Gonadal and Extragonadal Germ Cell Tumors, Sex Cord Stromal and Rare Gonadal Tumors

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Dominik T. Schneider, Monica Terenziani, Giovanni Cecchetto, and Thomas A. Olson

Contents

D.T. Schneider (✉)
Klinik für Kinder- und Jugendmedizin, Clinic of Pediatrics, Beurhausstr. 40, Klinikum Dortmund, 44137 Dortmund, Germany
e-mail: dominik.schneider@klinikumdo.de

M. Terenziani
Pediatric Oncology, Istituto Nazionale Tumori, Milan, Italy

G. Cecchetto
Department of Pediatrics, Pediatric Surgery, University of Padua, Padua, Italy

T.A. Olson
Division Pediatric Hematology/Oncology, Children`s Healthcare of Atlanta at Egleston, Atlanta, GA, USA
e-mail: thomas.olson@choa.org

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39.1 Overview on Epidemiology, Biology, Histology, and Clinic

Dominik T. Schneider,
Monica Terenziani, and Thomas A. Olson

Germ cell tumors include a group of tumors that are highly heterogeneous regarding their clinical and histologic appearance. Altogether they comprise approximately 2–3% of cancers diagnosed in children and adolescents younger than 15 years (Ries LAG et al. 1999a; Kaatsch 2004a). During childhood and adolescence, approximately half of all germ cell tumors develop at extragonadal midline sites. Sacrococcygeal germ cell tumors constitute the most frequent tumor in neonates, and extracranial germ cell tumors account for 14% of all cancers in adolescents of the 15–19 age group. An epidemiological analysis of patients reported to the German GCT trials from 1981 to 2000 showed a bimodal age distribution with a small peak during infancy and a larger peak after puberty, to be continued among adults, among which germ cell tumors constitute the most common cancer in young men (Schneider et al. 2004a). During the first year of life, teratomas predominate, with a slight female preponderance (Fig. 39.1.1a, b). After the first 6 months of life, yolk sac tumors are the most frequent histologic subtype. This histology is slightly more often seen in boys than in girls. Tumors with germinoma histology (syn. seminoma or dysgerminoma) are first observed in girls at 5 years of age and show a gradually increasing incidence during adolescence. Seminomas are not seen in boys, until they reach puberty. The same accounts for other nongerminomatous histologies such as embryonal carcinoma and choriocarcinoma, which are mainly seen during and after puberty, in most cases as components of mixed malignant germ cell tumors (Fig. 39.1.1c) (Schneider et al. 2004a).

This bimodal age distribution is also demonstrated by the Surveillance Epidemiology and End Results Registry (SEER). Of note, there appears to be a significant increase of the incidence in specific subgroups such as adolescent boys and prepubertal girls (Poynter et al. 2010). This study suggests that the biology of germ cell tumors may differ between different populations and clinical subgroups.

Separate groups are marked by distinct clinical and molecular features. The distribution of gonadal and extragonadal tumor sites by age is shown in

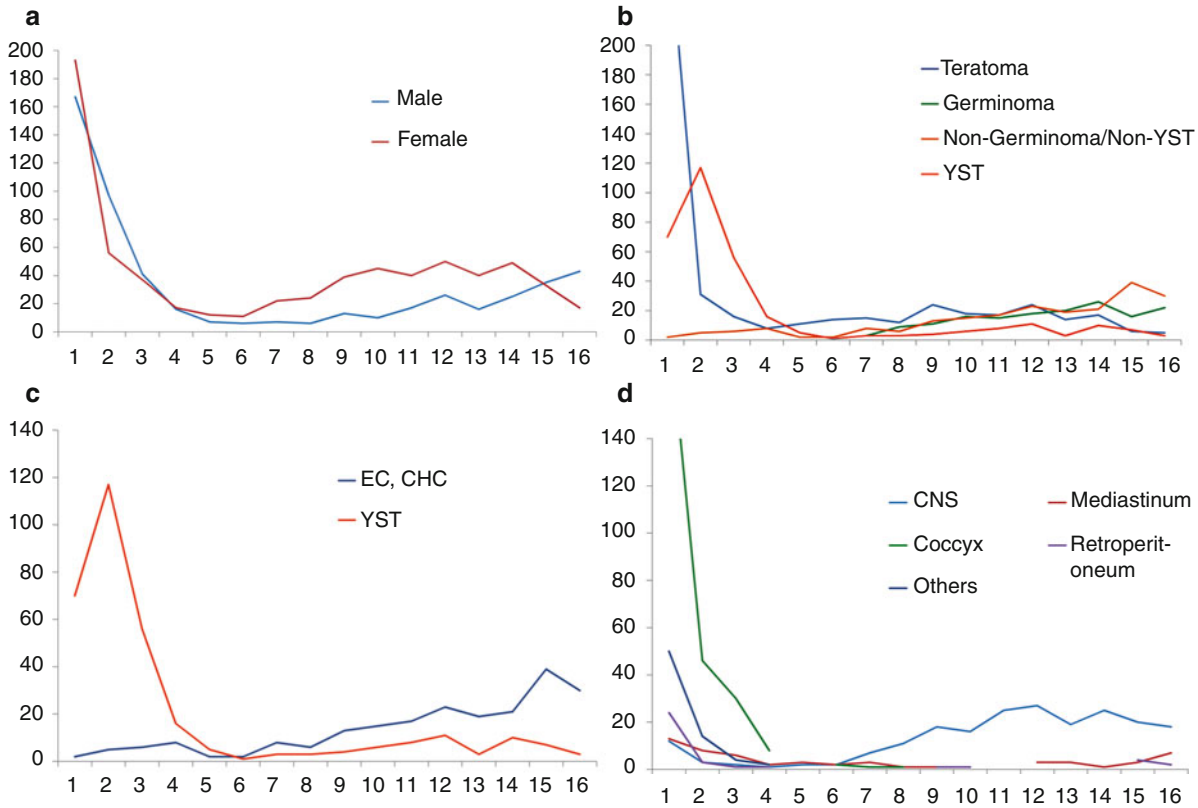


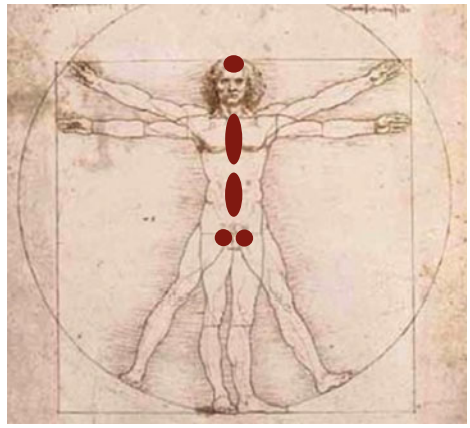
Fig. 39.1.1 (**a**) Age distribution of germ cell tumors by age and sex. (**b**) Age distribution of germ cell tumors by histology – teratomas. (**c**) Age distribution of germ cell tumors by histology – nongerminomatous. (**d**) Age distribution of germ cell tumors by site

Fig. 39.1.1d. This figure illustrates that for some specific tumor sites such as the testis and the mediastinum, a bimodal age distribution can be recognized, with a subgroup occurring during infancy and a separate group developing after the onset of puberty (Schneider et al. 2002a). In contrast, no separate epidemiological groups can be appreciated in CNS and ovarian germ cell tumors, which only show an incidence peak after the onset of puberty. Lastly, some germ cell tumors such as vaginal and sacrococcygeal germ cell tumors only develop during infancy and childhood but not after the onset of puberty (Fig. 39.1.2) (Schneider et al. 2004a).

The survival of children with pediatric germ cell tumors has greatly improved with the application of lessons from adult GCT. For some patients with GCT, a reduction in therapy may be warranted. However, there is still a small population for which more intensive or adaptive therapy is warranted. The paucity of such events suggests that international collaborations and advances in molecular understanding of GCT may be crucial.

39.1.1 Histogenesis and Biology of Extragonadal Germ Cell Tumors

As we investigate molecular differences in GCT from children and adolescents, it should be recognized that few pediatric tumors have been studied (Palmer et al. 2007). When addressing tumor-specific genetic changes, the heterogeneity of the pediatric germ cell tumors is evident also in studies investigating their genetic and molecular properties. Biologically distinct subcategories have been described in the pediatric population (Bussey et al. 1999a; Perlman et al. 2000; Schneider et al. 2006; Palmer et al. 2007).



	<10	>10 years
CNS	10%	35%
Ovary	15%	45%
Testis	25%	10%*
Coccyx	35%	0%
Others	15%	10%

1,442 patients from the MAHO/MAKEI/SIOP CNS GCT registry

*Due to the age cut-off, testicular GCTs during puberty are under-reported to this registry. Last, it should be noted that this figure cites data from Schneider et al. Ped Blood Cancer 2004

Fig. 39.1.2 Distribution of germ cell tumors by site and age

39.1.2 Sex-Chromosomal Abnormalities in Germ Cell Tumors

Sex-chromosomal abnormalities have been associated with the development of germ cell tumors. The most recognized association is the one of ovarian germ cell tumors with Turner syndrome, in particular, in patients with microscopic residues of Y-chromosomal sequences. In these patients, dysgerminomas may develop within gonadoblastomas, which therefore constitutes a precursor lesion of invasive germ cell (Cools et al. 2006). Moreover, testicular feminization and Swyer syndrome, a disorder characterized by a female appearance but with gonadal dysgenesis, i.e., hypoplastic streak gonads in a cytogenetically male patient, are also associated with the development of gonadoblastoma and overt germ cell tumor over time. Therefore, prophylactic oophorectomy is recommended in these patients.

Moreover, some extragonadal germ cell tumors are also associated with sex-chromosomal aberrations. Thus, mediastinal GCT have been associated with Klinefelter's syndrome (47,XXY) (Nicholset al. 1987a). Approximately 50% of adolescents with mediastinal germ cell tumors have cytogenetic changes consistent with Klinefelter's syndrome (Schneider et al. 2002a) (see Chap. 24). In addition, a high frequency of numeric aberrations of sex chromosomes have been demonstrated in germ cell tumors of the central nervous system (Yu et al. 1995).

39.1.3 The Primordial Germ Cell Hypothesis of Extragonadal Germ Cell Tumors

More than 35 years ago, Teilum postulated that all different histologic entities of germ cell tumors develop from an omnipotent primordial germ cell that is capable of differentiation along the germ line and into embryonic and extraembryonic tissues (Teilum et al. 1975a) (Fig. 39.1.3). This so-called holistic concept of the histogenesis of germ cell tumors remains fascinating since it provides a very instructive theory that is able to explain both the apparent heterogeneity of germ cell tumors and the observation of tumors with mixed histology. Moreover, patients who at relapse present with a histology different from that at initial diagnosis can be explained based on this theory. Last, if the holistic concept is considered in the light of the knowledge of primordial germ cell migration during early embryonal development, even the development of seminomatous and nonseminomatous germ cell tumors at extragonadal sites can be explained. However, several aspects still remain elusive. For instance, it is unclear why the histologic differentiation of germ cell tumors is restricted to specific subtypes at specific sites, while it is not at others. At the sacrococcygeal region, teratomas and yolk sac tumors can be found, while vaginal germ cell tumors always present as pure yolk sac tumors. Therefore, it can be assumed that the microenvironment may play a substantial role in modulating tumor development and differentiation.

There has been considerable debate as to whether the heterogeneous germ cell tumors, in particular extragonadal teratomas may originate from midline somatic stem cells. This debate has been fostered by the experimental observation that teratoma like tumors may develop at the injection site of cultured embryonal stem cells (Thomson et al. 1998). Moreover, the development of an isochromosome 12p, the pathognomic marker of germ cell tumors in young men, has been described in long-term culture of embryonal stem cells (Draper et al. 2004).

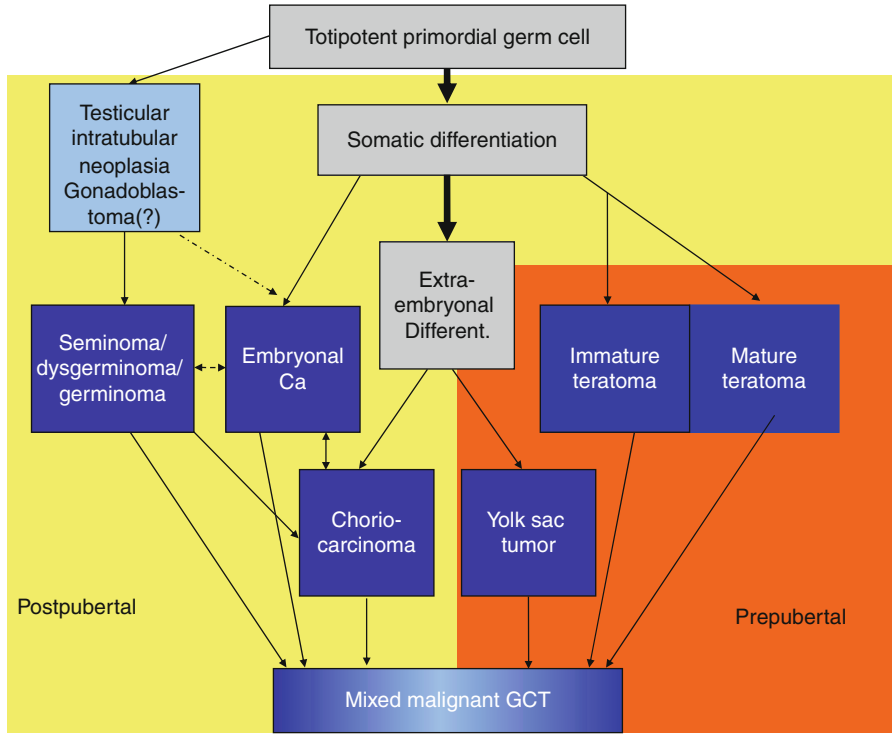


Fig. 39.1.3 Primordial germ cell hypothesis of extragonadal germ cell tumor development

On the other hand, there is molecular evidence that both gonadal and extragonadal germ cell tumors originate from primordial germ cells at different stages of development. Thus, the examination of the epigenetic control of genomic imprinting reveals a methylation pattern that is characteristic of primordial germ cells during and shortly after their migration during early embryonal development (Bussey et al. 1999a; Schneider et al. 2001a). Moreover, the tumors cells retain a specific embryonal stem-cell-like expression pattern, characteristic of primordial germ cells (Hoei-Hansen et al. 2006). However, this hypothesis has recently been challenged by the observation that neural stem cells may also show loss of the methylation imprint, e.g., of SNRPN, making these cells alternative candidates from which CNS germ cell tumors may be derived (Lee et al. 2010). The loss of methylation pattern of other genes such as IGF-2 however distinguishes germ cell tumors from other embryonal tumors with presumed stem cell origin such as nephroblastoma (Sievers et al. 2005a). This observation, as well as modern findings on the role of the microenvironment for the development of extragonadal germ cell tumors, still supports the hypothesis of a specific germ cell origin of these tumors (Oosterhuis et al. 2007).

The primordial germ cells first become evident in the extraembryonic yolk sac by the fourth week of gestation. By the fifth week, the germ cells migrate through the mesentery to the gonadal ridge. This migration appears to be mediated by the c-kit receptor and its ligand, stem-cell factor, or steel factor. Primordial germ cells express c-kit. Stem-cell factor is expressed with an increasing gradient from yolk sac to gonadal ridge, guiding germ cells to the gonadal ridge. In animal models, primordial germ cells not expressing c-kit are unable either to migrate to the gonad or to proliferate during this migration (Godin et al. 1991; Dolci et al. 1993; Orth et al. 1997).

The association of c-kit mutations (codon 816) with bilateral or familial germ cell tumors underlines the importance of this gene during germ cell development (Looijenga et al. 2003; Rapley et al. 2004). In addition, c-kit mutations or c-kit amplifications have also been reported in 27% of unilateral ovarian dysgerminomas (Cheng et al. 2010).

Germ cell migration is also controlled by additional mediators such as the chemokine soluble derived factor 1 (SDF-1) and its receptor CXCR-4 (Doitsidou et al. 2002). Germ cells express CXCR-4 and migration is directed by the expression and secretion of SDF-1 (CXCL-12) in the mesenchyme of the gonadal

Table 39.1.1 Histology and genetics

Group	Histology	Epigenetics	Genetics
GCTs of infancy and childhood	Teratoma Yolk sac tumor	Premeiotic Loss of imprinting	Normal −1p, + 1p, − 6p, + 20
GCTs of adolescence and adulthood	Teratoma Seminoma Mal. nonseminoma	Meiosis I Loss of imprinting	+12p
Spermatocytic seminoma (testis)		Meiosis II Gamet. imprinting	+9
Cystic teratoma (ovary)		Meiosis II Gamet. imprinting	(23,X)×2

ridges. Mice that lack either SDF-1 or CXCR-4 also fail to populate the gonadal ridges and may persist at extragonadal sites. Moreover, aberrant migration of germ cells can be induced by aberrant expression of SDF-1 (Molyneaux et al. 2003). Of note, expression analysis of SDF-1 and CXCR-4 has demonstrated aberrant expression of CXCR-4 in extragonadal germ cell tumors, which typically locate at sites known to express SDF-1 (Gilbert et al. 2009). These data from embryological and tumor genetic studies support the hypothesis that extragonadal germ cell tumors may arise from germ cells that have migrated aberrantly, and in which expression of growth factors aberrantly persists beyond the embryonal period. However, yet unpublished data indicate that no mutations of CXCR-4 can be detected in extragonadal germ cell tumors, thus indicating that aberration of the SDF-1 and CXCR-4 axis is not involved in the development of extragonadal germ cell tumors (D.T.S. unpublished data).

39.1.4 Complex Correlation of Biology, Site, and Histology

It should be noted that apart from the predominance of midline sites and the histologic similarity to the histologic spectrum of gonadal germ cell tumors, there are pronounced biologic and histologic differences between germ cell tumors at different anatomical sites.

Thus, during childhood the histologic appearance of germ cell tumors is almost exclusively restricted to teratoma and yolk sac tumor (Table 39.1.1). Tumors at other sites such as vaginal germ cell tumors only present as yolk sac tumors. Both tumors are not seen during adolescence. After the onset of puberty, mediastinal and central nervous system germ cell tumors predominate among extragonadal germ cell tumors. These tumors present with the whole spectrum of adult germ cell tumors, including seminomas, nonseminomas, and teratomas. Of note, mediastinal germ cell tumors may present with both patterns, one consisting of teratomas and yolk sac tumors during childhood and one with seminomas, nonseminomas, and teratomas during adolescence. These two groups are distinguished by different genetic profiles, both corresponding to the genetic aberrations seen in germ cell tumors at other anatomical sites during the corresponding age group (Schneider et al. 2002a).

Thus, genetic studies have substantially helped in categorizing the different distinct clinical entities of germ cell tumors and in defining childhood germ cell tumors at a distinct site, despite their heterogeneous clinical presentation at different anatomical sites. Genetic studies have also provided information regarding the pathogenesis of pediatric germ cell tumors including information on constitutional genetic changes that may lead to increased susceptibility and tumor-specific genetic changes. However, little is still known regarding the former, particularly with regard to infantile germ cell tumors. Nevertheless, it has become clear that with the onset of puberty, the spectrum of genetic changes is seen in germ cell tumors, and therefore the biology changes.

39.1.5 Genetics of Prepubertal Germ Cell Tumors

In children younger than 10 years, germ cell tumors arising in gonadal and extragonadal sites are similar in clinical presentation, histology, and genetics (Table 39.1.2). Most teratomas in this age group are diploid, have normal karyotypes, and, if completely resected, behave in a

Table 39.1.2 Histology and markers

Histology	AFP	β-HCG	Immunohisto-marker	Prepubertal	Postpubertal
Teratoma, mature	–	–	–	+	+
Teratoma, immature	(+)	–	–	+	+
Teratoma with mal. Transformation, e.g., carcinoma	(+)	–	–	–	+
Germinoma (syn. seminoma, dysgerminoma)	–	(+)	OCT3/4, c-kit	–	+
Embryonal Carcinoma	–	–	CD30 OCT3/4	–	+
Choriocarcinoma	–	+++	β-HCG	(+)	+
Yolk sac tumor	+++	–	AFP CD34	+	+
Mixed malignant GCT	–/+	–/+	As above	TER + YST	All comb.
Gonadoblastoma	–	–	OCT3/4	–	+
Polyembryoma	–	–	–	–	–

benign fashion regardless of degree of immaturity and site of origin (Kaplan et al. 1979a; Silver et al. 1994; Bussey et al. 1999a; Schneider et al. 2001b, c; Harms et al. 2006a). Malignant germ cell tumors in these young children are almost exclusively yolk sac tumors, may arise from a preexisting teratoma, and most often are diploid or tetraploid (Perlman et al. 1994a; Silver et al. 1994; Bussey et al. 1999a). Recurrent cytogenetic abnormalities involve chromosomes 1, 6, and 20 among others, but only rarely the 12p (Bussey et al. 1999a; Perlman et al. 1994a, 2000; Mostert et al. 2000; Schneider et al. 2001b, c, 2006; Palmer et al. 2007).

In situ hybridization and loss of heterozygosity studies have demonstrated deletion of 1p36 in 80–100% of infantile malignant germ cell tumors arising from testicular and extragonadal sites (Jenderny et al. 1995; Bussey et al. 2001; (Zahn et al. 2006; Perlman et al. 1996). Genetic surveys of regions of gain or loss in these infantile yolk sac tumors document recurrent loss of 6q24-qter, gain of 20q and 1q, and loss of 1p. A small number of tumors show evidence for c-myc or n-myc amplification (Schneider et al. 2002a, Germ Cell Tumours V, 127–128). The clinical significance for these markers is however entirely unknown.

Recently, first expression studies of mRNAs and micro-RNAs in childhood germ cell tumors have been reported (Palmer et al. 2008, 2010). Germ cell tumors show recurrent mRNA and micro-RNA profiles that segregate tumors primarily according to histology. Furthermore, expression profiles distinguished between childhood and adult germ cell tumors. Of note, within a distinct histology, the yolk sac tumor, tumors had different expression profiles for different ages. In contrast, no site-specific differences were reported within a given histology and age group. Gene expression studies have also yielded insights into the molecular biology of childhood germ cell tumors. Thus, in pediatric yolk sac tumors, genes associated with activation of the canonical WNT pathway were expressed at high levels (Fritsch et al. 2006; Palmer et al. 2008). Additional studies have shown that this pattern is associated primarily with epigenetic dysregulation of WNT control genes among others, the adenomatosis poliposis gene and cell surface regulators of *wnt* signaling (unpublished data).

Figures 39.1.4 and 39.1.5 demonstrate a summary of CGH profiles of 116 malignant germ cell tumors and 32 pure teratomas, respectively. The results are separated by age, demonstrating frequent chromosomal imbalances of chromosomes 1p, 6q, and 20q in prepubertal tumors, irrespective of tumor site. Postpubertal tumors show recurrent gain of 12p and other less recurrent imbalances. Of note, all pure teratomas prior to puberty are balanced, while postpubertal teratomas may show recurrent imbalances, resembling a pattern seen in malignant germ cell tumors of the same age group. However, the number of chromosomal imbalances is smaller than in corresponding malignant tumors.

Fig. 39.1.4 CGH profiles of 116 malignant germ cell tumors (Schneider et al. 2006)

In conclusion, tumors in children younger than10 years of age are biologically distinct from those tumors that develop in adolescents and adults. This is true, even if the histology, e.g., yolk sac tumor, is microscopically undistinguishable.

39.1.6 Genetics of Postpubertal Germ Cell Tumors

Testicular germ cell tumors of the young adult constitute the best studied entity of germ cell tumors. These tumors appear to arise from a precursor lesion, which is histologically defined as testicular intratubular neoplasia (TIN). TIN may grow within the seminiferous tubules. Tumor cells express specific transcription factors such as c-kit and OCT3/4, indicating their origin from immature pluripotent gonocytes (Oosterhuis and Looijenga 2005a). Obviously, the progression of TIN to invasive germ cell cancer is associated with the development of additional cytogenetic events, including aberrations of chromosome 12p. Bilateral testicular (2–5%) and familial (2%) cases have been reported.

The isochromosome 12p constitutes the biologic hallmark of testicular and extragonadal germ cell tumors in adults (Atkin and Baker 1982; Rodriguez et al. 1992). It is formed by centromeric fusion of two short arms of chromosome 12, with loss of the long

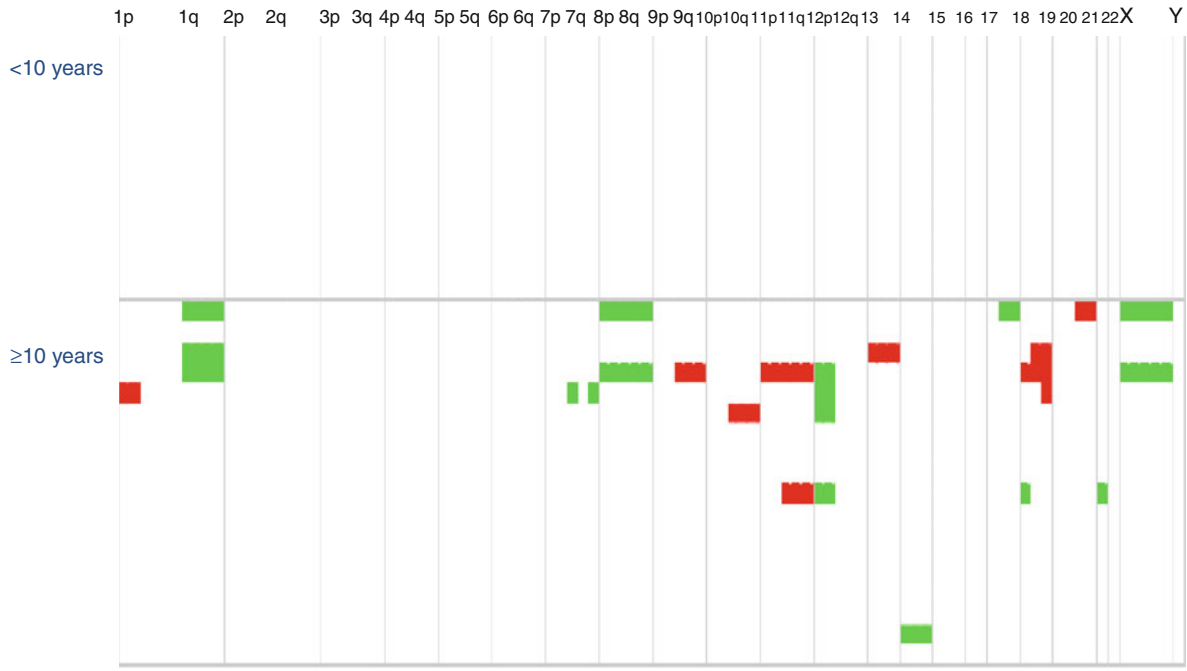


Fig. 39.1.5 CGH profiles of pure teratomas (Schneider et al. 2006)

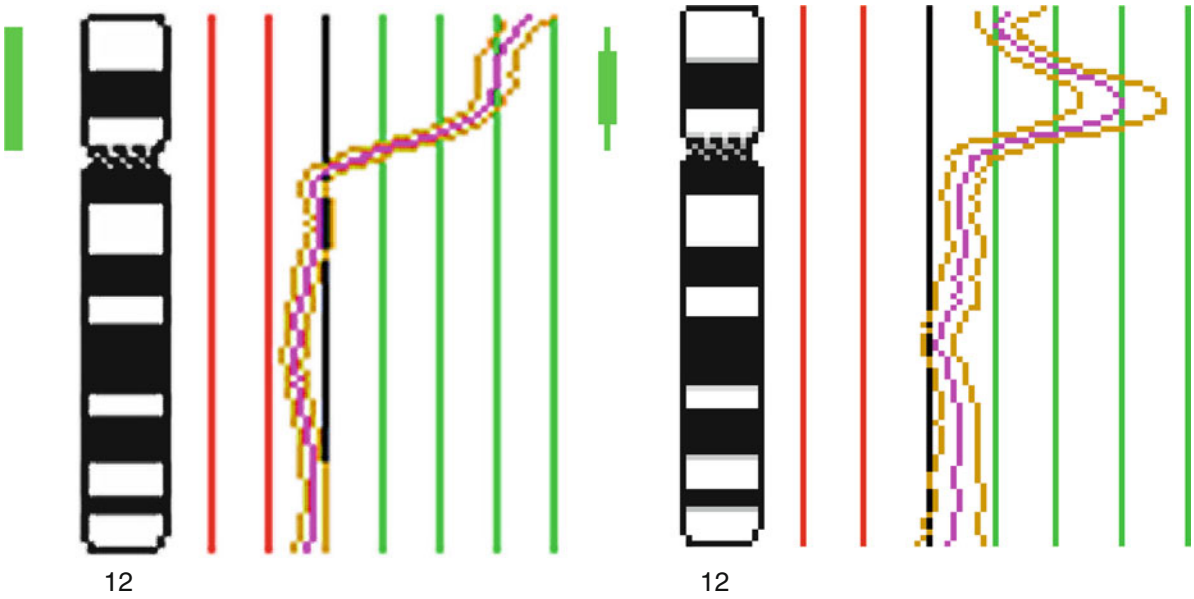


Fig. 39.1.6 CGH of CNS germ cell tumor with amplification at 12p22 (isochromosome 12p)

arms. The isochromosome 12p can be detected in approximately 80% of adult malignant germ cell tumors. In addition, in adults, even pure teratomas may display 12p aberrations. In those cases with no isochromosome 12p, amplification of 12p chromosomal material can be detected with molecular techniques such as fluorescence in situ hybridization or comparative genomic hybridization (Samaniego et al. 1990; Schneider et al. 2006). Figure 39.1.6 demonstrates a comparative genomic hybridization of a central nervous

system germ cell tumor with an amplicon at 12p22. The region from 12p11 to 12p12 has been defined as the region most commonly involved in amplification. Chromosomal amplification is cytogenetically recognizable as double minutes or homogeneously staining region, e.g., on marker chromosomes. In this chromosomal region, several candidate oncogenes such as *KRAS* and cyclin D2 are located. However, their etiopathogenetic role remains unclear. In addition, this region harbors stem cell genes such as *STELLAR* and *NANOG* (Oosterhuis and Looijenga 2005a).

The development of adult testicular germ cell tumors is associated with cryptorchidism and testicular dysgenesis, leaving a proportion of patients infertile (Skakkebaek et al. 2003; Skakkebaek 2004). In the context of a testicular dysgenesis syndrome, TIN and invasive germ cell tumors may be detected "accidentally" during medical evaluation of infertility. For general pediatricians and pediatric surgeons, question arises whether medical or surgical treatment of cryptorchidism may influence the risk of germ cell tumor development in the cryptorchid testis. The lifetime risk of later development of germ cell tumors in cryptorchid children is estimated to 2–18% (Buetow 1995). In this context, the biologic association between cryptorchidism and germ cell tumor is still elusive. It remains unclear if the risk of later germ cell tumor development can be reduced by early orchidopexy (and at what age) or whether it is inherent to an underlying testicular dysgenesis and maturation disorder.

While ovarian germ cell tumors are associated with testicular feminization, constitutional loss of one X chromosome, and presence of aberrant Y chromosomal genetic material, no such association has been reported in girls with extragonadal germ cell tumors. However, mediastinal germ cell tumors are associated with constitutional Klinefelter's syndrome (Nichols et al. 1987a). Compared to patients with normal constitutional karyotype, these tumors tend to occur at a younger age and predominantly with malignant nonseminomatous histology. Of note, the risk of germ cell tumors at other anatomical sites including the testis does not appear to be significantly increased in Klinefelter's syndrome (Hasle et al. 1995), although some single patients with CNS germ cell tumors and Klinefelter's syndrome have been reported (Prall et al. 1995).

The two most common sites for extragonadal germ cell tumors in adolescents and adults are mediastinum and brain. Cytogenetic analysis of central nervous system teratoma has shown a high frequency of sex-chromosome abnormalities, most commonly increased copies of the X chromosome (Yu et al. 1995). The i (12p) has been described in some, but not all, pineal germinomas, but it has not been seen in pineal teratoma (Schneider et al. 2006). Ploidy analyses of mediastinal germ cell tumors suggest that most are diploid or tetraploid (Oosterhuis et al. 1990), and those that are malignant contain the i (12p) and the other genetic changes seen in adolescent testicular germ cell tumors (Dal Cin et al. 1989; Schneider et al. 2002a). The extragonadal germ cell tumors (almost exclusively, nonseminomatous mediastinal tumors) in adolescents and adults are associated with hematopoietic malignancies of various cell lineages that present soon after the initial presentation of the germ cell tumors. The most common presentation is acute megakaryocytic leukemia, and the malignant hematopoietic clone commonly demonstrates i (12p).This differs from hematopoietic malignancies that arise secondary to therapy (Chaganti et al. 1994; Hartmann et al. 2000).

39.1.6.1 Pathology

Germ cell tumors comprise numerous histologic subtypes; however, the microscopic morphology of a distinct histologic subentity is undistinguishable regardless of age at diagnosis, tumor site, and genetic background (Hawkins and Perlman 1996a). Thus, tissue from ovarian cystic teratoma, a tumor arising from premeiotic cells, is undistinguishable from mature cystic teratoma of the sacrococcygeal region or the CNS.

Currently, germ cell tumors are most commonly classified according to the World Health Organization revised classification for testicular, ovarian, and central nervous system tumors. Still, there are some inconsistencies in the site-specific classification, in that different terms are used for histologically and biologically identical tumors, i.e., seminomas of the testis, dysgerminomas of the ovary, and germinoma of the CNS. These inconsistencies are mainly explained by the historical development of the site-specific classifications. However, in all classification systems, the approach to mixed malignant germ cell tumors composed of different histologic components is comparable. Thus, it is highly recommended that all different histologic entities present in each single tumor should be listed separately so that a specific

Table 39.1.3 Pediatric germ cell tumor – histology

- Teratoma
  - Mature teratoma
  - Immature teratoma (grades 1–3)
- Germinoma (seminoma and dysgerminoma)
- Embryonal carcinoma
- Choriocarcinoma
- Polyembryoma
- Mixed malignant germ cell tumor
  - Teratoma or immature teratoma with malignant GCT elements
  - Teratoma with other malignant elements (e.g., squamous cell carcinoma)

description is provided that may assist in the optimal planning of the multimodal therapy. For instance, in a mixed malignant germ cell tumor with germinoma and teratoma, a 2-cm tumor residue after chemotherapy should be interpreted differently from a 2-cm residue of a pure germinoma; the first could represent residual teratoma requiring resection, whereas a residue of pure germinoma may be pure scar to be followed only.

The histologic classification of these tumors is shown in Table 39.1.3. The pathologic features of each histologic subtype are discussed separately.

39.1.6.2 Mature Teratoma

Teratomas are the most common histologic subtype of childhood germ cell tumors (Dehner 1983a; Harms and Janig 1986; Hawkins 1990; Young and Scully 1990a). They can arise in the gonads and virtually all extragonadal locations. In fact, sacrococcygeal teratoma constitutes the most common tumor in neonates. Mature teratomas of the gonads are encapsulated and present as multicystic or solid tumors. Extragonadal teratomas differ from their gonadal counterparts in that they commonly lack a clearly defined external capsule, which interferes with surgical preparation and hence complete tumor resection. In sacrococcygeal teratoma, this characteristic requires the coccyx to be removed during surgery to reduce the risk of recurrence (Göbel et al. 1997a, 1998a). A simple enucleation of a mature teratoma may be possible in skilled surgical hands.

The mature teratoma is composed of mature representative tissues from one or up to all three germ cell layers: ectoderm, mesoderm, and endoderm (Fig. 39.1.7a). Although any tissue type may be seen, the most commonly found are skin and skin appendages, adipose tissue, mature brain, intestinal epithelium, and cystic structures lined by squamous, cuboidal, or flattened epithelium. Some tissue types are site-specific. For example, hematopoietic, pancreatic, or pituitary tissue frequently is found in mediastinal tumors and rarely in teratoma at other sites. Components of the mature teratoma occasionally may be biologically active, with secretion of enzymes or hormones, including insulin, growth hormone, prolactin, and vasopressin.

39.1.6.3 Immature Teratoma

Pediatric immature teratomas primarily occur in extragonadal sites in children and in the ovaries of girls near puberty (Göbel et al. 1998a; Marina et al. 1999a). Immature teratomas have a gross appearance similar to mature teratoma and are composed of representative tissues from all three germ layers. Unique to these tumors is the presence of various immature tissues, usually neuroepithelium, although immature ectodermal, mesodermal, and endodermal elements also may be observed (Fig. 39.1.7b). A number of grading systems have been established for immature teratoma, all of which are variations of the system originally devised by Thurlbeck and Scully (1960). All currently used grading systems, such as the one proposed by Gonzalez-Crussi (Gonzalez-Crussi et al. 1978), quantify the degree of immaturity in the lesion. Grade 0 contains only mature tissue, while grade 3 contains more than 3 areas of immature tissue per low power slide. This grading system to pediatric germ cell tumors has not consistently been applied. Only, within the German MAKEI studies, a consistent reference pathologic evaluation of mature and immature teratomas has been implemented, allowing for evaluating the clinical impact of immaturity and the detection of microfoci of yolk sac tumor within teratomas.

The prognostic impact of grading of immature elements in childhood immature teratoma is not clear. High immaturity itself does not confer a poor prognosis if the tumor is completely resected. However, the risk of incomplete resection is obviously higher in very immature teratomas that tend to show more infiltrative growth in the absence of a clearly distinguished tumor capsule (Göbel et al. 1997a, 1998a).

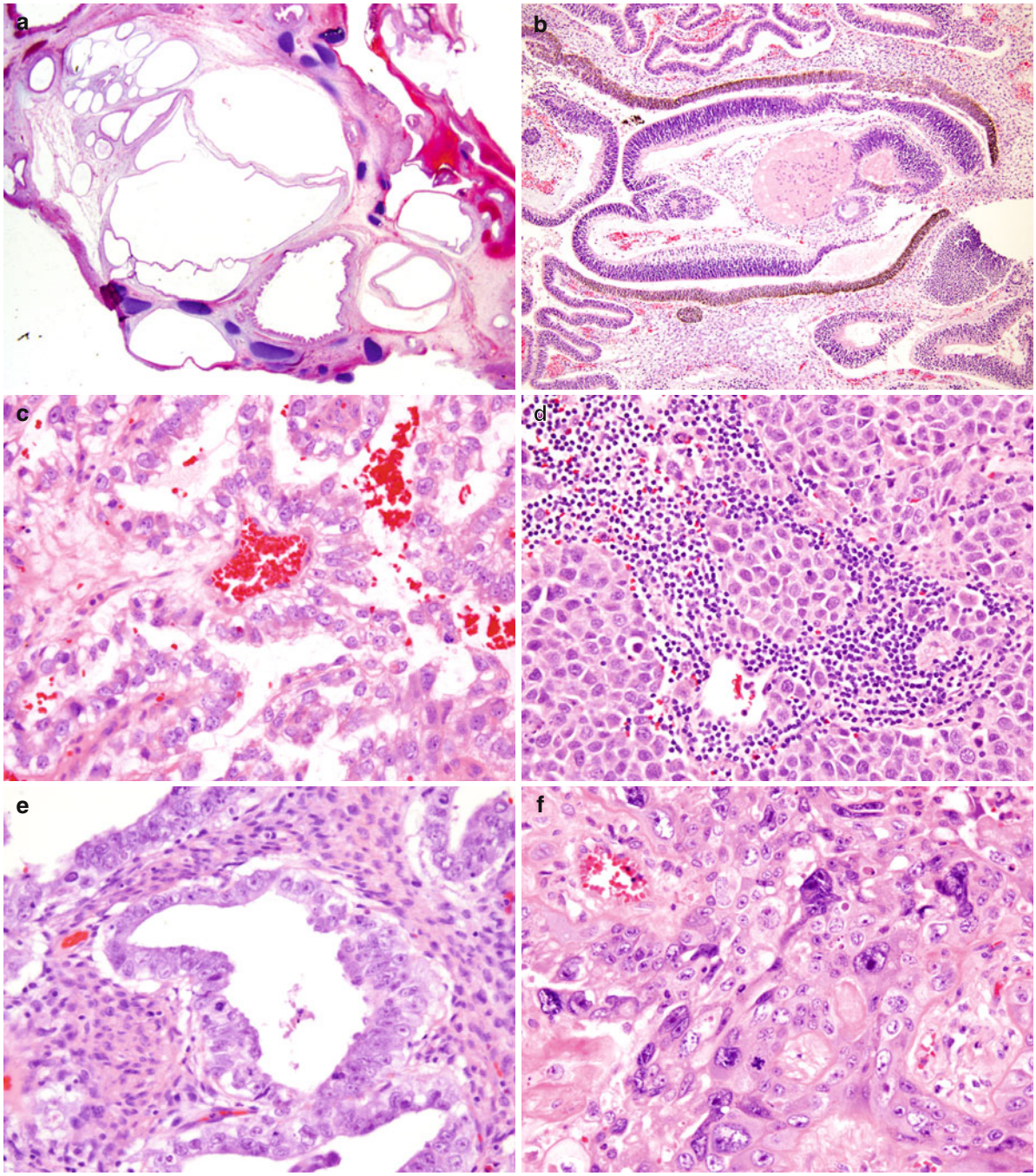


Fig. 39.1.7 (**a**) Teratoma – encapsulated cystic structure with ectoderm, mesoderm, and endoderm. In this area, cartilage and skin tissue is apparent. (**b**) Immature teratoma – myxoid background with large areas of immature neuroepithelium. (**c**) Yolk sac tumor showing Schiller-Duval body with central blood vessel surrounded by tumor cells and a space before next layer of tumor cells. (**d**) Germinoma showing monomorphic cells with abundant clear cytoplasm surrounded by lymphocytic infiltrate. (**e**) Embryonal carcinoma showing large overlapping nuclei with eosinophilic cytoplasm. (**f**) Choriocarcinoma showing small cells associated with large giant syncytiotrophoblasts

Immature teratomas in children behave in a malignant fashion only if foci of malignant germ cell elements (usually yolk sac tumor) are present, and if they are resected incompletely. Clusters of yolk sac tumor can be easily overlooked because they may be very small. Since these may not stain for AFP by immunohistochemistry, the experience of the pathologist is of crucial importance. Tumors containing such foci likely are responsible for the reports that immature teratoma may metastasize. Surgical resection is not always possible, and in some cases, a "benign" immature teratoma proves fatal.

39.1.6.4 Yolk Sac Tumor

Yolk sac tumors are the most common pure malignant GCT in young children (Young and Scully 1990a). Apart from very few exceptions, it is the only malignant GCT type occurring during infancy. Yolk sac tumors rarely occur in pure form in adolescents but more frequently are a component of the mixed malignant germ cell tumors occurring in these locations. Grossly, these tumors consist of friable, pale-gray, mucoid tissue with variable amounts of hemorrhage and necrosis. The microscopic features are also wide and have been characterized fully only in the last two decades. Four general patterns and a number of variations have been recognized. These patterns are useful in the recognition of yolk sac tumor, but their clinical relevance is currently unknown.

The pseudopapillary or festoon pattern and the microcystic or reticular patterns are the most common and widely recognized. Both contain Schiller-Duval bodies (Fig. 39.1.7c). The microcystic or reticular pattern is associated most often with eosinophilic globules and strands that only occasionally stain positively for AFP or α_1-antitrypsin. The pseudopapillary and parietal patterns often are observed after chemotherapy (Ulbright et al. 1990). The solid pattern usually is found only focally and may mimic embryonal carcinoma. A variant of the solid pattern is the hepatoid pattern, which closely resembles fetal liver (Nakashima et al. 1987). A fourth pattern is the polyvesicular vitelline pattern, characterized by small, empty cystic structures lined by a single layer of malignant cells that merge from cuboidal to flat. The cells often are embedded in a loose, frequently myxoid stroma. Two other patterns have been described. The enteric pattern resembles the fetal human gastrointestinal tract and typically stains positively for AFP and chorionic embryonic antigen (Clement et al. 1987; Cohen et al. 1987; Ulbright and Roth 1987). The mesenchyme-like pattern stains positively for cytokeratin and vimentin but not for AFP and has been implicated as the source of the sarcomas that occasionally occur in patients who have had a yolk sac tumor (Nakashima et al. 1987).

In general, AFP is the characteristic immunohistochemical (and clinical) marker of yolk sac tumors. Remarkably, it may not consistently stain all tumor cells but may rather show a spotty staining pattern, so that a negative AFP staining of yolk sac tumor microfoci may not exclude the presence of yolk sac tumor. Therefore, the measurement of AFP in the serum (and cerebrospinal fluid in case of a CNS tumor) is complementary to immunohistochemistry.

39.1.6.5 Germinoma

Germinomas, also termed dysgerminomas (ovary) or seminomas (testis), are the most common pure malignant germ cell tumors that occur in the ovary and central nervous system in adolescents (Talerman 1987; Ho and Liu 1992). Pure seminomas are unusual in men younger than 20 years and rarely occur prior to the onset of puberty. The exception is in patients with sex-chromosomal abnormalities or cryptorchidism, where tumors often present at an earlier age.

On gross pathology, germinomas are encapsulated, solid, gray-pink tumors with a rubbery consistency and occasional small foci of hemorrhage and necrosis (Fig. 39.1.7d). Microscopically, the tumor cells are arranged in nests separated by bands of fibrous tissue in which variable numbers of lymphocytes are identified. The cells are large, with clear cytoplasm, distinct cell membranes, and large round nuclei having one or two prominent nucleoli. Granulomas with giant cells frequently are present.

Syncytiotrophoblasts also may be present, but they do not alter the prognosis of the tumor unless they are associated with cytotrophoblasts in foci of choriocarcinoma. These tumors are then termed mixed malignant germ cell tumors. Immunohistochemically, the germinoma cells have strong staining for the stem cell marker OCT3/4, placental alkaline phosphatase (PLAP), and c-kit, whereas the syncytiotrophoblasts may stain for human chorionic gonadotropin beta-subunit (β-HCG). In such tumors, a slight elevation of β-HCG may be found in the serum or the cerebrospinal fluid ion case of CNS tumors.

39.1.6.6 Embryonal Carcinoma

Embryonal carcinoma rarely occurs in a pure form in children and is more often a component of a mixed malignant GCT of adolescents (Young and Scully 1990a; Hawkins and Perlman 1996a). This component is commonly seen in adult testicular GCT. They are characterized by large cells with large, overlapping nuclei and very large, round nucleoli. The major pattern is epithelial and consists of large nests of cells with varying amounts of central necrosis (Fig. 39.1.7e). Pseudotubular and papillary patterns that may be confused with those of yolk sac tumor are frequent, but the cells are AFP-negative, and the tumors typically lack the eosinophilic hyaline globules characteristic of yolk sac tumors. Unlike other germ cell tumors, embryonal carcinoma is consistently positive for CD30 by immunohistochemical staining. In addition, they stain positive for OCT3/4 (Looijenga et al. 2003).

39.1.6.7 Choriocarcinoma

Choriocarcinoma rarely occurs outside the context of malignant mixed germ cell tumors in adolescents (Young and Scully 1990a; Hawkins and Perlman 1996a). The rare case of pure choriocarcinoma detected in infants almost always represents metastasis from maternal or placental gestational trophoblastic primary tumor (Belchis et al. 1993). These tumors characteristically are very hemorrhagic and friable. Microscopically, two types of cells must be present to confirm the diagnosis: cytotrophoblasts, which classically appear as closely packed nests of relatively uniform, medium-sized cells having clear cytoplasm, distinct cell margins, and vesicular nuclei, and syncytiotrophoblasts, which represent multinucleate syncytial trophoblastic cells (Fig. 39.1.7f). The syncytiotrophoblastic elements stain positively for β-HCG, accounting for the associated high concentrations of serum β-HCG in these patients. If choriocarcinoma arises in the CNS, β-HCG may be detected both in the cerebrospinal fluid and the serum, sometimes with discrepant findings in the two compartments. Clinically, choriocarcinoma is associated with widespread hematogenic metastases including CNS metastases, which may be complicated by CNS hemorrhage.

39.1.7 Serum Tumor Markers

Due to their crucial importance for the categorization of childhood germ cell tumors, the serological markers α_1-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are discussed in detail. AFP, an α_1-globulin, is the earliest and predominant serum-binding protein in the fetus, reaching its peak concentration at 12–14 weeks' gestation and gradually falling to reach an adult normal level of less than 10 ng per dL at approximately age 1 year (Gitlin et al. 1972) (Table 39.1.4). In some patients, adult AFP normal serum levels of AFP are reached only at the end of the second year of life (Blohm et al. 1998a). As AFP levels begin to decline in fetal development, albumin becomes the principal serum-binding protein. In early embryogenesis, AFP is produced in the yolk sac and later by hepatocytes and the gastrointestinal tract. Since AFP may cross the placenta, AFP of pregnant mothers may be significantly elevated.

Table 39.1.4 Serum AFP levels in first year of life for preterm and term infants

Age	Preterm (<37 weeks)	Term
Birth	31,261–799,834	9,120–190,546
1 week	6,039–311,889	1,480–58,887
1 month	389–79,433	16–1,995
3–4 months	9–18,620	3–417
6–24 months	0–372	0.8–87

Adapted from report by Blohm et al. (1998)
AFP levels (ng/ml) reported as 95.5% intervals

In 1974, the association between serum elevation of AFP and the natural history of adult germ cell tumors was described. Elevated serum levels or positive immunohistochemical staining of germ cell tumors for AFP indicates the presence of malignant components, specifically yolk sac or embryonal carcinoma (Table 39.1.2). The serum half-life ($t_{1/2}$) of AFP is 5–7 days, but may be longer in particular at lower levels, e.g., during the second half of the first year of life (Blohm et al. 1998a). Because of the wide variation in levels at birth, especially with infants of less than 40 weeks' gestational age, and the wide variability in $t_{1/2}$ at different ages within the first year of life, difficulties arise in interpreting decay of serum AFP as an indication of residual or recurrent GCT in infants younger than 12 months (Blohm et al. 1998a; Schneider et al. 2001a).

Increasing levels of serum AFP, however, are not necessarily indicative of tumor progression. Abrupt escalation in serum AFP can occur after chemotherapy-induced tumor lysis. Spurious persistence of elevated serum AFP may reflect an alteration in hepatic

function from such conditions as viral hepatitis (hepatitis B, hepatitis C, and human immunodeficiency virus–associated hepatitis), cholestasis secondary to anesthesia, metabolic disease (e.g., tyrosinemia type I) or exposure to phenytoin or methotrexate. Other neoplastic conditions associated with elevated serum AFP include hepatoblastoma, hepatocellular carcinoma, pancreaticoblastoma, and pancreatic, gastrointestinal, or bronchial adenocarcinomas. AFP is not only helpful in detecting significant yolk sac tumor components but may also assist in prognostic assessment. During and after treatment, an elevation in AFP identifies progression or recurrence before tumor can be identified by imaging. In a large cooperative analysis of adult germ cell tumors, high AFP and/or β-HCG levels indicated poor prognosis (Group 1997a). In the British childhood cancer studies, high AFP levels above 1,000 μg/L were associated with unfavorable outcome (Mann et al. 1989a; Mann et al. 2000a). Furthermore, an inadequate decline of AFP that does not follow its half time of 5–7 days indicates pure response to chemo or tumor progression after tumor resection (Schneider et al. 2005a).

Human chorionic gonadotropin (HCG) is a glycoprotein comprised of α- and β-peptide subunits and normally is synthesized during pregnancy by syncytiotrophoblasts of the placenta to maintain viability of the corpus luteum. The α-subunit is similar to α-peptides of other hormones, such as luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone. The β-subunit is antigenically distinct, serving as the basis for the method of serum assay. Minute amounts, less than 5 mIU per mL, are detected in serum of healthy adults; serum $t_{1/2}$ of β-HCG is 24–36 h.

The most frequent for significant rise of β-HCG is pregnancy. Therefore, in case of suspected GCT and elevated β-HCG, pregnancy must be excluded with other techniques, e.g., ultrasound.

Elevation of serum β-HCG in patients with germ cell tumors implies the presence of clones of syncytiotrophoblasts, such as choriocarcinoma, or of syncytiotrophoblastic giant cells, found frequently in germinomas (pure seminomas or dysgerminomas) and occasionally in adult embryonal carcinoma.

Like serum AFP, sudden elevation of serum β-HCG occurs after cell lysis secondary to chemotherapy (Vogelzang et al. 1982). Iatrogenic hypogonadism secondary to bilateral orchiectomy, oophorectomy, or chemotherapy also may be associated with rising levels of serum β-HCG because of an increase in luteinizing hormone that results in immunologic cross-reactivity. Other conditions in which modest elevations of serum β-HCG have been reported include multiple myeloma and other malignancies of liver, pancreas, gastrointestinal tract, breast, lung, and bladder. Simultaneous elevation of serum AFP and β-HCG has been described in ovarian embryonal carcinoma in an 11-year-old and in patients with polyembryoma.

39.1.7.1 Other Markers

Because some germ cell tumors with identifiable malignant elements do not produce measurable amounts of serum AFP or β-HCG, other markers with potential prognostic value have been investigated. Serum LDH, a glycolytic enzyme that appears to correlate with growth and regression of various solid neoplasms, has not shown specificity for a specific histologic subtype of germ cell tumors. In patients with dysgerminoma, serum levels of the LDH isoenzyme 1, the gene which resides on 12p, correlate with the tumor burden and aid in the planning and assessment of surgical management (Schwartz and Morris 1988). Elevated serum LDH levels have not been prognostic in germ cell tumors of prepubertal children.

Human placenta like alkaline phosphatase (PLAP) is a fetal isoenzyme of alkaline phosphatase that is elevated in the sera of up to 30% of patients with stage I disease and of almost 100% of cases with advanced seminoma (Koshida et al. 1991). As with AFP and β-HCG, immunohistochemical staining for PLAP sometimes is useful in determining the origin of histologically undifferentiated tumors.

Although elevated serum levels of carcinoembryonic antigen (CEA) are reported in patients with ovarian tumors, the usefulness of this antigen has been hampered by lack of tumor specificity and correlation to disease natural history.

The carbohydrate antigen CA-125, which is related to the tissues of the coelomic epithelium and müllerian ducts, has been assessed in ovarian cancers of germ cell and epithelial origin. CA-125 has been reported to have some correlation with other tumor markers and to be of value in monitoring patients with ovarian tumors of germ cell, epithelial, and stromal origin (Altaras et al. 1986), although its utility in these patients remains to be defined because of the limited numbers of patients studied to date.

Table 39.1.5 Sensitivity to treatment

	Histologic grading	Sensitivity to chemo	Sensitivity to radiation
Seminoma/ germinoma	Malignant	+++	>24 Gy
Embryonal carcinoma	Malignant	+++	>45 Gy
Yolk sac tumor	Malignant	+++	>45 Gy
Choriocarcinoma	Malignant	+++	>45 Gy
Teratoma, mature/ immature	Benign/ potential for malignant development	?	?

39.1.8 Treatment Overview

The treatment of benign and malignant germ cell tumors requires a coordinated multimodality approach. The strategy is chosen based on data on site, staging, biology, histology, and marker levels (Table 39.1.5). The development of effective chemotherapy regimens has allowed a more adaptive surgical approach that is specific to anatomic site of germ cell tumors. These specifics will be discussed in sections that follow on testicular, ovarian, and extragonadal germ cell tumors. A few guiding principles can be outlined.

39.1.9 Surgical Treatment of Germ Cell Tumors in the Context of Multimodal Therapy

Surgery is a mainstay in the treatment of germ cell tumors. Complete surgical resection is the standard treatment for benign tumors, such as teratomas. There is no evidence that chemotherapy has any significant therapeutic effects in pure teratoma (Göbel et al. 1998a; Marina et al. 1999a). The complete surgical removal of malignant lesions is indicated, if possible. However, the surgical approach to malignant germ cell tumors may be influenced by effective neoadjuvant chemotherapy. In this situation, biopsy may be appropriate.

It must be emphasized that surgical recommendations may differ significantly for children and adolescents and for gonadal and extragonadal germ cell tumors. In general, gonadal tumors are more assessable to complete tumor resection, since most present with a clearly defined tumor capsule often in combination with the organ capsule of the gonad. Therefore, most gonadal tumors are resected completely and the local relapse rate is low. In contrast, extragonadal tumors more often show infiltrating growth and a poorly defined pseudocapsule. These tumors present with considerable size and often develop in anatomically problematic regions such as the brain, mediastinum, or the pelvic floor. Therefore, complete resection with free margins of extragonadal germ cell tumors is often impossible. In this situation, neoadjuvant chemotherapy may substantially facilitate complete resection on delayed surgery.

Malignant germ cell tumors may respond dramatically to neoadjuvant chemotherapy, allowing a less aggressive surgical approach at specific sites such as vaginal yolk sac tumors (Mauz-Körholz et al. 2000). Therefore, resection should not be undertaken to the point of sacrificing vital structures. Chemotherapy may allow a patient to be spared mutilating surgery. In many large extragonadal malignant germ cell tumors, neoadjuvant chemotherapy may increase the chance of complete resection. Eventual complete resection (post-chemotherapy) is the goal if cure of an extragonadal germ cell tumor is to be achieved (Schneider et al. 2000a; Göbel et al. 2001a). Stable radiologic disease with marker normalization may not suggest resistant disease.

The question "is a biopsy needed prior to neoadjuvant chemotherapy?" is approached differently by various groups. Most physicians are more comfortable treating with chemotherapy when a pathologic diagnosis is confirmed. In addition, material for molecular studies of germ cell tumor may be crucial to future treatments. However, it may be in the patient's interest not to biopsy, for example, in the presence of respiratory distress due to mediastinal disease. This strategy must be reserved for secreting tumors. Surgery also plays a significant role in relapsed germ cell tumors.

39.1.9.1 Radiotherapy

Radiotherapy has been used to effectively treat germ cell tumors of germinomatous origin including germinoma (CNS), seminoma (testis), and dysgerminoma (ovarian). Radiation sensitivity correlates with histology (Table 39.1.5). However, the role of radiation in seminoma and dysgerminoma has been reduced by the advent of platinum-based chemotherapy. Nevertheless, radiation therapy, applied as craniospinal irradiation, remains standard treatment for CNS germinoma. However, currently new strategies have been developed

that combine chemotherapy with irradiation to reduced fields and with reduced doses, in order to reduce the risk of long-term radiotherapy-associated sequelae. Radiation therapy may also play a role in the treatment of recurrent germ cell tumors, in particular, if tumors still cannot be resected completely after up-front salvage chemotherapy.

39.1.10 Chemotherapy

The prognosis of germ cell tumors has improved significantly with the development of cisplatin-based therapy in adult testicular GCT patients (DFS 68–92%) (Einhorn and Donohue 1977a; Logothetis et al. 1985; Bosl et al. 1988; Einhorn et al. 1989a). Prior to this effective chemotherapy, children with extracranial malignant germ cell tumors had 3-year survival rates of 15–20% with surgery and radiation therapy (Kurman and Norris 1976a; Billmire and Grosfeld 1986). However, boys with localized testicular tumors did well with surgical resection (Hawkins et al. 1986). Prognosis and appropriate treatment depend on factors such as histology (e.g., seminomatous vs. nonseminomatous), age (young children vs. adolescents), stage of disease, and primary site (Baranzelli et al. 1999a; Marina et al. 2006a). Cisplatin-based chemotherapy has dramatically improved the outcome for children with extracranial GCT, with 5-year overall survival rates of more than 90% (Mann et al. 2000a; Göbel et al. 2001a; Cushing et al. 2004a; Rogers et al. 2004a). Table 39.1.6 describes successful regimens developed by various national pediatric groups. In general, the clinical outcome is comparable with the different protocols; however, the toxicity profile may vary. To develop an optimal consensus treatment strategy, an international meta-analysis would be beneficial. However, such a project is still problematic due to several issues such as different staging systems, different histopathologic classification systems, as well as considerable differences in risk stratification.

In general, substantial reduction of cumulative chemotherapy has become possible with the optimization of multimodal therapeutic strategies, including optimal timing of surgical resection in locally advanced tumors. Thus, acute and long-term side effects can be minimized while maintaining excellent survival. This goal can only be achieved through ongoing cooperative group studies. Advances in molecular understanding of these rare pediatric tumors may additionally help in the development of risk-adapted strategies. Site-specific details will be discussed.

39.1.11 Salvage Therapy

The treatment of recurrent germ cell tumors in children has not been studied systematically. Recurrent disease must be categorized based on histology (benign or malignant) and extent (local or distant). In addition, the first-line treatment has a substantial impact on both the choice of salvage treatment and prognosis. Thus, tumors that progress after surgery and watch-and-wait strategy commonly have a favorable prognosis with standard platin-based chemotherapy. In contrast, malignant tumors that relapse after first-line treatment are often resistant to further therapy, and prognosis is poor. Recurrent benign tumors (mature teratomas and most immature teratomas) must be treated with surgery. Chemotherapy has not yielded significant improvement in these benign tumors. One example that demonstrates this phenomenon is the "growing teratoma syndrome." A mixed tumor with teratoma and yolk sac tumor continues to grow despite normalization of markers. At surgery, only viable mature teratoma persists (Afifi et al. 1997). Of note, these growing teratomas retain the cytogenetic aberrations also present in malignant germ cell tumors (van Echten et al. 1997a, b). It may be concluded that in these tumors, terminal differentiation presents a way to evade cytotoxic treatment and to induce resistance to chemotherapy (Mayer et al. 2003a). For these tumors, alternative strategies with either immunomodulation (interferon) (van der Gaast et al. 1991) or antiangiogenetic therapy (Calaminus et al. 2009) have been applied with some success. Nevertheless, surgical resection is always required, even if intermittent stable disease can be achieved with such strategies. In 3–6% of adult cases, somatic transformation is evident.

The prospective assessment of salvage therapies in recurrent or refractory malignant pediatric germ cell tumors is limited by the small numbers of patients.

The treatment of recurrent malignant pediatric germ cell tumors is anecdotal. In contrast to adult patients, many children have local relapses and treatment may include intensive chemotherapy and local therapy (Schneider et al. 2001d). For these purposes a strategy that utilizes up-front chemotherapy followed by

Table 39.1.6 Pediatric treatment strategies

Drug	Doses	No. of cycles
US Children's Oncology Group: PEB (9048/8891;9049/8890)		
Cisplatin	20 mg/m^2, day 1, 2, 3, 4, 5 or 33 mg/m^2, day 1, 2, 3	3–4 cycles
Etoposide	100 mg/m^2, day 1, 2, 3, 4, 5 or 167 mg/m^2, day 1, 2, 3	
Bleomycin	15 U/m^2, day 1	
German MAKEI study group: PE and PEI (MAKEI 96)/SIOP CNS GCT I-II		
Cisplatin	20 mg/m^2, day 1,2,3,4,5	2–4 cycles
Etoposide	100 mg/m^2, day 1,2,3	
Ifosfamide	1500 mg/m^2, day 1,2,3,4,5	
French TGC study group: PVB and VIP (TGM 2011)		
Cisplatin	20 mg/m^2, day 1,2,3,4,5	Up to 3 cycles
Vinblastin	3 mg/m^2, day 1,2	
Bleomycin	15 U/m^2, day 1	
Cisplatin	20 mg/m^2, day 1,2,3,4,5	Up to 4 cycles
Etoposide	75 mg/m^2, day 1,2,3,4,5	
Ifosfamide	3,000 mg/m^2, day 1,2	
Italian GCT study group (PEB)		
Cisplatin	25 mg/m^2, day 1,2,3,4	Up to 4 cycles
Etoposide	100 mg/m^2, day 1,2,3,4	
Bleomycin	15 mg/m^2, day 2	
Brazilian TCG [PE (high-dose PE), IVB] (Lopes, 2009)		
Cisplatin	20 mg/m^2, day 1,2,3,4,5	5 cycles
Etoposide	100 mg/m^2, day 1,2,3,4,5	
HD-Cisplatin	30 mg/m^2, day 1,2,3,4,5	5 cycles
HD-Etoposide	120 mg/m^2, day 1,2,3,4,5	
Ifosfamide	1,500 mg/m^2, day 1,2,3	3 cycles
Velban	3 mg/m^2, day 1	
Bleomycin	15 mg/m^2, day 1	
SIOP central nervous system germ cell tumor protocol (SIOP CNS GCT) (HD-PEI) (Schmoll 2003)		
Cisplatin	100 mg/m^2, day 1,2,3,4,5	3 cycles (after one initial cycle of conventional PEI)
Etoposide	300 mg/m^2, day 1,2,3,4,5	
Ifosfamide	2,000 mg/m^2, day 1,2,3,4,5	
Plus autologous stem cell support plus G-CSF at day 7		
SIOP central nervous system germ cell tumor protocol (SIOP CNS GCT) (Carbo-PEI)		
Carboplatin	600 mg/m^2, day 1	2 cycles
Etoposide	100 mg/m^2, day 1,2,3,22,23,24	
Ifosfamide	1800 mg/m^2, day 22,23,24,25,26	
UK CCLG (Mann 2000)		
Carboplatin	600 mg/m^2, day 2	Until remission + 2 cycles
Etoposide	120 mg/m^2, day 1,2,3	
Bleomycin	15 mg/m^2, day 3	

During cisplatin therapy, intensive infusion therapy with 3 l/m^2/day accompanied by mannitol forced diuresis is mandatory. During ifosfamide, uroprotection with mesna is recommended

delayed tumor resection has proven effective. In selected patients, locoregional control can be supported by the combination of cisplatin chemotherapy and regional deep hyperthermia (Wessalowski et al. 1997a, 2003a). In addition, it is certainly helpful to concentrate surgical therapy of patients with recurrent malignant germ cell tumors in specific national surgical centers. This provides the opportunity to centralize

experience in these often delicate surgical procedures and to advance scientific research on salvage surgery.

Radiation therapy with at least 45 Gy for nonseminomatous germ cell tumors (Table 39.1.5) may also be considered to improve local control, in particular, in tumors not assessable to complete resection (Schneider et al. 2001d).

A multimodal strategy that combines chemotherapy, surgery, and possibly radiotherapy is necessary for recurrent malignant tumors. Trials in adult patients with recurrent or persistent malignant germ cell tumors have provided potential strategies for salvage chemotherapy. Complete responses from 50% to 77% have been obtained in patients, who relapsed after cisplatin therapy (Motzer et al. 2000). Combinations of paclitaxel, ifosfamide, and cisplatin; vinblastine, ifosfamide, and cisplatin; or vincristine, bleomycin, and cisplatin have been used. Autologous marrow transplantation has also been used to treat these adult patients (Einhorn et al. 2007). However, in particular, for extragonadal germ cell tumors, the therapeutic impact of high-dose chemotherapy is limited, if no local control can be achieved (Schneider et al. 2001d).

Retroperitoneal lymph node dissection (RPLND) has not been part of standard pediatric germ cell tumor treatment. Post-chemotherapy followed by RPLND may be an integral part of treatment in adolescent and adult males. These tumors may progress in the retroperitoneal lymph nodes, and residual teratoma may dedifferentiate into malignant germ cell tumor or somatic malignant differentiation (Carver et al. 2007a, b, c). Site-specific salvage therapies will be discussed with anatomic sites.

39.1.12 Late Effects

In the study of late effects of therapy, attention must be paid to those late effects from tumor and local therapy and those effects secondary to systemic therapy (Table 39.1.7).

Among the various possible late effects of germ cell tumors, local sequelae after surgery and/or radiotherapy must be distinguished from systemic late effects as a consequence of chemotherapy. Local effects can be caused both by tumor and by local treatment. For instance teratomas of the head and neck can involve the thyroid gland, which must then be removed with the tumor. As a consequence a proportion of children with cervical teratoma may suffer from insufficiency of the thyroid or parathyroid glands (Bernbeck et al. 2009a). Chronic endocrine insufficiency is also characteristic of hypophyseal germ cell tumors. In these tumors, diabetes insipidus may be the key symptom of the tumor. Diabetes insipidus will usually persist even after successful treatment of the germ cell tumors. Hypophyseal insufficiency may also result in other hormone deficiencies such as growth hormone deficiency.

Table 39.1.7 Potential late treatment effects

I. Late effects from tumor and local therapy
– CNS
Diabetes insipidus, GH, and other endocrine deficiencies
Hemianopsia, cranial nerve palsies, bone growth
– Head and neck tumors – hypothyroid, tracheal malacia
– SCT – incontinence
– Gonadal – sterility, lack of function
– Polyembryoma
– Mixed malignant germ cell tumor
Teratoma or immature teratoma with malignant GCT elements
Teratoma with other malignant element (e.g., squamous cell carcinoma)
II. Late effects from systemic therapy
– Cisplatin – ototoxicity and renal toxicity, secondary malignancy
– Bleomycin – pulmonary dysfunction and cutaneous toxicity
– Etoposide – secondary leukemia
– Ifosfamide – renal toxicity

Sacrococcygeal teratomas are often very large at presentation. They may distort the anatomic situation of the pelvic floor so that the muscles of the pelvic floor have to be reconstructed during tumor resection. However, still some patients may develop palsy of the pelvic floor, in particular, if a malignant tumor infiltrates the nerves of the sacral plexus. As a result, these patients may be incontinent for stool and/or urine, or they may suffer from chronic obstipation. The risk of recurrent urinary infections is also increased. Since many germ cell tumors grow to a considerable size, a broad surgical approach is required, thus giving rise to scars at considerable size. Nevertheless, as presented in the respective chapters, most patients even with gross tumors grow up with a good quality of life and without mutilation. To achieve this goal, the possibility to apply up-front chemotherapy prior to surgery should be considered in all malignant germ cell tumors.

The issue of chemotherapy-related late effects is multifactorial and varies with the different chemotherapy combinations applied according to the different protocols.

Cisplatin era has greatly improved survival in children with malignant germ cell tumors. However, significant toxicity and late effects have occurred. Hearing impairment, in particular, high tone loss, was noted in a substantial proportion of pediatric patients treated with high-dose cisplatin (Cushing et al. 2004a). However, individual audiograms have already documented significant hearing loss with both standard- and high-dose cisplatin (Li et al. 2004). Amifostine, as a protectant, did not lessen ototoxicity (Marina et al. 2003). Young children are particularly sensitive to toxic effects of cisplatin. Importantly, ototoxicity in a young child may significantly impair speech, academic, and social development (Knight et al. 2005).

A study in adults suggests that cisplatin ototoxicity may be associated with specific glutathione S-transferase genotypes (Oldenburg et al. 2007). In addition, genetic polymorphism of the megalin gene (Riedemann et al. 2008) may eventually provide a diagnostic tool to assessing the risk of ototoxicity prospectively. These markers have not yet been studied in children.

Nephrotoxicity may be enhanced when cisplatin and ifosfamide are used concurrently.In particular, children may develop tubulopathy with loss of electrolytes and glucose (secondary Fanconi syndrome). Therefore, renal function and urinary excretion of electrolytes should be monitored during follow-up in order to prevent renal osteopathy.

The risk of pulmonary toxicity of bleomycin in toddlers and infants is controversial. In adult germ cell tumors, there are reports on an increased risk of cardiovascular disease, including atherosclerosis and coronary disease. However, there are no comparable long-term follow-up data available for patients treated for a germ cell tumor during childhood. However, in the German MAKEI registry, two patients are documented, who developed lethal pulmonary fibrosis and pulmonary failure after bleomycin and anesthesia required for tumor resection (Göbel et al. 2000a). In adults, the risk of lethal pulmonary toxicity is estimated to be approximately 1% (Osanto et al. 1992). Most adult patients develop some gradual impairment of pulmonary function during bleomycin chemotherapy. However, these changes are mostly intermittent and resolve after cessation of chemotherapy. Nevertheless, since an increased pulmonary sensitivity is suspected for children and since pulmonary function cannot be monitored in infants, most pediatric protocols have either reduced bleomycin doses, reduced chemotherapy to a two-agent regimen, or replaced bleomycin with ifosfamide.

The risk of secondary neoplasms such as therapy-related acute myelogenous leukemias has been debated intensively, both for adult and pediatric patients treated with etoposide. According to the MAKEI series, the 10-year cumulative risk of secondary leukemia can be estimated to be approximately 1% in patients treated with chemotherapy alone and 4.2% in patients treated with both radio- and chemotherapy (Schneider et al. 1999). In the US pediatric intergroup study, there were four cases of acute myelocytic leukemia. None were associated with 11q23 abnormality, supporting that the regimen commonly prescribed for childhood germ cell tumors only have a low leukemogenic potential.

In this context, it should also be noted that some malignant germ cell tumors, in particular, malignant mediastinal nonseminomatous germ cell tumors, may be associated with concurrent or metachronous leukemia. However, this leukemic clone is intrinsic to the germ cell tumor and presents a somatic malignant transformation within the germ cell tumor. This is proven by the observation that the isochromosome 12p, which is pathognomic of the germ cell tumor, is also detectable in the leukemic cell (Orazi et al. 1993).

In adult patients, chemotherapy for malignant germ cell tumors is associated with a significant long-time risk of cardiovascular disease. Thus, the risk of myocardial infarction, angina pectoris, and heart failure is increased compared to healthy adults of the same age group (Gietema et al. 1992; Bokemeyer et al. 1996; van den Belt-Dusebout et al. 2006). Compared to adults, no comprehensive data on long-term cardiovascular risk for children treated with chemotherapy is currently available. However, considerable research activities are currently focusing on the issue of cancer survivorship. This data may then assist in evaluating different therapeutic strategies for childhood germ cell tumors that take both the therapeutic efficacy and long-term sequelae of therapy into account. The quality of semen is very poor in adults, even in those patients not treated with chemotherapy. This has not been well investigated in adults who were treated for germ cell tumors as children.

39.2 Extragonadal Germ Cell Tumors

Dominik T. Schneider,
Giovanni Cecchetto, and Thomas A. Olson

Germ cell tumors include a group of tumors that is highly heterogeneous regarding their clinical and histologic appearance. During childhood and adolescence, approximately half of all germ cell tumors develop at extragonadal midline sites. Sacrococcygeal germ cell tumors constitute the most frequent tumor in neonates, and extracranial germ cell tumors account for 14% of all cancers in adolescents of the 15–19 age group. Accordingly, an epidemiological analysis of patients reported to the German GCT trials from 1981 to 2000 showed a bimodal age distribution with a small peak during infancy and a larger peak after puberty (Schneider et al. 2004b). These separate groups were marked by distinct clinical and molecular features. The distribution of extragonadal tumor sites by age is shown in Figs. 39.1.1 and 39.1.2 of Sect. 39.1.1.

Experience gained in the successful chemotherapy of testicular germ cell tumors in adults has successfully been translated to the treatment of childhood extragonadal germ cell tumors. Several prospective trials of different national study groups have demonstrated that cis- or carboplatin-based combination chemotherapy is effective in extragonadal germ cell tumors, too (Kapoor et al. 1995, Cushing et al. 2004b; Göbel et al. 2000b; Lopes et al. 2009a; Mann et al. 2000b). In addition, substantial reduction of cumulative chemotherapy has become possible with the optimization of multimodal therapeutic strategies, including optimal timing of surgical resection in locally advanced tumors. Thus, acute and long-term side effects can be minimized, while maintaining excellent survival. This goal can only be achieved through ongoing cooperative group studies. Advances in molecular understanding of these rare pediatric tumors may additionally help in the development of risk-adapted strategies (Oosterhuis and Looijenga 2005b).

39.2.1 Histogenesis, Biology, and Histology of Extragonadal Germ Cell Tumors

These aspects are extensively discussed in Sect. 39.1. In summary, the histologic appearance of extragonadal germ cell tumors is undistinguishable from that of their gonadal counterparts. Moreover, within the corresponding age groups, they share the same genetic aberrations such as the isochromosome 12p or deletion of 1p and 6q. At the epigenetic level, both gonadal and extragonadal germ cell tumors show erasure of genomic imprinting, substantiating the holistic concept of Teilum that all germ cell tumors arise from primordial germ cells (Teilum et al. 1975b).

Nevertheless, some peculiar and site-specific features have to be considered. Thus, the histologic differentiation may be restricted to specific subtypes such as teratoma and yolk sac tumor in the coccygeal region (Göbel et al. 2001; Harms and Jänig 1986) and yolk sac tumor in the vagina (Mauz-Körholz et al. 2000). At these sites, no germinomatous tumors can be observed.

In addition, the development of germ cell tumors may be restricted to specific age groups. Sacrococcygeal or vaginal germ cell tumors only develop in prepubertal children, while ovarian and central nervous system germ cell tumors mainly develop during and after puberty (Schneider et al. 2004b). Last, some extragonadal germ cell tumors may be associated with specific genetic aberrations such as Klinefelter's syndrome in mediastinal germ cell tumors, while this constellation is not observed at other sites (Nichols et al. 1987b; Schneider et al. 2002b). These clinical observations illustrate that some yet unknown site-specific environmental factors significantly modulate the development as well as histologic and clinical appearance of extragonadal germ cell tumors. In how far such factors also impact on therapy is currently speculative.

39.2.2 Pathology

Germ cell tumors show numerous histologic subtypes; however, the microscopic morphology of a distinct histologic subentity is undistinguishable regardless of age at diagnosis, tumor site, and genetic background (Dehner 1983b). Thus, tissue from ovarian cystic teratoma, a tumor arising from premeiotic cells, is undistinguishable from mature cystic teratoma of the sacrococcygeal region or the central nervous system. Currently, germ cell tumors are most commonly classified according to the World Health Organization revised classification for testicular, ovarian, and central nervous system tumors (Young 2005a; Kleihues et al. 1993; Mostofi and Sobin 1993; Serov and Scully 1973). Still, there are some

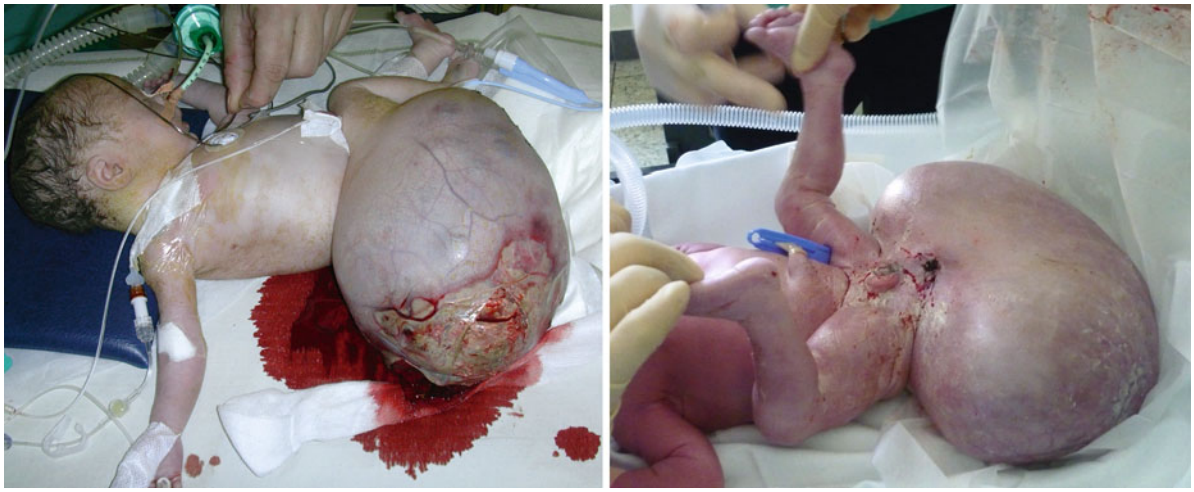


Fig. 39.2.1 Clinical presentation of neonatal sacrococcygeal teratomas. The tumor shown to the left is incompletely covered with skin and ruptured during delivery (cesarean section), leading to hemorrhagic shock

inconsistencies in the site-specific classification, in that different terms are used for histologically and biologically identical tumors, i.e., seminomas of the testis, dysgerminomas of the ovary, and germinoma of the CNS. These inconsistencies are mainly explained by the historical development of the site-specific classifications. However, in all classification systems, the approach to mixed malignant germ cell tumors composed of different histologic components is comparable. Thus, all different histologic entities present in each single tumor are listed separately so that a specific description is provided that may assist in the optimal planning of the multimodal therapy. For instance, in a mixed malignant germ cell tumor with germinoma and teratoma, a 2-cm tumor residue after chemotherapy should be interpreted different from a 2-cm residue of a pure germinoma; the first could represent residual teratoma, whereas a residue of pure germinoma may be pure scar tissue.

The histologic classification of these tumors is shown in Table 39.1.3 of Sect. 39.1.1. The pathologic features of each histologic subtype are discussed separately in Sect. 39.1.1 too.

39.2.3 Clinical Diagnosis

39.2.3.1 Clinical Symptoms

The diagnosis of extragonadal germ cell tumors primarily depends on the clinical and radiographic assessment as well as the evaluation of the "specific" tumor markers AFP and β-HCG. In most patients, germ cell tumors present as considerably large indolent tumors. In contrast, childhood testicular germ cell tumors are mainly diagnosed at a comparably small size, since in young infants these tumors are detected by the parents while the diapers are changed. In analogy, vaginal yolk sac tumors are mostly diagnosed at comparable moderate size, because these may become apparent after vaginal bleeding.

Regardless of benign or malignant histology, large tumors may result in significant local complications. Thus, head and neck teratomas may result in acute life-threatening airway obstruction, requiring an anticipating and qualified perinatal management [Fig. 19.1 in Chap. 19. (Head and Neck Teratomas)]. Sacrococcygeal teratomas may cause tumor bleeding if extrapelvic cysts rupture during vaginal delivery (Fig. 39.2.1). On the other hand, sacrococcygeal germ cell tumors may lead to chronic obstipation if they show predominantly intrapelvic extension (Fig. 39.2.2). Some sacrococcygeal yolk sac tumors may lead to skeletal metastases including the vertebral columns (Fig. 39.2.3). Spinal invasion may then lead to acute paralysis. Vaginal yolk sac tumors may lead to vaginal bleeding.

At other sites, the diagnosis even of small tumors is also guided by local symptoms and complications. Thus, CNS germ cell tumors of the hypophyseal region frequently present with diabetes insipidus, or pineal tumors may result in symptoms resulting from increased intracranial pressure or in vertical ocular

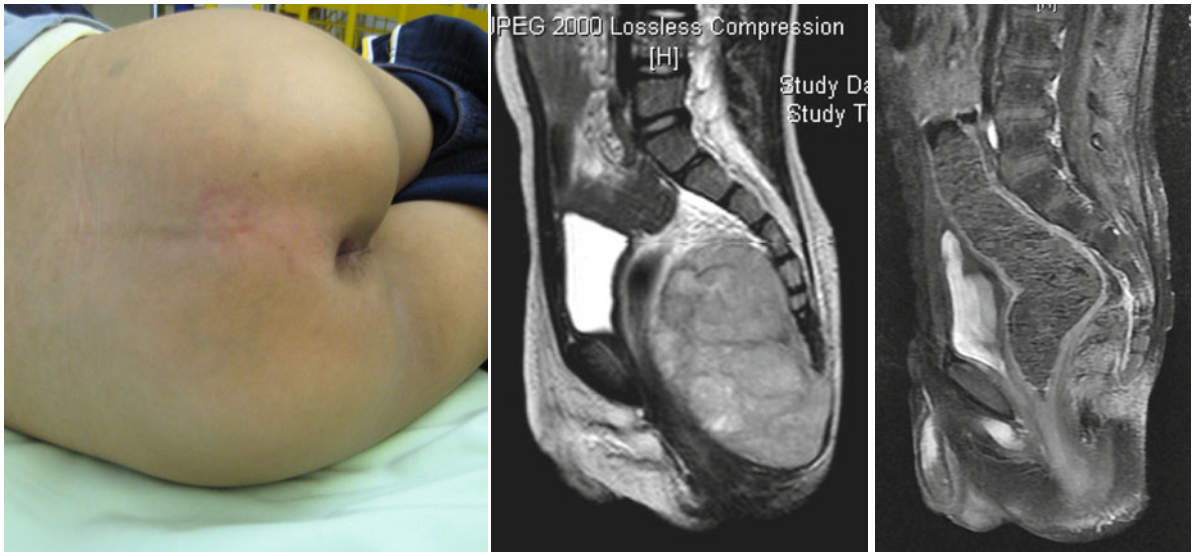


Fig. 39.2.2 Sacrococcygeal yolk sac tumor (Altman III/IV) in a 3-year-old boy: clinical presentation and MRI prior to (*left*) and after (*right*) chemotherapy with three cycles of cisplatin, etoposide, and etoposide

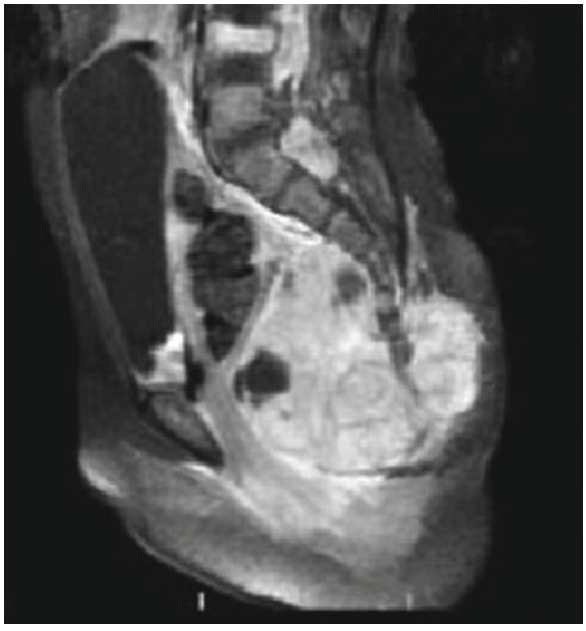


Fig. 39.2.3 Sacrococcygeal yolk sac tumor (Altman III) of a 2-year-old girl with bone metastasis in lumbar spine

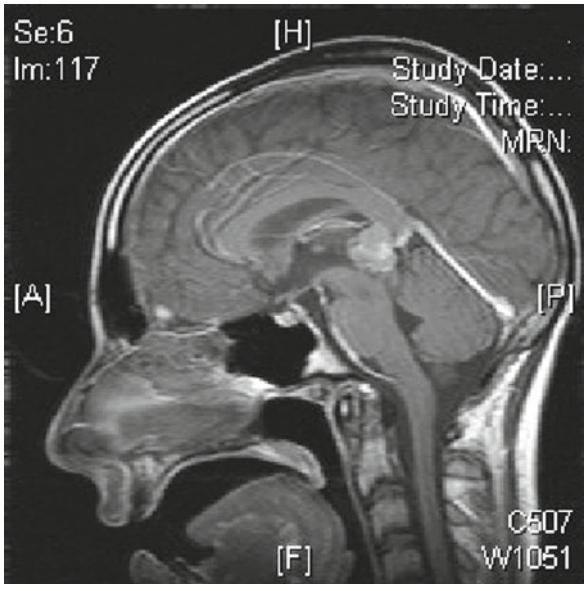


Fig. 39.2.4 Pineal mixed malignant germ cell tumor in a 15-year-old male

paralysis (Parinaud's syndrome) (Fig. 39.2.4) (Cho et al. 1998; Diez et al. 1999; Hieda and Fukui 2008). Apart from this, unspecific personality changes have also been reported. Rarely, differentiated elements within teratomas may result in endocrinological pertubances, e.g., by inadequate hormone secretion (Esik et al. 1994; Lam and Cheung 1996; Yassa et al. 2008). Last, due to their specific location at very sensible midline sites, CNS germ cell tumors often lead to obstructive hydrocephalus, as it is demonstrated in Fig. 39.2.5, showing an infant with a huge teratoma.

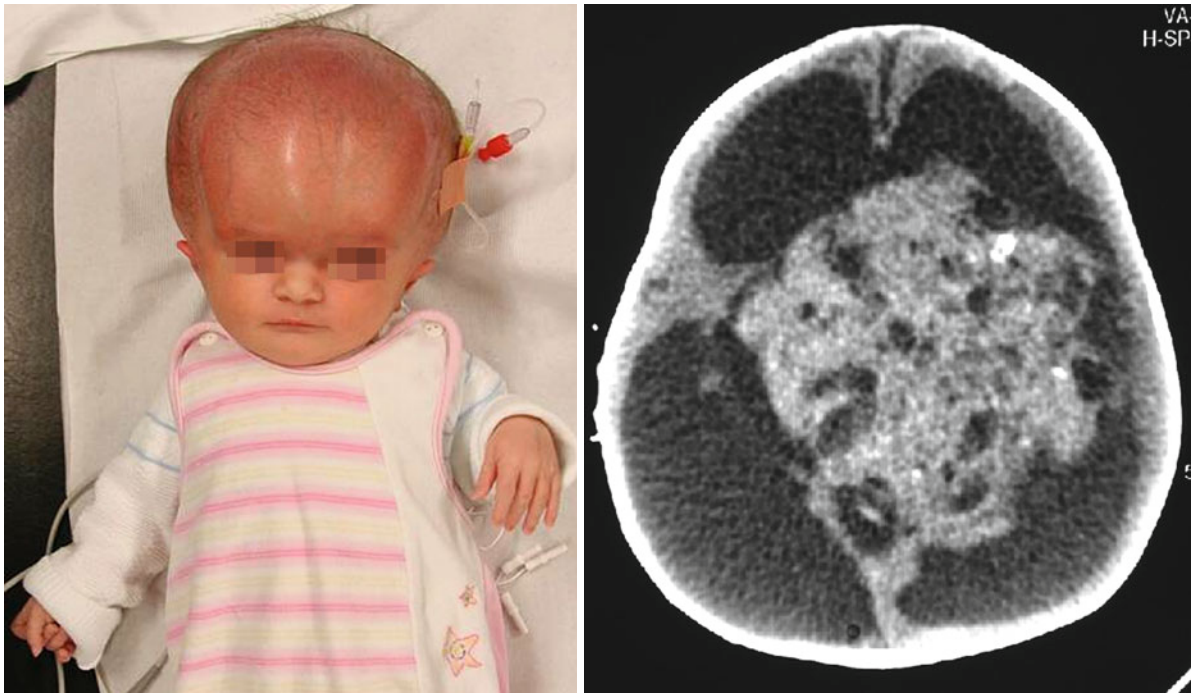


Fig. 39.2.5 One-month-old infant with an unresectable intracranial teratoma

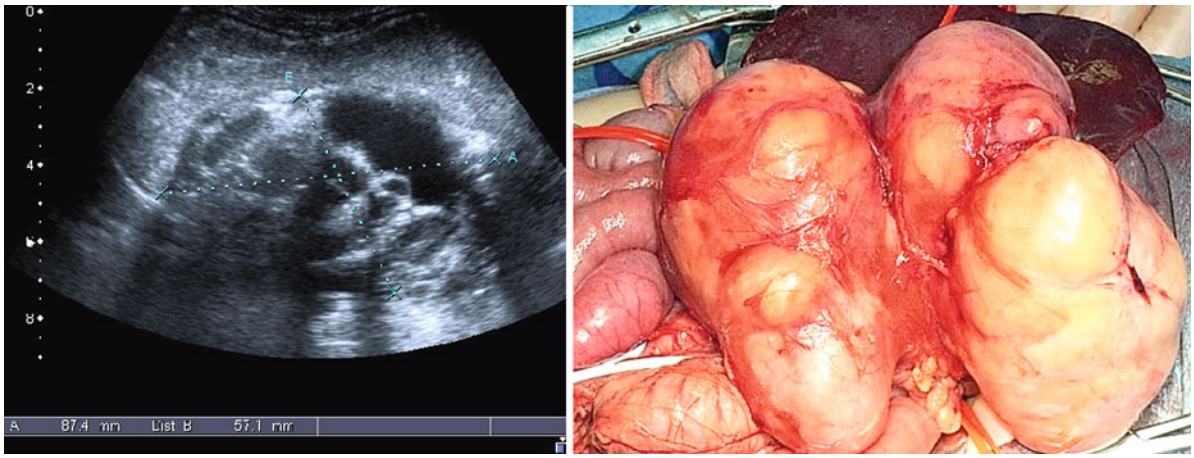


Fig. 39.2.6 Retroperitoneal teratoma in a 1-year-old girl: ultrasound and operative situs

39.2.4 Diagnostic Assessment

The diagnostic assessment is also outlined for sacrococcygeal, retroperitoneal, and central nervous system germ cell tumors in Tables 39.2.1–39.2.3. The medical history and physical examinations should consider signs of congenital malformations such as anal atresia (Currarino et al. 1981) or sex-chromosomal aberrations such as Ullrich-Turner and Klinefelter's syndrome, which may be associated with specific subtypes of germ cell tumors. In each child, the pubertal status has to be documented. Both testes have to be palpated. Rarely, a retroperitoneal teratoma may interfere with testicular descensus, so that a "retroperitoneal" tumor may arise in an undescended testis (Schwabe et al. 2000).

In sacrococcygeal tumors (Table 39.2.1), a rectal examination should be performed to palpate for

Table 39.2.1 Specific diagnostic strategy in sacrococcygeal germ cell tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Obstipation? Continence? Urinary retention? Anal atresia/malformation?
Phys. examination	Rectal examination: intrapelvic tumor component/relation to rectum. Anal sphincter tone?
Audiometry	Sensorineural hearing loss?
Laboratory assessment	
– Creatinine clearance/cystatin c	Assessment of renal function
– AFP	Malignant GCT with yolk sac tumor (consider age-related reference values)
– LDH	Unspecific marker with prognostic impact
Radiographic assessment	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to rectum, extension into spinal canal, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to rectum, extension into spinal canal, lymph node metastases, vertebral metastases
Chest X-ray	Lung metastases
Chest CT	Lung (micro-) metastases
Brain MRI	CNS metastases (indicated in case of pulmonary or visceral metastases and/or neurological symptoms)
Bone scan	Skeletal metastases (indicated in case of pulmonary or visceral metastases and/or bone pain)
Histologic assessment	
H&E	Classification according to WHO, in teratoma grading of immaturity according to Gonzalez-Crussi or Skullbeck
AFP	Yolk sac tumor (microfoci in teratoma)

Table 39.2.2 Specific diagnostic strategy in retroperitoneal germ cell tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Obstipation? Klinefelter's syndrome? Maldescensus testis? Ullrich-Turner syndrome? Gynecological anamnesis?
Phys. examination	Tumor size, pubertal status, testicular palpation
Audiometry	Sensorineural hearing loss?
Laboratory assessment	
– Creatinine clearance/cystatin c	Assessment of renal function
– AFP	Malignant GCT with yolk sac tumor (consider age-related reference values)
– β-HCG	Malignant GCT with choriocarcinoma
– LDH	Unspecific marker with prognostic impact
Radiographic assessment	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to the intestine, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to the intestine, lymph node metastases
Chest X-ray	Lung metastases
Chest CT	Lung (micro-) metastases
Brain MRI	CNS metastases (indicated in case of choriocarcinoma and/or pulmonary or visceral metastases and/or neurological symptoms)
Bone scan	Skeletal metastases (indicated in case of pulmonary or visceral metastases and/or bone pain)
Histologic assessment	
H&E	Classification according to WHO, in teratoma grading of immaturity according to Gonzalez-Crussi or Skullbeck
AFP	Yolk sac tumor (microfoci in teratoma)
β-HCG	Choriocarcinoma
HPLAP, OCT3/4	Seminoma
CD30	Embryonal carcinoma

Table 39.2.3 Specific diagnostic strategy in central nervous system germ cell tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Signs of intracranial hypertension? Signs of diabetes insipidus. Pubertal development
Phys. examination	Complete neurological assessment: cerebral palsy? Parinaud's phenomenon? Klinefelter's syndrome? Pubertal status? Testicular palpation
Ophthalmology including perimetry	Intracranial hypertension? Hemianopsia?
Audiometry	Sensorineural hearing loss?
Phys. examination	Complete neurological assessment: cerebral palsy? Parinaud's phenomenon? Klinefelter's syndrome? Pubertal status? Testicular palpation
Laboratory assessment	
– Serum and urine osmolarity	Diabetes insipidus
– Serum sodium	Diabetes insipidus
– Creatinine clearance	Assessment of renal function
– AFP (serum + CSF)	Malignant GCT with yolk sac tumor (cutoff 25 µg/L)
– β-HCG (serum + CSF)	Malignant GCT with choriocarcinoma (cutoff 50 U/µl)
– HPLAP	Malignant GCT with germinoma
– LDH	Unspecific marker with prognostic impact
– CSF cytology	Detection of (micro-) metastatic spread
Radiographic assessment	
Brain MRI	Tumor extension, uni- or bifocal disease, ventricular or brain metastases
Spinal MRI	Spinal metastases
Chest X-ray	Lung metastases
Abdominal ultrasound	Liver metastases, exclusion of renal disease
Bone scan	Skeletal metastases (indicated in case of pulmonary or visceral metastases and/or bone pain)
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)

intrapelvic tumor extension and to consider a potential proximity to or infiltration of the rectum. The anal sphincter tone should also be documented preoperatively, since in some rare patients, paralysis of the pelvic floor may develop following surgery. These examinations should also be performed during follow-up investigations.

The first radiographic assessment is usually made by ultrasound, which should always include the draining lymph nodes. Sonography is the most commonly applied initial imaging technique and is usually followed by magnetic resonance imaging, which should always depict the tumor in all three dimensions. For sacrococcygeal tumors, the intrapelvic anatomy, i.e., the association to the rectum, has to be carefully considered, since this may have important implications for surgical therapy. In addition, any extension into the spinal canal should be excluded with MRI (Jelin et al. 2009; Ribeiro et al. 1999). Rarely intrapelvic teratomas may develop as a manifestation of the Currarino triad, which describes the association of anal atresia, sacral hemiagenesis, and intrapelvic masses such as dermoid cyst or teratoma (Currarino et al. 1981).

Due to their crucial importance for the categorization of childhood germ cell tumors, the serological markers alpha$_1$-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are discussed in detail in Sect. 39.1.1. Because of the wide variation in levels at birth, especially with infants of less than 40 weeks' gestational age, and the wide variability in $t_{1/2}$ at different ages within the first year of life, difficulties arise in interpreting decay of serum AFP as an indication of residual or recurrent GCT in infants younger than 12 months (Schneider et al. 2001f; Blohm et al. 1998b).

Increasing levels of serum AFP, however, are not necessarily indicative of tumor progression. Abrupt escalation in serum AFP can occur after chemotherapy-induced tumor lysis (Schneider et al. 2001f). Otherwise, the decline of AFP during chemotherapy of yolk sac tumor strongly indicates a favorable response to therapy and thus favorable prognosis (Calaminus et al. 1991). Spurious persistence of

elevated serum AFP may reflect an alteration in hepatic function from such conditions as viral hepatitis (hepatitis B, hepatitis C, and human immunodeficiency virus–associated hepatitis), cholestasis secondary to anesthesia, metabolic disease (e.g., tyrosinemia type I), or exposure to phenytoin or methotrexate. Other neoplastic conditions associated with elevated serum AFP include hepatoblastoma, hepatocellular carcinoma, pancreaticoblastoma, pancreatic, gastrointestinal, and bronchial adenocarcinomas (Schneider et al. 2001f).

AFP is not only helpful in detecting significant yolk sac tumor components but may also assist in prognostic assessment. In a large cooperative analysis of adult germ cell tumors, high AFP and/or β-HCG levels indicated poor prognosis (International-Germ-Cell-Cancer-Collaborative-Group 1997). In the British childhood cancer studies, high AFP levels above 1,000 μg/L were associated with unfavorable outcome (Mann et al. 1989b, 2000b). Furthermore, an inadequate decline of AFP that does not follow its half time of 5–7 days indicates pure response to chemo or tumor progression after tumor resection (Calaminus et al. 1991).

The most frequent for significant rise of β-HCG is pregnancy. Therefore, in case of suspected GCT and elevated β-HCG, pregnancy must be excluded with other techniques, e.g., ultrasound. Elevation of serum β-HCG in patients with germ cell tumors implies the presence of clones of syncytiotrophoblasts, such as choriocarcinoma, or of syncytiotrophoblastic giant cells, found frequently in germinomas (pure seminomas or dysgerminomas) and occasionally in adult embryonal carcinoma. Immunoperoxidase staining of tumor for β-HCG detects these hormone-containing elements.

39.2.5 Staging of Extracranial Extragonadal Germ Cell Tumors

Pure teratomas of childhood do not metastasize. However, since they may include microscopic foci of malignant yolk sac tumor, the draining lymph nodes should be examined with ultrasound or MRI, and an initial chest X-ray can be performed in order to document absence of metastases. It should be noted that teratomatous tumors arising after puberty may sometimes be associated with metastatic spread. Thus, clinical staging with ultrasound, MRI, and chest X-ray is certainly justified. If absence of metastases is documented, the follow-up of childhood teratomas should primarily focus on the primary tumor site, since relapses most commonly develop locally.

Malignant yolk sac tumors of childhood show a tendency to metastasize into the locoregional lymph nodes and into the lungs, justifying a limited staging assessment focusing on these sites. Currently, there is no prospectively proven evidence as to whether pulmonary micrometastases detected with CT scans of the lungs are therapeutically and prognostically relevant. In fact, pulmonary metastases commonly of childhood yolk sac tumor commonly show a favorable response to platin-based chemotherapy and extremely rarely require surgical treatment. However, germ cell tumors with pulmonary micrometastases are certainly eligible to intensive chemotherapy with four cycles of chemotherapy so that CT scans are commonly used and currently recommended in order to increase the accuracy of clinical staging.

Rarely, metastases at other sites such as the liver, the bones, or the CNS are noted. However, these metastases almost never present in the absence of lung metastases or site-specific symptoms such as bone pain (Calaminus et al. 2003). Therefore, clinical staging should be expanded to bone scan and MRI of the brain if lung metastases are diagnosed or if specific symptoms such as bone pain are reported.

39.2.6 Clinical Staging Systems for Extracranial Germ Cell Tumors

Different staging systems are used for extragonadal malignant germ cell tumors, which all have several advantages and disadvantages. The main problem is that extragonadal germ cell tumors may arise at different anatomical size, which of course cannot be considered in a general staging system. Therefore, the currently applied staging systems reflect general characteristics such as infiltration into neighboring organs and metastatic spread into the lymph nodes or the lungs or other visceral organs. The German MAKEI group is currently applying a modified TNM staging system for soft tissue sarcomas, according to which tumor size (<5 cm vs. >5 cm diameter) and local infiltration are considered for T-staging. Lymph node and distant metastases are counted separately as either negative or positive (Table 39.2.4). For therapy stratification, the completeness of resection is considered as a separate variable.

In contrast, the staging system according to the US COG also integrates information on resection status as well as the initial surgical procedure. Thus, all patients who undergo a biopsy prior to the start of chemotherapy are considered stage III (Table 39.2.5). A main advantage of this staging system is that it is similarly applied to gonadal germ cell tumors, facilitating comparison of prognostic and therapeutic data regardless of site. However in contrast to the TNM system, biopsy procedures will always upstage tumors to stage III, irrespective of anatomical stage.

39.2.7 Germ Cell Tumors of the Central Nervous System

Since CNS germ cell tumors are described extensively in this series' book on CNS tumors, only a brief description of the general diagnostic and therapeutic strategies is provided in this chapter.

Primary intracranial germ cell tumors primarily develop during adolescence and young adulthood. They may be located in the pineal gland (62%) or suprasellar region (31%), or they may span both areas (7%) (Balmaceda and Finlay 2004; Bamberg et al. 1999; Calaminus et al. 2005). Symptomatology depends on site, growth pattern, and histology of the tumor and may include personality changes, visual disturbances, diabetes insipidus, hypopituitarism, Parinaud's syndrome (convergence nystagmus), anorexia, and precocious puberty. Histologically, two thirds of the tumors are germinomas, and the rest are nongerminomatous, some mixed with yolk sac tumor, choriocarcinoma, or teratocarcinoma.

The clinical assessment of central nervous system germ cell tumors is outlined in Table 39.2.3. Since hypophyseal germ cell tumors may induce diabetes insipidus, specific attention should be paid to the serum electrolytes as well as serum and urine osmolarity. The presence of diabetes insipidus would have significant impact on infusion therapy during chemotherapy, since severe electrolyte imbalances may develop during intensive infusion therapy required during platin chemotherapy (Bryant et al. 1994).

It is important to note that CNS germ cell tumors show a marked tendency to metastasize through the cerebrospinal fluid. Thus, metastases within the ventricular system as well as drop metastases to the spine may occur (Alapetite et al. 2002, 2010; Calaminus et al. 2002). Extracranial spread to lung and bones has also been reported, however very rarely. Considering their tendency to spread within the cerebrospinal fluid, cytological evaluation after lumbar tap or of cerebrospinal fluid collected during surgery is absolutely mandatory for initial staging. If cytological examination is not performed perioperatively, tumors should be considered potentially metastatic, with a significant impact on local treatment, i.e., radiotherapy (Calaminus et al. 1997a).

Table 39.2.4 Staging system for extragonadal germ cell tumors adapted from the TNM staging system for soft tissue sarcomas

Category		Parameters	
Local stage			
T	1a	No infiltration of neighboring organs	<5 cm
	1b		>5 cm
	2a	Infiltration of neighboring organs	<5 cm
	2b		>5 cm
N	0	No lymphatic metastases	
	1	Lymphatic metastases	
M	0	No distant metastases	
	1	Distant metastases	

Table 39.2.5 US COG staging system for gonadal and extragonadal germ cell tumors

Children's Oncology Group staging of extragonadal germ cell tumors	
I	Complete resection at any site, coccygectomy for sacrococcygeal site, negative tumor margins. No evidence of metastases. Appropriate marker decline
II	Microscopic residual; lymph nodes negative
III	Gross residual disease or biopsy ony; Lymph node involvement with metastatic disease; retroperitoneal nodes positive or negative
IV	Metastatic disease including liver

There is no specific staging system for central nervous system germ cell tumors. Thus, they are staged in analogy to other CNS tumors such as medulloblastoma (Chang et al. 1969). Mainly, the presence of tumor cells in the cerebrospinal fluid as well as metastases to different sites of the CNS is considered. Local radiotherapy is planned according to this initial staging, with inclusion of craniospinal irradiation in micrometastases and an additional boost to any visible metastases apparent on MRI.

AFP and β-HCG should be measured both in the serum and the cerebrospinal fluid, because they indicate secreting malignant nonseminomatous germ cell tumors. Of note, discrepant levels between serum and cerebrospinal fluid may be detected in some patients. There is considerable debate regarding the appropriate cutoff levels for AFP and β-HCG, since in some rare patients histologically pure germinoma may be associated with significant β-HCG secretion. However, in the current international SIOP study on CNS germ cell tumors, cutoff levels of AFP, 25 μg/l, and β-HCG, 50 IU/μl, have been defined (Calaminus et al. 1994, 2005, 2002). Tumors associated with higher levels either in the serum or the cerebrospinal fluid are considered secreting tumors and selected for more intensive chemotherapy with cisplatin instead of carboplatin and higher irradiation doses. Of note, these tumor markers also assist in establishing a clinical diagnosis in that a significant elevation is considered sufficient for the clinical diagnosis of a malignant germ cell tumor even without biopsy. Last, high AFP levels above 1,000 μg/L may be used for therapy stratification in the current SIOP protocol.

39.2.8 Treatment Overview

For all extragonadal germ cell tumors, an individualized multimodal treatment plan has to be chosen that takes histology, the site of origin, and stage into account. The treatment of teratoma is surgical; apart from single-case reports (Garre et al. 1996), there is no evidence of significant therapeutic effects of chemotherapy in pure teratomas (Göbel et al. 1997, 1998a; Marina et al. 1999b). In malignant germ cell tumors, surgical resection is also of vital importance for successful treatment, since extragonadal germ cell tumors show a high tendency to relapse at the site of origin. Therefore, complete resection constitutes the mainstay of treatment (Göbel et al. 2001; Schneider et al. 2000b). In rare, circumscribed, and nonmetastatic malignant germ cell tumors, patients may not require additional chemotherapy following complete surgical resection. However, in most extragonadal germ cell tumors, chemotherapy is indicated to consolidate remission after initial resection. Alternatively, up-front chemotherapy may be applied to facilitate complete resection on delayed surgery. Radiotherapy is rarely applied in extragonadal germ cell tumors. In contrast, it is commonly applied in central nervous system germ cell tumors, in which it may partly replace surgical resection as a measure to achieve local tumor control (Bamberg et al. 1999; Calaminus et al. 2005).

Chemotherapy is given according to the regimens also administered for gonadal germ cell tumors (see Table 39.1.4 in Sect. 39.1.1).

39.2.9 Principles of Surgery of Extragonadal Extracranial Germ Cell Tumors

Surgical resection is the therapy of choice in benign tumors, such as teratomas. With malignant lesions, removal is indicated, if possible. However, given the availability of effective chemotherapy, resection should not be undertaken to the point of sacrificing vital structures. In this situation, biopsy may be appropriate. Biopsy will not only support, confirm, and specify clinical diagnosis but also opens perspectives for genetic analysis and molecular research.

It must be emphasized that surgical recommendations may differ significantly for children and adolescents. After initial chemotherapy, second-look surgery serves to assist in achieving complete response in selected patients. Specific surgical strategies for specific extragonadal germ cell tumors of the mediastinum and the head and neck region are described in Chap. 19 and below for sacrococcygeal germ cell tumors.

39.2.10 Principles of Chemotherapy for Extragonadal Germ Cell Tumors

Substantial improvements in the cure rates for pediatric germ cell tumors have occurred, stemming in large part from the evolution of effective chemotherapeutic

strategies, most developed for the larger adult population with these neoplasms. Most pediatric germ cell tumor trials are limited by the small numbers of tumors at each site of origin with specific histology and stage.

Most chemotherapeutic studies have been conducted in patients with testicular and extragonadal tumors, primarily with advanced or disseminated disease. These data indicated that extragonadal germ cell tumors show a similar response to cisplatin-based combination chemotherapy as gonadal germ cell tumors do (Mann et al. 2000b; Göbel et al. 2000). However, mediastinal germ cell tumors constitute the largest subgroup of extragonadal germ cell tumors in adults, and they commonly have an unfavorable prognosis (Ganjoo et al. 2000). Therefore, strategies for chemotherapy intensification have been proposed that incorporate dose-escalated chemotherapy as well as high-dose chemotherapy with autologous stem cell transplantation (Bokemeyer et al. 2003; Schmoll et al. 2003).

Pediatric studies have mirrored the adult experience. Combination chemotherapy has been found to be superior to single or dual agents, and the addition of cisplatin has increased the efficacy of these regimens (Billmire et al. 2003; Billmire et al. 2004a; Cushing et al. 2004b; Rogers et al. 2004b; Lopes et al. 2008, 2009a; Göbel et al. 2000). In the intergroup study conducted by the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG), PEB, as standard treatment, was compared to a combination of high-dose cisplatin plus etoposide and bleomycin (Cushing et al. 2004b). This regimen did differ from adult PEB treatments because bleomycin was not administered weekly. Patients with localized gonadal germ cell tumors were treated with standard PEB. All other gonadal and all extragonadal germ cell tumors were randomized to standard PEB or a regimen with high-dose cisplatin (200 mg/m^2). Although tumor control was better in high-risk patients who received high-dose cisplatin, significant toxicity appeared to limit its use.

Studies conducted by the United Kingdom Children's Cancer Study Group suggest the superiority of carboplatin over standard-dose cisplatin in reducing permanent toxicity. Comparison was not made, however, to high-dose cisplatin (Mann et al. 1998; Mann et al. 2000b).

The Brazilian pediatric germ cell tumor group applied a response-based strategy. Bleomycin was omitted for both intermediate- and high-risk patients (Lopes et al. 2008, 2009a). Cisplatin, at 30 mg/m^2/day for 5 days, was administered to high-risk patients. After three cycles patients from both risk categories, who did not achieve CR, were switched to ifosfamide, vinblastine, and bleomycin. Though the study was limited by small sample size, some patients were treated successfully without bleomycin. In addition, a rationale for response-based treatment was suggested (Lopes 2009). Marrow-ablative doses of carboplatin and etoposide followed by autologous marrow reinfusion may provide a method of salvaging patients who experience relapse or whose disease proves refractory to treatment.

The French group has utilized both carboplatin- and cisplatin-based regimen. In the late 1980s and 1990s, carboplatin-based regimen have been applied, with doses of carboplatin at 400 mg/m^2/cycle (Baranzelli et al. 1999b, 2000a), which is considerably lower than in the British studies. In this study, inferior response rates have been reported, in particular, for extragonadal germ cell tumors (Baranzelli et al. 1999b). However, patients could be salvaged with second-line cisplatin-based regimen. In the current studies, a combination of cisplatin, etoposide, and ifosfamide is applied, using a response-based strategy. Thus, patients receive two additional cycles after complete response, summing up to a median of three cycles in intermediate-risk patients and five cycles in high-risk patients.

In the German MAKEI protocols, therapy is stratified according to site, stage, and completeness of tumor resection (Göbel et al. 1999, 2000). In locally advanced and metastatic tumors, up-front chemotherapy after clinical diagnosis based on markers or biopsy is strongly advocated. In completely resected, low-stage tumors, a watch-and-wait strategy is chosen, or patients are treated with two to three cycles of a two-agent regimen including cisplatin and etoposide. In all other tumors, cisplatin and etoposide are combined with ifosfamide. In previous studies, bleomycin has substituted for ifosfamide. However, after two lethal pulmonary toxicities occurred in young infants, ifosfamide was chosen but is withheld in young toddlers (Göbel et al. 2000). Up to four cycles of PEI are administered to high-risk patients. For patients with unresectable tumors that respond inadequately to up-front chemotherapy or relapse, a local therapy intensification with locoregional hyperthermia and thermochemotherapy is recommended (Wessalowski et al. 2003b).

One difficulty of establishing clear recommendations for treatment of pediatric germ cell tumors is the inability to define risk groups. Most trials are small and have

been conducted by individual national groups. Most pediatric trials combine different sites of origin, staging, and histology to the same stratum for therapy to achieve adequate statistical power. In contrast, for adult germ cell tumors, a large international meta-analysis has led to the introduction of a risk categorization that is currently used for the development and comparison of therapeutic trials (International-Germ-Cell-Cancer-Collaborative-Group 1997). A recent analysis of the US Children's Oncology Group has shown that this prognostic staging system, when adopted to a pediatric cohort, leads to a different stratification (Frazier et al. 2008). This is mainly explained by the different biology of germ cell tumors, in particular, during early childhood. Thus, the impact of high AFP levels has to be evaluated critically and under the consideration of yolk sac tumor being the only malignant histology in childhood.

Based on this consideration, an international attempt with a combined analysis of the US and British study registries has been taken to develop a new prognostic stratification system. Preliminary analyses show that a highly unfavorable risk group is defined for extragonadal, in particular, mediastinal germ cell tumors in adolescents. In fact, age emerges as a prognostic factor for mediastinal germ cell tumors. In line with the previous report from the German MAKEI study and the molecular genetic study (Schneider et al. 2002b), mediastinal nonseminomatous germ cell tumors of adolescents older than 10 years of age are prognostically unfavorable, whereas the corresponding tumors in young infants are not (Hale et al. 2010).

Specific recommendations for incorporating chemotherapy into the management of pediatric extragonadal germ cell tumors are discussed separately for each tumor. The dosages and methods of administration of current regimens employed in pediatric germ cell tumors [cisplatin, vinblastine, and bleomycin (PVB); cisplatin, etoposide, and bleomycin (PEB); and carboplatin, etoposide, and bleomycin (JEB)] are shown in Table 39.1.4 in Sect. 39.1.1.

It should be noted that complete initial resection with wide margins is rarely achieved in malignant extragonadal germ cell tumors. Therefore, apart from teratoma, only rare extragonadal malignant tumors are eligible for a watch-and-wait strategy. Patients with moderate-risk gonadal tumors or progression of disease in untreated tumors may be managed adequately with three to four cycles of a platinum-containing regimen. For higher-risk patients (higher-stage extragonadal tumors), four (to six) cycles of a platinum-based or dose-intensified chemotherapeutic regimen is indicated.

39.2.11 Treatment of SC-GCT

39.2.11.1 Sacrococcygeal Tumors

Sacrococcygeal germ cell tumors constitute the most frequent germ cell tumors during childhood and adolescence. In fact, sacrococcygeal teratoma is the overall most frequent neonatal tumor. The risk of malignancy increases with age. The surgical approach strongly depends on the anatomical site according to the Altman classification (Altman et al. 1974a). This classification categorizes tumors with regard to the extrapelvic (dorsal to the coccyx) and intrapelvic extension of the tumor. It is hypothesized that malignant tumors show a higher tendency to grow inside the pelvis. Although this classification is not consistently used, the basic consideration to evaluate preoperatively for intra- and extrapelvic tumor extension has a significant impact on surgical access and strategy.

39.2.11.2 Resection of Neonatal Sacrococcygeal Teratomas

Most neonatal teratomas, both immature and mature, present as large exophytic tumors that may be as large as the rest of the neonate. If the tumor is diagnosed with prenatal ultrasound, the child should not be delivered through vaginal delivery, since tumor rupture and severe hemorrhage may develop (Fig. 39.2.1). If the tumor is intact, there is no need for immediate resection, and preoperative imaging can be completed.

If the tumor has ruptured, then a pressure bandage may diminish the blood loss for a limited period of time. Prior to surgical resection, the degree of abdominal extension should be accurately evaluated if possible with US and MRI, to plan the approach.

The patient is usually positioned in the prone position, with a roll under the hips. Surgical principles that lead to a complete removal include a posterior approach with an inverted V shape to allow for excision of the tumor and to facilitate an eventually satisfactory cosmetic closure. This approach affords the surgeon excellent exposure for most neonatal sacrococcygeal germ cell tumors and may obviate the need for intra-abdominal exposures. The incision should be placed as

to preserve as much normal skin as possible: Excess skin can always be trimmed later if necessary.

Immature lesions are more vascular with significantly greater blood loss during surgery, and it is often necessary to perform blood transfusions (Altman et al. 1974a). The tumor is dissected from gluteus muscles, the coccyx is dissected at the sacrococcygeal joint, and the middle sacral vessels are controlled to minimize intraoperative hemorrhage. Failure to resect the complete coccyx is associated with increased risk of local recurrence (Göbel et al. 1997, 1998a).

The presacral extent of the tumor can compress the perineal structures forward; since the tumor may be adherent to the rectum, sharp dissection can be directed by placing a finger or a Hegar dilator in the rectum. The mass should be mobilized close to its pseudocapsule and removed, without spillage, en bloc with the coccyx. Then the anorectal and the retrorectal muscles are reconstructed. Closed suction drainage is adopted to evacuate fluid, and the wound is closed in layers.

If the tumor extends deeply through the bony pelvis into the retroperitoneum, an abdominal approach allows the mobilization of the mass and the control of the sacral artery. In some patients, a combined posterior and abdominal approach has to be chosen.

The tumor is eventually removed from the perineum. If the tumor has been ruptured and is actively bleeding, preliminary abdominal exploration is required: The aim is to find and ligate the middle sacral vessels; if this is not possible, an occlusive sling is placed across the aorta below the origin of the inferior mesenteric artery (Lindahl 1988).

Intraoperative hemorrhage and postoperative wound infections constitute the most frequent complications of excision of sacrococcygeal teratoma. The major cause of mortality is hemorrhagic shock, since an unsuspected teratoma may rupture during delivery. Neonatal teratomas need accurate clinical follow-up since local recurrences are observed in 4–20% of cases, in particular, if the coccyx is not removed. Of note, 50% of relapses are malignant (Fig. 39.2.7) (Göbel et al. 1998a). The infant should be followed with visits (including rectal examination), ultrasound, and AFP at 3-month intervals for at least 3 years and then annually. Recurrences rarely develop after the age of 2 years. The development of a malignant recurrence may be the result of an incomplete resection or a pathologic sampling error.

In a study from UK, the 5-year event-free survival for both mature and immature sacrococcygeal teratomas was approximately 75% (Mann et al. 2008a). Accordingly, the recurrence rate was 23% in 132 patients reported to the German MAKEI studies. Of note, the risk of malignant relapse with yolk sac tumor was minimized when postoperative chemotherapy was administered to patients with incomplete initial resection. However, the overall relapse rate was not reduced by chemotherapy (Göbel et al. 1998a). Cautious monitoring of such patients is required, because malignant germ cell tumors are well recognized to recur either from unnoticed malignant elements in the original tumor or from malignant transformation in residual tissue. Until recently, only a 10% salvage rate for malignant lesions was expected.

39.2.11.3 Resection of Malignant Sacrococcygeal Germ Cell Tumors in Toddlers

At the sacrococcygeal region, the risk of malignant germ cell tumor increases with age. However, even in neonates, malignant components may be detected histologically, the so-called yolk sac tumor microfoci (Harms and Jänig 1986). Therefore, accurate preoperative evaluation of the tumor markers and radiographic staging are necessary. The strategy for postoperative follow-up or adjuvant treatment and estimated prognosis is illustrated in Fig. 39.2.8.

Tumors are frequently non-capsulated and may develop in close proximity to the rectum. When invasion of the pelvic structures and/or extension into the spine are found or uncertain, the mass should be considered unresectable and a primary excision is discouraged. In these patients, an initial biopsy followed by neoadjuvant chemotherapy is the best choice (Göbel et al. 2000). Tumor shrinkage from platinum-based chemotherapy is highly successful and increases the achievement of complete resection with negative margins (Göbel et al. 2001).

Primary or delayed excision can be performed with posterior or combined (abdominal plus posterior) approach, depending on the site and extension of the tumor [according to Altman classification (Altman et al. 1974a)], and the surgical principles are the same, adopted for neonatal germ cell tumors, taking into consideration the crucial importance of a microscopically complete resection in patients with malignant lesions. The mass is removed with the coccyx, and multiple biopsies on the tumor bed should be performed to verify the completeness of the excision.

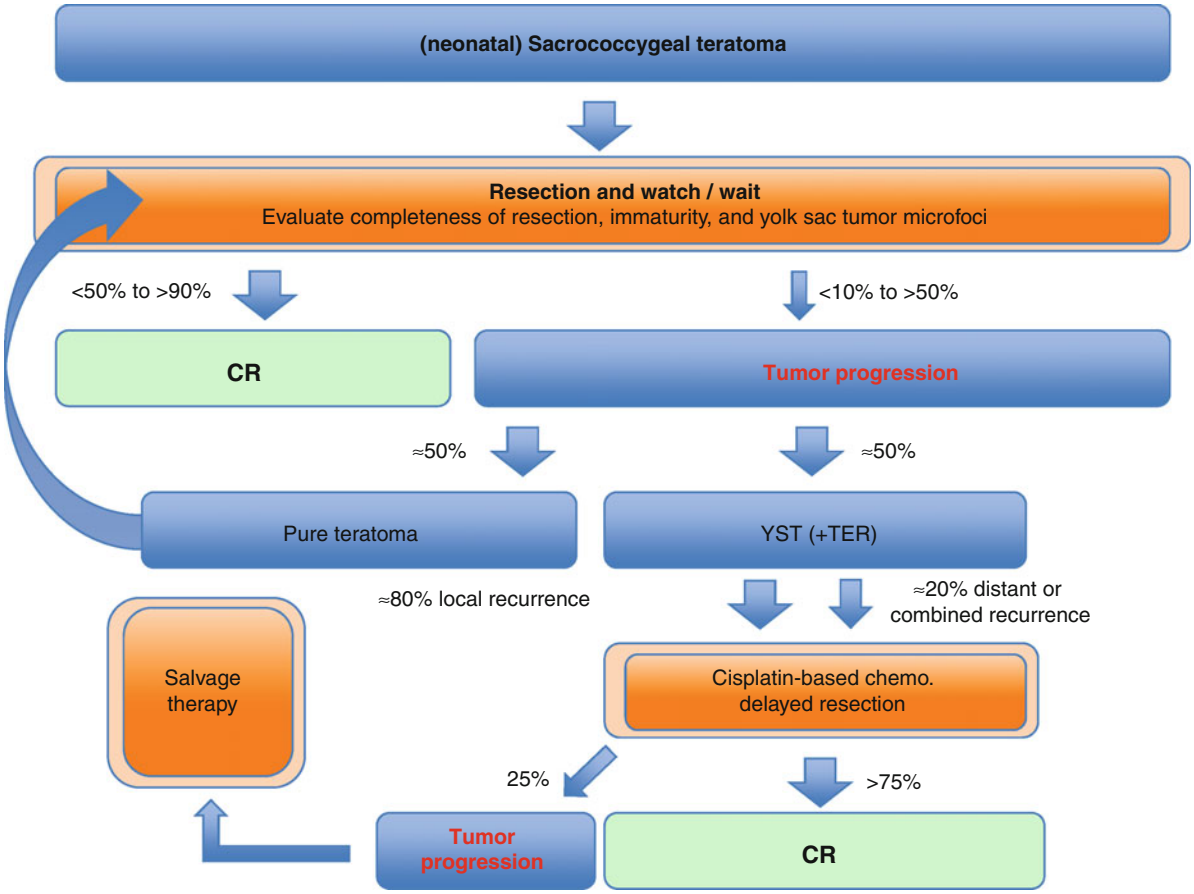


Fig. 39.2.7 Therapeutic algorithm in sacrococcygeal teratomas

Biopsy of suspected regional nodes (pelvic or inguinal) is recommended. If no residual disease is visible at imaging after neoadjuvant chemotherapy, coccygectomy is still required.

Surgery for extragonadal malignant germ cell tumors may be difficult due to the invasiveness of the tumor and the involvement of pelvic structures. Temporary colostomies may be required if rectal damages are caused during the resection. Neuropathic bladder or bowel disorders are reported in up to 30% of cases after major procedures (Rescorla 2008).

39.2.12 Surgical Resection of Intra- and Retroperitoneal Germ Cell Tumors

Compared to sacrococcygeal germ cell tumors, abdominal intra- or retroperitoneal germ cell tumors are rare and account for less than 5% of childhood germ cell tumors (Billmire et al. 2003) (Fig. 39.2.6). Histology and biology are comparable to other childhood germ cell tumors such as mediastinal tumors, with teratoma predominating in neonates and yolk sac tumors in toddlers. Mixed malignant germ cell tumors are observed in postpubertal patients. A testicular primary should always be excluded by clinical and ultrasound examination. In prepubertal patients, testicular biopsy is not recommended. However, it is often performed in postpubertal patients and in adults. Differential diagnosis is problematic, in particular, if the tumors are located in the upper retroperitoneum. In these tumors, the tumor marker AFP is equivocal, since other upper retroperitoneal tumors such as pancreatic tumors and metastases of hepatic tumors may also be associated with elevated AFP (Schneider et al. 2001e).

As for germ cell tumors arising at other sites, retroperitoneal germ cell tumors should also be resected in

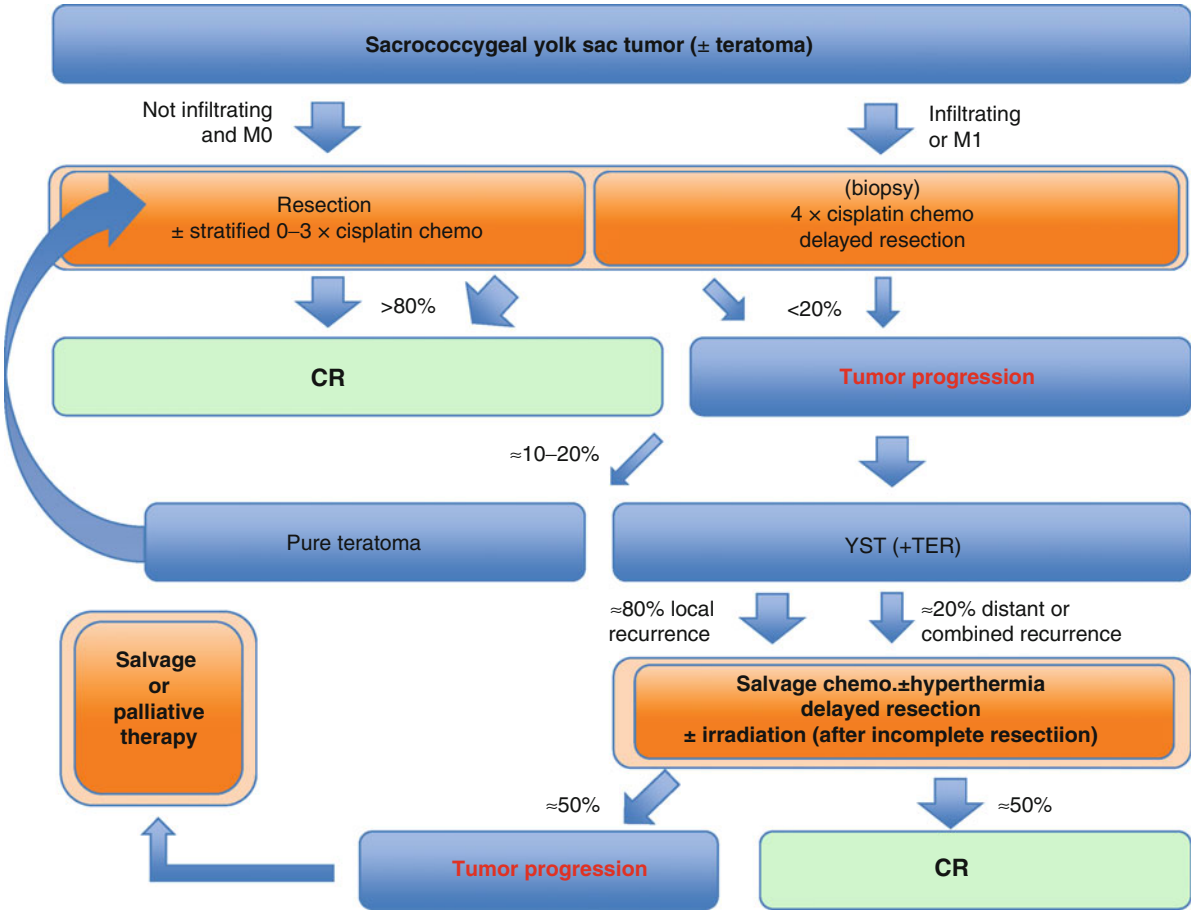


Fig. 39.2.8 Therapeutic algorithm in malignant sacrococcygeal yolk sac tumors

one piece and without spillage. In order to facilitate complete resection, a median laparotomy is chosen based on the anatomical situation of the tumor. Benign teratomas are usually well capsulated and not attached to retroperitoneal organs (Fig. 39.2.6). The excision represents the only therapy, and usually it is not difficult because they have a modest blood supply which is simply interrupted during the dissection. Adjacent lymph node should be sampled.

For large and invasive GCTs, the most important initial step is to establish the diagnosis clinically or with a biopsy, without performing extensive surgery. After neoadjuvant chemotherapy, mutilating surgery may be avoided in most cases.

Intraperitoneal GCT may be located in the liver or attached to the stomach or omentum. Gastric teratomas require the removal of a part of the gastric wall, which depend on the size of the tumor and the depth of the attachment (Billmire et al. 2003).

39.2.12.1 Surgical Resection of Vaginal Germ Cell Tumors

Although vaginal germ cell tumors are extraordinarily rare, they constitute a specific subgroup that is characterized by its limitation to yolk sac tumor histology in the absence of teratoma (Mauz-Körholz et al. 2000; Lopes et al. 1999). Moreover, these tumors show a low incidence of metastases. In the pre-platinum era, these tumors have been considered prognostically unfavorable, and extensive surgical resection including hysterectomy has been advocated. With the development of intensive platin-based combination chemotherapy, prognosis has dramatically improved. In fact, vaginal yolk sac tumors belong to the most curable subtypes of childhood germ cell tumors with a low relapse rate and excellent overall survival (Mauz-Körholz et al. 2000b). The prerequisite of this success has been the implementation of up-front chemotherapy, which usually induces excellent tumor response,

thus allowing for only limited resection on delayed surgery.

In most patients, enucleation of the pretreated tumor, often in combination with partial vaginectomy, is performed. In contrast to sacrococcygeal germ cell tumors, in which microscopically incomplete resection is associated with a high rate of local recurrences, microscopic residues obviously do not bear a dismal prognostic impact in vaginal yolk sac tumors.

Last, germ cell tumors may also rarely arise at other urogenital sites such as the penis or the prostate. In these tumors, complete surgical resection is considered a prerequisite of cure. In order to avoid mutilating surgery, a preoperative chemotherapy is recommended after initial diagnostic biopsy. The surgical strategy follows the general guidelines for oncologic surgery at the specific site.

39.2.12.2 Germ Cell Tumors of the Central Nervous System

Since CNS germ cell tumors are described extensively in this series' book on CNS tumors, only a brief description of the general therapeutic strategies is provided in this chapter.

As CNS germ cell tumors may develop at different, mostly midline sites, they may pose a significant challenge to the neurosurgeon (Figs. 39.2.4 and 39.2.5). In fact, large neonatal midline teratomas may be completely inassessable to treatment (Fig. 39.2.5). On the other hand, malignant germ cell tumors show a favorable response to chemotherapy and radiotherapy, in particular, in case of germinoma. Therefore, an initial surgical procedure should not be performed at the risk of provoking neurological damage or of sacrificing structures of vital importance such as vessels (Nicholson et al. 2002). Moreover, venous plexus may be in close neighborhood to, e.g., larger pineal tumors so that surgery may be complicated by hemorrhage. Last, surgical resection of hypophyseal tumors will lead to hypophyseal insufficiency with a lifelong need of hormone replacement.

In addition, it should always be considered in brain tumors that secreting germ cell tumors may easily be diagnosed based on serum and CSF tumor markers AFP and β-HCG. In patients with unequivocally elevated tumor markers, the clinical diagnosis may be established on markers and imaging even without surgical procedure and histologic confirmation. As a consequence, only a subset with marker of negative tumors requires histologic confirmation. The neurosurgical resection should be limited to initial (stereotactic, endoscopic, or open) biopsy. In patients with significant intracranial hypertension, biopsy may be combined with insertion of a ventricular-peritoneal drainage, or ventricular drainage can ideally be combined with biopsy during endoscopic surgery. There is no convincing evidence that aggressive surgical resection at diagnoses improves patients' oncologic prognosis, but there is considerably a concern that it may be associated with significant sequelae. Thus, many patients can be spared major brain surgery and can be cured with chemo- and/or radiotherapy.

The adjuvant chemo- and radiotherapy treatment heavily depends on histology and stage. Evidence of secreting tumor (AFP 25 μg/l and β-HCG 50 IU/μl) will lead to more intensive chemotherapy and higher radiotherapy doses. Evidence of (micro-) metastases on the cerebrospinal fluid will justify extended radiation fields including the cerebrospinal axis. Therefore, complete initial diagnostic assessment and staging constitutes the mainstay of treatment stratification. Moreover, the presence of diabetes insipidus has significant impact on infusion therapy during chemotherapy, since severe electrolyte imbalances may develop during hyperhydration required during platin chemotherapy.

Germinomas have traditionally been treated with radiotherapy, consisting of craniospinal irradiation with a tumor boost to 36 Gy (Bamberg et al. 1999). More recently, several studies from the US and Europe reported that both germinomas and secreting germ cell tumors can be successfully managed with a carboplatin-based chemotherapeutic regimen (Balmaceda et al. 1996; da Silva et al. 2010; Kellie et al. 2004; Khatua et al. 2010; Alapetite et al. 2002). However, omitting radiotherapy is associated with an increased risk of local recurrence. In analogy, the omission of craniospinal irradiation in patients receiving radiochemotherapy including focal irradiation is associated with an increased risk of ventricular recurrences (Alapetite et al. 2010). Therefore, the current international SIOP protocol will propose ventricular irradiation after carboplatin-based combination chemotherapy, in order to minimize this risk of ventricular relapse. For metastatic germinomas, craniospinal irradiation is proposed. The prognostic impact of residual tumor following chemo- and radiotherapy has to be considered carefully and in the context of the histology, in

particular, the presence of additional teratomatous components.

For secreting tumors, a combination of four cycles of cisplatin-based chemotherapy (PEI) supplemented by local (localized tumor) or craniospinal (metastatic tumors) irradiation with 45 Gy is recommended. In tumors with high AFP levels, chemotherapy is intensified with dose escalation of ifosfamide and etoposide.

39.2.13 Salvage Strategies

Therapy of malignant extragonadal germ cell tumors depends on histology at diagnosis and at relapse, site of recurrence, and first-line treatment (Figs. 39.2.7 and 39.2.8). In general, extragonadal germ cell tumors tend to recur at the primary tumor site. Nevertheless, prognosis of malignant extragonadal germ cell tumors that recur after platin-based chemotherapy is poor. This is primarily related to the fact that these tumors may develop resistance to chemotherapy (Mayer et al. 2003b). Second, the (surgical) chances to obtain a complete local control are usually significantly impaired at second-look surgery. Thus, scarring and changes in the normal anatomy after first surgery may impair surgical access to the recurrent tumor. Therefore, salvage strategy must always take both the local surgical situation and the general oncologic situation (metastases) into account. In general, salvage strategy must be planned and performed following an interdisciplinary approach.

The chances to successfully treat a malignant recurrence of a neonatal sacrococcygeal teratoma are good, in particular, if recurrence is detected at an early stage during regular follow-up. These tumors are usually treated with up-front cisplatin-based chemotherapy, followed by delayed tumor resection, which should be reserved to experienced pediatric surgeons (Fig. 39.2.7). If complete resection is obtained, the prognosis is comparable to that of primary sacrococcygeal yolk sac tumor.

In contrast, the outlook of recurrence after first-line chemotherapy is impaired. A switch, ideally an intensification of chemotherapy, is indicated in case of recurrence after first-line chemotherapy. In case of carboplatin-based first-line therapy, carboplatin can be replaced with cisplatin, and studies have shown that a substantial proportion of patients can be salvaged after the introduction of cisplatin (Baranzelli et al. 1999). Otherwise, salvage chemotherapy regimens in children including high-dose chemotherapy strategies are commonly derived from studies performed in adult patients. This experience is extensively reviewed in Sect. 39.1.1.

Ideally, a strategy should be developed that allows both to overcome resistance of tumor cells to chemotherapy and to facilitate local tumor control (Fig. 39.2.8). In this context, regional deep hyperthermia may provide promising aspects. Wessalowski and colleagues have treated children and adolescents with recurrent gonadal but mostly extragonadal germ cell tumors with cisplatin, etoposide, and ifosfamide in combination with regional deep hyperthermia (Wessalowski et al. 1997b, 2003b). The majority of patients were suffering from recurrent malignant sacrococcygeal germ cell tumors. Therapy was administered in a neoadjuvant strategy, with a delayed resection usually performed after the third or fourth cycles of thermochemotherapy. Of note, surgical resection was centralized to few experienced pediatric surgical centers, and in case of still incomplete resection, a proportion of patients additionally received local radiotherapy (Schneider et al. 2001e). With this approach, response to thermochemotherapy was favorable, as demonstrated by reduction of tumor size and decline of tumor markers. In addition, complete resection could be obtained in a proportion of patients, and in those not assessable to complete resection, radiotherapy appeared to enhance local tumor control additionally. With this strategy, a salvage rate almost comparable to that in first-line treatment was obtained – however, such favorable outcome was only achieved in patients referred to thermochemotherapy at first relapse. In later relapses, thermochemotherapy strategies are not as promising. This indicates that in case of relapse, early treatment intensification and stringent multimodal treatment strategies are an absolute prerequisite of cure (Schneider et al. 2001e). Unfortunately, thermochemotherapy is available only in few pediatric oncologic centers. Even more, any salvage strategy should nevertheless aim for the best possible tumor control. For this purpose, careful planning of surgical resection and, if required, radiotherapy is essential.

These considerations can be transferred to recurrent extragonadal germ cell tumors at any other site, including retroperitoneal, mediastinal, and vaginal germ cell tumors. For intracranial germ cell tumors, the same biologic and clinical observations can be made. They

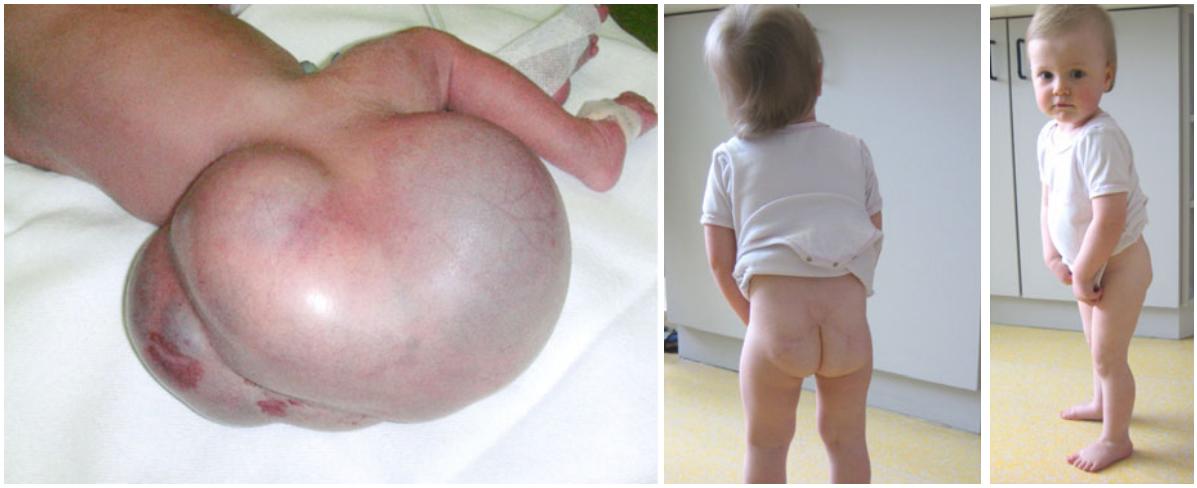


Fig. 39.2.9 Clinical presentation of a neonatal sacrococcygeal teratoma in a preterm girl delivered in the 32th week of pregnancy. The girl has become continent for both urine and stool at the age of 2 years

only rarely metastasize outside of the central nervous system. However, metastases within the ventricular system are not infrequent (Alapetite et al. 2010). In addition, local recurrences can be observed, in particular, in nonseminomatous germ cell tumors. Unfortunately, the chances to intensify local and systemic tumor control in recurrent central nervous system germ cell tumors are very restricted. Thus, most patients have been treated with intensive first-line chemotherapy. Only in case of carboplatin-based chemotherapy, a switch to cisplatin regimen opens the perspective to intensive chemotherapy significantly. If tumors recur outside of the radiation field, irradiation can be administered to these areas. However, it should be considered that usually such tumors present as metastatic tumors, thus requiring consolidating irradiation of the whole craniospinal axis. If high cumulative doses are required, toxicity may thus interfere with this approach. Thus, alternative strategies including intraventricular chemotherapy can also be administered, however, with currently only limited experience. Therefore, any salvage strategy in recurrent central nervous system germ cell tumors should be discussed with the respective study coordinator. Ideally, clinical data should be collected centrally in order to support the development of standardized and effective strategies including new irradiation techniques (e.g., protons), alternative chemotherapy strategies (e.g., high-dose chemotherapy), and alternative drugs (e.g., kinase inhibitors or antiangiogenetic drugs).

39.2.14 Prognosis and Late Effects

The prognosis of extragonadal teratomas is excellent if complete tumor resection is obtained. If tumor resection is incomplete, the risk of recurrence correlates with the grade of immaturity. Last, the recurrence risk also correlates with site, with incompletely resected sacrococcygeal teratomas being at the highest risk. Of note, half of recurrences present with malignant histology so that monitoring of AFP during follow-up is helpful in detecting these malignant relapses (Göbel et al. 1998a, b). It should be considered that despite the "benign" histology, teratomas are potentially lethal tumors. In a large series of 270 extracranial non-testicular teratomas, relapse rates of mature and immature teratoma were 10% and 18%, respectively. 25% of patients with tumor recurrence died, and almost half of the survivors underwent mutilating surgery with long-term sequelae such as palsy of the pelvic floor and incontinence (Göbel et al. 1998a). In contrast, the long-term outcome of patients who were successfully operated at initial diagnosis is favorable. Only a minority of patients with sacrococcygeal teratoma suffer from neurologic sequelae related to the tumor infiltrating the spinal canal, such as weakness of the lower limbs or incontinence, illustrated by the little girl of Fig. 39.2.9, who presented with a giant neonatal teratoma and was continent at the age of 2 years. Nevertheless, a proportion of patients may describe episodal or chronic constipation, which may rarely be significant (Draper et al. 2009).

The prognosis of teratomas at other extragonadal sites is comparably favorable and clearly exceeds 90% long-term survival (Göbel et al. 1998a; Marina et al. 1999b). Fortunately, the surgery-associated risks are tolerable, too. In head and neck teratomas, secondary hypothyroidism or parahypothyroidism has been reported (Bernbeck et al. 2009b).

A comparably favorable outcome has been reported for patients with malignant extragonadal yolk sac tumors. Certainly, vaginal yolk sac tumors appear to have the best overall prognosis with a cure rate exceeding 95%. This therapeutic success is the result of the exquisite chemotherapy sensitivity of these tumors so that even less-radical surgical procedures such as partial vaginectomy can be performed that may potentially lead to less long-term functional deficits (Lopes et al. 1999; Mauz-Körholz et al. 2000). In contrast, the prognosis of sacrococcygeal yolk sac tumors heavily depends on a radical surgical therapy with microscopically complete resection. If resection is incomplete, long-term outcome falls below 50%, whereas cure rates above 85% can be achieved after complete resection (Göbel et al. 2001). Accordingly, outcome is more favorable even in high-stage tumors if a neoadjuvant strategy with up-front chemotherapy and delayed resection is chosen, since at delayed resection a higher chance of complete resection can be obtained. Even if published experience is limited, there is no evidence that the cosmetic and functional outcome of malignant sacrococcygeal germ cell tumors is significantly different from that of sacrococcygeal teratomas. The most adverse indicator is invasion of the spinal canal and the sacral nerve plexus by the tumor, which may lead to pelvic palsy be it by the tumor or the surgeon (Draper et al. 2009).

Long-term toxicity related to chemotherapy is extensively discussed in Sect. 39.1.1. The same considerations can be taken into account for gonadal and extragonadal germ cell tumors.

39.3 Testicular Germ Cell Tumors

39.3.1 Introduction

Gonadal and extragonadal germ cell tumors (GCT) comprise approximately 2–3% of cancers diagnosed in children and adolescents younger than 15 years (Ries LAG et al. 1999b; Kaatsch 2004b). The survival of boys with testicular germ cell tumors has greatly improved with the application of lessons from adult GCT trials. However, significant differences exist between germ cell tumors from prepubertal boys and adolescents and young adults. Long-term toxicity may be a significant problem especially with treatment as a young child. We will explore the molecular basis of testicular germ cell tumor and risk-adaptive strategies that may be applicable to young boys and adolescents with malignant testicular germ cell tumors.

39.3.1.1 Testicular Germ Cell Tumors of Young Children – Genetics

In children younger than 4 years, germ cell tumors arising in gonadal and extragonadal sites are histologically, clinically, and genetically similar (for more details see Sect. 39.1.1). Most teratomas in this age group are diploid, have normal karyotypes, and, if completely resected, behave in a benign fashion regardless of degree of immaturity and site of origin (Kaplan et al. 1979b; Bussey et al. 1999b; Harms et al. 2006b). Malignant GCTs in prepubertal children are almost exclusively yolk sac tumors (Perlman et al. 1994b). Cytogenetic abnormalities involving chromosomes 1, 3, and 6 have been reported (Oosterhuis et al. 1988; Bussey et al. 1999b). In situ hybridization and loss of heterozygosity studies have demonstrated deletion of 1p36 in 80–100% of infantile malignant germ cell tumors arising from testicular and extragonadal sites (Stock et al. 1994; Sievers et al. 2005b).

39.3.1.2 Testicular Tumors in Adolescents and Adults – Genetics

Adolescent testicular germ cell tumors most commonly become clinically evident several years after puberty, suggesting that a critical genetic event occurs with, or is unmasked at, puberty. Germ cell tumors of the adolescent and adult testis demonstrate homogeneous genetic patterns including aneuploid DNA content and the isochromosome 12p or i (12p) (Oosterhuis et al. 1989; Atkin and Baker 1992; el-Naggar et al.

1992). Postpubertal testicular teratomas may have cytogenetic evidence of i (12p) and spread as a malignant GCT (Harms et al. 2006b).

The i (12p) can be found in 80% of postpubertal GCT and is comprised of two copies of the short arm of chromosome 12, fused at the centromere (Fig. 39.1.6 from gonadal chapter). Testicular tumors lacking i (12p) often show gain of 12p material within marker chromosomes (Rodriguez et al. 1993). The i (12p) has been documented by fluorescent in situ hybridization. This finding of i (12p) in intratubular germ cell neoplasia, a precursor lesion of testicular germ cell tumors, suggests that this genetic alteration occurs early in germ cell tumor pathogenesis (Looijenga et al. 1993). Testicular GCTs also have exhibited loss of chromosome 13 (38%), gain of chromosome 21 (45%), gain of chromosome 8 (45%), gain of chromosome 1q (36%), and high-level gain of 12p11.2–12.1 (Mostert et al. 1996). Other less frequent genetic changes have been noted. Adolescent testicular germ cell tumors, like normal embryonic germ cells, demonstrate biallelic expression of multiple imprinted genes including H19 and insulin-like growth factor-2 (van Gurp et al. 1994).

39.3.1.3 Pathology

Germ cell tumors comprise several histologic subtypes. The histologic features of each subtype are independent of presenting clinical characteristics. Both tumor biology and clinical behavior vary with site of origin, stage, and age of the patient (Altman et al. 1974b; Hawkins and Perlman 1996b). In contrast to mature teratomas which are almost always benign and diploid in infants or located in the ovary, the same histologic features are aneuploid and potentially malignant in the adult testis (Young and Scully 1990b). The histologic and pathologic classifications and descriptions have been previously described in Table 39.1.3 and Fig. 39.1.7 from gonadal chapter.

There are several points that are particular to testicular GCT. Teratomas and yolk sac tumors are the predominant histology prior to puberty. After puberty, other elements, seminoma, choriocarcinoma, and embryonal carcinoma are demonstrated. Pediatric immature teratomas primarily occur in extragonadal sites in children and in the ovaries of girls near puberty (Marina et al. 1999c). They are not usually present in the male testis. Yolk sac tumors (YST) are the most common pure malignant germ cell tumor in young children and are the most common GCT, benign or malignant, in the testes of infants and young boys (Young and Scully 1990b). Pure seminomas represent the most common malignant germ cell tumor in men older than 20 years. However, pure seminomas are unusual in men younger than 20 years. Embryonal carcinoma rarely occurs in a pure form in children and is more often a component of a mixed malignant germ cell tumor (Young and Scully 1990b; Hawkins and Perlman 1996b). This component is seen in adolescent testicular germ cell tumor (Fig. 39.1.7e, Sect. 39.1.1).

Table 39.3.1 Testicular germ cell tumor – presentation

– Teratoma	– Enlarging non-painful scrotal mass, surgery alone
– Volk sac tumor	– Most common pediatric GCT histology, enlarging non-painful scrotal mass
– Embryonal carcinoma	– More common in adolescents, may require more extensive surgery, similar presentation to above
– Mixed	– Less common in young males, combination of yolk sac tumor, embryonal carcinoma, and teratoma in postpubertal males
– Teratocarcinoma	– Adolescents
– Gonadoblastoma	– Bilateral 30%, poor sexual development
– Choriocarcinoma	– Rare, seen in mixed tumors, in adolescents, findings consistent with Klinefelter's

39.3.2 Clinical Diagnosis

The signs and symptoms of GCT are dependent on the site of origin of the tumor (Table 39.3.1). Pain especially is associated with testicular torsion (Giwercman et al. 1987). The absence of clinical findings often delays the diagnosis. Testicular GCTs present in two peaks during childhood and adolescence. The first peak is usually under age 4 years. Parents generally note these lesions, and patients may be brought to the attention of primary care physician in timely fashion (Fig. 39.3.1, left). Postpubertal males usually identify a mass but often delay reporting to their family or physician so that tumors are diagnosed at considerable size (Fig. 39.3.1, right). Perhaps this may also increase the risk for metastases. Diagnostic strategies specific

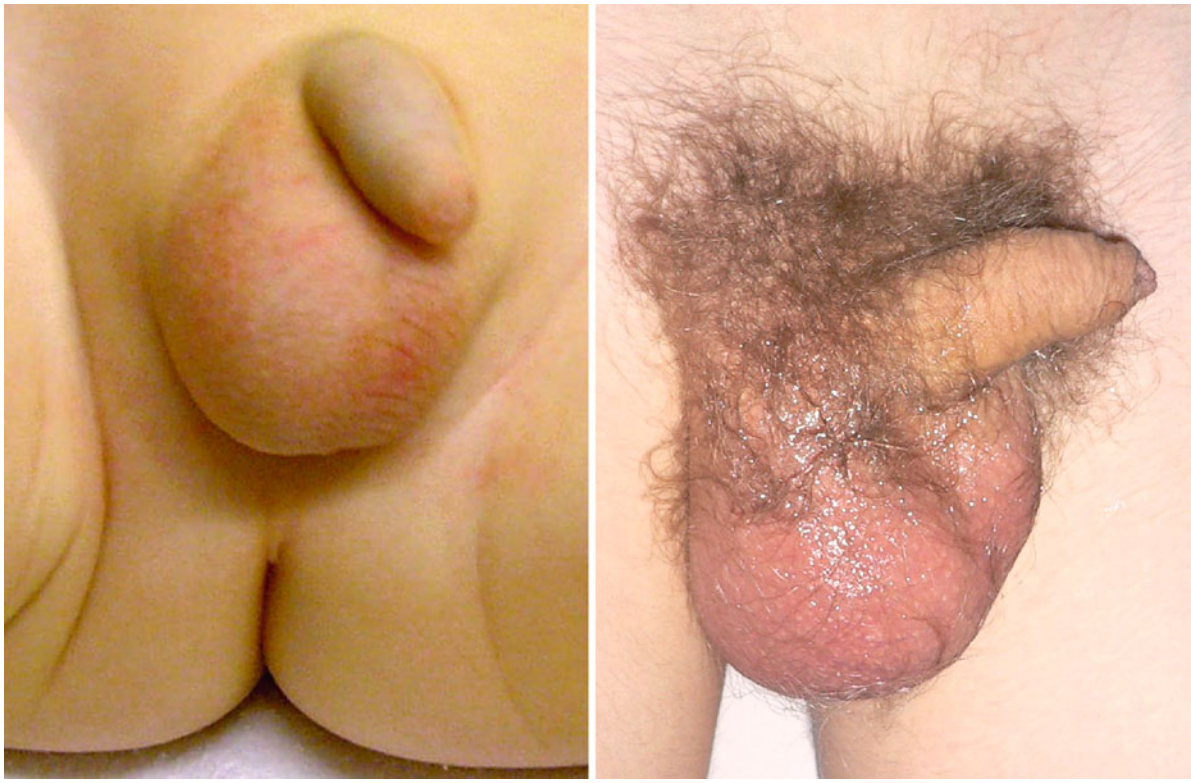


Fig. 39.3.1 Clinical presentation of testicular germ cell tumor in an infant (6 months old, immature teratoma + yolk sac tumor) and adolescent boy (15 years old, mixed malignant germ cell tumor with nodal metastases)

for testicular germ cell tumors are described in Table 39.3.2. A crucial point in the diagnosis and treatment of testicular GCT is referral to an appropriate surgeon. Testicular GCTs, in particular, in prepubertal children, can often be treated with surgery and observation. If the wrong surgical approach is taken, the patient may require chemotherapy. This will be discussed further in treatment section.

39.3.3 Staging

Staging of testicular germ cell tumors is closely linked to treatment. An improper diagnostic procedure, for example, a trans-scrotal biopsy with contamination, will upstage a patient. This patient will then require chemotherapy. Table 39.3.3 shows the clinical surgical staging system as defined by intergroup pediatric trials from the US. Ideally, patients with testicular masses should have appropriate imaging and marker studies prior to diagnostic biopsy or orchiectomy.

Several features must be considered in stage I testicular germ cell tumor. The surgical approach may determine stage and need for further treatment. An inguinal approach with high ligation of spermatic cord and vessels may ensure complete resection and classification of stage I disease. An additional feature is marker decay. Most prepubertal males have yolk sac tumor with elevated AFP as the predominant histology. An appropriate AFP decline (half-life, 5–7 days) would confirm stage I disease. An AFP that does not return to normal or rises would suggest stage II disease in the absence of positive imaging. This patient would need to be treated with chemotherapy. The prognosis is excellent for stage I with approximately 70% of patients requiring no chemotherapy. The remaining patients can usually be salvaged with standard cisplatin chemotherapy. The treatment of postpubertal males must be informed by adult GCT studies, which will incorporate histology (embryonal carcinoma associated with a worse prognosis) and vascular invasion. Testicular germ cell tumors have a

Table 39.3.2 Specific diagnostic strategy in testicular GCT

Procedure	Specific questions
Clinical assessment	
Phys. examination	Non-tender testicular mass, suspected torsion of testis, undescended testis, Klinefelter's syndrome
Laboratory assessment	
– AFP (β-HCG)	Malignant GCT with yolk sac tumor – consider age-related reference range (or choriocarcinoma)
– LDH	May be prognostic in older males
Radiographic assessment	
Chest, abdomen, pelvis – CT scan	Most common sites of metastatic spread from testis are retroperitoneal lymph nodes and lungs
Testicular ultrasound	Examine both testes (bilateral cases possible)
Bone scan	Not usually required in young boys but may need evaluation in older males
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)
(β-HCG)	Exclusion of choriocarcinoma
(CD-30)	Exclusion of embryonal carcinoma
(OCT3/4)	Exclusion of seminoma (embryonal carcinoma)

Table 39.3.3 Testicular germ cell tumor – staging

I	Complete resection. Disease limited to testis. Surgical approach – high inguinal ligation or trans-scrotal (with no spillage). No evidence of metastases. Appropriate marker decline
II	Microscopic disease in scrotum or spermatic cord (≤5 cm from proximal end). Trans-scrotal with spillage
III	Retroperitoneal involvement (>2 cm sized nodes) or biopsy positive
IV	Metastatic

propensity to metastasize to retroperitoneal lymph nodes. Postpubertal males, in particular, often have residual teratomatous material that has the potential to dedifferentiate later into malignant disease. For this reason, many physicians, treating adult patients with GCT, recommend removal of residual tissue. Figure 39.3.2 demonstrates the full extent of nodal metastases from an initial testicular primary. A mixed YST and embryonal carcinoma spread to retroperitoneal nodes, posterior mediastinal nodes, and eventually to left supraclavicular nodes. The last finding brought patient to medical attention, as the testicular primary was small.

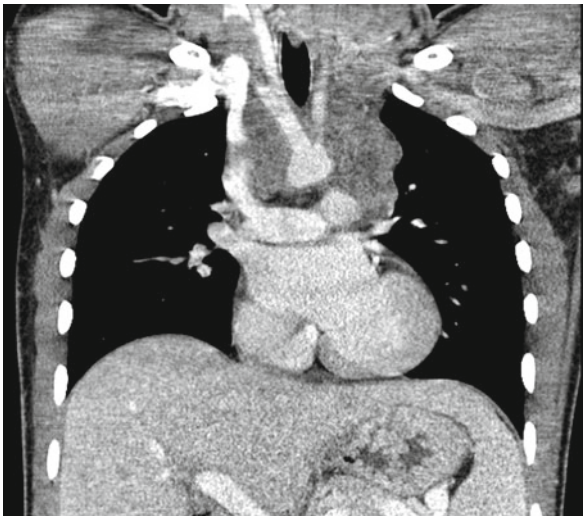


Fig. 39.3.2 Testicular germ cell tumor with YST and embryonal carcinoma histology metastatic throughout retroperitoneal and posterior mediastinal lymph nodes to supraclavicular nodes

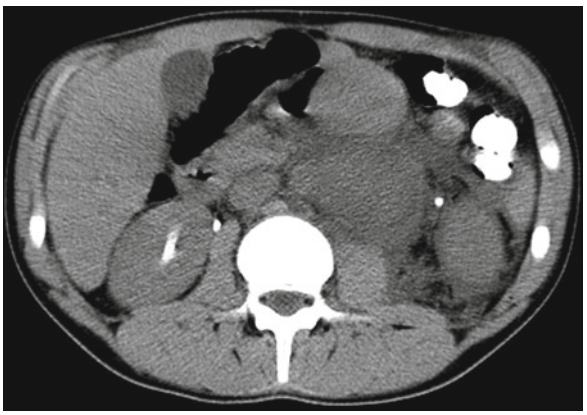


Fig. 39.3.3 Recurrent retroperitoneal seminoma, 4 years after surgery for stage I seminoma

The question of retroperitoneal lymph node dissection for accurate staging of testicular GCT has been long standing and complex. In boys less than 4 years of age, there are no data to suggest that this surgical approach is warranted. The outcome, even in stage IV, is excellent, and residual teratoma is not usually present. In adolescent males, this is still an important question. Figure 39.3.3 shows recurrence of seminoma in an adolescent who did not have RPLND or return for observational studies.

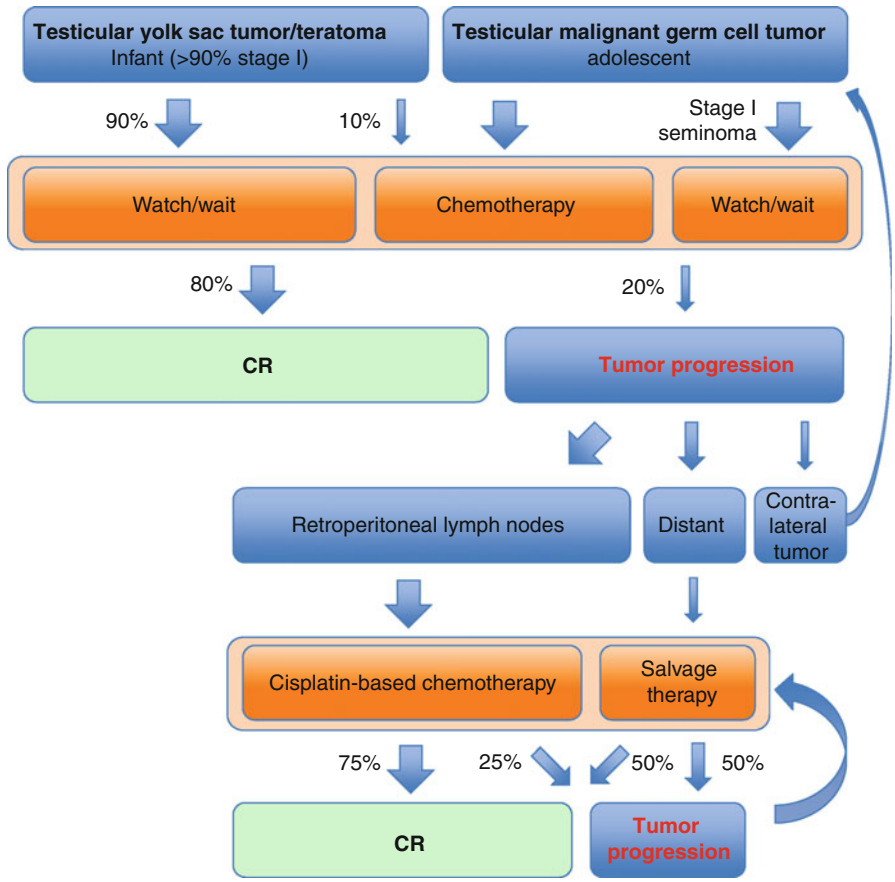


Fig. 39.3.4 Treatment algorithm for malignant testicular GCT

39.3.4 Therapy

An individualized, multimodality treatment plan is necessary due to the heterogeneity of pediatric germ cell tumors relative to site of origin, age, histology, and stage. Different subsets have been being described for childhood and adolescent germ cell tumors (Schneider et al. 2004c). Most patients are referred after orchiectomy, and treatment will be directed based on staging. In the US, the Children's Oncology Group staging for testicular GCT reflects other pediatric tumors. The advent of effective chemotherapy may mitigate the need for initial extensive surgery. Figure 39.3.4 details practical options in the treatment of testicular germ cell tumors.

Surgery represents the cornerstone of the management of testicular GCT. Generally, a primary complete excision is feasible. Protocols recommend an inguinal approach with vascular control before mobilization of the testis (Schmidt et al. 2002a; Lo Curto et al. 2003). If a malignant GCT is confirmed by frozen section examination of the mass, en bloc resection of testis and spermatic structures with ligation of the cord at the inguinal ring is required (Schlatter et al. 2003). Patients with scrotal skin involvement and those operated or biopsied through a scrotal approach should undergo a hemiscrotectomy to ensure local control. Some authors state that this procedure can be avoided if patient is upstaged from stage I to stage II and receives chemotherapy (Billmire 2006a). Primary retroperitoneal lymph node dissection (RPLND) is not indicated in prepubertal boys, since malignant GCTs are highly responsive to chemotherapy (Haas et al. 1999). Limited biopsy may be necessary to define staging when the involvement of retroperitoneal lymph nodes is uncertain after imaging. However, RPLND may be necessary when enlarged nodes remain after chemotherapy. Inguinal node exploration is indicated only in patients with scrotal involvement.

Patients with completely resected testicular GCT do not require chemotherapy. The "watch-and-wait" approach requires scheduled serial physical examination, tumor marker determination, and primary tumor imaging to ensure that a recurrent tumor is detected without delay. A discussion of tumor marker is warranted, especially in

testicular stage I germ cell tumor. Tumor markers, especially AFP in prepubertal male, must fall according to AFP half-life. While it is usually 5–7 days, some patients will have longer half-life. The failure to normalize or any significant rise in AFP suggests the presence of residual tumor, and patient should receive chemotherapy even without imaging or biopsy confirmation. In a few cases AFP can show minimal rise and fall secondary to other causes. Many investigators agree that in this population, five times the upper limit or normal is too high.

The prognosis of GCT has improved significantly with the development of cisplatin-based therapy in adult testicular GCT patients (DFS 68–92%) (Einhorn and Donohue 1977b; Ozols et al. 1988; Einhorn et al. 1989b). Prior to this effective chemotherapy, children with extracranial malignant germ cell tumors (GCT) had 3-year survival rates of 15–20% with surgery and radiation therapy (Kurman and Norris 1976b). However, boys with localized testicular tumors do well with surgical resection (Schlatter et al. 2003). Prognosis and appropriate treatment depend on factors such as histology (e.g., seminomatous vs. nonseminomatous), age (young children vs. adolescents), stage of disease, and primary site (Baranzelli et al. 1999c; Marina et al. 2006b). Children with extracranial malignant GCT should be cared for at pediatric cancer centers with experience treating these rare tumors, to maximize the likelihood of long-term survival while minimizing the likelihood of treatment-related long-term sequelae (e.g., secondary leukemias, infertility, hearing loss, renal dysfunction).

Cisplatin-based chemotherapy has dramatically improved the outcome for children with extracranial GCT, with 5-year survival rates of more than 90% (Mann et al. 2000c; Göbel et al. 2002a; Cushing et al. 2004c; Rogers et al. 2004c). Chemotherapy strategies developed by various international pediatric germ cell tumor committees were previously described in Table 39.1.6 (gonadal chapter). The standard chemotherapy regimen for both adults and children with malignant nonseminomatous GCT includes cisplatin, etoposide, and bleomycin (PEB), though children receive fewer doses of bleomycin than adults. The combination of carboplatin, etoposide, and bleomycin (JEB) has undergone clinical investigation in the United Kingdom in children younger than 16 years and is reported to have a similar event-free survival (EFS) by site and stage as PEB (Mann et al. 2000c). It must be noted that these were not randomized trials. The use of JEB appears to be associated with less ototoxicity and nephrotoxicity than PEB.

In an intergroup study conducted by the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG), the benefit of increasing the dose of cisplatin [high-dose (HD)-PEB: 200 mg/m^2 vs. PEB: 100 mg/m^2 of cisplatin] was studied in a randomized manner in patients with extragonadal and advanced gonadal GCT (Cushing et al. 2004c). Intensification of cisplatin in the HD-PEB regimen provided some improvement in EFS; however, the use of HD-PEB was associated with a significantly higher incidence and severity of ototoxicity and nephrotoxicity. In a subsequent study, amifostine was not effective in preventing hearing loss in patients who received HD-PEB (Marina et al. 2005).

Other groups (Germany, Brazil, France) have studied the omission of bleomycin from front-line therapies. Regimens without bleomycin were developed for favorable-risk germ cell tumors. Excellent outcomes were maintained.

The treatment of testicular GCT in adolescents and adults has been informed by a large meta-analysis study. Postpubertal males with testicular GCT should be treated according to these guidelines (Group 1997b).

There are several points that should be made concerning treatment approaches in patients with testicular germ cell tumors containing specific benign or malignant elements.

39.3.4.1 Teratoma

Immature teratomas are rarely found in the prepubertal testis. Teratomas, in prepubertal males, almost always take a favorable clinical course. Surgery is the treatment for these patients and all patients with such benign teratomas. Inguinal orchiectomy is usually required for mature and immature GCT (Mann et al. 2008b). However, testis-sparing procedure through the inguinal canal may be considered when markers and investigations suggest a benign process. The feasibility of a conservative resection (tumorectomy) depends on size and location. Re-excision may be necessary for residual tumor. Inguinal orchiectomy may be required for mature and immature germ cell tumors (Mann et al. 2008b). The postpubertal adolescent patient with a germ cell tumor presents additional challenges. Residual teratomatous material has been associated with significant malignant GCT recurrence within 10 years. Therefore, several institutions advocate resection of all residual material in postpubertal males. This may include RPLND (Carver et al. 2005, 2007d).

39.3.4.2 Seminoma

Seminomas of the testis are almost exclusive to the postpubertal male. Seminomas display an outstanding response to treatment, both chemotherapy and radiation therapy. In most patients, residual tumor after chemotherapy is resected. Nevertheless, the therapeutic impact of tumor resection in highly regressive tumors is controversial. In these instances, post-chemotherapy PET assessment may assist in decision making. Any PET positive tumors should be resected irrespective of size. In contrast, PET negative tumors smaller than 1–2 cm can be followed, whereas larger tumors should also be excised. In unresectable viable seminomas, irradiation constitutes a promising salvage therapy. However, it is not recommended for first-line therapy, since the long-term side effects associated with mediastinal irradiations may be significant. Patients with stage I seminomas must be observed carefully for at least 5 years, as late retroperitoneal recurrence is possible (Fig. 39.3.3).

39.3.4.3 Embryonal Carcinoma

Embryonal carcinoma is usually seen in postpubertal males with testicular germ cell tumors as part of a mixed tumor. In postpubertal males, an increased percentage of embryonal carcinoma histology in a mixed tumor correlates with worse prognosis and possibly suggests a need for chemotherapy. The infrequent incidence of this histology in prepubertal males makes conclusions difficult.

39.3.5 Prognosis

Patients with mature and immature teratomas will have an EFS of near 100% with surgery alone (Mann et al. 2008b).With a multidisciplinary approach, boys with malignant testicular GCT have an outstanding prognosis. In the US intergroup studies, boys (pre- and postpubertal) with stage I, II, and III testicular GCT had an overall survival rate of 100% (Schlatter et al. 2003; Cushing et al. 2004c; Rogers et al. 2004c). Other pediatric groups have reported similar results (Göbel et al. 1990; Baranzelli and Patte 1998; Mann et al. 2000c; Göbel et al. 2002a; Lopes et al. 2009b). The US trial included boys up to age 18 years. Overall survival rates for boys <15 and >15 years were 100% and 84%, respectively (Cushing et al. 2004c). It must be noted that most of the boys >15 had pure yolk sac histology.

39.4 Germ Cell Tumors of the Ovary

39.4.1 Introduction

The general aspects of germ cell tumors (GCTs) common to all GCTs occurring at different sites have been previously discussed in general gonadal chapter. Ovarian tumors are rare, accounting for only about 1% of childhood malignancies (Bernstein et al. 1999). The incidence increases after 8 years and peaks at 19 years. Ovarian GCT development parallels gonadotropin release (Cronen and Nagaraj 1988; Walker et al. 1988; dos Santos Silva and Swerdlow 1991). In contrast to adult ovarian tumors, most pediatric ovarian tumors are of germ cell origin. Few children present with tumors of epithelial and stromal origin, as seen in adult patients (Lovvorn et al. 1998). Approximately 5% of ovarian germ cell tumors develop bilaterally. Thus, bilateral tumors may be present at diagnosis (synchronous manifestation) or develop during follow-up (metachronous manifestation).

39.4.2 Ovarian Tumors GCT in Adolescents and Adults – Genetics

The genetic biology of ovarian germ cell tumors is more complex than that of testicular germ cell tumors and is considered separately for mature teratomas, immature teratomas, and malignant ovarian germ cell tumors. There is a considerable association with sex-chromosomal abnormalities such as Ullrich-Turner syndrome and testicular feminization (Sect. 39.1.1).

39.4.2.1 Teratomas

Mature teratomas demonstrate karyotypically balanced cytogenetics (95%), with only 5% showing gains of single whole chromosomes (Parrington et al. 1984; Surti et al. 1990). Characteristically, they may show an isodisomic karyotype (23,X ×2). A methylation profile of imprinted genes (e.g., hypermethylation of SNRPN), also consistent with a postmeiotic origin, is often seen in ovarian teratomas (Schneider et al. 2001g).

39.4.2.2 Immature Teratomas

Ovarian immature teratomas are heterogeneous with evidence of a meiotic stem cell origin or mitotic origins. This suggests failure of early meiotic arrest (Ohama et al. 1985). Immature and mature teratomas may represent different biologic entities, rather than simply a

spectrum of maturation. Chromosomal abnormalities are more common in immature teratoma. Patients with cytogenetically abnormal immature teratomas often develop recurrence. In contrast, patients with karyotypically normal immature teratomas do not (Ohama et al. 1985; King et al. 1990; Gibas et al. 1993).

39.4.2.3 Malignant Ovarian Germ Cell Tumors

Malignant ovarian GCTs in postpubertal girls have similar genetic findings when compared to testicular malignant GCTs, including presence of i (12p) (75%), gains of chromosomes 21 and 1q (42% and 32% respectively), and loss of chromosomes 13 and 8 (25% and 42% respectively) (Speleman et al. 1990; Hoffner et al. 1994; Thompson et al. 1994; Riopel et al. 1998). Although malignant ovarian germ cell tumors appear to be equivalent to their adolescent testicular counterparts, immature and mature ovarian teratomas remain as unique subcategories of germ cell tumors likely to have a different mechanism of origin.

39.4.3 Histopathology

Pathologic characteristics are described in Sect. 39.1.1. The majority of ovarian germ cell tumors are either mature teratomas or immature teratomas. Significant distribution differences do not exist in pre- and postpubertal females. Yolk sac tumor is the most common malignant element seen in mixed germ cell tumors. It is usually associated with immature teratoma.

39.4.4 Clinical Diagnosis

Clinical features of ovarian germ cell tumors are detailed in Table 39.4.1. Abdominal pain is the most common presenting symptom (80%) (Cronen and Nagaraj 1988; Gribbon et al. 1992; Lovvorn et al. 1998). The pain is usually chronic but some patients present with an acute abdomen, often secondary to torsion. Other signs and symptoms include a palpable or even visible abdominal mass (Fig. 39.4.1), abdominal distension, fever, constipation, amenorrhea, vaginal bleeding, and rarely frequency and dysuria (Harris and Boles 1974; Lovvorn et al. 1998). Precocious puberty can be seen in most malignant GCT, though it is more frequent in ovarian sex cord stromal tumors. AFP levels are increased in patients with yolk sac tumors.

Table 39.4.1 Ovarian cell tumor – presentation

– Teratoma Mature Immature	Palpable mass, abdominal pain 15%, bilateral Implants
– Dysgerminoma	Pain, rapid growth, ovarian torsion
– Yolk sac tumor	Pain, mass, torsion
– Embryonal carcinoma	Rare, precocious puberty
– Choriocarcinoma	Part of mixed tumor
– Mixed germ cell tumor	30% precocious puberty
– Gonadoblastoma	Dysgenetic ovaries, bilateral

Mixed ovarian germ cell tumors with elevated AFP are usually composed of immature teratoma and varying amounts of yolk sac elements. Specific diagnostic strategies for ovarian tumors are described in Table 39.4.2.

39.4.5 Staging

Ultrasound is most often used for the initial evaluation of patients with abdominal or pelvic masses and will differentiate cystic from solid masses (Surratt and Siegel 1991). Although the presence of a solid ovarian mass raises the suspicion of malignancy, the majority are benign teratomas (Cronen and Nagaraj 1988). Computed tomography (CT) is helpful in identifying the site of origin, the extent of tumor, the presence of calcifications or fat, and metastatic disease. Many children with teratomas do not have evidence of fat on CT scan (Jabra et al. 1993). Neuroglial implants, containing mature or immature teratomatous elements, may be identified. They do not usually affect prognosis. Figures 39.4.2–39.4.4 show CT findings of ovarian teratoma, yolk sac tumor, and dysgerminoma, respectively, illustrating that tumors are hardly distinguishable by imaging. Staging evaluation should include a chest CT and bone scan, though metastases to bones are rare. Central nervous system metastasis is unusual, and routine imaging of central nervous system is not indicated.

Serum tumor markers AFP and β-HCG are essential because the majority of pediatric patients with ovarian germ cell tumors have a yolk sac tumor component, and mixed malignant germ cell tumors may also include significant choriocarcinoma components (Mann et al. 1989b; Marina et al. 1992).

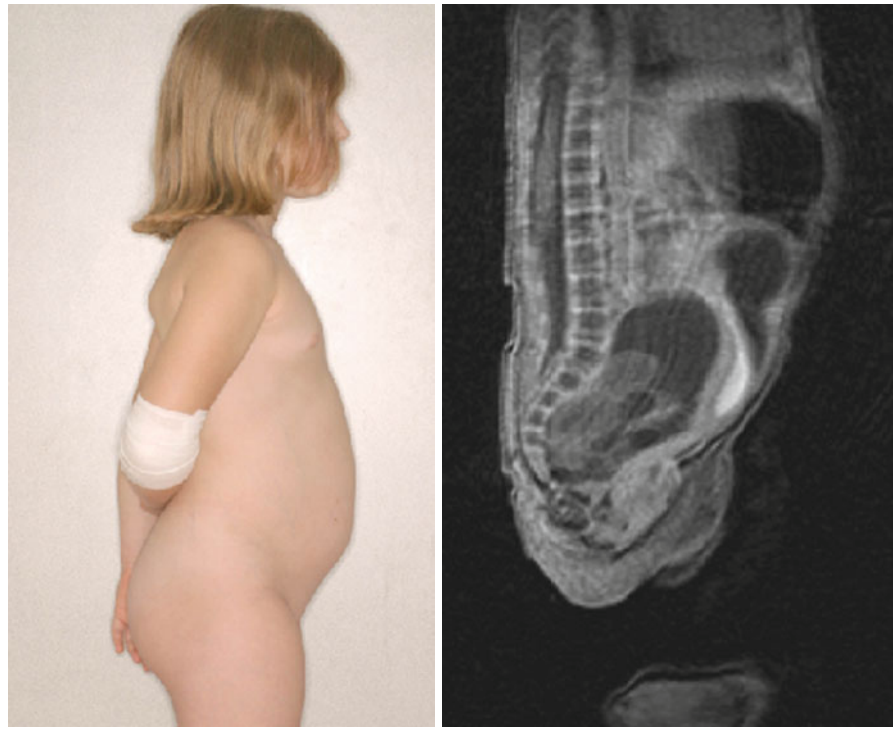


Fig. 39.4.1 11 year old girl presenting with a large abdominal teratoma

Table 39.4.2 Specific diagnostic strategy in ovarian tumors

Procedure	Specific questions
Clinical assessment	
Phys. examination	Abdominal pain (acute or chronic), rapidly developing abdominal mass, sexual precocious
Laboratory assessment	
– AFP (β-HCG)	Malignant GCT with yolk sac tumor – consider age-related reference range (or choriocarcinoma)
– Catecholamines	Exclusion of neuroblastoma
– LDH	May have prognostic significance
Radiographic assessment	
Abdominal ultrasound	Examination of both ovaries, presence of cysts or solid components
CT chest, abdomen, pelvis	Site, size, organ of origin, cystic structures, calcification, metastases
Bone scan	Rare
Histologic assessment	
H&E	Classification according to WHO
AFP	Yolk sac tumor (microfoci in teratoma)
(β-HCG)	Exclusion of choriocarcinoma
(CD-30)	Exclusion of embryonal carcinoma
(OCT3/4)	Exclusion of dysgerminoma (embryonal carcinoma)

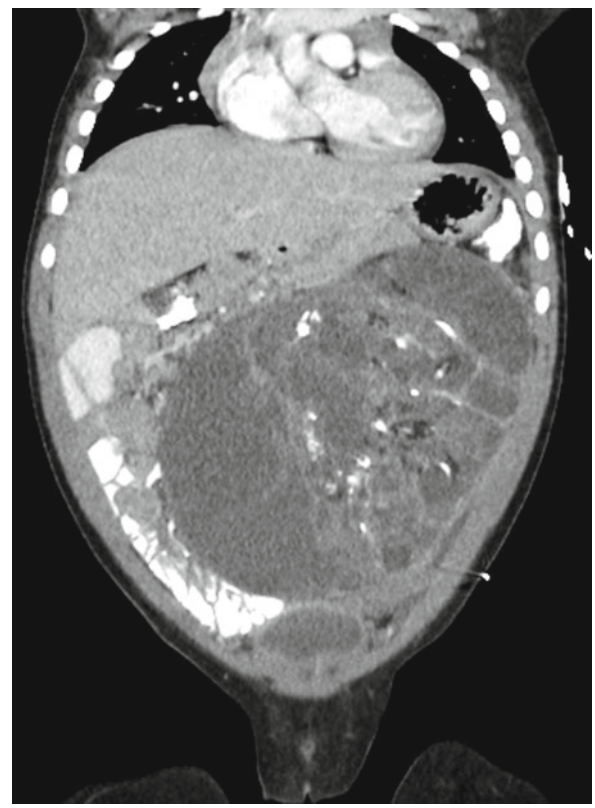


Fig. 39.4.2 Ovarian teratoma in a 2 year old

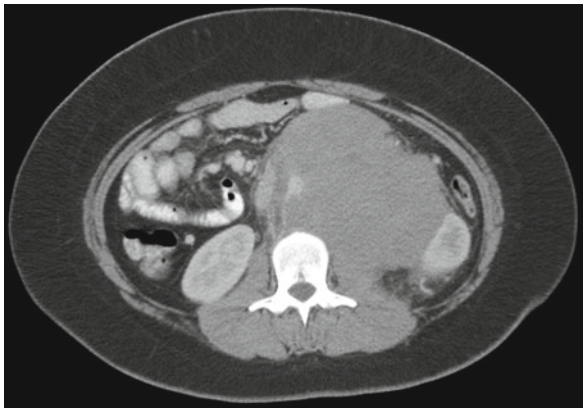


Fig. 39.4.3 Large ovarian yolk sac tumor involving retroperitoneal nodes. After chemotherapy, second surgery revealed only scar and no residual tumor

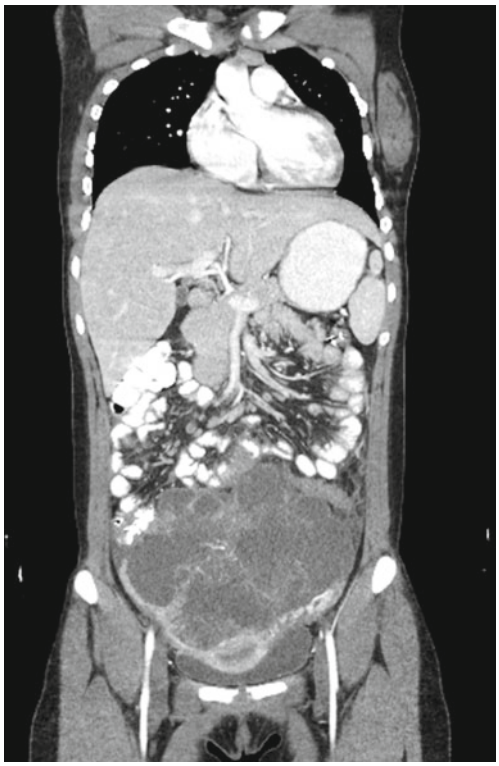


Fig. 39.4.4 Large ovarian dysgerminoma in adolescent

Staging systems modeled after the by FIGO system (Table 39.4.3) may be the most useful because different strategies must be followed for different histologies (Cannistra 1993). This system includes cytological examination of any thoracic or peritoneal fluid. The FIGO staging system has been used in several international pediatric germ cell studies. The US intergroup study used a surgicopathologic system to refine the FIGO system. In the US staging system, strict guidelines are required for an ovarian tumor to be categorized as stage I. Unless all surgical guidelines are followed or in the event of peritoneal contamination, such as seen in rupture, the patient will be upstaged to stage III and receive chemotherapy. If chemotherapy is to be administered for any ovarian germ cell tumor, the FIGO staging system is not necessary.

Table 39.4.3 Ovarian germ cell tumor – staging according to FIGO

Stage	Extent of disease	
I		Limited to the ovaries
	Ia	To one ovary, no ascites. No tumor on external surface, capsule intact
	Ib	Both ovaries, no ascites. No tumor on external surface, capsule intact
	Ic	One or both ovaries but with tumor on surface of one or both ovaries, or capsule ruptured, or positive ascites or positive peritoneal washings
II		Tumor involving one or both ovaries with pelvic extension
	IIa	Extension and/or metastases to uterus and/or tubes only
	IIb	Extension to other pelvic tissues
	IIc	As in IIa or IIb but with positive ascites or positive peritoneal washings, or with capsule ruptured
III		Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal lymph nodes, extension to small bowel or omentum, superficial liver metastases
	IIIa	Limited to true pelvis grossly with negative nodes but histologically confirmed microscopic seeding of abdominal peritoneal surfaces
	IIIb	Limited to one or both ovaries with negative nodes but histologically confirmed implants of abdominal peritoneal surfaces, not < 2 cm diameter
	IIIc	Abdominal implants >2 cm diameter and/or positive retroperitoneal or inguinal nodes
IV		Tumor of one or both ovaries with distant metastases outside of peritoneal cavity, parenchymal liver metastases; pleural effusion, if present, must have positive cytology

39.4.6 Therapy

The background for treatment of ovarian GCT can be informed from previous discussions in general gonadal chapter. There are features that are unique to ovarian tumors. Most recommendations relate to surgical options based on distinct histology. Surgery has a prominent role in the treatment of patients with ovarian tumors. However, since malignant germ cell tumors are very chemosensitive, primary excision should be attempted only when the surgeon thinks a complete resection can be obtained without a mutilating procedure (Billmire et al. 2004b; Billmire 2006b). If imaging shows invasion of other structures (i.e., bladder, uterus, vagina) or bilateral ovarian involvement, a tumor biopsy is the best option. The biopsy may be "open" or with a tru-cut needle. Under ultrasound guidance, multiple biopsies should be obtained from different sites for histologic diagnosis and collection of material for biology studies. If AFP and β-HCG are elevated, biopsy may not be necessary. After neoadjuvant chemotherapy, the patient will undergo delayed surgery.

Primary excision of ovarian tumors can be approached from a Pfannenstiel incision, an infraumbilical transverse incision or a midline approach. Since malignant tumors and benign tumors cannot be distinguished based on gross features alone, all tumors should be staged according to current staging principles (Göbel et al. 1998d; Billmire 2006b).

- Aspiration of ascitis, if present, or peritoneal washing for histology.
- Examination of omentum and removal of suspected nodules.
- Inspection of peritoneum and abdominal organs, with biopsy of abnormal areas. Peritoneal implants (gliomatosis peritonei) may be associated with mature and immature teratomas.
- Examination and palpation of contralateral ovary with biopsy of suspicious areas.
- Complete removal of involved ovary, avoiding spillage. Ipsilateral fallopian tube may be spared if not adherent to mass.
- Inspection of iliac and aorto-caval nodes with biopsy of suspicious nodes.

Laparoscopy is usually discouraged for removal of malignant tumors, as the violation of capsule or rupture can result in upstaging the tumor. Secondary excision should be done if the initial approach was a biopsy followed by chemotherapy (Schmidt et al. 2002b). Most authors recommend a conservative approach for bilateral tumors (if possible on least affected side) to preserve ovarian function. Bilateral oophorectomies and other extensive surgeries should be reserved when tumors do not respond to chemotherapy.

Special mention should be made concerning ovarian torsion. Approximately 10% of ovarian tumors present as acute abdomen secondary to torsion or rupture of tumor. Most ovarian masses associated with torsion are benign (Pienkowski et al. 2004). Ovarian torsion is an emergency and laparoscopy is preferred. If a tumor is suspected, immediate oophorectomy should be done. If a mass is found incidentally, a thorough abdominal inspection must be done (Hayes-Jordan 2005).

39.4.6.1 Teratoma and Immature Teratoma

The majority of ovarian germ cell tumors are either mature teratomas or immature teratomas. In the first months of life, most ovarian tumors are benign (Bagolan et al. 1992). Most teratomas (but also some mixed malignant germ cell tumors) are cystic and may present with considerable size (Fig. 39.4.5). Surgery is the treatment of choice, whether or not they contain malignant elements (Templeman and Fallat 2005). The procedure often requires oophorectomy due to size and pathologic uncertainty. However, in selected case, tumor enucleation may be possible. Every effort should be made to preserve hormonal and reproductive function in patients with bilateral benign germ cell tumors. Several authors recommend ovary-sparing procedures in patients with unilateral appearing lesions (Cass et al. 2001; Pienkowski et al. 2004). However, since many ovarian germ cell tumors have mixed histology, the approach should be cautious. If suspicion for malignancy is low and a pediatric surgeon is expert in minimal invasive surgery, a laparoscopic approach may be considered for benign lesions (Templeman and Fallat 2005; Ehrlich et al. 2007). In general, immature teratomas in children do not respond to chemotherapy (Mann et al. 2008c), so an attempt at complete resection should be undertaken. Figure 39.4.2 shows a large ovarian teratoma in a 2-year-old. A complete resection was accomplished. There have been reports that high-grade immature teratomas in postpubertal women may respond to chemotherapy (Norris et al. 1976). In a pediatric study of teratomas, gliomatosis peritonei was not associated with poor outcome (Göbel et al. 1998d).

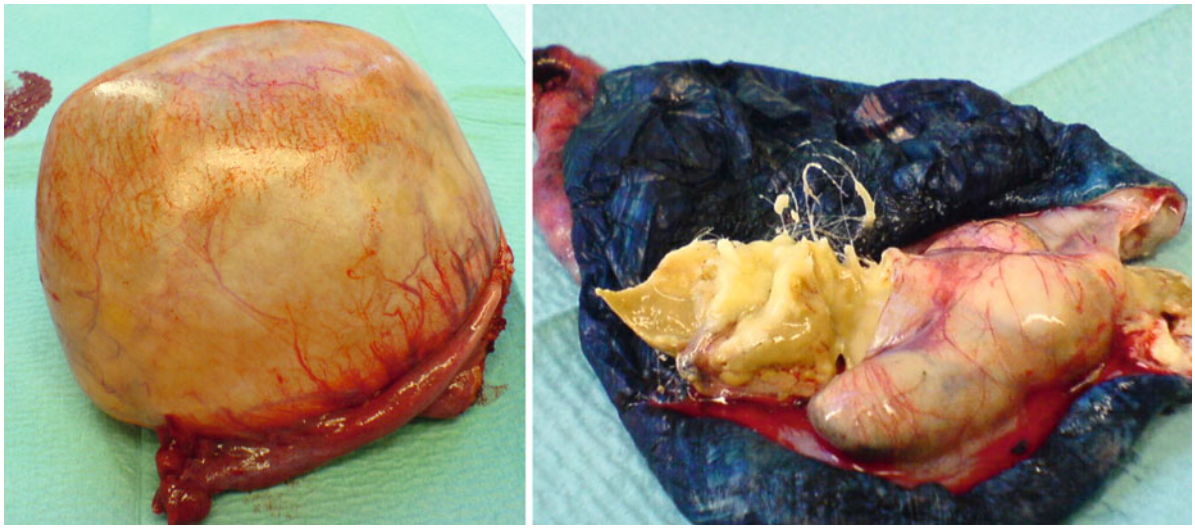


Fig. 39.4.5 Macroscopic presentation of a 2 kg cystic ovarian teratoma prior to and after ink impragnation and opening of the cyst

39.4.6.2 Yolk Sac Tumor and Embryonal Carcinoma of the Ovary

One difficulty in treating ovarian germ cell tumors is that delay in diagnosis often leads to higher-stage disease at presentation. The most common sites of metastases are lymph nodes and lungs. Patients identified as stage I may be managed with surgery and observation. This should be done under the auspices of a clinical trial. In this case overall survival should be the clinical endpoint, rather than event-free survival (tumor events to be specific). What would be an acceptable recurrence rate? In the treatment of many adults with a wide range of cancers, where observation is an option, most patients would choose 50% chance of recurrence, as a determining factor in deciding to receive chemotherapy. Are parents willing to use the same determination for their daughters? If the salvage rate is greater than 95%, observation would make sense. In this way 50% patients would not require toxic chemotherapy Fig. 39.4.6.

The definition of stage I is important. Surgical guidelines are very specific and require careful attention to the other ovary, integrity of the capsule, spillage, and peritoneal washings. However, these strict guidelines for assessing surgical pathologic stage are often violated. This has been documented in a recent pediatric study (Billmire et al. 2004b). Chemotherapy was administered to all stage I and II patients and 100% survived. If chemotherapy is to be omitted, it is an issue. Surgical guidelines as described above should be followed. The strategy of observation with stage I ovarian tumors should be evaluated in clinical trial. Current experience of the MAKEI studies indicates that with a watch-and-wait strategy, progression rate is approximately 20–30%, but overall survival after cisplatin combination chemotherapy is higher than 95%.

If imaging studies show disease beyond the ovary, neoadjuvant chemotherapy must be administered. Subsequent surgery may be required to resect residual disease. This may be important in girls where malignant tumors are often part of a mixed tumor, containing mature or immature teratoma. Surgery is the only treatment for residual mature or immature teratoma. Surgery is often not required for residual gliomatosis peritonei.

Chemotherapy, as previously described in Fig. 39.1.6 from gonadal chapter, should be administered to all patients with stage II–IV ovarian germ cell tumor. A large ovarian yolk sac tumor with retroperitoneal nodal metastases is shown in Fig. 39.4.3. This patient responded to PEB, and a second-look surgery showed no viable tumor.

39.4.6.3 Dysgerminomas

Stage I ovarian dysgerminomas may be treated with surgery alone. Dysgerminomas of the ovary are very sensitive to chemotherapy and radiation therapy.

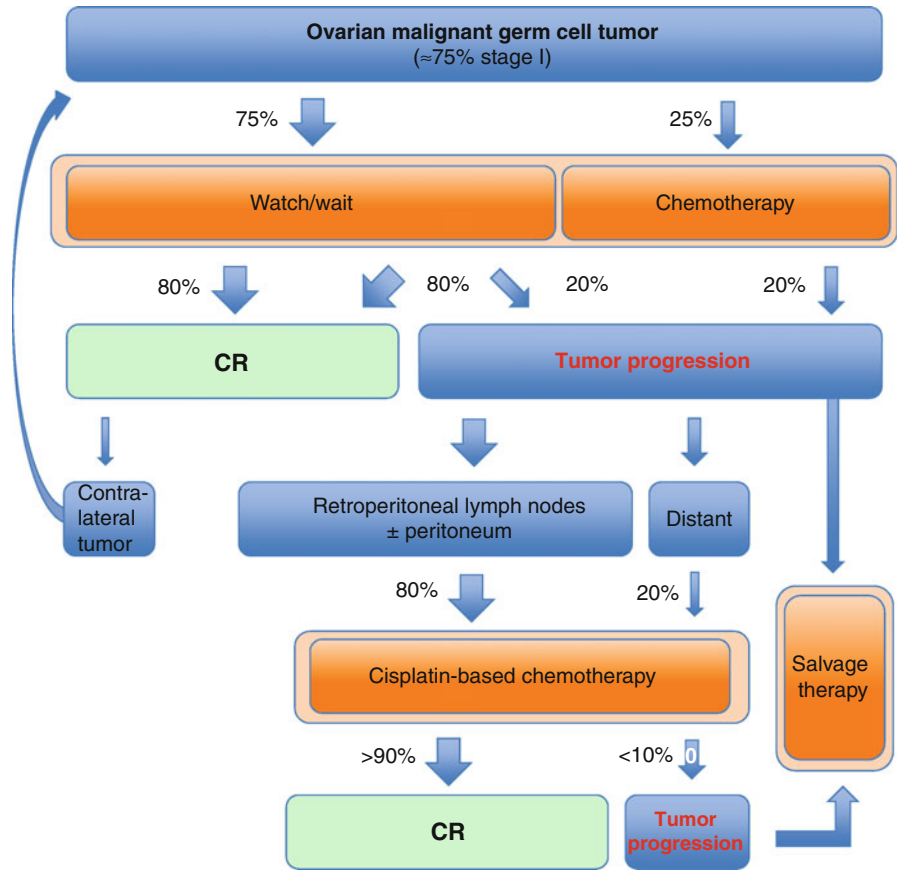


Fig. 39.4.6 Treatment of ovarian malignant germ cell tumors

However, radiation therapy should be avoided due to significant toxicities. It can be used in salvage strategies for recurrence. Chemotherapy regimens have been previously described in Sect. 39.1.1.

39.4.7 Prognosis

Mann et al. reported a 97% 5-year event-free survival rate in girls <15 years of age with mature teratoma and immature teratoma (Mann et al. 2008c). Patients were treated with surgery alone, and no mature or immature teratoma showed any response to chemotherapy. It is recommended that mature teratomas and immature teratomas, in girls less than 15 years of age, be managed without chemotherapy. The management of gliomatosis peritonei is not clear. The German MAKEI study showed no clear association with prognosis (Göbel, Calaminus et al. 2006). The prognosis of ovarian germ cell tumors has improved significantly with the advent of platinum-based chemotherapy. Results, from many international pediatric groups, have been very encouraging (Baranzelli et al. 2000b; Mann et al. 2000d; Göbel et al. 2002b; Cushing et al. 2004d; Rogers et al. 2004d; Schultz et al. 2005). In a US intergroup study, which did not include lymph node sampling or extensive mutilating surgery, greater than 90% EFS was obtained in all stages (stages I–IV). However, if one is to attempt a "watch-and-wait" approach to stage I ovarian germ cell tumors, caution must be observed. In that US trial, adherence to surgical guidelines was poor. Patients survived because they all received chemotherapy (Billmire et al. 2004b).

39.5 Sex Cord Stromal Tumors of the Testis and Ovary

Dominik T. Schneider,
Giovanni Cecchetto, and Thomas A. Olson

39.5.1 Introduction

Sex cord stromal tumors are a heterogeneous group of rare gonadal tumors. Overall, sex cord stromal tumors represent approximately 10% of all gonadal tumors during childhood. However, the true incidence of sex cord stromal tumors may be underestimated, most likely as a result of incomplete tumor registration. In the Pediatric Tumor Registry of the German Society of Pediatric Oncology and Hematology, sex cord stromal tumors contribute almost 20% to all testicular and ovarian tumors (Schneider et al. 2003b). Accordingly, a continuous rise in the registration rate of ovarian and testicular sex cord stromal tumors has been observed after the development of uniform diagnostic and therapeutic guidelines. Thus, sex cord stromal tumors constitute an illustrative example that with the development of study structures, more patients with rare tumors can be integrated into the clinical and scientific network of pediatric oncology.

Sex cord stromal tumors, in particular, juvenile granulosa cell tumors, constitute characteristic tumors of childhood. Ovarian sex cord stromal tumors may contribute up to one third of all ovarian tumors in early childhood, probably due to the low incidence of germ cell tumors. In the German MAKEI studies (children ≤5 years registered to the MAKEI studies between 1983 and 2000), there were 18 ovarian sex cord stromal tumors compared to 35 ovarian germ cell tumors (Schneider et al. 2003b). Therefore, the clinical management and scientific evaluation of these tumors belong into the hands of pediatric oncologists and not to other subspecialists.

Sex cord stromal tumors develop from the non-germ-cell component of the ovary and may present with a histologic differentiation that in some tumors, may be paradox for the host. Cellular elements, characteristic of the testis, may be seen in ovarian sex cord stromal tumors and vice versa. The rarity of tumors, the heterogeneity, and the difficulty in the correct histopathologic classification of these tumors leave a significant uncertainty with regard to the correct clinical approach to patients with testicular and ovarian sex cord stromal tumors.

39.5.2 Biology

During early embryonic development (fourth week of development), the sex cords arise from the primitive genital ridge or coelomic epithelium. During female gonadal development, the germ cells retain at the periphery of the gonad, enter meiosis, and are surrounded by granulosa cells. The sex cords ultimately develop into ovarian follicles. The development of granulosa cells is dependent on the expression of the winged-helix transcription factor *FOXL2* (Schmidt et al. 2004). In male embryos, sex cords give rise to the rete testis cords that later develop into the seminiferous tubules, thus accompanying the germ cells that further migrate into the gonadal stroma and are surrounded by Sertoli cells. Sertoli cell differentiation and survival depends on the expression of the microRNA processing enzyme *DICER1* (Kim et al. 2010).

Thus, sex cord stromal tumors may develop from sex cord cells or from ovarian stromal cells of the developing gonad. Accordingly, they are histologically heterogeneous and include granulosa cell tumors, Sertoli-Leydig cell tumors, pure Sertoli cell and Leydig cell tumors, as well as theca and granulosa-theca tumors, sclerosing stromal tumors, sex cord stromal tumors with annular tubules, and gynandroblastomas with simultaneous Sertoli and granulosa cell differentiation.

Sex cord stromal tumors may develop in the context of several defined hereditary disorders. Juvenile granulosa cell tumors may be associated with multiple enchondromatosis, syn. Ollier's disease (Clement et al. 1991; Plantaz et al. 1992; Young et al. 1984a). The pathogenetic mechanism has not yet been elucidated to date. In the German series of now more than 150 sex cord stromal tumors, only two patients with Ollier's disease and juvenile granulosa cell tumor have been reported. Adult granulosa cell tumors consistently show mutations of the *FOXL2* gene, a key regulator of granulosa cell development. However, *FOXL2* mutations are only rarely found in juvenile granulosa cell tumors (Shah et al. 2009; Al-Agha et al. 2011). Notably, aberrant *FOXL2* expression may also be observed in some testicular granulosa cell tumors, although no

adult but only juvenile granulosa cell tumors are observed in the testis (Kalfa et al. 2008). Otherwise, no pathognomic genetic aberration has been defined for juvenile granulosa cell tumors, but approximately one third of tumors may show point mutations of stimulatory G proteins (Kalfa et al. 2006). Moreover, the development of juvenile granulosa cell tumors appears to be associated with aberrations in wnt signaling (Boyer et al. 2009).

Genetic analysis of sporadic juvenile ovarian granulosa cell tumors with comparative genomic hybridization has not revealed frequent or characteristic chromosomal imbalances. The majority of tumors show balanced karyotypes. In approx. 25% of patients, chromosomal imbalances, such as gain of the whole chromosome 12, can be found. This analysis has not revealed any correlation between karyotype and clinical outcome (Schneider et al. 2005b). This finding is in line with a previous DNA ploidy analysis of juvenile granulosa cell tumors. In this study, almost half of the tumors showed aneuploid DNA indices. However, no correlation with clinical stage was observed (Jacoby et al. 1992).

Recently, the second most frequent group of ovarian sex cord stromal tumors, the Sertoli-Leydig cell tumors, have been shown to be associated with mutations of the *DICER*1 gene, in particular, in the context of familial multinodular goiter (Rio Frio et al. 2011; Slade et al. 2011). *DICER*1 mutations are associated with pleuropulmonary blastoma (Hill et al. 2009). Of note, a significant proportion of Sertoli-Leydig cell tumor patients suffer from familial multinodular goiter (Whitcomb et al. 1986) or rarely even thyroid cancer (Poiana et al. 2010). In the German series of sex cord stromal tumors, approximately one third of patients with Sertoli-Leydig cell tumors show thyroid disease, and two have developed differentiated thyroid cancer during follow-up of Sertoli-Leydig cell tumor.

There is a pronounced association of Peutz-Jeghers syndrome with sex cord stromal tumors with annular tubules (SCTAT) of both the testis and ovary (Young et al. 1982; Young 2005b; Chang et al. 1998). Approximately one third of SCTAT appear to develop in the context of Peutz-Jeghers syndrome. These tumors usually develop at a younger age than in otherwise healthy patients, and they may develop bilaterally. In contrast, predominantly large cell calcifying Sertoli cell tumors can be found in boys with Peutz-Jeghers syndrome.

39.5.3 Pathology

Testicular and ovarian sex cord stromal tumors present as solid, sometimes lobulated, and partly cystic masses. Tumors are commonly encapsulated, and in the majority of patients, tumors do not grow beyond the gonadal capsule. Thus, testicular sex cord stromal tumors virtually always present as stage I tumors, without local or distant spread. The size of testicular sex cord stromal tumors is low and rarely exceeds 5 cm in diameter. In contrast, ovarian sex cord stromal tumors may present with considerable size. Diameters of more than 20 cm are not uncommon. Some of these large tumors may rupture spontaneously, with tumor spread within the peritoneal cavity. Approximately 5% of ovarian sex cord stromal tumors may develop bilaterally, either as simultaneous or metachronous contralateral tumors. Some tumors may locally infiltrate the Fallopian tube. If tumor spread occurs, it is most commonly observed within the pelvis and the peritoneal cavity and to the locoregional lymph nodes. Hematogenic metastases may develop to the liver, most commonly in relapse situations. In the German MAKEI series of now more than 150 patients, no metastases to lungs, central nervous system, or the skeletal system have been observed.

Since no specific staging system has been developed for sex cord stromal tumors, they are usually staged according to the corresponding germ cell tumors and epithelial cancers (see Sect. 39.1). Testicular tumors are staged either according to the Lugano or COG staging system. Ovarian tumors are staged according to the FIGO or COG staging system.

Histologically, sex cord stromal tumors are categorized according to the predominant cell type of the tumor (Table 39.5.1) (Young 2005a, b). Of note, the histologic differentiation does not follow sex differentiation. Thus, some paradoxical differentiation patterns can be found. Characteristically, sex cord stromal tumors stain positive for inhibin, indicating that these are hormone-producing tumors (Schneider et al. 2003b). Therefore, the immunohistochemical detection of inhibin constitutes a reliable diagnostic marker that distinguishes sex cord stromal tumor from the more frequent germ cell tumors, ovarian carcinoma, or other tumors of different cellular origin (Distelmaier et al. 2006a). Tumors may also stain positive for cytokeratins and vimentin.

Table 39.5.1 Histologic differentiation of testicular and ovarian sex cord stromal tumors and their relative frequencies and characteristic age at presentation

Histology	Testis	Ovary	Age @ presentation
Juvenile granulosa cell tumor (JGCT)	+++	+++	Childhood
Adult granulosa cell tumor (AGCT)	–	++	Adulthood
Sertoli-Leydig cell tumor (SLCT)	–	+++	Adolescence
Sertoli cell tumor	+++	(+)	Childhood/ Adulthood
Large cell calcifying Sertoli cell tumor	+++	–	Childhood
Sclerosing stroma tumor (SCLER)	–	+	Adolescence
Sex cord tumor with annular tubules (SCTAT)	–	+	Adol/ Adulthood
Steroid tumor (STER)	–	+	Adolescence
Thecoma (THEC)	–	++	Adolescence

Granulosa cell tumors constitute the most frequent subtype of sex cord stromal tumors during childhood. In the ovary, adult and juvenile granulosa cell tumors are distinguished by their histologic appearance. Adult granulosa cell tumors only develop within the ovary. These tumors grow slowly, are diagnosed most frequently after the third decade of life, and may develop late recurrences even later than 10 years after diagnosis. In the literature, Call-Exner bodies, formed by a ring of granulosa cells with grooved nuclei and central eosinophilic material, have been often considered the morphologic hallmark of these tumors. Mitotic activity is usually low, and if elevated, has been associated with higher aggressiveness of the tumor. In contrast, juvenile granulosa cell tumors do not display such Call-Exner bodies. They commonly show microfollicular structures with follicle-like structures of variable sizes that are filled with homogeneous eosinophilic material (Young et al. 1984a). Juvenile granulosa cell tumors may show nuclear atypia and high mitotic activity which may sometimes be pronounced. In tumor stage beyond Ia, high mitotic rate (≥20/10 high power fields) correlates with adverse outcome (Schneider et al. 2003a, 2004d). Juvenile granulosa cell tumors of the testis are undistinguishable from their ovarian counterparts.

Sertoli cells constitute the characteristic component of testicular sex cord stromal tumor. Sertoli cell tumors have a peak frequency in the fourth decade of life. However, they may also be diagnosed in childhood. They present with a high variability of well, or poorly tubular, Sertoli cell aggregates. Sertoli cell tumors of childhood are well differentiated and show a favorable outcome. Large cell calcifying Sertoli cell tumors of the testis are characterized by a pronounced fibrosis that may separate the tumor cells into thin cords. Approximately, one fifth of these tumors may develop bilaterally. These tumors are typically associated with Carney's complex (Young 2005b).

Comparable tumors with pure Sertoli cell differentiation are only rarely observed in the ovary. Here, Sertoli cell differentiation is characteristically seen only within Sertoli-Leydig cell tumors (SLCT), which include both cellular components (Young and Scully 1985). Of note, this tumor type is not observed within the testis. SLCTs may show a highly variable grade of differentiation. In highly differentiated SLCTs, tubular structures with Sertoli cells predominate and are accompanied by sheets of Leydig cells. As a result of hormone production, the ovarian stroma may show luteinization. Tubular structures are lost with lower grade of differentiation. Retiform and microtubular differentiation may be described, and by some authors, are considered distinct histopathologic patterns (Young et al. 1984b). In some tumors, heterologous differentiation, e.g., with intestinal epithelium, may develop. These histologic features, low differentiation, retiform pattern, and heterologous differentiation, have all been associated with adverse outcome (Young and Scully 1985).

Other very rare sex cord stromal tumors include sex cord stromal tumors with annular tubules, sclerosing stroma tumors, thecomas, and steroid cell tumors. Considering the heterogeneity of these tumors and the difficulties in distinguishing them from germ cell tumors or small cell ovarian carcinomas, a reference pathologic evaluation at an experienced paidopathologic or gynecopathologic center is strongly recommended.

Characteristic histologic samples of JGCT and SLCT are demonstrated in Figs. 39.5.1–39.5.3.

39.5.3.1 Clinical Presentation

Testicular sex cord stromal tumors typically present as an indolent scrotal mass. Since juvenile granulosa cell tumors often develop within the first months of life,

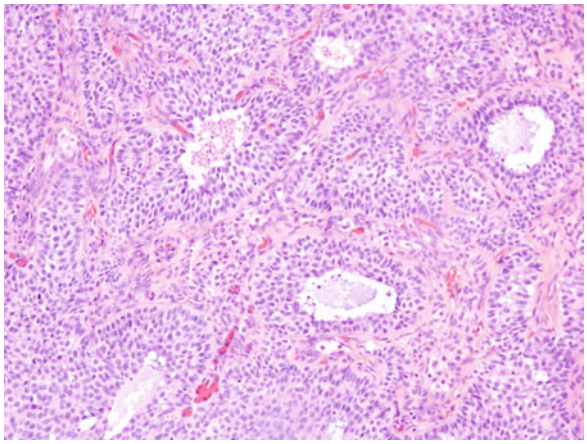


Fig. 39.5.1 Histologic samples from juvenile granulosa cell tumors (H+E)

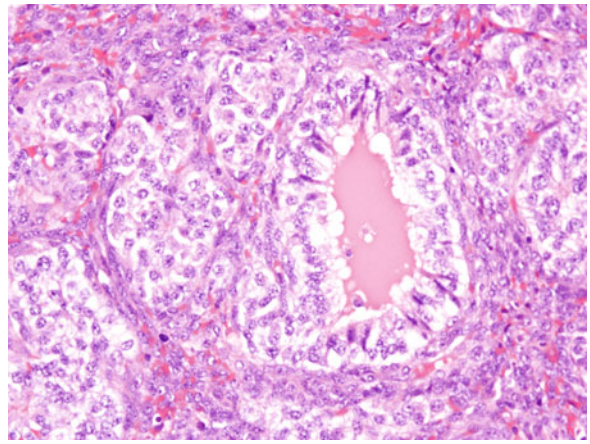


Fig. 39.5.3 Histologic samples from juvenile granulosa cell tumors (H+E)

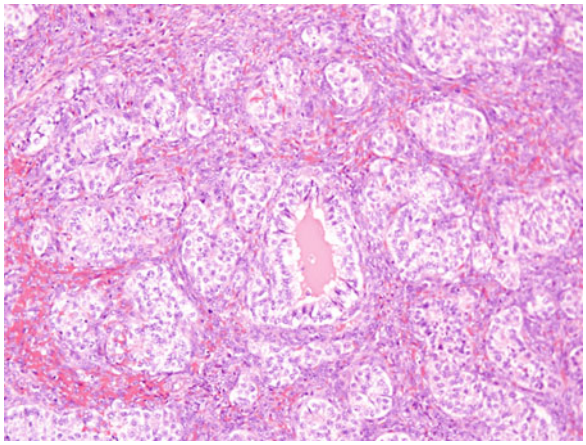


Fig. 39.5.2 Histologic samples from juvenile granulosa cell tumors (H+E)

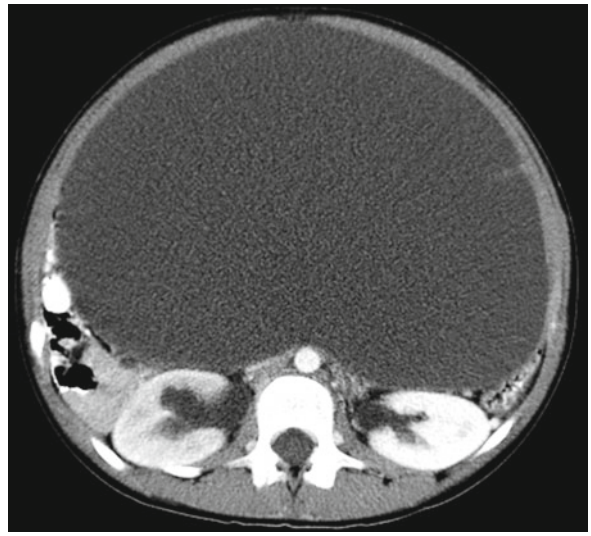


Fig. 39.5.4 CT scan of a large cystic juvenile granulosa cell tumor

these tumors may be present at birth. In contrast, only one in four ovarian sex cord stromal tumors are apparent as a large indolent mass (Fig. 39.5.4). Almost half of the patients have abdominal pain. Approximately 10% of patients present with an acute abdomen, caused either by spontaneous tumor rupture or ovarian torsion. Two thirds of ovarian sex cord stromal tumors were associated with clinical symptoms related to production of sex hormones by the tumor (Schneider et al. 2003a). Characteristically, infants and children may present with signs of isosexual precocity, including breast enlargement, pubarche, and vaginal bleeding. In postpubertal girls, tumors may lead to primary or secondary amenorrhea and unspecific signs of virilization such as pronounced acne. These are characteristic signs of Sertoli-Leydig cell tumors (Schneider et al. 2003a).

As other steroid hormone–producing cells, OSCST also produce inhibin. Free inhibin can be measured in the serum and may serve as a serological tumor marker during follow-up. However, the diagnostic value may sometimes be hampered by the physiologically broad normal range in healthy prepubertal children (Crofton et al. 2002a, b).

In some rare patients, SLCT may produce AFP, which can be detected serologically. Histologically, most of these tumors resemble SLCT with retiform, often hepatoid, differentiation and heterologous elements (Young et al. 1984b).

39.5.4 Diagnostic Assessment and Differential Diagnosis

Due to the rarity of sex cord stromal tumors, in most patients the diagnosis of sex cord stromal tumor will not be established until histologic confirmation. Nevertheless, in particular, in young children, with tumor marker (AFP, βHCG) negative gonadal tumors, sex cord stromal tumors should be considered. The diagnostic and radiographic assessment is almost identical to that of gonadal germ cell tumors (Table 39.5.2). Since these tumors do not metastasize beyond the abdomen, whole-body staging is not required.

OSCST have to be distinguished from ovarian germ cell tumors, epithelial ovarian cancer, including small cell carcinoma of the hypercalcemic type, and gonadal tumors of different histogenesis, such as leukemia/lymphoma or sarcoma. Tumors presenting with vaginal bleeding in infants must be discriminated from the rare vaginal yolk sac tumors. Clinically, the evaluation of serologic tumor markers alpha-fetoprotein (AFP) and β-human chorionic gonadotropin helps in the differential diagnosis of secreting malignant germ cell tumors. Therefore, it is mandatory to measure these tumor markers preoperatively (Schneider et al. 2001h).

In some rare patients, the distinction of juvenile granulosa cell tumors from small cell ovarian carcinoma of the hypercalcemic type may be particularly difficult, since the latter may mimic the pseudofollicular growth pattern characteristic of JGCTs (Distelmaier et al. 2006b). In these situations, the immunohistochemical detection of inhibin constitutes an important diagnostic hallmark of ovarian sex cord stromal tumors. Inhibin positivity has not been observed in small cell ovarian carcinoma, while virtually all sex cord stroma tumors stain positive (Schneider et al. 2003b).

Lastly, mutation testing for DICER1 may be performed in Sertoli-Leydig cell tumors within clinical studies. The clinical and prognostic impact is not yet evaluated prospectively, but positive findings may

Table 39.5.2 Specific diagnostic strategy in testicular or ovarian sex cord stromal tumors

Procedure	Specific questions
Clinical assessment	
Medical history	Gynecological and pubertal history? Vaginal bleeding, breast development, etc.? Thyroid disease? Inherited syndromes (Mb. Ollier's, Peutz-Jeghers, etc.)?
Phys. examination	Pubertal status, goiter, abdominal pain
Laboratory assessment	
AFP, β-HCG	Malignant germ cell tumor with yolk sac tumor (consider age-related reference values) or choriocarcinoma.
	Note: Some Sertoli-Leydig cell tumors may show AFP levels up to 1000 μg/L
Inhibin	Serological marker of hormone-secreting sex cord stromal tumors
Estrogen, DHEAS, LH, FSH	Endocrinological assessment
Clinical chemistry incl. calcium	Calcium may be elevated in ovarian small cell carcinoma (but also in rare germ cell or sex cord stromal tumors)
Creatinine clearance/ cystatin c	Assessment of renal function (in case of chemotherapy)
Radiographic assessment	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/ spermatic cord, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/ spermatic cord, lymph node or liver metastases
Chest X-ray	Lung metastases (extremely unlikely)
Note: Metastases beyond the abdomen are exceedingly rare. Therefore, extended radiographic assessment is required in case of clinical symptoms only	
Histologic assessment	
H&E	Classification and grading according to WHO
Mitotic rate per 10 HPF	Prognostic assessment (in particular, juvenile granulose cell tumors)
Inhibin	Positive for sex cord stromal tumors
AFP	Yolk sac tumor, may also be positive in retiform Sertoli-Leydig cell tumors

indicate association with thyroid disease or metachronous tumors (Rio Frio et al. 2011; Slade et al. 2011).

39.5.5 Treatment and Prognostic Markers – Review of the Literature

The current literature includes only a few and mostly retrospective series of patients with testicular sex cord stromal tumors. Most publications focus on adult patients with sex cord stromal tumors or represent case reports and small patient cohorts, collected at single centers. This may be explained by the lack of cooperative study structures for sex cord stromal tumors, as have successfully been established for germ cell tumors. Thus, many patients have been registered on either the corresponding national germ cell tumor trial or the national rare tumor study group.

The largest series of ovarian sex cord stromal tumors has been reported by the German MAKEI study group (Schneider et al. 2003a, b). This series has verily focused on the pathologic differential diagnosis and prognostic factors (Schneider et al. 2003b) and the prognostic impact of staging (Schneider et al. 2003a, 2004d). In this and other studies, the favorable outcome of completely resected stage I ovarian sex cord stromal tumors has been demonstrated (Cecchetto et al. 2011; Kalfa et al. 2005). In stage Ic or higher (i.e., microscopic tumor spread), prognosis was inferior if tumors ruptured spontaneously or showed malignant ascites compared to those with only intraoperative tumor violation, e.g., during laparoscopic surgery (Schneider et al. 2004d). In stage Ic or higher, pronounced mitotic activity (>20 mitoses per 10 high power fields) was also associated with adverse outcome. In stages II–III, the impact of cisplatin-based chemotherapy in accordance to current germ cell tumor protocols has been demonstrated (Schneider et al. 2002c; Cecchetto et al. 2011).

This experience is further supported by case reports that argue for adjuvant chemotherapy in advanced stage JGCT. Colombo reported on a girl with a stage III JGCT that achieved complete remission for at least 7 months after PVB chemotherapy (Colombo et al. 1986). Powell reported on a 13-year-old primigravida with a stage IIIb JGCT that was successfully treated with a combination of methotrexate, actinomycin, and chlorambucil. The patient has remained in complete remission for 7 years, during which time, she gave birth to further children. The same authors reported on two stage III tumors successfully treated with surgical debulking and carboplatin and etoposide. In addition, a patient with recurrent JGCT with liver metastases achieved complete remission for 44 months after surgery and six cycles of bleomycin and Taxol (Powell and Otis 1997; Powell et al. 1993, 2001).

The largest published series, focusing specifically on ovarian juvenile granulosa cell tumors, analyzed 125 adolescent and adult patients, with follow-up data in 83 patients (Young et al. 1984a). In this series, there were only 2/80 stage I tumors, but all three stage II tumors were fatal. Additional clinical and histologic parameters did not contribute to the prognostic assessment. The largest series of Sertoli-Leydig cell tumors has been reported by the same study group and included 207 patients. Follow-up information was available in 164 patients (Young and Scully 1985). Outcome correlated with both stage and histologic differentiation, and both parameters closely correlated with each other. All well-differentiated SLCT behaved clinically benign, whereas 11% of SLCT with intermediate differentiation and 59% of poorly differentiated SLCT (all stages II-III) showed a malignant course. In particular, those tumors with retiform differentiation and/or heterologous elements were unfavorable.

Two significant studies by the French Pediatric Oncology Group each report on 40 ovarian juvenile granulosa cell tumors treated between 1965 and 1990, and 1990 and 2004, respectively (Kalfa et al. 2005; Plantaz et al. 1992). The authors report that young (prepubertal) age appears to correlate with more favorable diagnosis, in particular, if early diagnosis is established based on assessment of isosexual precocity. However, delayed diagnosis is associated with a higher risk of tumor ruptures and higher tumor stage. Thus, manifestation with acute abdominal pain correlated with adverse outcome, both in prepubertal children and in postpubertal adolescents.

Data on pediatric Sertoli-Leydig cell tumors in children and adolescents are even more limited. Recently an international cooperative analysis of eXpert has been performed, which included 42 patients from Poland, Italy, France, and Germany. In this analysis, event-free survival was 0.66 and overall survival 0.83, which is inferior to that observed in juvenile granulosa cell tumors. Again, outcome was excellent in completely resected (stage Ia) tumors. Only two metachronous contralateral tumors have been reported in this

Table 39.5.3 Proposed therapeutic algorithm in testicular and ovarian sex cord stromal tumors

Site	Stage	Histology	Neoadjuvant chemotherapy	Surgical therapy	Adjuvant chemotherapy
Testis	I	All	–	Inguinal orchiectomy	Watch & wait
	>I	All	–	Inguinal orchiectomy	≥4×PEI/BEP
Ovary	Ia	All	–	Ovariectomy	Watch & wait
	Ic	Sertoli-Leydig	–		4×PEI/BEP
	Ic, intraop.	Juv. granulosa, others	–		Watch & wait
	Ic, preop.		–		4×PEI/BEP
	II–III	All	PEI/BEP	Adenectomy	>4×PEI/BEP[a]

[a]A total of 5–6 cycles of chemotherapy including preoperative chemotherapy is recommended

group. In contrast, almost half of patients with microscopic spread (e.g., malignant ascites, preoperative rupture) or even only intraoperative tumor rupture relapsed. Metastases are rare and are only found at diagnosis in approximately 10% of patients. Metastatic disease can successfully be managed with cisplatin-based chemotherapy (e.g., PEI).

Current literature indicates that the prognosis of testicular sex cord stromal tumors is excellent (Cecchetto et al. 2011; Harms and Kock 1997). Virtually, no patients develop metastases. If they do, these tumors show poorly differentiated histology and require aggressive therapy, comparable to that for metastatic germ cell tumors (Ross et al. 2002). Thus, if a metastatic testicular sex cord stromal tumor is diagnosed, the histopathologic diagnosis should first be questioned and be specified by reference evaluation. In the German series and in all currently published pediatric series, only very rare recurrences or fatal outcomes have been reported.

39.5.6 Proposed Therapeutic Strategy

It should be considered that the following recommendation is not based on prospective randomized trials but represents the experience gained in comparably small prospective series of patients. Basically, the following strategy is based on the concept of the MAKEI study, which has also been adopted as a consensus and guidance for the COG rare tumor group (Table 39.5.3). The therapeutic algorithm separates patients by tumor site, stage, and histologic parameters. The uniform treatment stratification, the incorporation of uniform central pathology review, and the central evaluation and documentation of clinical data may hopefully facilitate validation and further optimization of therapy of these rare tumors.

39.5.6.1 Testicular Sex Cord Stromal Tumors

Since virtually all tumors present as localized stage I tumors, resection will constitute the only therapy of these tumors. In principle, orchiectomy after high inguinal incision and ligation of the spermatic cord constitutes the gold standard. Considering the overall favorable diagnosis, there has been some debate as to whether tumor excision after scrotal excision and even organ sparing surgery (e.g., enucleation of the tumor) may also be appropriate. However, it should be noted that this strategy has not been validated prospectively. Moreover, it remains questionable whether organ-sparing surgery may indeed contribute to further reproductive function and quality of life (Tröbs et al. 2007). The extremely rare metastatic tumor should be treated according to the corresponding concept for ovarian sex cord stromal tumors.

39.5.6.2 Ovarian Sex Cord Stromal Tumors

In all patients, the tumor resection (tumor ovariectomy/tumor adnectomy) constitutes both a diagnostic and therapeutic procedure. The surgical resection should follow the same principles as that for malignant germ cell tumors. The MAKEI data do not indicate that radical retroperitoneal lymph node resection or extended lymph node sampling is required in all ovarian sex cord stromal tumors, because lymph node metastases have been observed only rarely and most commonly in (extended) relapse situations. However, if lymph node metastases are detected (e.g., in relapse situations), all visible metastases should be resected. Ideally, this should be done after preoperative chemotherapy. The German, French, and Italian data presented above suggest that no adjuvant therapy is necessary in stage Ia tumors.

The data reported by the German MAKEI study group represents the first cohort of patients prospectively registered and treated according to a uniform

strategy. Based on these data, a risk stratification for adjuvant chemotherapy can be proposed for patients with stage Ic, II, or III tumors:

39.5.6.3 Stage Ic

In stage Ic, the decision to add adjuvant chemotherapy is most difficult. Tumors in which a microscopic tumor spread is suspected or proven (but no pathologic evidence of peritoneal metastases) are classified as stage Ic. According to FIGO, tumors may be classified as stage Ic for several reasons: A preoperative tumor rupture may have occurred, and in others the cytological analysis of peritoneal washings or ascites provides evidence of malignant tumor cells. In contrast, a tumor may also be classified stage Ic if the tumor has been punctured or the capsule has otherwise been violated in situ. In this case the tumor capsule must be intact prior to surgery (intraoperative violation of tumor capsule).

The previous analysis of a cohort of patients, which predominantly included juvenile granulosa cell tumors, has demonstrated that intraoperative violation of the tumor capsule does not increase risk of recurrence. In contrast, a high relapse rate (comparable to stages II–III) has been observed in those patients whose tumor has been ruptured prior to surgery or if the ascites contains malignant cells.

This observation indicates that thorough documentation and critical evaluation of the clinical and surgical report are mandatory. Cytological analysis of ascites/peritoneal washings is indispensable. In cases with incomplete documentation or missing cytological evaluation, the assessment of the proliferative activity of the tumors may help with regard to risk assessment, but nevertheless a higher grade of uncertainty remains. In the current experience of the MAKEI study, the application of four cycles of cisplatin-based chemotherapy is sufficient to control microscopic tumor spread. In Germany, PEI (see Sect. 39.1, Table 39.1.4) is recommended. In other countries, PEB is applied according to the respective national germ cell tumor protocol. There are no data supporting which regimen is more effective. Data on carboplatin are limited.

As mentioned above, this experience is based on the analysis of cohorts that predominantly included juvenile granulosa cell tumors. The most current analysis, specifically focusing on Sertoli-Leydig cell tumors, has demonstrated that these may develop recurrences even after only minute intraoperative tumor violation (Schneider et al. 2010). Most of these recurrent tumors show additional prognostically unfavorable features such as low histologic differentiation, retiform pattern, or heterologous elements. Thus, the decision in favor of or against chemotherapy remains individual; however, the approach for these tumors obviously has to be more aggressive than that for juvenile granulosa cell tumors.

39.5.6.4 Stages II–III

In stages II–III, micro- or macroscopic spread with peritoneal or lymph node metastases has occurred. It is very obvious that surgical treatment alone will not be curative but must be supplemented with adjuvant chemotherapy. In the past, cure of ovarian sex cord stromal tumors has been reported in single cases only (Kudelka et al. 1998, Powell and Otis 1997; Powell et al. 1993, 2001). The MAKEI study group was the first to report a series of patients with advanced tumor stage, who were treated with adjuvant cisplatin-based combination chemotherapy (Calaminus et al. 1997b; Wessalowski et al. 1995; Schneider et al. 2002c). In these series on advanced juvenile granulosa cell tumors, high proliferative activity distinguishes patients with poor prognosis. In addition to proliferative index, age also appears prognostic (Schneider et al. 2003a).

There are several issues that remain to be addressed critically. The indication for chemotherapy and the minimum amount of chemotherapy necessary in stage Ic tumors are ill-defined. The German data suggest that among stage Ic patients, a subgroup of patients at high risk can be identified through histologic assessment. These patients may be suitable for adjuvant chemotherapy. However, the limited data available from our analysis does not allow definition of the required chemotherapy for tumors at stage Ic or higher. In the Germany study, all patients with stage II to III tumors received at least four cycles. Considering other studies with less favorable outcome, we would not advocate less but rather argue for extension to six cycles. Although to a certain extent, chemotherapeutic regimens varied with the consecutive MAKEI protocols. All but one patient received chemotherapy that included cisplatin and etoposide, mostly as part of three-agent regimens. Therefore, it appears meaningful to include these two drugs into a three-agent combination regimen such as cisplatin, etoposide, and ifosfamide (PEI).

Lastly, alternative strategies must be developed for refractory tumors. In our experience, regional deep hyperthermia has resulted in complete remissions in recurrent or refractory OSCST, although experience

with this approach is limited and responses did not translate into durable remissions longer than 2 years (Wessalowski et al. 1995).

39.5.7 A Call for International Collaboration

Sex cord stromal tumors are currently registered to germ cell tumor trials or rare tumor registries in a minority of countries. However, these tumors constitute a potentially deadly threat. It is mandatory to develop international networks for counseling, scientific evaluation, and validation of therapeutic concepts. The authors have been continuously contacted for consultation on a significant numbers of patients. However, if the data of these patients are not collected centrally and if the involved requesting partner does not provide follow-up data, this valuable clinical information will be lost to the scientific community. Future patients will not benefit from the experience gained in other patients in comparable, rare situations.

39.6 Ovarian Adenomas, Ovarian Carcinoma, and Ovarian Small Cell Carcinoma

Dominik T. Schneider and Thomas A. Olson

39.6.1 Introduction

In addition to the more common ovarian germ cell tumors and sex cord stromal tumors, there are several less frequent and poorly studied pediatric epithelial ovarian tumors. Their clinical spectrum varies from benign adenomas and borderline tumors to adenocarcinoma and highly aggressive tumors, such as ovarian small cell carcinoma of the hypercalcemic type (OSCCHT). The latter was first defined, as a distinct entity, 30 years ago (Dickersin et al. 1982). It may be the most aggressive ovarian tumor during childhood and adolescence. Until recently, OCCCHT has been considered almost inevitably fatal.

All these tumors usually fail to be identified in tumor registries. A remarkable gap between true incidence and registration exists. An epidemiological analysis of the North American Association of Cancer Registries revealed that in children younger than 15 years, ovarian carcinomas are three times more common than sex cord stromal tumors. In adolescents from 15 to 19 years of age, they were almost as common as germ cell tumors (Young et al. 2003). These epidemiologic data stand in stark contrast to the little experience reported in the literature. To a certain degree, this discrepancy can be attributed to the circumstance that epithelial ovarian tumors are not routinely registered on prospective studies of gonadal tumors, where the main focus is germ cell tumors. Even in a large pediatric oncologic ovarian tumor registry, the German MAKEI registry, an average of two to three epithelial or carcinomatous ovarian tumors is reported per year. This compares to more than ten sex cord stromal tumors. Other international pediatric study group, that register ovarian tumors experience comparably low registration rates, too. There is an obvious trend. These children and adolescents are seen, treated, and followed up by gynecologists. As a result, they are not evaluated by pediatric oncologists. Nevertheless, pediatric oncologists are often consulted, in particular, when these patients present with advanced

Table 39.6.1 Diagnostic assessment in ovarian epithelial tumors and ovarian small cell carcinoma, hypercalcemic type

Procedure	Specific questions
Clinical assessment:	
Medical history	Gynecological and pubertal history? Vaginal bleeding, breast development etc.? Familial cancer (ovary, breast)?
Phys. examination	Pubertal status, abdominal pain
Laboratory assessment:	
– AFP, ß-HCG	Malignant germ cell tumor with yolk sac tumor (consider age-related reference values) or choriocarcinoma; *Note:* Some Sertoli-Leydig cell tumors may show AFP levels up to 1000 µg/L
– Inhibin	Serological marker of hormone secreting sex cord stromal tumors
– Estrogen, DHEAS, LH, FSH	Endocrinological assessment
– Clinical chemistry incl. calcium	Calcium may be elevated in ovarian small cell carcinoma (but also in rare germ cell or sex cord stromal tumors)
– Creatinine clearance/ cystatin c	Assessment of renal function (in case of chemotherapy, renal impairment may occur as a complication of hypercalcemia)
Radiographic assessment:	
Ultrasound	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/spermatic cord, lymph node or liver metastases
Abdominal and pelvic MRI	Tumor size and extension in 3 dimensions, anatomical relation to ovary/testis and fallopian tube/spermatic cord, lymph node or liver metastases
Chest X-ray	Lung metastases (extremely unlikely)
Note: OSCCHT may show metastases beyond the abdomen. Therefore, extended radiographic assessment is required in case of clinical symptoms.	
Histologic assessment:	
H&E	Classification and grading according to WHO
Vimentin, cytokeratin	Double positive in OSCCHT
Inhibin	Positive for sex cord stromal tumors, negative in ov. carcinomas
AFP, β-HCG	Exclusion of secreting germ cell tumors

or recurrent disease. It is clearly important to early identify those patients that are at the highest risk to develop fatal disease. The best example might be OSCCHT, since these patients have to be treated intensively at any stage of disease.

39.6.2 Clinical Presentation and Diagnostic Assessment

Ovarian cystadenomas, borderline tumors, and most ovarian carcinomas present with local symptoms such as local swelling, obstipation, dysuria, or abdominal pain. Ovarian torsion or spontaneous rupture may mimic acute abdomen, necessitating emergency procedures. Paraneoplastic symptoms are rarely observed. Approximately, two thirds of OSCCHT may present with significant hypercalcemia, sometimes leading to renal failure. However, other ovarian neoplasms, such as dysgerminoma, may also be associated with hypercalcemia, though less frequently (Young et al. 1994) Table 39.6.1.

On histopathologic examination, most epithelial tumors present as cystic adenomas (cystadenomas) or borderline tumors. True classical ovarian carcinomas may be diagnosed, too. The majority of these tumors present at a low local stage. In contrast, OSCCHT may present with extensive intra-abdominal metastases. Two thirds of patients with OSCCHT may exhibit a paraneoplastic hypercalcemia. OSCCHT is predominantly a unilateral tumor that most commonly affects young women in the second and third decade of life. Less than 30% of tumors develop in patients younger than 20 years of age and less than 1% in children. The

youngest patient, reported to date, has been 14 months (Florell et al. 1999; Young et al. 1994).

The diagnostic work-up is comparable to ovarian germ cell tumors and sex cord stromal tumors (see Sect. 39.1.4, Table 39.4.2; Sect. 39.1.5, Table 39.5.1).

Tumor markers AFP and β-HCG serve to help exclude the diagnosis of malignant nondysgerminomatous germ cell tumors. Inhibin, androgens, and estrogens are within the normal range in epithelial tumors. CA125 is the characteristic tumor marker and can be utilized for follow-up monitoring. However, CA125 elevation may also be observed in germ cell tumors and sex cord stromal tumors (personal observation) or in benign conditions such as pregnancy, endometriosis, or Crohn's disease (Robertson et al. 2002).

Radiographic assessment includes abdominal ultrasound, supplemented with magnetic resonance tomography. The pattern of lymph node metastases may vary by site. Left ovarian tumors primarily metastasize to lymph nodes in the renal hilum, whereas right ovarian tumors metastasize to paracaval lymph nodes. A chest X-ray is indicated to exclude rare lung metastases. In OSCCHT, a brain MRI and bone scan should be performed if patients show clinical signs of skeletal or neurological involvement.

In case of classical ovarian carcinoma, the family history should specifically focus on a history of breast cancer. Genetic counseling and testing for BRCA gene mutations should be considered. However, one should be aware that OSCCHT might also occur in families without evidence of BRCA mutations (Distelmaier et al. 2006b) (Lamovec et al. 1995; Longy et al. 1996). In the German pediatric series, two pairs of siblings have been observed among a total of currently 15 patients.

The differential diagnosis of pelvic masses includes benign ovarian cysts, other ovarian tumors, and benign or malignant masses that develop from the bowel, urinary tract, or other pelvic structures. The most difficult diagnosis of cystadenomas may be benign ovarian cysts. Ovarian cysts are often asymptomatic and are detected accidentally during ultrasound. In a large series including more than 1,800 prepubertal patients, ovarian cysts were detected in 5% of patients (Millar et al. 1993). However, benign cysts rarely exceed 5 cm in diameter and often show spontaneous regression during follow-up. In contrast, ovarian tumors are most commonly diagnosed with a diameter of greater than 10. The spectrum of differential diagnoses of ovarian cysts in postpubertal adolescents is broader and includes pregnancy, tubal lesions, and genital obstruction, such as imperforate hymen.

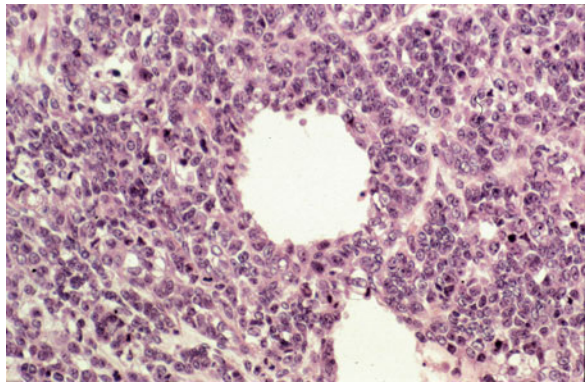


Fig. 39.6.1 Ovarian small cell carcinoma of the hypercalcemic type in a 16- year old girl (H&E, 400×). Histologically, the tumor is characterized by sheets of closely packed, small cells with scanty cytoplasm forming scattered follicle-like structures, and the morphologic similarity to sex cord stromal and germ cell tumors may pose significant problems in establishing the correct diagnosis

Pathologic examination follows the same principles as for ovarian germ cell and sex cord stromal tumors. It should be noted that the majority of OSCCHTs are first misdiagnosed (Distelmaier et al. 2006b). Therefore, consultation with a reference pathologist should be considered for all ovarian tumors, ideally prior to the start of chemotherapy.

On histopathologic examination, OSCCHTs show a solid growth pattern with admixed pseudofollicular structures and occasional areas of necrosis and hemorrhage (Fig. 39.6.1). The mitotic rate is usually high with an average of 23 mitoses of 10 high power fields (range 17–29/10 HPF) in the German series. Some tumors are classified as a large cell variant. Others may show a pronounced hemangiopericytic growth pattern or pronounced rhabdoid features. The most important and difficult histopathologic differential diagnosis is juvenile granulosa cell tumor, which in contrast to OSCCHT, shows inhibin positivity (Schneider et al. 2003c). All OSCCHT centrally examined at the German Childhood Tumor Registry stained negative for inhibin, alpha-fetoprotein, human placental like alkaline phosphatase, and beta-human chorionic gonadotropin upon immunohistochemical examination. Characteristically, the tumors show co-expression of cytokeratins and vimentin.

Tumors are staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (Benedet et al. 2000) (see Sect. 39.1.4, Table 39.4.3).

39.6.3 Therapy

In cystadenomas, borderline tumors, and carcinomas, complete tumor resection constitutes the cornerstone of treatment. In most gynecology-oncology centers, tumor resection is done laparoscopically. However, this technique has not been validated in children and adolescents with ovarian tumors. No prospective studies have compared conservative and laparoscopic approaches in children and adolescents. The tumor-bearing ovary is removed in most patients. Again, organ-sparing surgery is not validated in children and adolescents. However, in bilateral tumors, it remains the only (but still experimental) approach to conserve fertility. During surgery, it must be decided whether the fallopian tube has to be removed, too. Since most tumors are limited to the ovary, routine adenectomy and hysterectomy are not justified. Given the perspective of chemosensitive tumors, hysterectomy is obsolete in children and adolescents.

Normalization of renal function must be the first therapeutic intervention when OSCCHT presents with hypercalcemia. This can be achieved with aggressive hydration and diuretic therapy with furosemide. In OSCCHT, complete resection is a prerequisite for cure. However, resection alone is often not sufficient for definite cure: In the German series, all four stage I patients, followed according to a watch-and-wait strategy, relapsed (Distelmaier et al. 2006b). In the report by Young, less than 10% of adolescent stage I patients survived (Young et al. 1994). Nevertheless, mutilating surgery, such as hysterectomy, should be avoided, even in OSCCHT with pelvic and peritoneal metastases, as recent data indicate that these tumors are chemosensitive. Thus, in a multimodal therapy, the aim is cure with preservation of a chance of fertility.

Ovarian cystadenomas and borderline tumors usually present as stage I tumors and require no additional adjuvant therapy. Metastatic ovarian carcinomas are most commonly treated with a combination of carboplatin and Taxol, in accordance to current gyne-oncology protocols. The pediatric experience in these tumors is limited. During the last decade, nine cystadenomas and borderline tumors as well as two ovarian carcinomas have been reported to the German study group. All were stage one and have been observed without adjuvant treatment. No relapses were reported (unpublished information).

39.6.4 Review on Multimodal Therapy of OSCHHT in Adults and Children

The prognosis of OSCCHT is generally believed to be poor and almost inevitably fatal. In the largest series reported to date, event-free survival was 33% in stage Ia, 10% in stage Ic, and 6.5% in stages II–IV. Notably, half the registered patients showed abdominal or peritoneal tumor spread, corresponding to FIGO stages II–III. In addition, young age was associated with a particularly poor prognosis, even in low-stage tumors. Less than 10% of children and adolescents with stage IA OSCCHT survived (Young et al. 1994).

The ideal multimodal treatment for OSCCHT has not yet been defined. However, it is apparent from the above-mentioned data that treatment of this tumor type requires a multimodal aggressive approach.

Senekjian et al. first reported on five patients with ovarian small cell carcinomas treated with a combination of vinorelbine, cisplatin, cyclophosphamide, bleomycin, Adriamycin, and etoposide (Senekjian et al. 1989). Despite initial promising responses to chemotherapy, four of five patients died of disease.

In the largest series on OSCCHT, Young et al. mention that the most patients received some form of adjuvant chemotherapy (Young et al. 1994). However, detailed information on only seven patients with favorable response to therapy, either during first- or second-line therapy, is provided. As outlined in Table 39.6.2, patients received combination chemotherapy with various regimens that included anthracyclins, etoposide, cisplatin, and alkylating agents. Three patients had radiation therapy. One of the seven patients is in first complete remission (CR).Three are in second CR. One is alive with disease and two are dead (Table 39.6.2) (Young et al. 1994). However, this report includes no information regarding the single and cumulative doses of either radio- or chemotherapy. Therefore, no specific conclusions can be drawn other than that some selected patients may benefit from adjuvant therapy.

Table 39.6.2 Summary of therapeutic regimen administered in series using coventional chemotherapy ± radiotherapy but without high dose chemotherapy (this table includes only drugs included in the first-line chemotherapy)

Study	No	Stage	Irradiation	Taxol	Platin derivates	VP-16	Alkylat. Agents	Anthra-cyclins	Best status	Outcome	Follow-up (months)
Young[a]	1	Ia	+	–	+	–	–	–	CR	CR-2	45
	2	Ia	–	–	+	–	–	–	CR	CR-2	53
	3	Ia	–	–	+	+	–	+	CR	DOD	81
	4	IIb	+	–	+	+	+	+	CR	CR-2	84
	5	III	+	–	–	–	–	–	CR	DOD	66
	6	III	–	–	+	+	+	+	CR	AWD	24
	7	III	–	–	+	+	–	+	CR	NED	30
Harrison	1	I	–	–	+	+	–	–	CR	NED	10
	2	Ia	45 Gy	–	+	+	–	–	CR	NED	60
	3	Ic	45 Gy	–	+	+	–	–	CR	NED	51
	4	Ic	–	–	+	–	+	+	CR	DOD	29
	5	Ic	–	+	+	+	–	–	CR	CR-2	16
	6	Ic	45 Gy	–	+	+	–	–	CR	NED	71
	7	Ic	40 Gy	+	+	+	–	–	CR	NED	59
	8	Ic	45 Gy	–	+	+	–	–	CR	NED	65
	9	Ic	50 Gy	+	+	+	–	–	PR	AWD	8
	10	Ic	–	+	+	–	–	–	CR	AWD	16
	11	III	–	+	+	+	–	–	SD	DOD	6
	12	IIIc	–	+	+	-	–	–	CR	DOD	11
	13	IIIc	50 Gy	–	+	+	–	–	CR	NED	5
	14	IIIb	–	–	+	+	–	–	CR	DOD	7
	15	IIIb	–	+	+	–	–	–	PD	DOD	3
	16	IIIc	–	–	+	–	–	–	CR	DOD	13
	17	n.d.	–	+	+	–	–	–	PD	DOD	2
Senekijan	1	Ia	–	–	+	+	+	+	CR	NED	29
	2	Ia	–	–	+	+	+	+	CR	DOD	18
	3	IIc	45 Gy	–	+	+	+	+	CR	DOD	11
	4	IIIa	45 Gy	–	+	+	+	+	PR	DOD	13
	5	IIIa	–	–	+	+	+	+	CR	DOD	15

[a]Only the patients with "favourable response" to therapy

Additional detailed and more encouraging information can be retrieved from the more recent report by Harrison et al. which included 17 adult patients treated in Australia, Canada, and Europe between 1989 and 2004 (Table 39.6.2) (Harrison et al. 2006). Ten patients had stage I tumors, six with stage III, and one patient with an unknown tumor stage. Surgical resection included oophorectomy (six patients), unilateral adenectomy (three patients), or hysterectomy with (bilateral) adenectomy (seven patients). After surgery and prior to the start of adjuvant chemotherapy, three patients had tumor residues larger than 1 cm. In accordance with recommendation discussed above, all patients received adjuvant chemotherapy regardless of initial tumor stage. The main drugs are listed in Table 39.6.2. Briefly, cisplatin-based regimens, in combination with etoposide according to strategies applied in malignant germ cell tumors, were administered. Notably, Taxol-based regimens, which are commonly used in other types of ovarian carcinoma, did not prove successful. Only one of eight patients treated with Taxol remains in continuous remission. This finding is in line with the observation, from the German series, that Taxol demonstrates only limited efficacy both in first-line and salvage therapy. The authors conclude that radiotherapy has a significant therapeutic impact. In their experience, the outcome of stage I tumors was better after irradiation. However, there is one patient, who received radiation, with active disease 8 months after diagnosis. In stage

III tumors, no comparable observation supporting the impact of radiotherapy has been made.

A French study group reported on 27 adolescent and adult OSCCHT patients treated with a combination of cisplatin, Adriamycin, cyclophosphamide, and etoposide, then consolidated with high-dose chemotherapy and autologous stem cell transplantation. In this series that included four stage II, 14 stage II, and three stage IV patients, event-free survival was 34% and overall survival 49% (Pautier et al. 2007).

In the German pediatric series, the adjuvant chemotherapeutic regimens were heterogeneous and ranged from sarcoma (CEVAIE) to ovarian cancer (Carbo-Taxol) and germ cell tumor protocols (PEI). Response to chemotherapy was heterogeneous. The best results were achieved with sarcoma or germ cell tumor regimens, while classic ovarian carcinoma regimens were ineffective. Despite initial responses, six of eleven patients suffered recurrence. However, all five patients who underwent high-dose chemotherapy with autologous stem cell transplantation achieved long-term remission. The outcome of this series is comparable to that of the French series. Event-free survival is 0.28 ± 0.15 (4/11 patients), and 5-year survival is 0.49 ± 0.15 (6/11 patients) (Distelmaier et al. 2006b).

Based on this published experience, four additional patients have been treated with a combination of cisplatin, ifosfamide, and Adriamycin, followed by high-dose chemotherapy. All four currently remain in complete remission. Thus, combining all patients reported to the MAKEI registry, all nine patients treated with high-dose chemotherapy are alive and well, while all treated without high-dose chemotherapy have died from their tumor. On recurrence, OSCCHTs characteristically show a diffuse metastatic spread within the peritoneal cavity and involved abdominal and pelvic lymph nodes. A few patients may develop distant metastases to the liver and the skeletal system.

39.6.5 Approach to a Multimodal Therapy of OSCCHT of Children and Adolescents

In summary, the optimal management of OSCCHT still remains unknown. The only clear evidence is that after the diagnosis of OSCCHT, there is no role for expectant follow-up, even in completely resected stage Ia disease. Obviously, at least microscopic tumor spread has to be assumed in virtually all tumors, so that all require adjuvant therapy. It is also evident that adjuvant chemotherapy may successfully eradicate such subclinical disease, and according to the study by Harrison, Pautier, and the German series, a platin-based regimen that includes etoposide, alkylating agents, and anthracyclins currently appears to be the most promising combination regimen (Distelmaier et al. 2006b; Harrison et al. 2006; Pautier et al. 2007).

Preliminary information indicates that high-dose chemotherapy may indeed be useful in consolidating a complete clinical remission previously achieved with surgery and conventional chemotherapy. For locally intensive tumor control, either abdominal irradiation of locoregional hyperthermia may be considered (Distelmaier et al. 2006b; Harrison et al. 2006).

This positive development and the anticipation that more patients with OSCCHT will be registered in the future have encouraged the German MAKEI germ cell tumor study group to incorporate a therapeutic recommendation for patients with OSCCHT in the upcoming MAKEI protocol. Thus, further patients can hopefully be evaluated prospectively. According to this protocol, a timely histopathologic review of all ovarian tumors will be mandatory. In the case of an OSCCHT, all patients will receive adjuvant chemotherapy with a combination of cisplatin, ifosfamide, and Adriamycin for six cycles. Therapy will be completed with high-dose chemotherapy including carboplatin and etoposide, thus avoiding intolerably high cumulative doses of etoposide. In case of gross tumor residues after resection, a local deep hyperthermia will be discussed. The authors can be contacted for further details regarding therapy, and they would appreciate exchange of experience.

In conclusion, ovarian small cell carcinoma of the hypercalcemic type must still to be considered a prognostically unfavorable disease. However, data are accumulating, which open encouraging perspectives for cure through the use of adjuvant multiagent chemotherapy and consolidating high-dose chemotherapy. In addition, further genetic research on the biology of this rare neoplasm with recurrent familial clustering may uncover new therapeutic targets. However, these goals can only be achieved if patients are registered centrally and prospectively. The difficulty in collecting data from rare pediatric tumors must be emphasized. In the case of OSCCHT, clinicians often query experts on the appropriate treatment. Yet, scarce follow-up data are provided. These data might help inform future treatments, but the opportunity is lost without communication Thus, this

rare tumor type is an ideal candidate for international cooperation in order to achieve standardization of treatment and data collection in a registry ("Get friends!").

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