Virchows Archiv (2025) 486:65–79
https://doi.org/10.1007/s00428-025-04023-7

REVIEW

Germ cell tumors in children

Peter Karl Bode[1] · Luis Blasco-Santana[2] · Isabel Colmenero[2] · Miguel Reyes-Múgica[3]

Received: 8 December 2024 / Revised: 27 December 2024 / Accepted: 31 December 2024 / Published online: 9 January 2025

Abstract
Pediatric germ cell tumors represent a rare but biologically diverse group of neoplasms arising from pluripotent primordial germ cells. The 2022 edition of the *WHO Classification of Pediatric Tumors* introduced the first organ independent classification of germ cell tumors, reflecting advances in molecular biology, histopathology, and clinical practice. This review highlights the key changes, including the refined distinctions between the different subtypes. These updates enhance diagnostic accuracy and provide a framework for understanding age-dependent differences in tumor biology and behavior. Emphasis is placed on integrating the new classification into multidisciplinary care, particularly in addressing diagnostic challenges in pre- and post-pubertal-type germ cell tumors. By bridging the gap between histopathology and oncology, the updated classification represents a pivotal step forward in improving outcomes for children with germ cell tumors.

Keywords Germ cell tumors · WHO classification of pediatric tumors · Germinoma · Teratoma · Yolk sac tumor · OCT3/4

Introduction

Primordial germ cells represent a population that undergoes significant migration from their initial location in the yolk sac to their final location in the gonads, crossing vast territories usually following the midline of the developing organism. This extensive migratory phenomenon explains the occurrence of germ cell tumors (GCTs) in seemingly disparate locations, affecting predominantly the gonads, but involving also the sacral, retroperitoneal, mediastinal, and midbrain regions [1].

The WHO Classification of Tumours volumes have followed traditionally a system based on the organ of origin, incorporating a crucial aspect in classifying: their phenotypic differentiation. Like epithelial, mesenchymal, or hematopoietic tumors, GCTs also represent a separate tumor class due to their specific neoplastic cell of origin. However, while epithelial tumors are classified by their organ of origin, mesenchymal and hematopoietic tumors occur throughout the body, and consequently, both are addressed in separate WHO classification volumes. GCTs usually develop in the gonads; therefore, they have been covered in the WHO volumes addressing classification of testicular and ovarian tumors. However, and due to the above-mentioned extensive migration of primordial germ cells, GCTs also occur independently of the organ.

GCT can present in early childhood, but are also common in adolescents and young adults. They are rare in old age (with the exception of spermatocytic tumor). Incidence rates are summarized in Table 1 [2]. Bringing all this together, an organ-independent GCT WHO classification was established for the first time. It integrates seamlessly into the newly created blue book of pediatric tumors by explicitly emphasizing developmental aspects [3]. The challenge was to take into account existing classifications and terminologies on the one hand, and to emphasize the common characteristics of this tumor class on the other. The aim was to standardize communication between pathologists and clinicians, which ultimately benefits patient management and research into these relatively rare tumors. Nevertheless, since all classifications evolve over time, this new GCT classification may also have some limitations that must be addressed in future developments.

✉ Peter Karl Bode
peter.bode@ksw.ch

[1] Department of Pathology, Kantonsspital Winterthur, Winterthur, Switzerland

[2] Department of Histopathology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

[3] Department of Pathology and Laboratory Medicine, University of Miami Miller School of Medicine, Miami, FL, USA

Table 1 Incidence rates of GCT per 1,000,000 by sex (age adjusted), sites, and histological types (germinoma vs non-germinoma). Table adopted and adjusted from [2]

	Male			Female		
	Total	Germinomas	Non-germinomas	Total	Germinomas	Non-germinomas
Gonadal GCT	62.1	36.9	25.3	2.5	0.9	1.7
Extragonadal GCT	1.81	0.90	0.91	1.19	0.22	0.97
-Central nervous system	0.62	0.51	0.12	0.17	0.14	0.03
-Mediastinum	0.51	0.21	0.30	0.07	0.01	0.05
-Intraabdominal	0.38	0.10	0.27	0.79	0.03	0.76

The evolution of GCT classifications

GCT vary in their levels of differentiation and are subdivided into germinomas and non-germinomas. Germinomas resemble early germ cells and retain pluripotent potential. Non-germinomas encompass a wide range of subtypes, including undifferentiated forms like embryonal carcinoma and differentiated forms. The differentiated non-germinomas may exhibit some degree of embryonic (teratoma) or extra-embryonic pattern, such as in yolk sac tumor and choriocarcinoma [4].

Two decades ago, Oosterhuis and Looijenga proposed a comprehensive GCT classification, which was based on molecular and developmental data and also implemented clinical and anatomical aspects [5]. An update was published in 2019 [6]. They defined different GCT types depending on epigenetics (genomic imprinting) and karyotypes. The differentiation between pre- and post-pubertal GCT was particularly relevant for the revision of testicular GCT classification in the 4th edition of WHO classification on Tumors of the Urinary System and Male Genital Organs in 2016. It introduced two main GCT groups: GCT derived from the precursor lesion germ cell neoplasia in situ (GCNIS; Fig. 1) and GCT unrelated to GCNIS. The first group represents post-pubertal-type GCT. At the molecular level, they are characterized by the presence of an isochromosome i(12p) or by 12p gains.

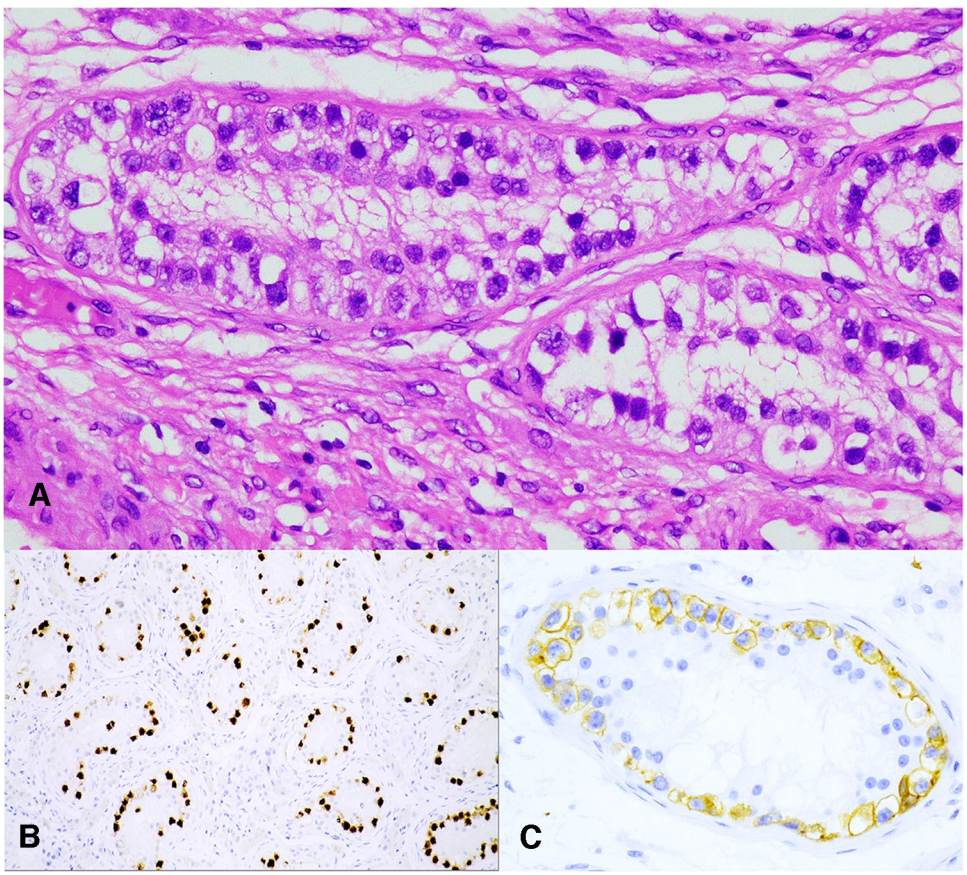

Fig. 1 Germ cell neoplasia in situ (GCNIS). Neoplastic cells are located along the basement membrane of seminiferous tubules. The cells are large and atypical, with abundant clear cytoplasm, large hyperchromatic nuclei, coarse chromatin, angulated nuclear borders, and prominent nucleoli (**A**). These cells can be highlighted with immunohistochemical markers such as OCT3/4 (**B**) and KIT (**C**)

Pre-pubertal-type GCT usually lack 12p alterations and are included in the second group (together with the spermatocytic tumor of the testis). The distinction between pre- and post-pubertal-type GCT is reflected in their different tumor biology. While pre-pubertal-type GCT usually are benign or mostly indolent, post-pubertal-type GCT may show an aggressive behavior due to their metastatic potential. For this reason, the determination of 12p status (e.g., by fluorescence in situ hybridization) can be used to differentiate between pre- and post-pubertal-type GCT, especially in teratomas (see below). For the sake of completeness, oncogenic mutations will be briefly addressed in the Germinoma-family section; however, they do not play a significant role in the practical classification of GCT.

The disadvantage of the revised testicular GCT classification was its incompatibility with GCT classification in other organs (e.g., ovary), since GCNIS is unique to the testis and does not exist in extratesticular sites. Therefore, the pediatric GCT classification continues to rely on the histological GCT subtypes and highlights the differences between pre- and post-pubertal-type GCT in the particular sections on teratoma and yolk sac tumor. Table 2 summarizes the entities covered in the pediatric GCT classification. A comparison between the pediatric GCT classification and the GCT classification by Oosterhuis and Looijenga [6] is given in Table 3.

Table 2 Overview of the entities in the new GCT classification (WHO classification of pediatric tumors)

Non-invasive germ cell neoplasia
Intratubular germ cell neoplasia (male gonad)
Gonadoblastoma (mostly in dysgenetic gonad)
Germinoma-family tumours
Germinoma/dysgerminoma/seminoma (GDS)
Non-germinomatous germ cell tumours
Teratoma family
Mature cystic teratoma
Extragonadal teratoma
Fetus in fetu
Teratomas of the female gonad
Monodermal teratomas
Immature teratoma
Pre-pubertal-type testicular teratoma
Post-pubertal-type teratoma
Embryonal carcinoma
Yolk sac tumor (pre- and post-pubertal type)
Choriocarcinoma (non-gestational)
Malignant mixed germ cell tumors

New: gonadoblastoma in the precursor lesion section

According to the latest WHO Classification of Tumours in both the Urinary and Male Genital Tumours (5th ed.) and the Classification of Paediatric Tumours, gonadoblastoma represents the in situ stage of several GCTs, including seminoma in the testis and dysgerminoma in the ovary. Gonadoblastoma includes in its cellular composition a mixture of transformed germ cells and incompletely differentiated cells from the sex cords, which are equivalent of Sertoli/granulosa cells. Therefore, the diagnosis of gonadoblastoma ideally requires the demonstration by immunohistochemistry of both germ cells (positive for SALL4 and OCT3/4) and cells positive for so-called sex cord differentiation, e.g., SOX9, inhibin, or calretinin. These combined cellular elements may appear in two patterns: First, as irregular, incompletely developed cords, which sometimes are referred to as "undifferentiated gonadal tissue," although others prefer to designate them as "dissecting gonadoblastoma." Second, as well-developed round nodules with germ cells, alternating with sex cord elements, expressing the above-mentioned markers (Fig. 2). Within these nodules, there are prominent pink or eosinophilic aggregates of basement membrane hyaline deposits that, when prominent, impart a "mulberry" appearance to gonadoblastoma. When these nodules progress, the proliferating cells may break through the basement membrane and invade the surrounding stroma, usually accompanied by a growing population of infiltrating lymphocytes. At this state, gonadoblastoma has progressed from its in situ stage, toward the invasive stage of seminoma or dysgerminoma. These tumors have been grouped in the same category independently of the gonad from which they develop (testis, ovary, or more frequently a dysgenetic gonad), since they represent a spectrum with similar features wherever they develop.

GCT associated with differences/disorders of sex development

As previously mentioned, gonadoblastoma typically develops in dysgenetic gonads, placing differences/disorders of sex development (DSD) patients at an elevated risk of post-pubertal-type GCTs. Research has identified a critical region on the Y chromosome, particularly near the centromere (the GBY region), as pivotal in the development of this tumor type. This may be an explanation that the risk of developing GCTs varies significantly among clinical subgroups of DSD patients. The high-risk group (15–60%) includes individuals with gonadal dysgenesis carrying the GBY region, partial androgen insensitivity with non-scrotal gonads, and syndromes such as Frasier and Denys–Drash. An intermediate risk (12–28%) is described in persons with Turner syndrome

Table 3 Comparison between the classification by Oosterhuis and Looijenga [6] and the current GCT classification (WHO classification of pediatric tumors)

GCT classification by Oosterhuis and Looijenga [6]	WHO classification of pediatric tumors	Location	Age
GCT type 0	Fetus in fetu	Midline/sites of attachment of conjoined twins	In utero/congenital
GCT type 1	Pre-pubertal-type testicular teratoma Mature cystic teratoma Extragonadal teratoma Yolk sac tumor (pre-pubertal type)	Testis Gonads and midline Midline (from sacrococcygeal to brain) Gonads and midline	Congenital or in early childhood before puberty, rarely in adults (testis and other sites), broad age range in the ovary
GCT type 2	Germinoma-family tumors: Germinoma/dysgerminoma/seminoma Non-germinomatous GCT: • Embryonal carcinoma • Yolk sac tumor (post-pubertal type) • Choriocarcinoma (non-gestational) • Post-pubertal-type teratoma • Malignant mixed GCT	Gonads, anterior mediastinum, midline of the brain (predominantly in the pineal gland)	Adolescence and adulthood (decreasing incidence beyond the 5th decade) Rarely before puberty in DSD
GCT type 3	Not covered (Spermatocytic Tumor in WHO classification of Urinary and Male Genital Tumors)	Testis	Adulthood (3rd–9th decade, median age of 72)
GCT type 4	Mature cystic teratoma Monodermal teratomas (female gonadal) Immature teratoma (female gonadal)	Ovary	Adolescence and young adulthood
GCT type 5	Not covered (Gestational trophoblastic disease in WHO Classification of Female Genital Tumors)	Uterus/placenta	Adulthood
In situ *lesions* not covered, but related to GCT type 2	Non-invasive germ cell neoplasia: • Intratubular germ cell neoplasia (male gonadal)/germ cell neoplasia in situ (GCNIS) • Gonadoblastoma	Testis/dysgenetic gonad	Testis: Adolescence and adulthood (decreasing incidence beyond the 5th decade) Gonadoblastoma: Childhood (DSD)

GCT germ cell tumor, *DSD* differences/disorders of sex differentiation

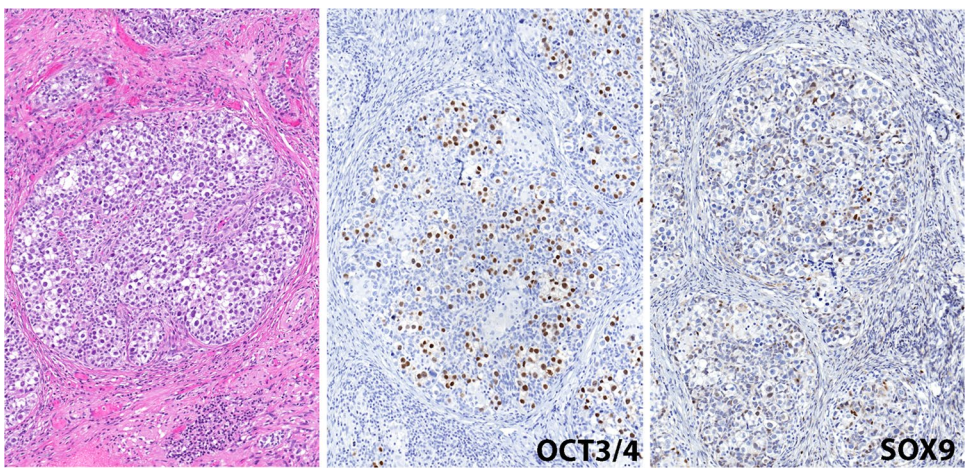

Fig. 2 Left: representative area of a *gonadoblastoma* with a well-developed nodule of germ cells and stromal cord elements. Note the pink hyaline basement membrane material. Center: OCT3/4 immunohistochemistry highlights the nuclei of germ cell in gonadoblastoma. Right: SOX9 immunohistochemistry stains the nuclei of many of the Sertoli cells

with Y chromosomes, 17β-HSD deficiency, and cases of androgen insensitivity or gonadal dysgenesis with scrotal gonads containing the Y chromosome. The low-risk group (< 3%) encompasses patients with complete androgen insensitivity, ovotesticular DSD, and Turner syndrome without Y chromosomes. This stratification highlights the importance of genetic and clinical factors in assessing the risk of GCT development among DSD patients [7, 8].

Germinoma-family tumors

Theoretically, the terms testicular or ovarian germinoma would be correct, but seminoma and dysgerminoma are so firmly established in the literature that no change in terminology has been made. Therefore, the category Germinoma-family of tumors was created to encompass germinoma, dysgerminoma, and seminoma (GDS). Despite the different terminology and anatomic location (seminoma/testis and mediastinum; dysgerminoma/ovary; germinoma/brain), they represent morphologically, immunophenotypically, and genetically the same tumor type. Apart from very few exceptions (especially disorders/differences of sex development [9]), they develop after puberty (post-pubertal-type GCT). GDS can manifest in pure form or as a component of mixed GCT (see below).

In the brain, most GCTs are germinomas with a median age of 18 years [10]. Central nervous system (CNS) GCTs are more prevalent in eastern Asia than in Europe and the USA [11–13]. Pure germinomas outside the brain usually occur at an older age [14]. Seminoma, the most common testicular germ cell neoplasm, occurs most frequently in patients aged 35–45 years and originates from GCNIS. Higher rates are noted in patients with cryptorchidism [15]. Dysgerminoma accounts for one third of malignant ovarian germ cell tumors [16], predominantly arising in adolescents and young women aged 15–20 years [14]. As already discussed, these can develop from gonadoblastoma in DSD patients [17]. Pure germinomas are the second most common GCT in the mediastinum after teratomas, typically affecting males, with sporadic cases in females [18]. They are often diagnosed in the 3rd and 4th decades [14]. Klinefelter syndrome is identified in up to 20% of males with primary mediastinal germ cell tumors, but usually associated with non-germinomatous GCT [19]. There is no specific serum marker for GDS, although human chorionic gonadotropin may be slightly increased in 10–20% of tumors with admixed syncytiotrophoblast cells. Serum lactate dehydrogenase (LDH) is not specific but increased levels are mostly associated with advanced-stage disease.

Macroscopically, GDS show solid, relatively homogeneous, often lobulated, pale gray to tan or pale-yellow nodules with a soft texture (Fig. 3A). Foci of necrosis and hemorrhage may be present but are usually not extensive. GDS typically displays tumor cells in a diffuse arrangement, interrupted by fibrovascular septa with lymphocytes (Fig. 4). Tumor cells have pale to clear cytoplasm due to abundant glycogen, demonstrable with periodic acid-Schiff stain. Nuclei are polygonal with finely granular

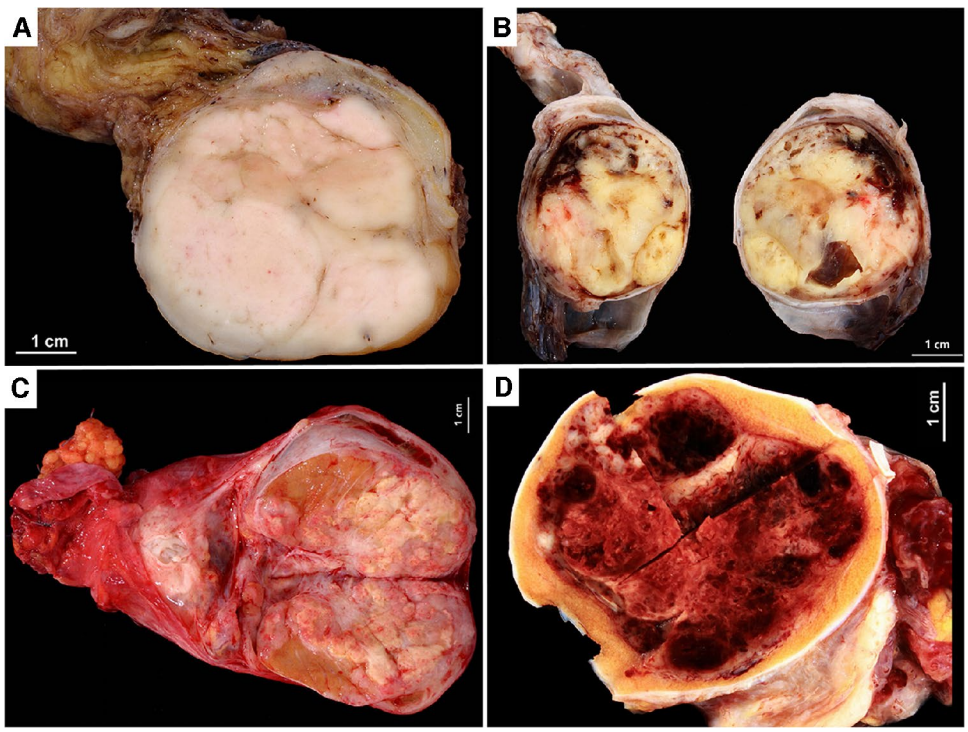

Fig. 3 Macroscopic features of testicular GCT. **A** Seminoma: Homogenous, white, and lobulated tumor replacing the entire testis. **B** Yolk sac tumor, pre-pubertal type: Lobulated tumor with brownish cut surface, featuring areas of necrosis and fibrotic scars. **C** Embryonal carcinoma: Yellow tumor with cystic areas and hemorrhagic foci. **D** Choriocarcinoma: Large testicular tumor mass characterized by extensive hemorrhage

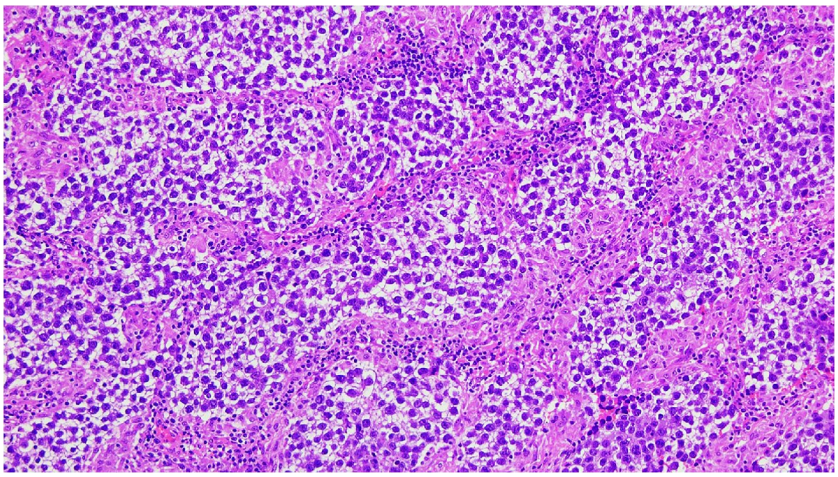

Fig. 4 Germinoma/dysgerminoma/seminoma (GDS). Tumor cells are arranged in nests separated by fibrovascular septae containing lymphocytes. The cells are polygonal with clear cytoplasm, distinct cell membranes, large nuclei exhibiting vesicular chromatin, and prominent nucleoli

chromatin and centrally located nucleoli. Mitotic activity and extent of necrosis vary. Granulomatous reaction is present in many cases. GDS stain for antigens characteristic of immature germ cells, including CD117 (c-KIT) [20, 21], OCT3/4 [22–25], SALL4 [26, 27], SOX17 [28, 29], and podoplanin [30]. Cytokeratin AE1/AE3 immunoreactivity varies [31]. Placental alkaline phosphatase (PLAP) is positive in 86–95% of cases, but also in other GCTs. GDS can be mistaken for solid-pattern embryonal carcinoma or yolk sac tumor (OCT3/4 negative), but differences include well-defined cytoplasmic membranes, less crowded nuclei, fibrous septa, and more prominent lymphocytic infiltrate in GDS. CD30 and AFP are always negative in GDS [32]. Scattered syncytiotrophoblastic elements may appear in GDS and should not lead to a choriocarcinoma diagnosis. Such tumors are reported as germinoma with syncytiotrophoblastic giant cells. Lymphoma is distinguished by irregular nuclear contours, lymphoid marker expression, and negative immunoreactivity for OCT3/4.

GDS harbor 12p alterations, typical for all post-pubertal-type GCT [33–37]. Oncogene mutations vary by anatomical location. KIT is most frequently mutated, followed by KRAS and NRAS. The mutation rate is low in seminoma (20%) [38, 39], around 50% in dysgerminomas [40, 41] as well as mediastinal germinomas [42] and up to 80% in CNS germinomas [43, 44]. KIT mutations are mainly in exon 17, unlike gastrointestinal stromal tumors (exons 11 and 9), so GDS do not respond to imatinib [45].

The prognosis of GDS is excellent due to high sensitivity to chemotherapy and radiation with > 95% 5-year survival rates in seminoma [46] and dysgerminoma [47]. Patients in early stage can be cured by surgery alone [48]. Long-term disease-free survival in germinoma of the mediastinum and brain reach 90% [49, 50].

Non-germinomatous GCT

Teratoma

Teratomas exhibit the greatest heterogeneity among GCT, as in principle any tissue type of the three blastodermal germ cell layers can occur (Fig. 5). In contrast to embryonal carcinoma, whose neoplastic cells reflect the early stages of embryonic development, the tumor cells of teratomas are usually fully mature. Like yolk sac tumor, teratoma can present as pre-pubertal and post-pubertal-type GCT, although in the latter case they rarely occur as a pure form and are more likely part of mixed GCT [51]. Despite extremely close morphological similarities, they exhibit an enormous range in terms of age, anatomical location, and tumor biology.

Extragonadal teratoma typically presents as pre-pubertal-type GCT. The sacrococcygeal area is the most common site (Fig. 6A), followed by head and neck, CNS (Fig. 6B), and mediastinum [52, 53]. Sacrococcygeal teratoma (SCT), which accounts for 40–50% of extragonadal teratomas, has not yet been included in any WHO tumor classification as a single entity. However, SCT is one of the most common congenital tumors [54, 55]. Beyond the age of 6 months, the incidence of pure teratoma decreases, while the frequency of yolk sac tumor rises [51]. Pure extragonadal teratomas do not metastasize, although prognosis can be fatal in a congenital setting, especially depending on size, which can reach > 15 cm [53] and the presence of hydrops fetalis [56]. Extragonadal teratomas do not harbor driver mutations [6, 57]. Whereas 12p alterations are a common feature of post-pubertal-type GCT [33], extragonadal pre-pubertal-type teratomas, especially SCT, lack chromosome 12p abnormalities [58, 59].

In the testis, pre-pubertal-type teratoma usually manifest before the age of 6 years [60], although in recent studies

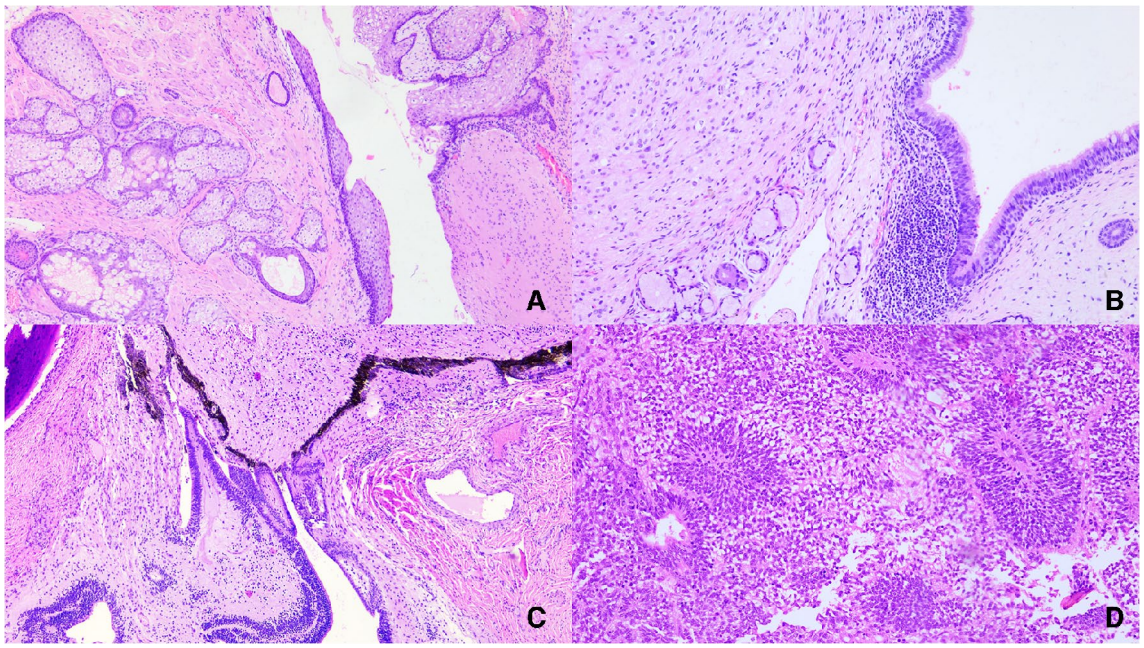

Fig. 5 Mature and immature ovarian teratoma. **A**, **B** Mature elements, including squamous epithelium, sebaceous glands, hair follicles, smooth muscle, respiratory epithelium, and mucous glands. Mature glioneuronal tissue and retina should not be misinterpreted as immature neuroepithelial components (**C**). **D** Immature neuroepithelium forming multilayered rosettes composed of atypical cells with brisk mitotic activity

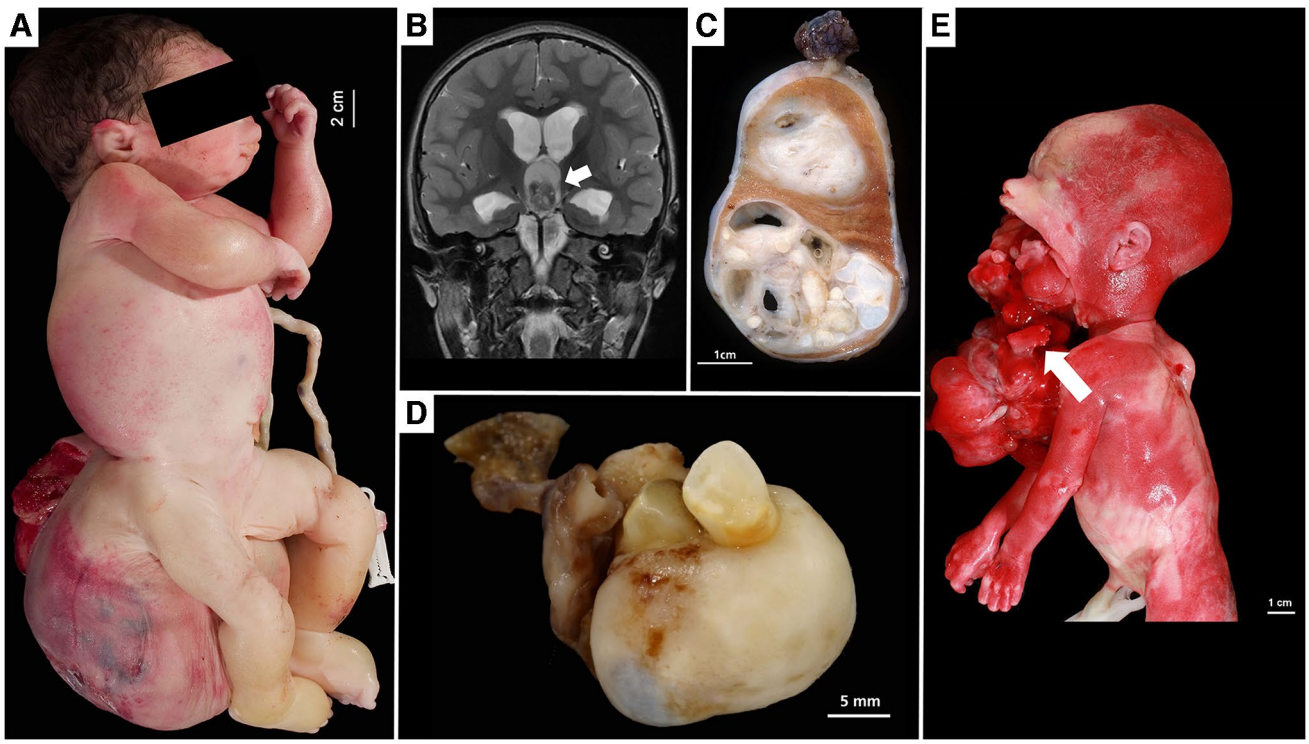

Fig. 6 Macroscopic spectrum of teratoma subtypes. **A** Congenital sacrococcygeal teratoma. **B** MRI of the brain showing a heterogeneous, partially cystic teratoma in the pineal region (arrow). **C** Prepubertal-type testicular teratoma: Cystic areas, partially filled with keratinaceous material and bluish cartilage (right part). **D** Bony protuberance with fully developed teeth from a mature cystic teratoma of the ovary. **E** Fetiform tumor mass (fetus in fetu) protruding from the mouth of fetus at 18 gestational week, showing a foot-like structure (arrow)

they have also been described more and more in older men [61]. In general, testicular teratoma in adults represents a post-pubertal-type GCT and is often a component of mixed GCT [51]. In the case of pure testicular teratoma in adults, the distinction between pre- and post-pubertal type can only be made by the presence of GCNIS in the adjacent testicular tissue or by the assessment of 12p status. This is important since prepubertal-type teratomas are benign [61–63] and are adequately treated with surgical (testis-sparing) excision alone [64].

Tumor markers are typically not elevated in teratomas. However, it is important to note that neonates and infants in the first months of life have physiologically elevated serum levels of alpha-fetoprotein (AFP), which do not necessarily indicate the presence of yolk sac tumor components [53].

Teratomas may be solid or have a variably prominent cystic component filled with keratinaceous or mucoid material (Fig. 6C). Grossly identifiable hair may be present in the dermoid subtype (mature cystic teratoma) identical to its much more common ovarian counterpart [62]. Other mature tissue components such as bone, teeth, or fat tissue may also be observed upon macroscopic examination (Fig. 6D). This appearance has not been described in post-pubertal-type teratomas of the testis.

Testicular and ovarian teratomas exhibit several key differences. In ovarian teratomas, special forms known as monodermal teratomas can occur. These are unique in that they consist predominantly of a single type of tissue, usually derived from one blastodermal layer. Mature cystic teratoma is technically a type of monodermal teratoma and falls within this category. Other examples include struma ovarii and carcinoid/neuroendocrine tumors, which develop when specific tissue components within a mature cystic teratoma undergo overgrowth. Monodermal teratomas are distinct to the ovary, originating from meiotic oocytes, which sets them apart from other germ cell tumors [65]. Consequently, they have been classified as a separate type (type IV GCT in the classification system proposed by Looijenga and Oosterhuis [4, 5]). In contrast, mature cystic teratomas arising outside the ovary are considered benign pre-pubertal-type teratomas.

Another unique concept in ovarian teratomas is the notion of immaturity, which is not recognized in teratomas at other anatomical locations. Immature tissue (e.g., primitive neuroectodermal component; Fig. 5D) is frequently present in congenital teratomas, yet immaturity is not associated with malignant behavior in sacrococcygeal teratomas [66]. Similarly, in testicular teratomas, the distinction between immature and mature teratomas has been abandoned due to the lack of therapeutic consequences. The only time immaturity becomes important in testicular teratomas is when differentiating post- from pre-pubertal-type teratomas, as immature elements (along with GCNIS and atrophy) are exclusion criteria for a benign pre-pubertal-type teratoma diagnosis.

There is a lack of consensus regarding the best approach to grade ovarian immature teratomas, with two well-known systems, a two-tier scale and a three-tier one. Reproducibility of the grading is also questionable and current efforts are underway to improve this difficult issue, for which there have been some preliminary analysis [67]. Hopefully, a new consensus will be reached to apply it in the grading of these tumors. It is generally agreed that low-grade tumors confined to the ovary do not require systemic treatment. Notably, opinions differ between pediatric and gynecologic oncologists regarding the role of chemotherapy in higher grade immature teratomas. In one series of ovarian GCT, there were no radiological responses to chemotherapy in immature teratomas and grade did not predict event-free survival, with no deaths occurring from immature teratomas [68]. Other authors have also highlighted these classification challenges [69]. Until these issues are resolved, the WHO have decided, for harmonization purposes, to include the category of immature teratomas, but limiting it to ovarian teratomas.

Somatic malignant transformation in GCT

In recent discussions, some authors have proposed that so-called grade 3 immature ovarian teratomas might represent a form of somatic malignant transformation (SMT) [69]. SMT in GCT, although rare, holds significant clinical relevance. The WHO classification defines SMT as a secondary tumor component, such as adenocarcinoma, embryonal neuroectodermal tumor (ENET), or rhabdomyosarcoma, that occupies at least one low-power field. The management of SMT presents considerable challenges. Studies indicate that the prognosis is generally not adversely impacted when SMT is confined to the primary tumor. However, the presence of SMT in metastatic sites is associated with a poorer prognosis [70, 71]. Although SMT is predominantly documented in post-pubertal-type GCT of the testis, it can also occur in prepubertal teratomas [72]. A particularly notable variant, the vasculogenic mesenchymal tumor, has recently been identified in GCT of the mediastinum [73], whereas vascular tumors as SMT are rare in other locations. Diagnosis of SMT can be challenging, but the detection of 12p alterations remains a valuable tool for confirming the GCT origin [70, 71]. This diagnostic marker is crucial for distinguishing SMT from secondary malignancies and ensuring accurate treatment planning. The emerging understanding of SMT in GCT underscores the need for continued research and nuanced approaches to therapy, tailored to the unique characteristics of these complex cases.

Fetus in fetu

Fetus in fetu (FIF) is a new diagnostic category included exclusively in the WHO Classification of Paediatric

Tumours [2]. It is a developmental anomaly in which a parasitic fetus is contained within the body of its twin. Most cases occur at the sites of attachment of conjoined twins, such as the sacral region, abdomen, retroperitoneum, face, neck, and orbit. The majority of cases are intra-abdominal, although other sites may also be affected [74].

FIF is currently classified as a so-called type 0 germ cell tumor (GCT) in the classification system proposed by Oosterhuis and Looijenga [5]. More than 15% of cases have a familial history of twinning and it is currently thought to result from an abnormality in the development of monozygotic twins. Furthermore, it is hypothesized to arise from alterations in the development of blastomeres at the two-cell stage, during which they are totipotent [5]. Several cases report genotypic identity between the host and the FIF [75].

Macroscopic features include a tumor mass with fetiform characteristics in varying degrees of development (Fig. 6E). Radiological examination may show the presence of vertebral organization suggestive of metameric segmentation. Some cases may strikingly resemble a developing fetus and have even shown spontaneous limb movement [76]. Histopathological features are similar to those of a mature teratoma but display a higher degree of organization. Most cases can be cured through surgical resection. However, there are reports of malignant recurrence, particularly in the form of yolk sac tumors [77].

Yolk sac tumor

Yolk sac tumor (YST) is a malignant neoplasm resembling extraembryonic structures, including the yolk sac, allantois, and extraembryonic mesenchyme. Testicular YST is subclassified into pre- and post-pubertal-type YST. Post-pubertal-type YST in testis is related to GCNIS and harbors 12p alterations. Pre-pubertal-type YST of the testis may represent progression from teratoma, usually showing recurrent gains of 1q, 12p13 (but not isochromosome 12p), 20q, and 22 as well as losses of 1p, 4, and 6q [5, 78]. There are differences in age of incidence, with pre-pubertal-type YST rarely arising beyond 6 years of age (median, 16–20 months), also showing no association with cryptorchidism or GCNIS. Testicular post-pubertal-type YST does not present in a pure form and shares the age distribution of other post-pubertal-type GCT. Elevation of serum AFP is classic. However, caution is advised as AFP may be physiologically elevated in neonates and young infants, as mentioned above.

Macroscopically, YSTs are usually solid and relatively homogeneous with a yellow cut surface (Fig. 3B). On histopathology, pre- and post-pubertal-type YSTs are identical, showing a wide range of histological patterns. Combinations of patterns are frequent (Fig. 7). AFP immunohistochemistry is an important diagnostic tool, although teratoma may show positivity in glandular epithelium and liver tissue. Many other markers have been reported (e.g., Glypican 3 [79, 80], SALL4 [81, 82], HNF1β [83, 84], FoxA2 [85]), but all of them

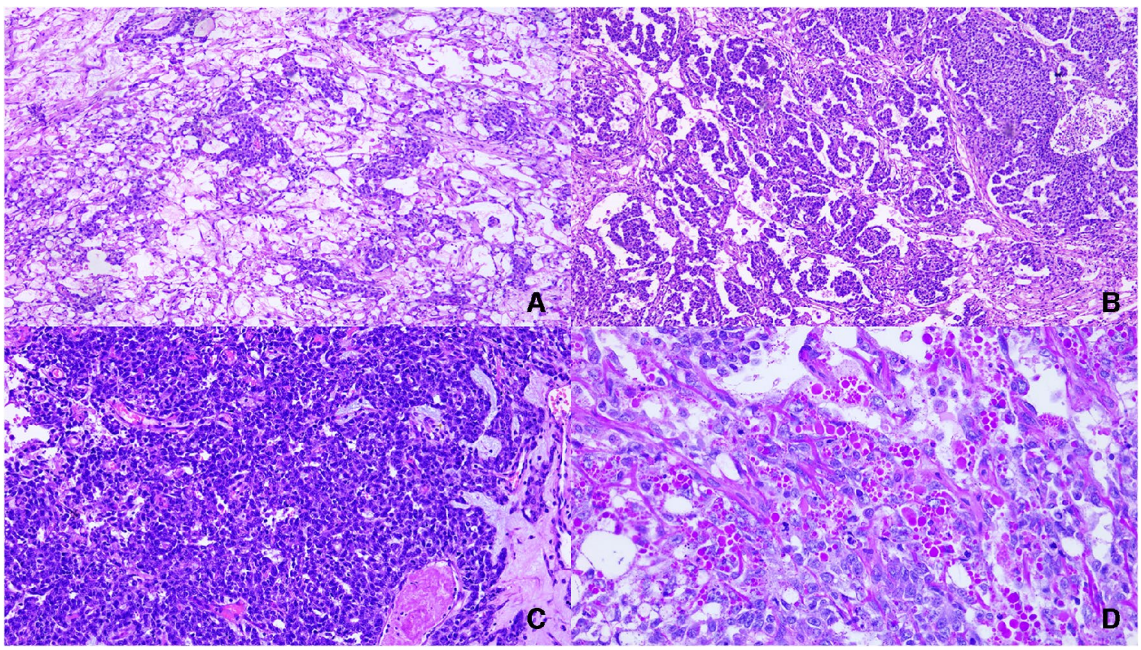

Fig. 7 *Yolk sac tumor* showing different histological patterns (**A** microcystic/reticular; **B** papillary; **C** solid). PAS highlights the presence of eosinophilic, PAS-positive, diastase-resistant intracellular and extracellular hyaline bodies (**D**)

share a heterogeneous expression pattern. In the testis, pre-pubertal-type YST may be found in combination with prepubertal teratoma, whereas post-pubertal-type YST is usually a component in mixed GCT.

Embryonal carcinoma

In contrast to teratoma, embryonal carcinoma (EC) is an undifferentiated GCT subtype that resembles embryonic stem cells. It belongs to the post-pubertal-type GCT category with 12p alterations and can arise in any midline location or in the gonads. EC usually appears as a component of malignant mixed GCT and pure EC is rare (Fig. 3C). It does not occur in childhood, except in DSD patients [9]. Serum β-hCG and AFP are generally not elevated, though LDH can be. EC cells are epithelioid with vesicular nuclei, dense amphophilic cytoplasm and poorly defined cytoplasmic membranes. Mitoses (atypical), necrotic foci, nuclear crowding, and pleomorphism are characteristic (Fig. 8). The most frequent patterns are solid, glandular, and papillary in any combination. EC can mimic germinoma. It may contain syncytiotrophoblast cells and lymphocytic infiltrates, although a granulomatous reaction is rare [86].

Immunohistochemically, EC expresses cytokeratin AE1/AE3, OCT3/4, SOX2, CD30 (which may be lost after chemotherapy) [87], and SALL4. Prognosis correlates with stage. Pure embryonal carcinoma behaves more aggressively than mixed GCT, with frequent lymphovascular invasion and higher metastatic potential. Postoperative combination chemotherapy is recommended in many cases [88]. For CNS embryonal carcinoma, outcomes are poor, but combined irradiation and chemotherapy can increase 5- and 10-year survival rates to 75–80% [50].

Choriocarcinoma

Choriocarcinoma is composed of cells, which reflect the extraembryonic chorion. Although morphologically similar, deep biological differences exist among non-gestational choriocarcinoma and its gestational counterpart that mostly occur in the uterus of women in reproductive age [89]. Genetically, gestational cases are androgenetic XX choriocarcinomas, usually following complete moles [90].

Non-gestational choriocarcinoma, as in other GCT, is related to gains in 12p [91], although CNS tumours may show fewer cases with gains of 12p, when compared to testicular and mediastinal examples [92]. Pure testicular choriocarcinoma is rare and is associated with other GCT in most cases. It may occur in the gonads, mediastinum, and CNS, with predominance in the pineal region. Symptoms will be related to location, metastatic disease, and tumoral hemorrhage [93]. Elevation of serum b-hCG is the norm, often up to > 50,000 IU/L [94]. Macroscopically, solid, hemorrhagic, and necrotic nodules with more grayish-tan areas are typical (Fig. 3D). Histologically, combinations of mononucleated trophoblasts (cytotrophoblasts and intermediate trophoblasts) and multinucleated syncytiotrophoblasts (usually capping the mononucleated trophoblasts) immersed in a hemorrhagic background are characteristic (Fig. 9). β-hCG expression remains an invaluable diagnostic tool, although caution is advised in GCT that may have admixed syncytiotrophoblasts, like GDS.

Malignant mixed GCT

Malignant mixed GCTs are composed of more than one histological element. They represent the majority of non-germinomatous tumors, even though GDS may occasionally be one of the components. Any combination of elements can occur,

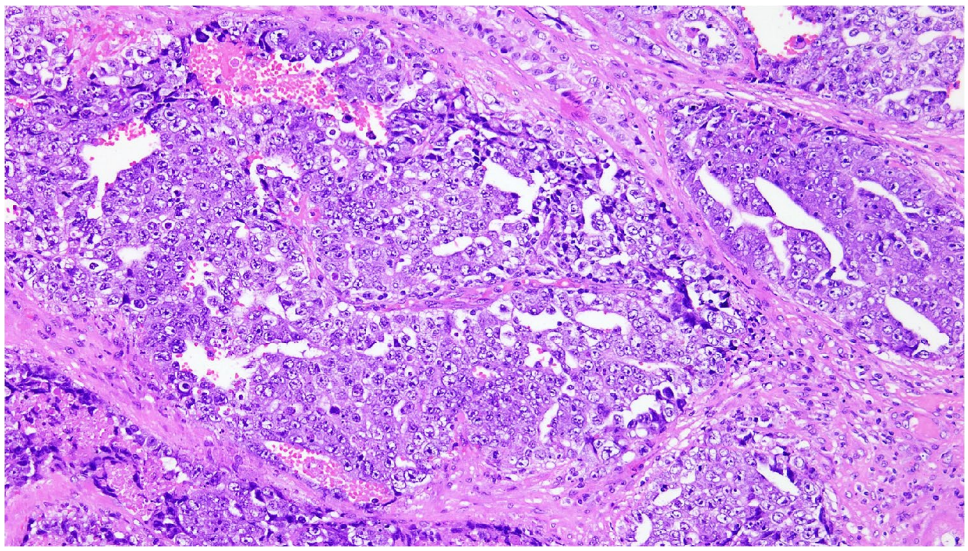

Fig. 8 *Embryonal carcinoma* predominantly composed of sheets of large, pleomorphic cells with amphophilic cytoplasm. The nuclei exhibit irregularly distributed chromatin, one or more prominent nucleoli, and nuclear crowding. Mitotic activity is high, with frequent atypical mitoses. Focally, gland-like structures are observed

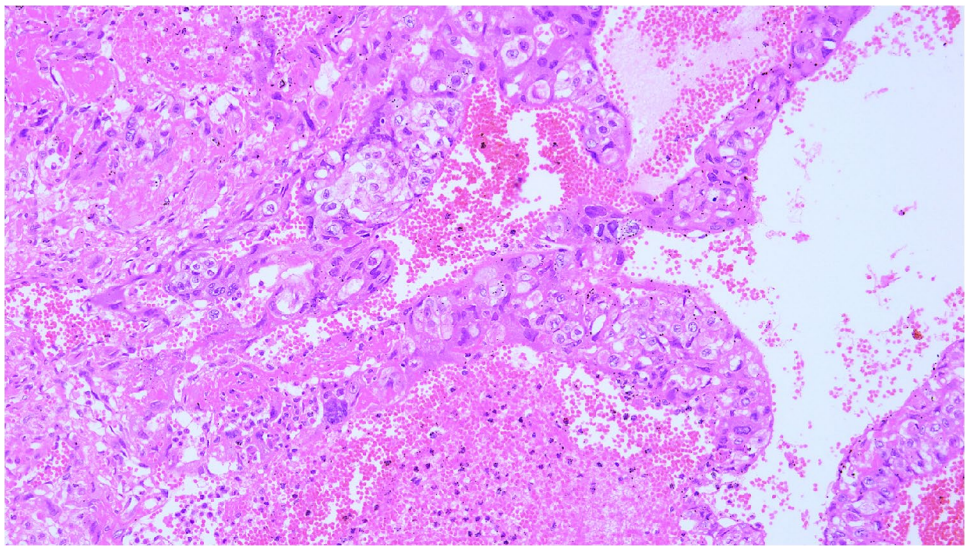

Fig. 9 Non-gestational choriocarcinoma. Biphasic admixture of cytotrophoblasts (inhibin-positive) and syncytiotrophoblasts (HCG-positive) is characteristic of choriocarcinoma. Note the hemorrhagic background frequently accompanying this tumor

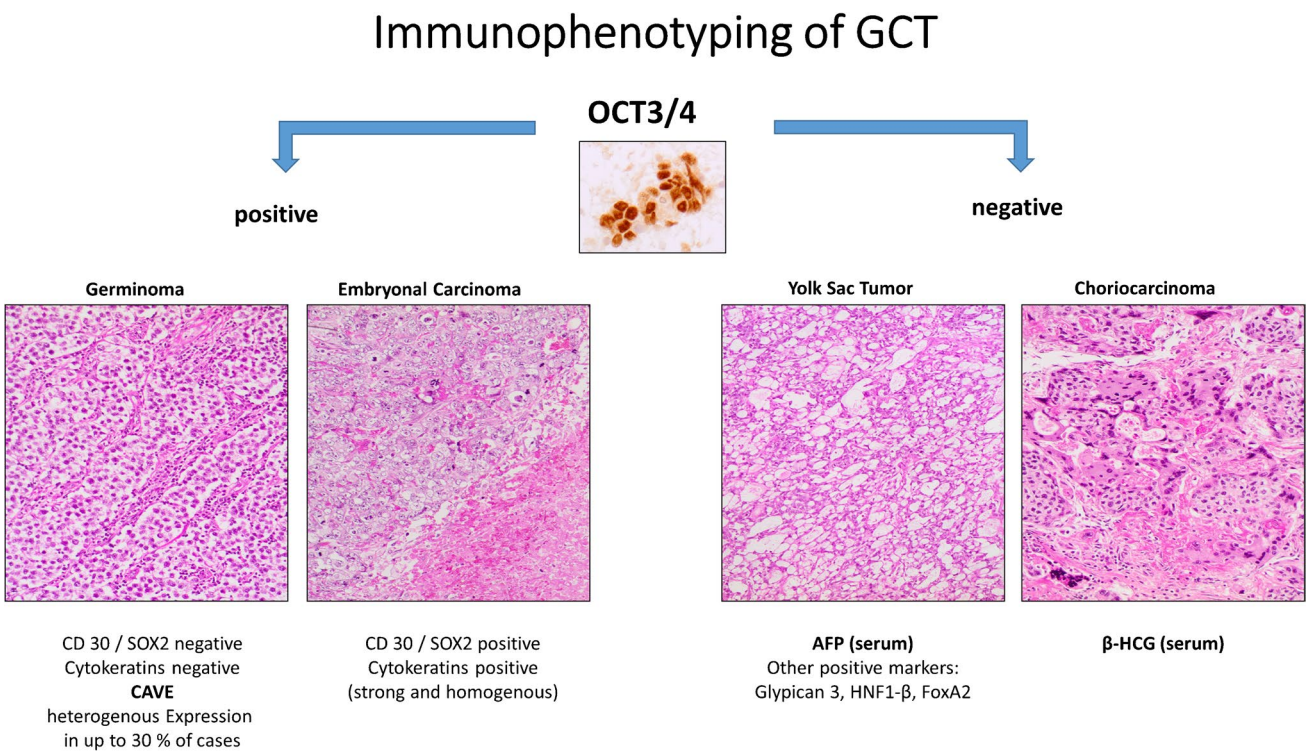

Fig. 10 Immunohistochemical algorithm for the diagnosis of the different GCT subtypes

although embryonal carcinoma mixed with teratoma, GDS, or yolk sac tumor is the most frequent. Identification of each malignant component has prognostic implications and should be reported appropriately. Corresponding tumor markers, such as alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-hCG), may be elevated. Macroscopically, mixed GCTs display heterogeneous morphology, reflecting the varying proportions of each element. On histopathological examination, the characteristic features of each subtype are present. An immunohistochemical algorithm for the distinction of the different subtypes is summarized in Fig. 10.

Conclusion

Significant effort has been made to establish an organ-independent classification, which has been quite successful thanks to the research of many who have increasingly

unraveled the pathogenesis of these fascinating tumors. For example, the integration and harmonization of teratoma classification across testis, ovary, and extragonadal sites represent a significant step forward in the understanding and management of these tumors. However, there remains potential for further refinement and improvement, as we have discussed above.

Engaging in a dialog with authors of the other WHO classifications has been pivotal in ensuring that our proposed revisions are both comprehensive and cohesive. However, the integration of spermatocytic tumors remains an open question. Given their exclusive occurrence in the testes of older patients, it is a compelling argument to retain them within the WHO classification of testicular tumors.

As we move forward, continuous evaluation and potential updates to this classification will be essential. This will accommodate emerging scientific insights and maintain alignment with evolving diagnostic and therapeutic practices. The ongoing collaboration among experts in this field is vital for addressing the remaining challenges and refining the classification to further enhance the care and prognosis of patients with pediatric GCT.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Zambrano E, Reyes-Múgica M (2023) Pediatric germ cell tumors. Semin Diagn Pathol 40(1):52–62
2. Trama A, Berrino F (2017) The epidemiology of malignant germ cell tumors: the EUROCARE study. In: Nogales FF, Jimenez RE (eds) Pathology and Biology of Human Germ Cell Tumors. pp 11–22. https://doi.org/10.1007/978-3-662-53775-6_2
3. WHO Classification of Tumours Editorial Board (2022) Paediatric tumours. (WHO classification of tumours series, vol 7, 5th edn.). International Agency for Research on Cancer, Lyon
4. Ulbright TM (2005) Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. Mod Pathol 18:S61–S79. https://doi.org/10.1016/S0893-3952(22)04459-3
5. Oosterhuis JW, Looijenga LHJ (2005) Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer 5:210–222. https://doi.org/10.1038/nrc1568
6. Oosterhuis JW, Looijenga LHJ (2019) Human germ cell tumours from a developmental perspective. Nat Rev Cancer 19:522–537. https://doi.org/10.1038/s41568-019-0178-9
7. Looijenga LHJ, Hersmus R, Oosterhuis JW et al (2007) Tumor risk in disorders of sex development (DSD). Best Pract Res Clin Endocrinol Metab 21:480–495. https://doi.org/10.1016/j.beem.2007.05.001
8. van der Zwan YG, Biermann K, Wolffenbuttel KP et al (2015) Gonadal maldevelopment as risk factor for germ cell cancer: towards a clinical decision model. Eur Urol 67:692–701. https://doi.org/10.1016/j.eururo.2014.07.011
9. Savage MO, Lowe DG (1990) Gonadal neoplasia and abnormal sexual differentiation. Clin Endocrinol (Oxf) 32:519–533. https://doi.org/10.1111/j.1365-2265.1990.tb00893.x
10. Gittleman H, Cioffi G, Vecchione-Koval T et al (2019) Descriptive epidemiology of germ cell tumors of the central nervous system diagnosed in the United States from 2006 to 2015. J Neurooncol 143:251–260. https://doi.org/10.1007/s11060-019-03173-4
11. Ostrom QT, Cioffi G, Gittleman H et al (2019) CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. Neuro Oncol 21:v1–v100. https://doi.org/10.1093/neuonc/noz150
12. Kang J-M, Ha J, Hong EK et al (2019) A nationwide, population-based epidemiologic study of childhood brain tumors in Korea, 2005–2014: A Comparison with United States Data. Cancer Epidemiol Biomarkers Prev 28:409–416. https://doi.org/10.1158/1055-9965.EPI-18-0634
13. Kaatsch P, Rickert CH, Kühl J et al (2001) Population-based epidemiologic data on brain tumors in German children. Cancer 92:3155–3164. https://doi.org/10.1002/1097-0142(20011215)92:12%3c3155::aid-cncr10158%3e3.0.co;2-c
14. Arora RS, Alston RD, Eden TOB et al (2012) Comparative incidence patterns and trends of gonadal and extragonadal germ cell tumors in England, 1979 to 2003. Cancer 118:4290–4297. https://doi.org/10.1002/cncr.27403
15. Ferguson L, Agoulnik AI (2013) Testicular cancer and cryptorchidism. Front Endocrinol (Lausanne) 4:32. https://doi.org/10.3389/fendo.2013.00032
16. Smith HO, Berwick M, Verschraegen CF et al (2006) Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol 107:1075–1085. https://doi.org/10.1097/01.AOG.0000216004.22588.ce
17. Ulbright TM, Young RH (2014) Gonadoblastoma and selected other aspects of gonadal pathology in young patients with disorders of sex development. Semin Diagn Pathol 31:427–440. https://doi.org/10.1053/j.semdp.2014.07.001
18. Takeda S, Miyoshi S, Ohta M et al (2003) Primary germ cell tumors in the mediastinum: a 50-year experience at a single Japanese institution. Cancer 97:367–376. https://doi.org/10.1002/cncr.11068
19. Völkl TMK, Langer T, Aigner T et al (2006) Klinefelter syndrome and mediastinal germ cell tumors. Am J Med Genet A 140:471–481. https://doi.org/10.1002/ajmg.a.31103
20. Leroy X, Augusto D, Leteurtre E, Gosselin B (2002) CD30 and CD117 (c-kit) used in combination are useful for distinguishing embryonal carcinoma from seminoma. J Histochem Cytochem 50:283–285. https://doi.org/10.1177/002215540205000216
21. Izquierdo MA, Van der Valk P, Van Ark-Otte J et al (1995) Differential expression of the c-kit proto-oncogene in germ cell tumours. J Pathol 177:253–258. https://doi.org/10.1002/path.1711770307

22. Hattab EM, Tu P-H, Wilson JD, Cheng L (2005) OCT4 immunohistochemistry is superior to placental alkaline phosphatase (PLAP) in the diagnosis of central nervous system germinoma. Am J Surg Pathol 29:368–371. https://doi.org/10.1097/01.pas.0000149709.19958.a7
23. Cheng L, Thomas A, Roth LM et al (2004) OCT4: a novel biomarker for dysgerminoma of the ovary. Am J Surg Pathol 28:1341–1346. https://doi.org/10.1097/01.pas.0000135528.03942.1f
24. Looijenga LHJ, Stoop H, de Leeuw HPJC et al (2003) POU5F1 (OCT3/4) identifies cells with pluripotent potential in human germ cell tumors. Cancer Res 63:2244–2250
25. Jones TD, Ulbright TM, Eble JN et al (2004) OCT4 staining in testicular tumors: a sensitive and specific marker for seminoma and embryonal carcinoma. Am J Surg Pathol 28:935–940. https://doi.org/10.1097/00000478-200407000-00014
26. Cao D, Guo S, Allan RW et al (2009) SALL4 is a novel sensitive and specific marker of ovarian primitive germ cell tumors and is particularly useful in distinguishing yolk sac tumor from clear cell carcinoma. Am J Surg Pathol 33:894–904. https://doi.org/10.1097/PAS.0b013e318198177d
27. Cao D, Li J, Guo CC et al (2009) SALL4 is a novel diagnostic marker for testicular germ cell tumors. Am J Surg Pathol 33:1065–1077. https://doi.org/10.1097/PAS.0b013e3181a13eef
28. Nonaka D (2009) Differential expression of SOX2 and SOX17 in testicular germ cell tumors. Am J Clin Pathol 131:731–736. https://doi.org/10.1309/AJCP7MNCNBCRN8NO
29. Bode PK, Barghorn A, Fritzsche FR et al (2011) MAGEC2 is a sensitive and novel marker for seminoma: a tissue microarray analysis of 325 testicular germ cell tumors. Mod Pathol 24:829–835. https://doi.org/10.1038/modpathol.2011.6
30. Lau SK, Weiss LM, Chu PG (2007) D2–40 immunohistochemistry in the differential diagnosis of seminoma and embryonal carcinoma: a comparative immunohistochemical study with KIT (CD117) and CD30. Mod Pathol 20:320–325. https://doi.org/10.1038/modpathol.3800749
31. Cheville JC, Rao S, Iczkowski KA et al (2000) Cytokeratin expression in seminoma of the human testis. Am J Clin Pathol 113:583–588. https://doi.org/10.1309/5fu2-8yq9-q12r-y0ku
32. Ulbright TM, Tickoo SK, Berney DM et al (2014) Best practices recommendations in the application of immunohistochemistry in testicular tumors: report from the International Society of Urological Pathology consensus conference. Am J Surg Pathol 38:e50–e59. https://doi.org/10.1097/PAS.0000000000000233
33 Looijenga LHJ, Zafarana G, Grygalewicz B et al (2003) Role of gain of 12p in germ cell tumour development. APMIS 111:161–71. https://doi.org/10.1034/j.1600-0463.2003.11101201.x. (discussion 172-3)
34. Sung M-T, Maclennan GT, Lopez-Beltran A et al (2008) Primary mediastinal seminoma: a comprehensive assessment integrated with histology, immunohistochemistry, and fluorescence in situ hybridization for chromosome 12p abnormalities in 23 cases. Am J Surg Pathol 32:146–155. https://doi.org/10.1097/PAS.0b013e3181379edf
35. Atkin NB, Baker MC (1982) Specific chromosome change, i(12p), in testicular tumours? Lancet 2:1349. https://doi.org/10.1016/s0140-6736(82)91557-4
36. Cossu-Rocca P, Zhang S, Roth LM et al (2006) Chromosome 12p abnormalities in dysgerminoma of the ovary: a FISH analysis. Mod Pathol 19:611–615. https://doi.org/10.1038/modpathol.3800576
37. Terashima K, Yu A, Chow W-YT et al (2014) Genome-wide analysis of DNA copy number alterations and loss of heterozygosity in intracranial germ cell tumors. Pediatr Blood Cancer 61:593–600. https://doi.org/10.1002/pbc.24833
38. Litchfield K, Summersgill B, Yost S et al (2015) Whole-exome sequencing reveals the mutational spectrum of testicular germ cell tumours. Nat Commun 6:5973. https://doi.org/10.1038/ncomms6973
39. Cutcutache I, Suzuki Y, Tan IB et al (2015) Exome-wide sequencing shows low mutation rates and identifies novel mutated genes in seminomas. Eur Urol 68:77–83. https://doi.org/10.1016/j.eururo.2014.12.040
40. Hoei-Hansen CE, Kraggerud SM, Abeler VM et al (2007) Ovarian dysgerminomas are characterised by frequent KIT mutations and abundant expression of pluripotency markers. Mol Cancer 6:12. https://doi.org/10.1186/1476-4598-6-12
41. Hersmus R, Stoop H, van de Geijn GJ et al (2012) Prevalence of c-KIT mutations in gonadoblastoma and dysgerminomas of patients with disorders of sex development (DSD) and ovarian dysgerminomas. PLoS ONE 7:e43952. https://doi.org/10.1371/journal.pone.0043952
42. Przygodzki RM, Hubbs AE, Zhao F-Q, O'Leary TJ (2002) Primary mediastinal seminomas: evidence of single and multiple KIT mutations. Lab Invest 82:1369–1375. https://doi.org/10.1097/01.lab.0000032410.46986.7b
43. Wang L, Yamaguchi S, Burstein MD et al (2014) Novel somatic and germline mutations in intracranial germ cell tumours. Nature 511:241–245. https://doi.org/10.1038/nature13296
44. Fukushima S, Otsuka A, Suzuki T et al (2014) Mutually exclusive mutations of KIT and RAS are associated with KIT mRNA expression and chromosomal instability in primary intracranial pure germinomas. Acta Neuropathol 127:911–925. https://doi.org/10.1007/s00401-014-1247-5
45. Einhorn LH, Brames MJ, Heinrich MC et al (2006) Phase II study of imatinib mesylate in chemotherapy refractory germ cell tumors expressing KIT. Am J Clin Oncol 29:12–13. https://doi.org/10.1097/01.coc.0000195086.47548.ef
46. Oliver RTD, Mead GM, Rustin GJS et al (2011) Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 29:957–962. https://doi.org/10.1200/JCO.2009.26.4655
47. Duhil de Bénazé G, Pacquement H, Faure-Conter C et al (2018) Paediatric dysgerminoma: results of three consecutive French germ cell tumours clinical studies (TGM-85/90/95) with late effects study. Eur J Cancer 91:30–37. https://doi.org/10.1016/j.ejca.2017.11.030
48 Honecker F, Aparicio J, Berney D et al (2018) ESMO consensus conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol 29(8):1658–1686. https://doi.org/10.1093/annonc/mdy217
49. Bokemeyer C, Nichols CR, Droz J-P et al (2002) Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol 20:1864–1873. https://doi.org/10.1200/JCO.2002.07.062
50. Takami H, Fukuoka K, Fukushima S et al (2019) Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. Neuro Oncol 21:1565–1577. https://doi.org/10.1093/neuonc/noz139
51. Schneider DT, Calaminus G, Koch S et al (2004) Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer 42:169–175. https://doi.org/10.1002/pbc.10321
52. Harms D, Schmidt D, Leuschner I (1989) Abdominal, retroperitoneal and sacrococcygeal tumours of the newborn and the very young infant. Report from the Kiel paediatric tumour registry. Eur J Pediatr 148:720–728. https://doi.org/10.1007/BF00443094

53. Heerema-McKenney A, Harrison MR, Bratton B et al (2005) Congenital teratoma: a clinicopathologic study of 22 fetal and neonatal tumors. Am J Surg Pathol 29:29–38. https://doi.org/10.1097/01.pas.0000146006.46468.ef
54. Swamy R, Embleton N, Hale J (2008) Sacrococcygeal teratoma over two decades: birth prevalence, prenatal diagnosis and clinical outcomes. Prenat Diagn 28:1048–1051. https://doi.org/10.1002/pd.2122
55. Hambraeus M, Arnbjörnsson E, Börjesson A et al (2016) Sacrococcygeal teratoma: a population-based study of incidence and prenatal prognostic factors. J Pediatr Surg 51:481–485. https://doi.org/10.1016/j.jpedsurg.2015.09.007
56. Ayed A, Tonks AM, Lander A, Kilby MD (2015) A review of pregnancies complicated by congenital sacrococcygeal teratoma in the West Midlands region over an 18-year period: population-based, cohort study. Prenat Diagn 35:1037–1047. https://doi.org/10.1002/pd.4641
57. Harms D, Zahn S, Göbel U, Schneider DT (2006) Pathology and molecular biology of teratomas in childhood and adolescence. Klin Padiatr 218:296–302. https://doi.org/10.1055/s-2006-942271
58. Mylonas KS, Kao C-S, Levy D et al (2019) Clinicopathologic features and chromosome 12p status of pediatric sacrococcygeal teratomas: a multi-institutional analysis. Pediatr Dev Pathol 22:214–220. https://doi.org/10.1177/1093526618798771
59. Gurda GT, VandenBussche CJ, Yonescu R et al (2014) Sacrococcygeal teratomas: clinico-pathological characteristics and isochromosome 12p status. Mod Pathol 27:562–568. https://doi.org/10.1038/modpathol.2013.171
60 Ross JH, Rybicki L, Kay R (2002) Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. J Urol 168:1675–8. https://doi.org/10.1097/01.ju.0000030749.27823.f5. (discussion 1678-9)
61. Wagner T, Scandura G, Roe A et al (2020) Prospective molecular and morphological assessment of testicular prepubertal-type teratomas in postpubertal men. Mod Pathol 33:713–721. https://doi.org/10.1038/s41379-019-0404-8
62. Zhang C, Berney DM, Hirsch MS et al (2013) Evidence supporting the existence of benign teratomas of the postpubertal testis: a clinical, histopathologic, and molecular genetic analysis of 25 cases. Am J Surg Pathol 37:827–835. https://doi.org/10.1097/PAS.0b013e31827dcc4c
63. Semjen D, Kalman E, Tornoczky T, Szuhai K (2014) Further evidence of the existence of benign teratomas of the postpubertal testis. Am J Surg Pathol 38:580–581. https://doi.org/10.1097/PAS.0000000000000186
64. Shukla AR, Woodard C, Carr MC et al (2004) Experience with testis sparing surgery for testicular teratoma. J Urol 171:161–163. https://doi.org/10.1097/01.ju.0000101185.90327.b4
65. Kaku H, Usui H, Qu J, Shozu M (2016) Mature cystic teratomas arise from meiotic oocytes, but not from pre-meiotic oogonia. Genes Chromosomes Cancer 55:355–364. https://doi.org/10.1002/gcc.22339
66. Göbel U, Schneider DT, Calaminus G et al (2001) Multimodal treatment of malignant sacrococcygeal germ cell tumors: a prospective analysis of 66 patients of the German cooperative protocols MAKEI 83/86 and 89. J Clin Oncol 19:1943–1950. https://doi.org/10.1200/JCO.2001.19.7.1943
67. Pashankar F, Hanley K, Lockley M et al (2022) Addressing the diagnostic and therapeutic dilemmas of ovarian immature teratoma: Report from a clinicopathologic consensus conference. Eur J Cancer 173:59–70. https://doi.org/10.1016/j.ejca.2022.06.006
68. Newton C, Murali K, Ahmad A et al (2019) A multicentre retrospective cohort study of ovarian germ cell tumours: evidence for chemotherapy de-escalation and alignment of paediatric and adult practice. Eur J Cancer 113:19–27. https://doi.org/10.1016/j.ejca.2019.03.001
69. Berney DM, Stoneham S, Arora R et al (2020) Ovarian germ cell tumour classification: views from the testis. Histopathology 76:25–36. https://doi.org/10.1111/his.14016
70. Lobo J, Rodrigues Â, Henrique R et al (2022) Morphological spectrum and molecular features of somatic malignant transformation in germ cell tumours. Histopathology 81:84–98. https://doi.org/10.1111/his.14667
71. Wyvekens N, Sholl LM, Yang Y et al (2022) Molecular correlates of male germ cell tumors with overgrowth of components resembling somatic malignancies. Mod Pathol 35:1966–1973. https://doi.org/10.1038/s41379-022-01136-1
72. Terenziani M, D'Angelo P, Bisogno G et al (2010) Teratoma with a malignant somatic component in pediatric patients: the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) experience. Pediatr Blood Cancer 54:532–537. https://doi.org/10.1002/pbc.22397
73. Levy DR, Agaram NP, Kao C-S et al (2021) Vasculogenic mesenchymal tumor: a clinicopathologic and molecular study of 55 cases of a distinctive neoplasm originating from mediastinal yolk sac tumor and an occasional precursor to angiosarcoma. Am J Surg Pathol 45:463–476. https://doi.org/10.1097/PAS.0000000000001615
74. Sathe PA, Ghodke RK, Kandalkar BM (2014) Fetus in fetu: an institutional experience. Pediatr Dev Pathol 17:243–249. https://doi.org/10.2350/14-01-1424-OA.1
75. Kim JW, Park S-H, Park S-S et al (2008) Fetus-in-fetu in the cranium of a 4-month-old boy: histopathology and short tandem repeat polymorphism-based genotyping. Case report J Neurosurg Pediatr 1:410–414. https://doi.org/10.3171/PED/2008/1/5/410
76. Jones DC, Reyes-Múgica M, Gallagher PG et al (2001) Three-dimensional sonographic imaging of a highly developed fetus in fetu with spontaneous movement of the extremities. J Ultrasound Med 20:1357–1363. https://doi.org/10.7863/jum.2001.20.12.1357
77. Hopkins KL, Dickson PK, Ball TI et al (1997) Fetus-in-fetu with malignant recurrence. J Pediatr Surg 32:1476–1479. https://doi.org/10.1016/s0022-3468(97)90567-4
78 Veltman IM, Schepens MT, Looijenga LHJ et al (2003) Germ cell tumours in neonates and infants: a distinct subgroup? APMIS 111:152–60. https://doi.org/10.1034/j.1600-0463.2003.11110119_1.x. (discussion 160)
79. Ota S, Hishinuma M, Yamauchi N et al (2006) Oncofetal protein glypican-3 in testicular germ-cell tumor. Virchows Arch 449:308–314. https://doi.org/10.1007/s00428-006-0238-x
80. Zynger DL, McCallum JC, Luan C et al (2010) Glypican 3 has a higher sensitivity than alpha-fetoprotein for testicular and ovarian yolk sac tumour: immunohistochemical investigation with analysis of histological growth patterns. Histopathology 56:750–757. https://doi.org/10.1111/j.1365-2559.2010.03553.x
81. Wu P, Luo R, Sun B et al (2020) SALL4 is a useful marker for pediatric yolk sac tumors. Pediatr Surg Int 36:727–734. https://doi.org/10.1007/s00383-020-04652-w
82. Wang F, Liu A, Peng Y et al (2009) Diagnostic utility of SALL4 in extragonadal yolk sac tumors: an immunohistochemical study of 59 cases with comparison to placental-like alkaline phosphatase, alpha-fetoprotein, and glypican-3. Am J Surg Pathol 33:1529–1539. https://doi.org/10.1097/PAS.0b013e3181ad25d5
83. Rougemont A-L, Tille J-C (2018) Role of HNF1β in the differential diagnosis of yolk sac tumor from other germ cell tumors. Hum Pathol 81:26–36. https://doi.org/10.1016/j.humpath.2018.04.025
84. Gallo A, Fankhauser C, Hermanns T et al (2020) HNF1β is a sensitive and specific novel marker for yolk sac tumor: a tissue microarray analysis of 601 testicular germ cell tumors. Mod Pathol 33:2354–2360. https://doi.org/10.1038/s41379-020-0597-x

85. Ricci C, Ambrosi F, Franceschini T et al (2023) FoxA2 is a reliable marker for the diagnosis of yolk sac tumour postpubertal-type. Histopathology 83:465–476. https://doi.org/10.1111/his.14968
86. Kao C-S, Ulbright TM, Young RH, Idrees MT (2014) Testicular embryonal carcinoma: a morphologic study of 180 cases highlighting unusual and unemphasized aspects. Am J Surg Pathol 38:689–697. https://doi.org/10.1097/PAS.0000000000000171
87. Berney DM, Shamash J, Pieroni K, Oliver RT (2001) Loss of CD30 expression in metastatic embryonal carcinoma: the effects of chemotherapy? Histopathology 39:382–385. https://doi.org/10.1046/j.1365-2559.2001.01226.x
88. Albers P, Siener R, Kliesch S et al (2003) Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German testicular cancer study group trial. J Clin Oncol 21:1505–1512. https://doi.org/10.1200/JCO.2003.07.169
89. Seckl MJ, Sebire NJ, Berkowitz RS (2010) Gestational trophoblastic disease. Lancet 376:717–729. https://doi.org/10.1016/S0140-6736(10)60280-2
90. Savage J, Adams E, Veras E et al (2017) Choriocarcinoma in women: analysis of a case series with genotyping. Am J Surg Pathol 41:1593–1606. https://doi.org/10.1097/PAS.0000000000000937
91. Schneider DT, Zahn S, Sievers S et al (2006) Molecular genetic analysis of central nervous system germ cell tumors with comparative genomic hybridization. Mod Pathol 19:864–873. https://doi.org/10.1038/modpathol.3800607
92. Sukov WR, Cheville JC, Giannini C et al (2010) Isochromosome 12p and polysomy 12 in primary central nervous system germ cell tumors: frequency and association with clinicopathologic features. Hum Pathol 41:232–238. https://doi.org/10.1016/j.humpath.2009.07.017
93. Jiang T, Raynald YH et al (2019) Predictive factors of overall survival in primary intracranial pure choriocarcinoma. J Clin Neurosci 61:93–101. https://doi.org/10.1016/j.jocn.2018.10.136
94. Alvarado-Cabrero I, Hernández-Toriz N, Paner GP (2014) Clinicopathologic analysis of choriocarcinoma as a pure or predominant component of germ cell tumor of the testis. Am J Surg Pathol 38:111–118. https://doi.org/10.1097/PAS.0b013e3182a2926e