secure tracheal access is procured (intubation or tracheostomy) or the patient is placed on extracorporeal membrane oxygenation. Once stabilized physiologically and adequate imaging has been obtained, treatment requires removal without compromising major

neurovascular structures. Achieving microscopically negative margins is often impossible without significant functional morbidity, and therefore, not necessary. If required, staged procedures to ensure complete removal of the entire tumor burden without rendering significant morbidity should be entertained by the treating physicians.[54] Outcomes are generally excellent with early surgical intervention and perinatal stabilization of the affected infants.

Abdominal Germ Cell Tumors

Abdominal GCT can be both intraperitoneal and retroperitoneal. Complete surgical resection is the procedure of choice, but resection with the intent of acquiring negative margins is often not possible or necessary. Although most tumors in this site are either mature or immature teratoma, when tumors at this site contain a malignant element, they can be challenging to treat.[55]

Thoracic Germ Cell Tumors

Most thoracic GCTs are located in the anterior mediastinum and originate in the thymus, although they can be found to rise from the posterior or middle mediastinum, heart, or epicardial structures. The tumors can be found on routine antenatal screening using standard fetal ultrasound, and the discovery of these lesions warrants further imaging with a dedicated fetal echocardiogram and MRI to document the extent of the tumor and involvement or compression of adjacent structures. Symptoms are related to the size of the tumor, and large lesions can cause fetal hydrops or airway compromise that may necessitate perinatal intervention.[56] Initial treatment consists of complete resection when possible, but gaining microscopically negative margins, again, is not necessary. Major neurovascular structures (great vessels, phrenic and recurrent laryngeal nerves) must be identified and preserved whenever possible, so as not to impair postoperative cardiorespiratory function and result in significant lifelong morbidity.[57]

CHEMOTHERAPY FOR MALIGNANT GERM CELL TUMORS

Chemotherapy is rarely indicated for neonatal GCTs. The advent of cisplatin-based chemotherapy in the treatment of advanced-stage malignant GCTs has led to excellent cure rates[46]; however, its success has been offset by the emergence of considerable long-term treatment-related morbidity and mortality affecting the quality of survivorship.[58,59] Over the last 25 years, the UK CCLG has used a carboplatin-based strategy in clinical trial design in an attempt to specifically minimize cisplatin-related toxicities.[60] A MaGIC database analysis comparing the outcomes of children and adolescents with extracranial malignant GCT treated with either carboplatin- or cisplatin-based regimens did not demonstrate a statistically significant difference in survival outcomes between the 2 regimens, even in analyses stratified by age, site, or stage.[61] The current COG trial, AGCT1531, aims to minimize toxicity by reducing therapy while maintaining current survival rates in patients with low- and standard-risk GCT. The trial will eliminate chemotherapy for low-risk patients who are likely cured with surgery and will observe the salvage rates among those who recur. Among standard-risk patients, the trial will evaluate whether cisplatin can be replaced with carboplatin.

SUMMARY

GCTs are derived from PGCs, which are destined to become either the egg or the sperm. Their intrinsic pluripotency results in a wide spectrum of benign and malignant

tumors, most of which are diagnosed antenatally. The clinical spectrum of GCTs is narrower in the neonatal period, predominantly comprising teratoma (mature and immature). Given the size, location, and complexity of these tumors, optimal management requires a multidisciplinary team. Surgical resection is the mainstay of therapy. Negative surgical margins are often difficult to obtain and should not be attempted if significant mortality or morbidity would be encountered. Relapse is an infrequent occurrence even in the setting of microscopic residual disease. In the rare instance of a newborn with malignant metastatic disease or unresectable malignant disease, neoadjuvant chemotherapy after a diagnostic biopsy is the preferred management, with demonstrated better survival outcomes with a delayed resection. The chemosensitivity of GCTs to cisplatin- or carboplatin-based regimens has contributed to excellent cure rates in malignant histologies, which in neonates is usually YST. If chemotherapy is indicated, a carboplatin-based regimen should be considered to minimize short- and long-term treatment-related toxicity.

CLINICS CARE POINTS

- Teratomas (mature or immature) account for a vast majority of the neonatal germ cell tumors, approximately 5% of which contain a malignant component that is predominantly yolk sac tumor.
- Given the size, location, and complexity of these tumors, optimal management requires multidisciplinary care with both surgical and oncologic input.
- Most neonatal germ cell tumors are curable with surgery alone.
- In the rare instance of a neonate with metastatic malignant disease or malignant disease for which upfront surgical resection is not feasible without significant morbidity, an initial biopsy followed by neoadjuvant chemotherapy and delayed surgical resection is recommended.
- If chemotherapy is indicated, a carboplatin-based regimen should be considered to minimize treatment-related toxicity.

DISCLOSURE

R. Shah: The author has nothing to disclose. B.R. Weil: The author has nothing to disclose. C.B. Weldon: The author has nothing to disclose. J.F. Amatruda: The author has nothing to disclose. A.L. Frazier: Clinical advisory board, Decibel Therapeutics.

REFERENCES

1. Isaacs HJMD. Congenital and neonatal malignant tumors: a 28-year experience at Children's Hospital of Los Angeles. Am J Pediatr Hematol Oncol 1987;9(2):121–9.
2. Isaacs H. Perinatal (fetal and neonatal) germ cell tumors. J Pediatr Surg 2004;39(7):1003–13.
3. Tang WWC, Kobayashi T, Irie N, et al. Specification and epigenetic programming of the human germ line. Nat Rev Genet 2016;17(10):585–600.
4. Pierce JL, Frazier AL, Amatruda JF. Pediatric germ cell tumors: a developmental perspective. Adv Urol 2018;2018:9059382.

5. Looijenga LHJ, Stoop H, de Leeuw HPJC, et al. POU5F1 (OCT3/4) identifies cells with pluripotent potential in human germ cell tumors. Cancer Res 2003;63(9): 2244–50.
6. Rakheja D, Teot LA. Pathology of Germ Cell Tumors. In: Frazier A, Amatruda J, editors. Pediatric Germ Cell Tumors. Pediatric Oncology, volume 1, 2014, Springer, Berlin, Heidelberg. https://doi-org.libproxy1.usc.edu/10.1007/978-3-642-38971-9_3 https://link-springer-com.libproxy1.usc.edu/chapter/10.1007/978-3-642-38971-9_3.
7. Aeckerle N, Drummer C, Debowski K, et al. Primordial germ cell development in the marmoset monkey as revealed by pluripotency factor expression: suggestion of a novel model of embryonic germ cell translocation. Mol Hum Reprod 2015; 21(1):66–80.
8. Mamsen LS, Brøchner CB, Byskov AG, et al. The migration and loss of human primordial germ stem cells from the hind gut epithelium towards the gonadal ridge. Int J Dev Biol 2012;56(10–12):771–8.
9. Poynter JN, Hooten AJ, Frazier AL, et al. Associations between variants in KITLG, SPRY4, BAK1, and DMRT1 and pediatric germ cell tumors. Genes Chromosomes Cancer 2012;51(3):266–71.
10. Doitsidou M, Reichman-Fried M, Stebler J, et al. Guidance of primordial germ cell migration by the chemokine SDF-1. Cell 2002;111(5):647–59.
11. Runyan C, Gu Y, Shoemaker A, et al. The distribution and behavior of extragonadal primordial germ cells in Bax mutant mice suggest a novel origin for sacrococcygeal germ cell tumors. Int J Dev Biol 2008;52(4):333–44.
12. Ross JA, Schmidt PT, Perentesis JP, et al. Genomic imprinting of H19 and insulin-like growth factor-2 in pediatric germ cell tumors. Cancer 1999;85(6):1389–94.
13. Cools M, Drop SLS, Wolffenbuttel KP, et al. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev 2006;27(5): 468–84.
14. Johnson KJ, Ross JA, Poynter JN, et al. Paediatric germ cell tumours and congenital abnormalities: a Children's Oncology Group study. Br J Cancer 2009;101(3):518–21.
15. Atkin NB, Baker MC. Specific chromosome change, i(12p), in testicular tumours? Lancet 1982;2(8311):1349.
16. Summersgill B, Goker H, Weber-Hall S, et al. Molecular cytogenetic analysis of adult testicular germ cell tumours and identification of regions of consensus copy number change. Br J Cancer 1998;77(2):305–13.
17. Veltman I, Veltman J, Janssen I, et al. Identification of recurrent chromosomal aberrations in germ cell tumors of neonates and infants using genomewide array-based comparative genomic hybridization. Genes Chromosomes Cancer 2005; 43(4):367–76.
18. Palmer RD, Foster NA, Vowler SL, et al. Malignant germ cell tumours of childhood: new associations of genomic imbalance. Br J Cancer 2007;96(4):667–76.
19. Palmer RD, Murray MJ, Saini HK, et al. Malignant germ cell tumors display common microRNA profiles resulting in global changes in expression of messenger RNA targets. Cancer Res 2010;70(7):2911–23.
20. Cancer incidence and survival among children and adolescents - pediatric monograph - SEER Publications 1975-1995. Available at: http://seer.cancer.gov/archive/publications/childhood/. Accessed March 16, 2016.
21. Williams LA, Frazier AL, Poynter JN. Survival differences by race/ethnicity among children and adolescents diagnosed with germ cell tumors. Int J Cancer 2020; 146(9):2433–41.

22. Poynter JN, Richardson M, Roesler M, et al. Family history of cancer in children and adolescents with germ cell tumours: a report from the Children's Oncology Group. Br J Cancer 2018;118(1):121–6.
23. Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. Pediatrics 2006;118(2):e488–500.
24. Huang H, Wang C, Tian Q. Gonadal tumour risk in 292 phenotypic female patients with disorders of sex development containing Y chromosome or Y-derived sequence. Clin Endocrinol (Oxf) 2017;86(4):621–7.
25. Dicken BJ, Billmire DF, Krailo M, et al. Gonadal dysgenesis is associated with worse outcomes in patients with ovarian nondysgerminomatous tumors: a report of the Children's Oncology Group AGCT 0132 study. Pediatr Blood Cancer 2018; 65(4):e26913.
26. Williams LA, Pankratz N, Lane J, et al. Klinefelter syndrome in males with germ cell tumors: a report from the Children's Oncology Group. Cancer 2018; 124(19):3900–8.
27. Thurlbeck WM, Scully RE. Solid teratoma of the ovary. A clinicopathological analysis of 9 cases. Cancer 1960;13(4):804–11.
28. Pashankar F, Hale JP, Dang H, et al. Is adjuvant chemotherapy indicated in ovarian immature teratomas? A combined data analysis from the Malignant Germ Cell Tumor International Collaborative. Cancer 2016;122(2):230–7.
29. Mann JR, Gray ES, Thornton C, et al. Mature and immature extracranial teratomas in children: the UK children's cancer study group experience. J Clin Oncol 2008; 26(21):3590–7.
30. Cushing B, Giller R, Ablin A, et al. Surgical resection alone is effective treatment for ovarian immature teratoma in children and adolescents: a report of the Pediatric Oncology Group and the Children's Cancer Group. Am J Obstet Gynecol 1999;181(2):353–8.
31. 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.
32. Witzleben CL, Bruninga G. Infantile choriocarcinoma: a characteristic syndrome. J Pediatr 1968;73(3):374–8.
33. Blohm MEG, Göbel U. Unexplained anaemia and failure to thrive as initial symptoms of infantile choriocarcinoma: a review. Eur J Pediatr 2004;163(1):1–6.
34. Johnson EJ, Crofton PM, O'Neill JMD, et al. Infantile choriocarcinoma treated with chemotherapy alone. Med Pediatr Oncol 2003;41(6):550–7.
35. Szavay PO, Wermes C, Fuchs J, et al. Effective treatment of infantile choriocarcinoma in the liver with chemotherapy and surgical resection: a case report. J Pediatr Surg 2000;35(7):1134–5.
36. Heath JA, Tiedemann K. Successful management of neonatal choriocarcinoma. Med Pediatr Oncol 2001;36(4):497–9.
37. Yoon JM, Burns RC, Malogolowkin MH, et al. Treatment of infantile choriocarcinoma of the liver. Pediatr Blood Cancer 2007;49(1):99–102.
38. Willis RA. The structure of teratomata. J Pathol Bacteriol 1935;40(1):1–36.
39. Spencer R. Parasitic conjoined twins: external, internal (fetuses in fetu and teratomas), and detached (acardiacs). Clin Anat 2001;14(6):428–44.
40. Ji Y, Song B, Chen S, et al. Fetus in fetu in the scrotal sac: case report and literature review. Medicine 2015;94(32):e1322.
41. Hing A, Corteville J, Foglia RP, et al. Fetus in fetu: molecular analysis of a fetiform mass. Am J Med Genet 1993;47(3):333–41.

42. Hopkins KL, Dickson PK, Ball TI, et al. Fetus-in-fetu with malignant recurrence. J Pediatr Surg 1997;32(10):1476–9.
43. Chen Y-H, Chang C-H, Chen K-C, et al. Malignant transformation of a well-organized sacrococcygeal fetiform teratoma in a newborn male. J Formos Med Assoc 2007;106(5):400–2.
44. Blohm MEG, Vesterling-Hörner D, Calaminus G, et al. Alpha1-fetoprotein (AFP) reference values in infants up to 2 years of age. Pediatr Hematol Oncol 1998; 15(2):135–42.
45. Wu JT, Book L, Sudar K. Serum alpha fetoprotein (AFP) levels in normal infants. Pediatr Res 1981;15(1):50–2.
46. Frazier AL, Hale JP, Rodriguez-Galindo C, et al. Revised risk classification for pediatric extracranial germ cell tumors based on 25 years of clinical trial data from the United Kingdom and United States. J Clin Oncol 2015;33(2): 195–201.
47. De Backer A, Madern GC, Hakvoort-Cammel FGAJ, et al. Study of the factors associated with recurrence in children with sacrococcygeal teratoma. J Pediatr Surg 2006;41(1):173–81.
48. Gross RW, Clatworthy HW, Meeker IA. Sacrococcygeal teratomas in infants and children; a report of 40 cases. Surg Gynecol Obstet 1951;92(3):341–54.
49. Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey—1973. J Pediatr Surg 1974;9(3):389–98.
50. Rescorla F, Billmire D, Stolar C, et al. The effect of cisplatin dose and surgical resection in children with malignant germ cell tumors at the sacrococcygeal region: a Pediatric Intergroup Trial (POG 9049/CCG 8882). J Pediatr Surg 2001; 36(1):12–7.
51. Göbel U, Schneider DT, Calaminus G, et al. Multimodal treatment of malignant sacrococcygeal germ cell tumors: a prospective analysis of 66 patients of the German Cooperative Protocols MAKEI 83/86 and 89. J Clin Oncol 2001;19(7): 1943–50.
52. Malone PS, Spitz L, Kiely EM, et al. The functional sequelae of sacrococcygeal teratoma. J Pediatr Surg 1990;25(6):679–80.
53. Schmidt B, Haberlik A, Uray E, et al. Sacrococcygeal teratoma: clinical course and prognosis with a special view to long-term functional results. Pediatr Surg Int 1999;15(8):573–6.
54. Azizkhan RG, Haase GM, Applebaum H, et al. Diagnosis, management, and outcome of cervicofacial teratomas in neonates: a Childrens Cancer Group study. J Pediatr Surg 1995;30(2):312–6.
55. Billmire D, Vinocur C, Rescorla F, et al. Malignant retroperitoneal and abdominal germ cell tumors: an intergroup study. J Pediatr Surg 2003;38(3):315–8.
56. Merchant AM, Hedrick HL, Johnson MP, et al. Management of fetal mediastinal teratoma. J Pediatr Surg 2005;40(1):228–31.
57. Billmire D, Vinocur C, Rescorla F, et al. Malignant mediastinal germ cell tumors: an intergroup study. J Pediatr Surg 2001;36(1):18–24.
58. Travis LB, Fosså SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 2005; 97(18):1354–65.
59. Travis LB, Beard C, Allan JM, et al. Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst 2010;102(15):1114–30.
60. Mann JR, Raafat F, Robinson K, et al. The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and

bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol 2000;18(22):3809–18.
61. Frazier AL, Stoneham S, Rodriguez-Galindo C, et al. Comparison of carboplatin versus cisplatin in the treatment of paediatric extracranial malignant germ cell tumours: a report of the Malignant Germ Cell International Consortium. Eur J Cancer 2018;98:30–7.