Virchows Arch [Pathol Anat] (1986) 409:223–239

Virchows Archiv A

Germ cell tumours of childhood

Report of 170 cases including 59 pure and partial yolk-sac tumours*, **

Dieter Harms and Ute Jänig

Abteilung Paidopathologie, Pathologisches Institut der Universität Kiel, Hospitalstrasse 42, D-2300 Kiel, Federal Republic of Germany

Summary. 170 germ cell tumours of childhood and adolescence were studied by light microscopy and immunohistochemistry. The male-to-female ratio was 1:1.3. 52 (30.6%) tumours were benign (mature teratoma), 30 (17.6%) potentially malignant (immature teratoma), and 88 (51.8%) unequivocally malignant. The main locations were ovary, testis and sacrococcygeal region. 92 tumours were located in a gonad, 78 tumours in extragonadal sites (ratio: 1.2:1). Of the frankly malignant tumours 40 were yolk-sac tumours (YST) and an additional 19 tumours of more than one histological type contained a YST component. Therefore, 67% of the malignant tumours had a YST component. Children with immature teratoma and pure YST showed the lowest median age (5 and 24 months, respectively), while children with germinomas of various locations had the highest median age (153 months). A festoon pattern was the predominant histological feature in all YST and in the YST component of mixed germ cell tumours. Hyaline globules were found in 33/37 YST and in 16/17 YST components. Immunohistochemically, alpha$_1$-fetoprotein (AFP) was demonstrated in 18/22 YST and in 6/7 YST components of mixed germ cell tumours. Hyaline globules were mostly AFP-negative (only 5 cases with AFP-positive globules in addition to many AFP-negative globules). In 3 cases beta-HCG-positive giant cells were seen. In most YST prekeratin intermediate filaments could be demonstrated in the epithelial cells. Follow-up data, available from 51 cases of YST and tumours with YST components showed disease-free survival in 37 cases (72.5%). 10 patients (19.6%) died of disease, and 4 patients (7.8%) are living with disease. The comparably high rate of survivors reflects the effectiveness of modern therapy, particularly polychemotherapy, in addition to surgery.

* Dedicated to Professor Karl Lennert, Kiel, on the occasion of his 65th birthday

** This study was supported in part by a grant from the Bundesminister für Arbeit und Sozialordnung

Offprint requests to: D. Harms at the above address

Key words: Germ cell tumours of childhood – Yolk-sac tumour – Endodermal sinus tumour – Teratomas – Mixed germ cell tumours – Immunohistochemistry

Introduction

Germ cell tumours in children differ in many respects from their counterparts in adults. Among these differences the most important are firstly, the anatomical site of the tumour. In a statistical study of a large number of cases Dehner (1983) found the following sites to be the most frequent in children: Sacrococcygeal region (42% of cases), ovary (24%), testis (9%), mediastinum (7%), the central nervous system (CNS) (6%), and retroperitoneum (4%). Secondly, the ratio of gonadal to extragonadal tumours differs in children. In the same study Dehner found a striking predilection (3:1) for extragonadal sites in children (see also Fraumeni et al. 1973). Thirdly, the proportion of benign to malignant tumours is very different. The vast majority of germ cell tumours in the sacrococcygeal region follows a benign course when excised immediately after diagnosis (Donnelan and Swenson 1968; Altman et al. 1974; Valdiserri and Yunis 1981; Bale 1984); the younger a patient with a germ cell tumour of the ovary, the greater the likelihood that the tumour will be malignant (Abell 1966, 1982; Norris and Jensen 1972). Testicular tumours of childhood show a higher relative incidence of mature (benign) teratomas than those occurring in the adult (Houser et al. 1965; Brown 1976; Harms 1982; Weißbach et al. 1982); and many tumours affecting other anatomical sites exhibit deviations in their biological behaviour (Gonzalez-Crussi 1982). Fourthly, the histological type of the most common germ cell tumours in childhood differs from that in adults. The most frequent type of malignant germ cell tumour occurring in children is the yolk-sac tumour (endodermal sinus tumour), both in gonadal and extragonadal sites (Marsden et al. 1981; Dehner 1983). Out of a total of 170 germ cell tumours of various histological types from the files of the Paediatric Tumour Registry in Kiel, 40 were found to be pure yolk-sac tumours (YST), and 19 were germ cell tumours with a YST component. These cases, a large number considering the relatively low incidence of YST, will form the basis of the present study.

Material and methods

The files of the Paediatric Tumour Registry were searched for cases of germ cell neoplasia over a period of 19 years and 8 months from February 1966 through October 1984. The tumours were classified according to the WHO classification of tumours of the ovary and testis (Serov et al. 1973; Mostofi and Sobin 1977) in conjunction with the classification of the (British) Testicular Tumour Panel (Pugh and Cameron 1976). Immature teratomas are designated as "potentially malignant" germ cell tumours (Gonzalez-Crussi 1982) in the tables.

Paraffin sections and paraffin blocks were available in most cases. Special stain (Giemsa, Goldner, Bielschowsky, and periodic acid Schiff) were, or already had been done on paraffin sections. Each section was examined several times and the various tumour components were noted. Additional immunological stainings with alpha$_1$-fetoprotein (AFP), beta-HCG and pre-

keratin were done on many histologically confirmed YST and tumours with a YST component or suspected YST pattern.

Immunohistochemical analyses were carried out using the peroxidase-antiperoxidase method of Sternberger et al. (1970). The following antibodies were used: Antihuman antibody against alpha$_1$-fetoprotein (AFP) from rabbit (Dakopatts, Hamburg), polyclonal antihuman antibody from rabbit against beta-HCG (Dakopatts), polyclonal antihuman antibody from rabbit against prekeratin (Euro Diagnostics, Apeldoorn, The Netherlands), and polyclonal antihuman antibody from rabbit against alpha$_1$-antitrypsin (Dakopatts).

Note was also made of the following data: Age of the patient at diagnosis, localization of the tumour, and, for YST, the type of treatment and outcome.

Results

Our material consisted of 170 children with germ cell tumours of different anatomical sites and histological types. With regard to the biological behaviour 52 (30.6%) tumours were considered to be benign (mature teratomas), 30 (17.6%) to be potentially malignant (immature teratomas), and 88 (51.8%) as frankly malignant germ cell tumours. The male-to-female-ratio in these groups was 1:1.6, 1:1.7, and 1:1.2, respectively (concerning all groups 1:1.3).

The distribution of the germ cell tumours according to anatomical site and histological type is given in Tables 1 (WHO classifications) and 2 (British classification).

The most frequently affected organs or regions were, in descending order, ovary, testis, sacrococcygeal and cervical region; additional tumour locations were the CNS, retroperitoneum and the mediastinum (another 6 cases in various locations). Overall, 92 tumours (54.1%) were located in a gonad and 78 tumours (45.9%) in extragonadal sites (ratio: 1.2:1).

Fourty (23.5%) were pure YST; next in frequency, tumours of more than one histological type ($n=26=15.3\%$) and germinomas (9 in the ovary, 5 in the CNS, but only one in the testis) were noted, whilst embryonal carcinomas of the adult type ($n=4$) and (pure) choriocarcinomas ($n=2$) occurred very rarely. 19 of the 26 tumours of more than one histological type (Table 3) contained YST elements. Therefore, out of 88 unequivocally malignant cases 59 (67.0%) had at least a YST component. According to the British classification (Table 3) most of the tumours of more than one histological type had to be classified as malignant teratoma intermediate (MTI; 17/26).

Distribution of the various types of tumour according to the age of the patients is given in Table 4. Children with immature teratoma and pure YST had the lowest median age (5 and 24 months, respectively), while children with a germinoma had the highest median age (153 months).

Pure YST ($n=40$) were located most often in the testis ($n=18=45.0\%$), followed by the sacrococcygeal region ($n=10=25.0\%$) and ovary ($n=7=17.5\%$), as shown in Table 5. Patients with testicular and sacrococcygeal tumours were clearly younger (median age 19 and 24 months, respectively) than patients with tumour of the ovary (median age 129 months).

Patients with tumours of more than one histological type and a YST component ($n=19$; Table 6) had a higher average age than patients with

Table 1. Germ cell tumours of childhood and adolescence. Localisation and histological tumour types (WHO classification). Relation of gonadal to extragonadal germ cell tumours = 1.2:1

Localisation	Number of cases	%	Teratoma		YST	EC	G	Chorio	Mixed
			mature	immature					
Ovarian	50	29.4	19	8	7	0	9	0	7
Testicular	42	24.7	10	4	18	1	1	0	8
Sacrococcygeal	38	22.4	12	8	10	0	0	0	8
Cervical	10	5.9	7	2	0	0	0	0	1
CNS	9	5.3	0	0	1	0	5	2	1
Retroperitoneal	8	4.7	1	3	2	1	0	0	1
Mediastinal	7	4.1	1	4	1	0	1	0	0
Other	6	3.5	2	1	1	2	0	0	0
Total	170	–	52	30	40	4	16	2	26
%	–	100.0	30.6	17.6	23.5	2.4	9.4	1.2	15.3

YST: Yolk-sac tumour; EC: Embryonal carcinoma; G: Germinoma/Dysgerminoma/Seminoma; Chorio: Choriocarcinoma; Mixed: Tumours of more than one histological type

Table 2. Germ cell tumours of childhood and adolescence. Localisation and histological tumour types (Classification of the British Testicular Tumour Panel; cf. Pugh and Cameron 1976)

Localisation	Number of cases	%	TD	T imm	YST	MTU	MTI	MTT		G	Comb
								pure	component		
Ovarian	50	29.4	19	8	7	0	3	0	2	9	2
Testicular	42	24.7	10	4	18	1	4	0	1	1	3
Sacrococcygeal	38	22.4	12	8	10	0	7	0	1	0	0
Cervical	10	5.9	7	2	0	0	1	0	0	0	0
CNS	9	5.3	0	0	1	0	1	2	0	5	0
Retroperitoneal	8	4.7	1	3	2	1	1	0	0	0	0
Mediastinal	7	4.1	1	4	1	0	0	0	0	1	0
Other	6	3.5	2	1	1	2	0	0	0	0	0
Total	170	–	52	30	40	4	17[a]	2	4	16	5
%	–	100.0	30.6	17.6	23.5	2.4	9.4	1.2	2.4	9.4	2.9

TD: Teratoma differentiated; T imm: Immature subtype of TD; YST: Yolk-sac tumour; MTU: Malignant teratoma undifferentiated; MTI: Malignant teratoma intermediate; MTT: Malignant teratoma trophoblastic; G: Germinoma/Dysgerminoma/Seminoma; Comb: G+ other germ cell tumour (excluding MTT component)

[a] In 15/17 cases a yolk-sac tumour component!

a pure YST (cf. Table 5). Germ cell tumours with a YST component occurred in the ovary and testis only in older children, while YST components in the sacrococcygeal region and other sites were observed only in very young children.

Macroscopically, the size of YST, including tumours with a YST compo-

Table 3. Malignant germ cell tumours of more than one histological type in childhood and adolescence ($n=26$). Any localisation. WHO classification and classification of the British Testicular Tumour Panel. Most cases of MTI contain a yolk-sac tumour component (15/17)! Relation of malignant tumours of one histological type ($n=62$) to tumours of more than one histological type = 2.4:1

Number of histological types	Histological types (WHO classification)	Number of cases	British classification
Two	T+YST	11	MTI
	T+Ec	2	MTI
	T+Chorio	1	MTT
	T+G	1	Comb
	G+YST	1	Comb
	G+EC	1	Comb
Three	T+YST+EC	4	MTI
	T+YST+Chorio	1	MTT
	T+EC+Chorio	1	MTT
	G+T+EC	1	Comb
Four	T+YST+EC+Chorio	1	MTT
	T+YST+EC+G	1	Comb

T: Teratoma; YST: Yolk-sac tumour; EC: Embryonal carcinoma; G: Germinoma/dysgerminoma/seminoma; Chorio: Choriocarcinoma; MTI: Malignant teratoma intermediate; MTT: Malignant teratoma trophoblastic; Comb: G + other germ cell tumour (excluding MTT component)

Table 4. Germ cell tumours of childhood and adolescence. Tumour types, number of cases and age distribution

Germ cell tumour	*n*	%	Age (mo)		
			Average	Range	Median
Benign	52	30.6	66.5	0–204	57
Potentially malignant[a]	30	17.6	47.2	0–192	5
Malignant	88	51.8	84.3	0–204	60
YST ("pure")	40	23.5	46.4	0–180	24
EC	4	2.4	124.3	60–193	122
G	16	9.4	148.6	76–190	153
Chorio	2	1.2	(138.0)	120–156	(138)
Mixed	26	15.3	91.5	0–192	99
Total	170				

[a] Immature teratoma
YST: Yolk-sac tumour; EC: Embryonal carcinoma; G: Germinoma/dysgerminoma/seminoma; Chorio: Choriocarcinoma; Mixed: Tumours of more than one histological type

nent, varied considerably; on the average, tumours located in the testis were smaller than tumours in the ovary or sacrococcygeal region. The cut surface of the tumour tissue was mostly solid and appeared greyish-white to yellowish in colour. Foci of hemorrhage and necrosis were found more often in large than in small tumours (Fig. 1).

Table 5. *Yolk-sac* (endodermal sinus) *tumours* in childhood and adolescence. Localisation, number of cases and age distribution

Localisation	*n*	Age (mo)		
		Average	Range	Median
Ovarian	7	119.4	42–180	129
Testicular	18	23.7	0–104	19
Sacrococcygeal	10	25.5	17– 36	24
Other	5	67.8	0–170	36
Total	40	46.4	0–180	24

Table 6. Mixed malignant germ cell tumours with a *yolk-sac tumour component*. Localisation, number of cases and age distribution

Localisation	*n*	Age (mo)		
		Average	Range	Median
Ovarian	5	129.2	91–147	144
Testicular	4	186.0	177–192	(187,5)
Sacrococcygeal	7	18.7	8– 30	22
Other	3	12.7	2– 18	(18)
Total	19	82.1	2–192	30

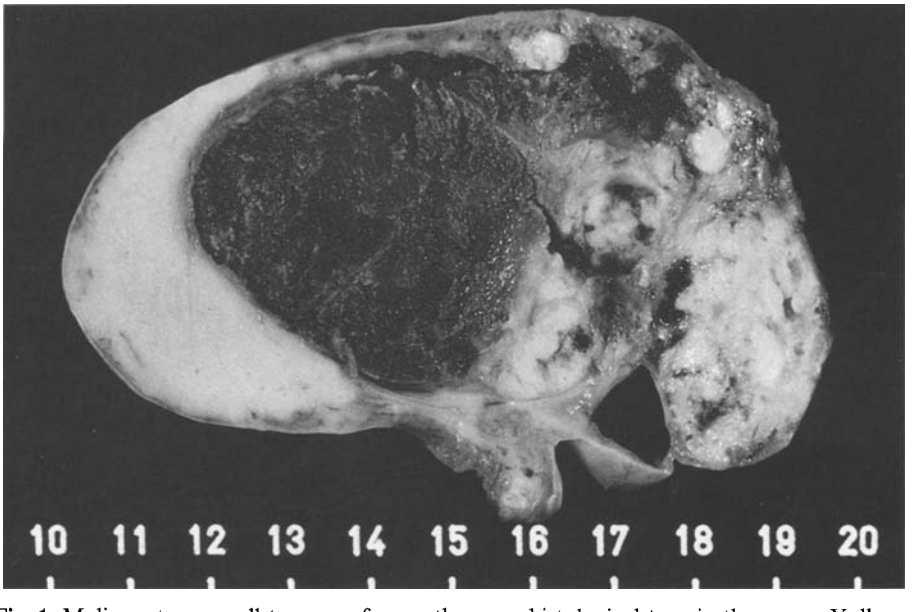

Fig. 1. Malignant germ cell tumour of more than one histological type in the ovary. Yolk-sac tumour with massive, partially haemorrhagic necroses and a small, semilunar, solid component of greyish-white coloured dysgerminoma (*left side*)

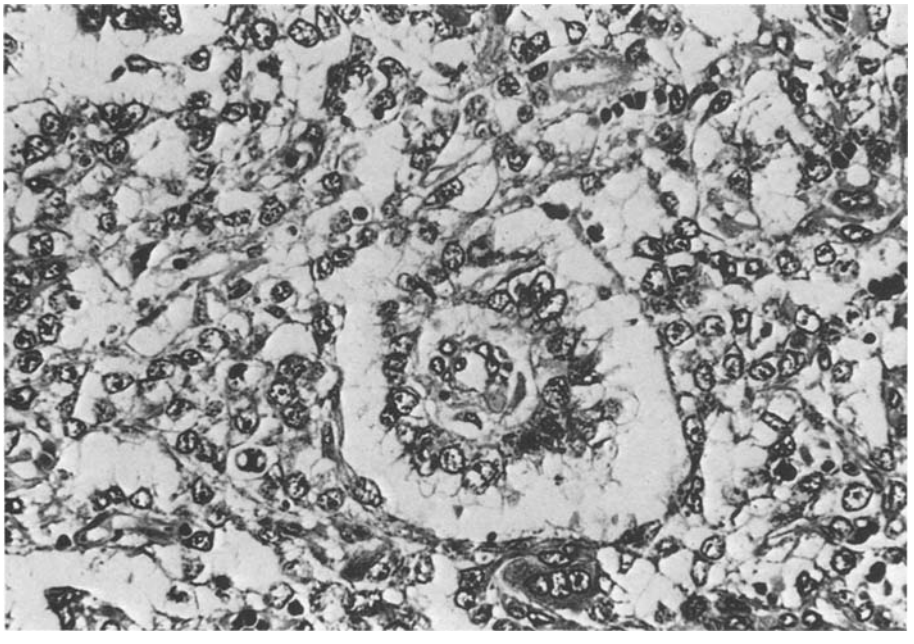

Fig. 2. Yolk-sac tumour. Predominantly reticular pattern and, additionally, a typical Schiller-Duval body (centre) (Goldner, ×350)

YST and the YST components in "mixed tumours" show basically the same histological picture (Figs. 2–5). The eight patterns named by Teilum (1976) can be combined into four basic patterns (Dehner 1983; Copeland et al. 1985): Festoon, reticular, solid, and polyvesicular. The distribution of these patterns (37 YST and 17 "mixed tumours" were evaluated) was as follows (Table 7): A festoon pattern was found in every tumour we examined; it was also the predominant pattern in all but 4 tumours evaluated semiquantitatively. The other three patterns occurred much less often, least of all the polyvesicular pattern (Fig. 5). No relation between predominant pattern and localization could be found. 49 of 54 tumours showed hyaline globules (Fig. 3), which can reach a size up to 30 μm. These show intense PAS-positivity and are mostly diastase resistant. In Goldner sections they stain partly red, partly orange and partly green. They can be localized either intra- or extracytoplasmically and are usually found in parts of the tumour showing a festoon or reticular pattern. Giant cells reminiscent of syncytiotrophoblast cells (Fig. 6) were found in 4 tumours (3 pure YST and 1 YST component).

Immunohistochemically 18 of 22 YST and 6 of 7 tumours with a YST component reacted positively for AFP (Fig. 7). In most cases hyaline globules were AFP negative. In only five cases were some AFP-positive globules seen in addition to many globules, which reacted negatively against antibody to AFP.

Single or small clusters of beta-HCG-positive giant cells were found

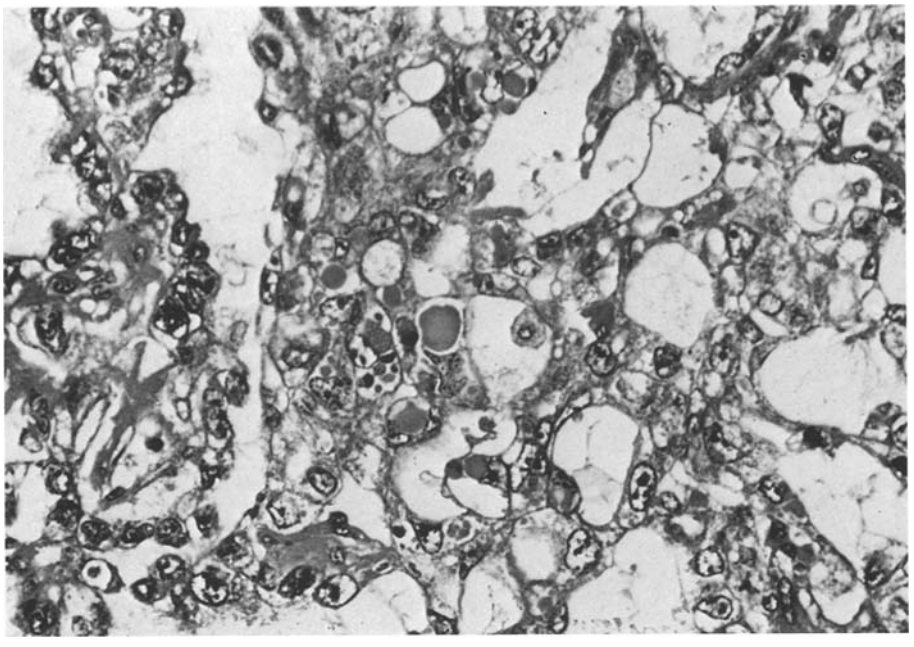

Fig. 3. Yolk-sac tumour with festoon pattern and hyaline globules (*centre*) (HE, ×350)

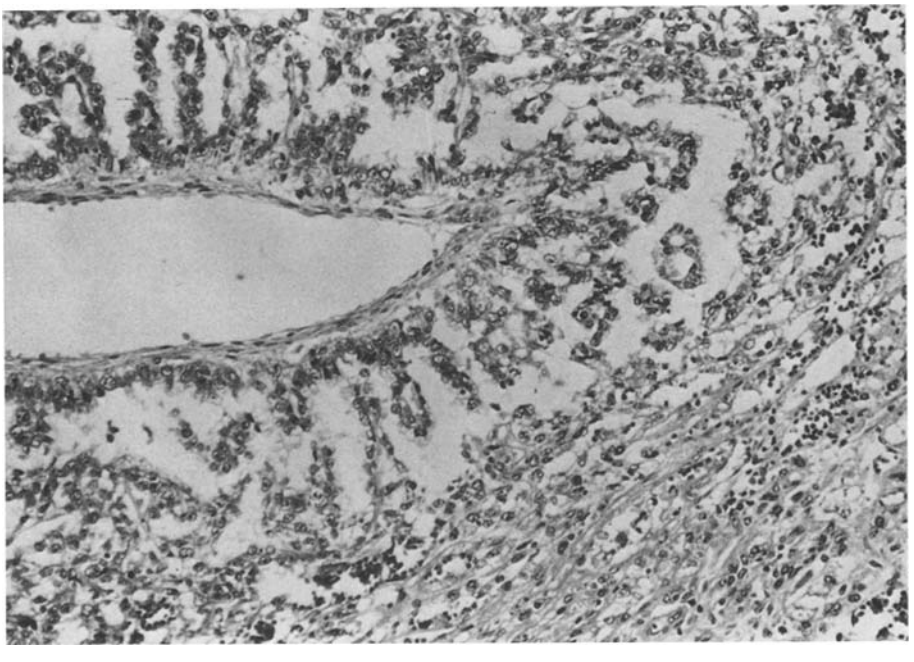

Fig. 4. Yolk-sac tumour. Periarterial festoon pattern (Goldner, ×140)

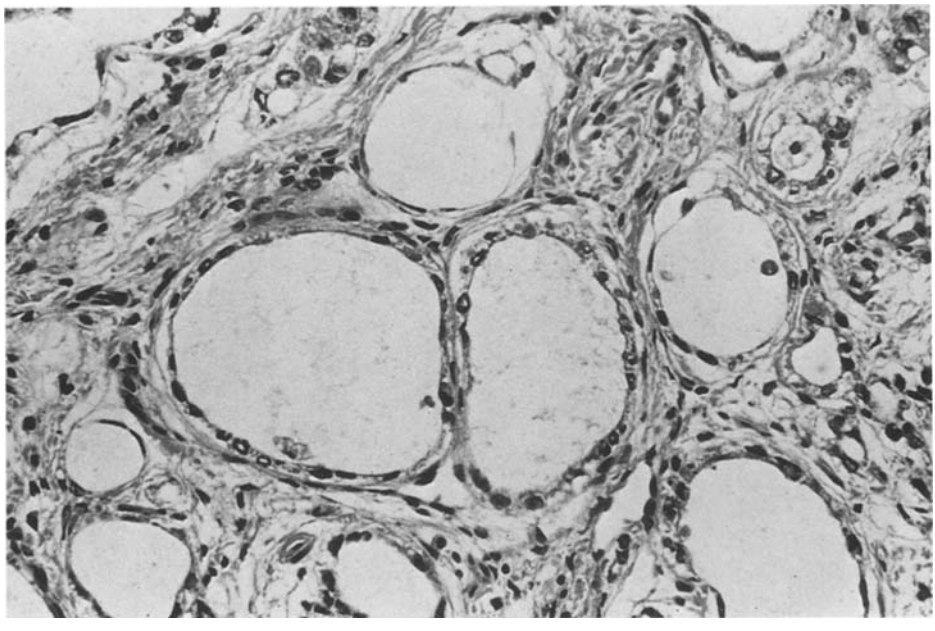

Fig. 5. Yolk-sac tumour. Polyvesicular pattern (Goldner, ×280)

Table 7. Histological patterns and results of immunohistochemical stainings in pure YST and in germ cell tumours with a YST component. Predominant pattern in brackets[a]

	Number of cases	
	YST, pure	YST component
Festoon pattern	37/37 (32)	17/17 (17)
Reticular pattern	32/37 (2)	15/17 (0)
Solid pattern	17/37 (2)	9/17 (0)
Polyvesicular pattern	6/37 (0)	5/17 (0)
Hyaline globules	33/37	16/17
Syncytial giant cells	3/37	1/17
AFP	18/22[b]	6/7[b]
β-HCG	1/20	1/7
Prekeratin	16/20[b]	6/6
α_1-Antitrypsin	7/7	5/5

[a] In one case there was no predominant pattern

[b] In three cases possibly false negative results. In these cases other immunohistochemical stains were negative too (inadequate fixation of the material)

in 3 cases (in two pure YST and in one YST component). (Typical syncytial trophoblastic giant cells were seen in one additional case, from which no material was available for immunohistochemistry; Fig. 6.)

In addition, prekeratin-positivity was observed in most cases studied (Fig. 8). On the whole, fixation in formalin produced a somewhat weaker reaction to prekeratin than fixation in alcohol, but the reaction product

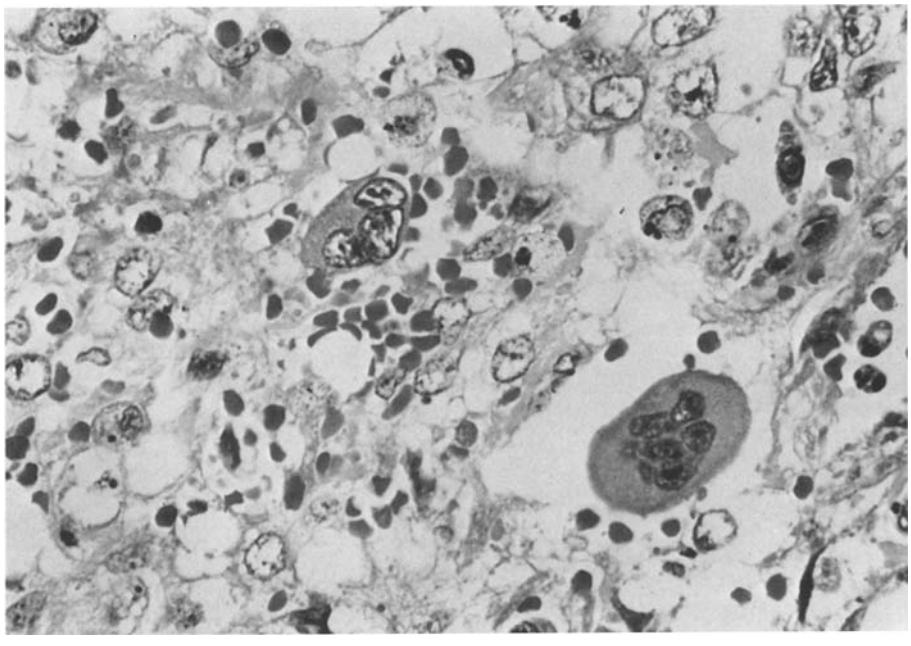

Fig. 6. Yolk-sac tumour with two syncytial trophoblast-like giant cells (Goldner, × 560)

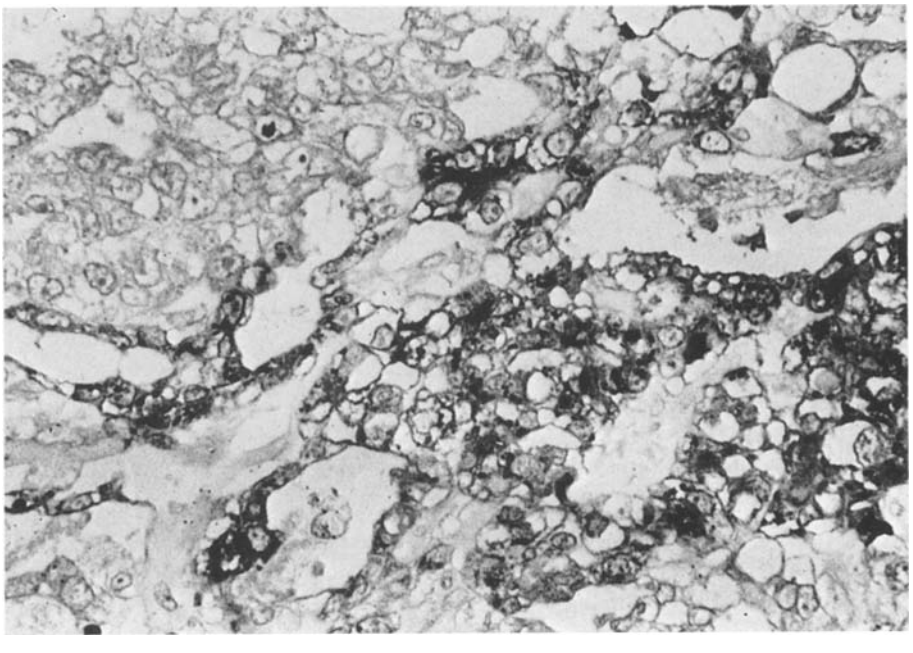

Fig. 7. Yolk-sac tumour. Many, but not all of the tumour cells stain positively with antibodies against alpha$_1$-fetoprotein (Immunoperoxidase method, × 350)

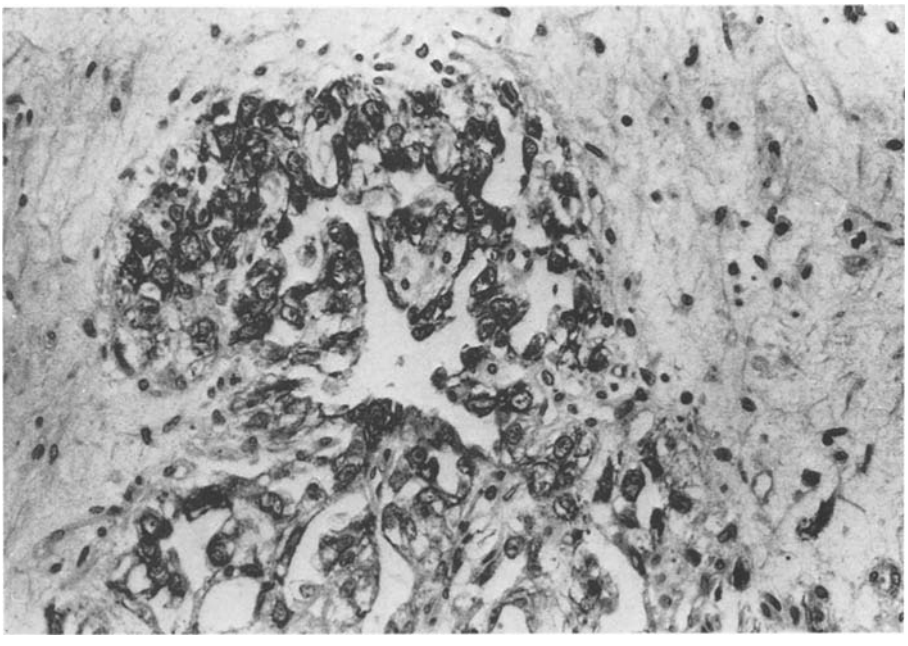

Fig. 8. Yolk-sac tumour with prekeratin-positive ephithelia (Alcohol fixation. Immunoperoxidase method, × 280)

Table 8. Clinical outcome in 51 cases of YST (35 pure YST and 16 germ cell tumours with a YST component). Not included are one stillbirth, one case with too short follow-up period (3 mo) and 6 cases without clinical data. Asteriks indicate 5 cases with short follow-up period due to early DOD

	n	CHT	RT	NED	LWD	DOD	Follow-up period (mo)		
							Average	Range	Median
YST, pure									
Testicular	16	11	2	*14*	2	0	44.6	17 – 72	51.0
Ovarian	7	5	2	6	0	1	42.9	1* – 80	38.0
Sacrococcygeal	8	7	1	5	2	1	28.0	3* – 88	17.5
Other	4	2	2	2	0	2	9.1	3.5*– 18	7.5
YST-component									
Testicular	4	1	1	4	0	0	77.5	28 –176	53.0
Ovarian	5	3	0	3	0	2	56.2	4* – 98	71.0
Sacrococcygeal	5	5	2	1	0	*4*	35.1	0.5*–121	14.0
Other	2	1	0	2	0	0	–	26 – 96	–
Total	51	35	10	37	4	10			

CHT: Chemotherapy; RT: Radiotherapy; NED: No evidence of disease; LWD: Living with disease; DOD: Dead of disease

after formalin fixation was suitable for interpretation. By contrast, AFP and beta-HCG could only be demonstrated in paraffin sections fixed in formalin. Lastly, the reaction with antibodies against alpha$_1$-antitrypsin was positive in all cases examined.

Table 8 shows the clinical outcome in cases with yolk-sac tumours. Follow-up data were available on 35 patients with pure YST. 27 patients (77.1%) are living without evidence of disease, 4 patients are living with disease (relapse or metastasis), and 4 patients died of disease. In the latter cases the primaries were localized in the ovary, sacrococcygeal region, mediastinum and retroperitoneum, respectively.

Follow-up data were further available on 16 patients with mixed germ cell tumours containing a YST component. In this group of patients only 10 patients were cured, whereas 6 patients died. Most deaths (4) occurred in patients with tumours located in the sacrococcygeal region.

In both groups – pure YST and tumours with a YST component –, 37 patients are living without evidence of disease (72.5%), 4 are living with disease (7.8%), and 10 patients have died (19.6%). All 20 patients with testicular tumours are living (two with disease), whilst 10 of 31 cases (32.3%) with extratesticular (including 12 ovarian) tumours have died.

Discussion

The present study is based on material from 170 children and adolescents (under 18 years) with germ cell tumours. For classification we used both the WHO and the British classification. The advantage of the British classification is that it contains only a few tumour types and is easily reproducible. The WHO classification on the other hand includes a larger number of tumour types, particularly when the numerous possibilities for combination in groups of tumours of more than one histological type are considered. Hence, the WHO classification is better able to document the variability of germ cell tumours or tumours with germ cell component. Furthermore, more consideration is given to histogenesis in the WHO scheme than in the British scheme (for extensive comparison and discussion of the two classification schemes see von Hochstetter and Hedinger 1982). Irrespective of their differences both classifications are applicable to paediatric cases regardless of the location of the tumour.

Germ cell tumours in children differ from those in adults in showing a higher incidence of extragonadal tumours (45.9%); a more "pure" YST (23.5%); a higher incidence of YST elements (67.0%) in cases of unequivocal malignancy; more immature teratomas (17.6%); a very low incidence of seminoma (0.6%) and a higher percentage of dysgerminoma (5.3%) and extragonadal germinoma (2.9%); and finally a higher percentage of malignancy in ovarian tumours (46.0%).

The relatively high incidence of extragonadal tumours is well known. It can range, depending on the composition of the study, from 86.2% (Carney et al. 1972), 81.3% (Berry et al. 1969), 78.5% (Bale et al. 1975) to 57.1% (Mahour et al. 1978) and 48.9% (Marsden et al. 1981). The corresponding

figures for the most frequent sacrococcygeal tumours in the same studies are 38.0%, 63.7%, 47.7%, 42.9% and 22.6%, respectively.

The data from our own study on the percentage of extragonadal germ cell tumours (45.9%) and sacrococcygeal teratoma (22.4%) were about as low as those from Marsden et al. (48.9% and 22.6%), which were also drawn from the files of a children's tumour registry (the Manchester University Children's Tumour Registry). In spite of the high percentage of sacrococcygeal tumours relative to that in adults, the data in the tumour registries regarding their localization and the percentage of the benign tumours – according to Bale (1984) about 80% of sacrococcygeal teratomas are benign – are too low and not representative. By contrast, the data on the unequivocally malignant tumours and the distribution of their histological types appear an accurate reflection of reality.

In agreement with the literature (Dehner 1983), our study found YST to be the most frequent kind of malignant germ cell tumour (45.5% of unequivocally malignant cases). Moreover, an additional 19 of 26 germ cell tumours of more than one histological type contained a YST component, so that altogether 67.0% of malignant tumours showed at least a YST component. Marsden et al. (1981) found 60.3% of malignant tumours to be either YST or to have a dominant YST component, a rate quite similar to our own, and saw YST elements "in 23 of the 34 tumours where the latter was the direct cause of death". Prognosis for YST is relatively favourable when the tumour is localized in the testis in early childhood (Houser et al. 1968; Weißbach et al. 1982; Wold et al. 1984). This was confirmed by our own follow-up data; pure YST of the testis lead to metastasis in only two cases, but up to now no death occurred. On the other hand, 10 of 31 patients with extratesticular YST have died. The relatively highest rate of deaths was observed in mixed germ cell tumours with a YST component (6/16; 37.5%), and 4 out of 10 deaths occurred in cases with mixed sacrococcygeal tumours. 19 of 31 patients with extratesticular pure or mixed YST are living without disease (61.3%), and 10 patients have died (32.3%). The number of deaths is considerably low concerning the general bad prognosis of these tumours (Altman et al. 1974; Bale et al. 1975; Kurman and Norris 1976; Gonzalez-Crussi 1979; Brodeur et al. 1981; Marsden et al. 1981; Talerman 1982), and therefore our comparably high rate of survivors reflects the effectiveness of modern therapy, particularly polychemotherapy, in addition to surgery. Similar results confirming the trend of improved outcome were recently reported, but mostly in small series of cases (Flamant and Lemerle 1982; Sartain et al. 1982). (For treatment strategy of the German Society of Paediatric Oncology see Göbel et al. 1983; Haas et al. 1983.)

The histological picture of YST is well known (Teilum 1950, 1959, 1965, 1976; Woodtli and Hedinger 1974; Kurman and Norris 1976; Gonzalez-Crussi 1979; Scully 1979; Talerman 1982). In agreement with Dehner (1983) and Copeland et al. (1985) we found the festoon pattern to be the most frequent. In a large number of cases we also found hyaline globules and, on immunohistochemistry, both a granular and diffusely positive reaction to alpha$_1$-fetoprotein in the cytoplasm of the tumour cells (Kurman et al.

1977; Wilke and Harms 1979; Mostofi 1980; Löhrs 1982). A few tumours also contained syncytial giant cells with evidence of beta-HCG. YST components in mixed germ cell tumours developed the same basic patterns as pure YST; these patterns had no apparent bearing on prognosis (which accords with the findings of Kurman and Norris 1976).

The exact nature of the hyaline globules is still unknown. While Itoh et al. (1974), Teilum et al. (1974) and Kurman et al. (1977) were able to detect AFP in hyaline globules, Talerman (1985), using the PAP method, detected no AFP, and Moringa et al. (1983) could detect it only occasionally. In the present study most hyaline globules were also predominantly negative for AFP upon immunohistochemical analysis. This result could hardly be due to the method employed, since the same sections also contained very often unequivocally AFP positive tumour cells. Although large numbers of hyaline globules are, indeed, often found in YST, they are "by no means diagnostic..., and they are not infrequently found in a number of unrelated neoplasms" (Talerman 1985). They may be the expression of a degenerative process, as is suspected of similar hyaline bodies "in undifferentiated hepatic sarcoma" (Keating and Tylor 1985), for example. Thus, AFP positive hyaline globules in YST could have the origin in the degeneration of AFP positive tumour cells and, conversely, AFP negative hyaline globules could originate from the degeneration of AFP negative cells; for even in clearly AFP positive YST some areas with a negative or only weakly positive immunohistochemical reaction to AFP can be found. This would, in any case, explain the different findings regarding the AFP content in the hyaline globules.

Cases with immature teratoma make up a significant number (30 = 17.6%) of our files. A relation of immature teratoma to unequivocally malignant germ cell tumours is 1:2.9, and the relation of immature teratoma to (pure) YST 1:1.3. These results confirm data from the literature, demonstrating a relatively high percentage of such tumours in germ cell tumours of infancy, childhood and adolescence (for references see Gonzalez-Crussi 1982; Dehner 1983; Harms and Jänig 1985).

Tumours of the germinoma group account for 9.4% of all germ cell tumours and for 18.2% of the unequivocally malignant germ cell tumours in our material. It is clear that seminoma of the testis is extremely rare in children (Viprakasit et al. 1977). By contrast, in this age group a considerable number of dysgerminomas of the ovary (9 of our own cases) and of extragonadally located germinomas (6 cases) was observed. Generally, the age of patients with dysgerminomas at time of diagnosis is lower than the age of patients with testicular seminoma (80% of the dysgerminomas occur in the second and third decades and further 5% already in children before the age of ten years (Scully 1979), whereas seminomas are seen most commonly in the fourth or fifth decade (Mostofi 1973)). Therefore, dysgerminomas are more frequent in childhood and adolescence than seminoma irrespective of the fact, concerning *all* age groups, that testicular seminomas are more frequent than dysgerminomas of the ovary.

The results of the current study demonstrate again that in childhood

the same types of germ cell tumours may occur as in the adult. However, the relative and absolute frequency of the various histological tumour types and their localizations in childhood is strikingly different from that in adulthood. The most important fact is, that among the malignant germ cell tumours of childhood YST is the most frequent and the most important histological type of tumour.

Acknowledgments. Information on clinical follow-up was kindly provided by PD Dr. J.D. Beck, Erlangen; Dr. A.I. v. Brenndorff, Heidenheim; Dr. D. Bürger, Hannover; Prof. Dr. J. Drescher, Oldenburg; Dr. H. Ehrle, Bochum; OA Dr. W. Ertelt, Stuttgart; OA Dr. Farahmand, Regensburg; Prof. Dr. H. Gadner, Wien; Prof. Dr. U. Goebel, Düsseldorf; Prof. Dr. E. Grundmann, Münster; Prof. Dr. H. Gunschera, Bremen; Prof. Dr. P. Gutjahr, Mainz; Prof. Dr. H. G. Hansen, Lübeck; Dr. B. Henkel, Hamm; Prof. Dr. G. Henze, Berlin; Prof. Dr. H. A. Hienz, Krefeld; Prof. Dr. H.-P. Jensen, Kiel; Prof. Dr. O. Klinge, Kassel; Prof. Dr. B. Kornhuber, Frankfurt; Dr. W. A. Maier, Karlsruhe; Prof. Dr. U. Matzander, Neumünster; Prof. Dr. W. Mengel, Kiel; Prof. Dr. C. Mittermayer, Aachen; Prof. Dr. Mortier, Wuppertal; Dr. G. Nessler, Karlsruhe; Prof. Dr. D. Niethammer, Tübingen; Dr. A. Nokolaidis, Steinfurt; Dr. P. Pfiester, Mannheim; PD Dr. U. Raute-Kreinsen, Mannheim; Prof. Dr. M. Rister, Kiel; Prof. Dr. G. Schellong, Münster; Dr. L. Schuster, München; PD Dr. U. Seppelt, Flensburg; Dr. K.-H. Stade, Kiel; OA Dr. W. Sternschulte, Köln; Prof. Dr. H. Wand, Kiel; Dr. W. Welte, Nürnberg; Dr. G. Wessler, Karlsruhe; Prof. Dr. K. Winkler, Hamburg. – Mrs. Irene Kiekbusch typed the manuscript. Mr. Jim Heywood translated parts of the manuscript.

References

Abell MR (1966) The nature and classification of ovarian neoplasms. Can Med Assoc J 94:1102–1124

Abell MR (1982) Ovarian neoplasms of childhood and adolescence. In: Blaustein A (ed) Pathology of the female genital tract, 2nd edn. Springer, New York Heidelberg Berlin, pp 665–704

Altman RP, Randolph JG, Lilly JR (1974) Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey – 1973. J Pediatr Surg 9:389–398

Bale PM (1984) Sacrococcygeal developmental abnormalities and tumors in children. Persp Pediatr Pathol 8:9–56

Bale PM, Painter DM, Cohen D (1975) Teratomas in childhood. Pathology 7:209–218

Berry CL, Keeling J, Hilton C (1969) Teratomata in infancy and childhood. A review of 91 cases. J Pathol 98:241–252

Brodeur GM, Howarth CB, Pratt CB, Caces J, Hustu O (1981) Malignant germ cell tumours in 57 children and adolescents. Cancer 48:1890–1898

Brown NJ (1976) Yolk-sac tumour ("orchioblastoma") and other testicular tumours of childhood. In: Pugh RCB (ed) Pathology of the testis. Blackwell, Oxford London Edinburgh Melbourne, pp 356–370

Carney JA, Thompson DP, Johnsson CL, Lynn HB (1972) Teratomas in children: clinical and pathologic aspects. J Pediatr Surg 7:271–282

Copeland LJ, Sneige N, Ordonez NG, Hancock KC, Gershenson DM, Saul PB, Kavanagh JJ (1985) Endodermal sinus tumor of the vagina and cervix. Cancer 55:2558–2565

Dehner LP (1983) Gonadal and extragonadal germ cell neoplasia of childhood. Hum Pathol 14:493–511

Donnellan WA, Swenson O (1968) Benign and malignant sacrococcygeal teratomas. Surgery 64:834–846

Flamant F, Lemerle J (1982) Aggressive treatment of stages III and IV yolk sac tumors (Abstract). XIVth meeting of the International Society of Pediatric Oncology. September 21–25, Bern, Switzerland

Fraumeni J Jr, Li FP, Dalager N (1973) Teratomas in children: Epidemiologic features. J Ntl Cancer Inst 51:1425–1430

Göbel U, Haas RJ, Harms D, Janka G, Brämswig J, Jürgens H, Weißbach L, Faber P, Müller E (1983) Behandlungsstrategie für nichttestikuläre maligne Keimzelltumoren bei Kindern und Jugendlichen – Konzept der Kooperativen Therapiestudie MAKEI 83 der GPO. Klin Pädiat 195:201–206

Gonzalez-Crussi F (1979) The human yolk sac and yolk sac (endodermal sinus) tumors. A review. Persp Pediatr Pathol 5:179–215

Gonzalez-Crussi F (1982) Extragonadal teratomas. Armed Forces Institute of Pathology, Washington (Atlas of tumor pathology, 2nd series, fasc 18)

Haas RJ, Brämswig J, Göbel U, Harms D, Janka G, Weißbach L (1983) Maligne Hodentumoren bei Kindern und Jugendlichen: Konzept der Kooperativen Therapiestudie MAHO 82 der GPO. Klin Pädiatr 195:196–200

Harms D (1982) Pathologische Anatomie kindlicher Hodentumoren. In: Hohenfellner R, Klippel KF (eds) Urologische Kinderonkologie. Enke, Stuttgart, pp 157–168

Harms D, Jänig U (1985) Immature teratomas of childhood. Report of 21 cases. Pathol Res Pract 179:388–400

Hochstetter AR von, Hedinger Chr E (1982) The differential diagnosis of testicular germ cell tumors in theory and practice. A critical analysis of two major systems of classification and review of 389 cases. Virchows Arch [Pathol Anat] 396:247–277

Houser R, Izant RJ Jr, Persky L (1965) Testicular tumors in children. Am J Surg 110:876–892

Itoh T, Shirai T, Naka A, Matsumoto S (1974) Yolk sac tumor and alpha-fetoprotein: Clinicopathological study of four cases. Gann 65:215–226

Keating S, Taylor GP (1985) Undifferentiated (embryonal) sarcoma of the liver: Ultrastructural and immunohistochemical similarities with malignant fibrous histiocytoma. Hum Pathol 16:693–699

Kurman RJ, Norris HJ (1976) Endodermal sinus tumor of the ovary. A clinical and pathologic analysis of 71 cases. Cancer 38:2404–2419

Kurman RJ, Scardino PT, McIntire KR, Waldmann TA, Javadpour N (1977) Cellular localization of alpha-fetoprotein and human chorionic gonadotropin in germ cell tumors of the testis using an indirect immunoperoxidase technique. A new approach to classification utilizing tumor markers. Cancer 40:2136–2151

Löhrs U (1982) Histologische Klassifikation der malignen Hodentumoren. In: Illger HJ, Sack H, Seeber S, Weißbach L (Hrsg) Nicht-seminomatöse Hodentumoren. Beitr Onkologie 8:2–18

Mahour GH, Landing BH, Wolley MM (1978) Teratomas in children: Clinicopathologic studies in 133 patients. Z Kinderchir 23:365–380

Marsden HB, Birch JM, Swindell R (1981) Germ cell tumours of childhood: a review of 137 cases. J Clin Pathol 34:879–883

Morinaga S, Ojima M, Sasano N (1983) Human chorionic gonadotropin and alpha-fetoprotein in testicular germ cell tumors. An immunohistochemical study in comparison with tissue concentrations. Cancer 52:1281–1289

Mostofi FK (1973) Testicular tumors. Epidemiologic, etiologic and pathologic features. Cancer 32:1186–1201

Mostofi FK (1980) Pathology of germ cell tumors of testis. A progress report. Cancer 45:1735–1754

Mostofi FK, Sobin LH (1977) Histological typing of testis tumours. International Histological Classification of Tumours No. 16. World Health Organization, Geneva

Norris HJ, Jensen RD (1972) Relative frequency of ovarian neoplasms in children and adolescents. Cancer 30:713–719

Pugh RCB, Cameron KM (1976) Teratoma. In: Pugh RCB (ed) Pathology of the testis. Blackwell, Oxford London Edinburgh Melbourne, pp 199–244

Sartain P, Ducore JM, Buchman GR (1982) Yolk sac tumors (YST) in childhood: Primary treatment with chemotherapy. Proc Am Soc Clin Oncol 1, 104

Scully RE (1979) Tumors of the ovary and maldeveloped gonads. Armed Forces Institute of Pathology, Washington (Atlas of tumor pathology, 2nd series, fasc 16)

Serov SF, Scully RE, Sobin LH (1973) Histological typing of ovarian tumours. International Histological Classification of Tumours No. 9. World Health Organization, Geneva

Sternberger LA, Hardy PH Jr, Cuculis JJ, Meyer HG (1970) The unlabeled antibody enzyme method of immuno-histochemistry. Preparation and properties of soluble antigen-antibody complex (horseradish peroxidase-antihorseradish peroxidase) and its use in identification of spirochetes. J Histochem Cytochem 18:315–333

Talerman A (1982) Germ cell tumors of the ovary. In: Blaustein A (ed) Pathology of the female genital tract, 2nd edn. Springer, Berlin Heidelberg New York, pp 602–664

Talerman A (1983) Hyaline globules in ovarian mixed mesodermal (Müllerian) tumors. Hum Pathol 14:562

Teilum G (1950) "Mesonephroma ovarii" (Schiller); extra-embryonic mesoblastoma of germ cell origin in ovary and testis. Acta Pathol Microbiol Scand 27:249–261

Teilum G (1959) Endodermal sinus tumors of the ovary and testis. Comparative morphogenesis of the so-called mesonephroma ovarii (Schiller) and extraembryonic (yolk-sac-allantoic) structures of the rat's placenta. Cancer 12:1092–1105

Teilum G (1965) Classification of endodermal tumour (Mesoblastoma vitellinum) and so-called "embryonal carcinoma" of the ovary. Acta Pathol Microbiol Scand 64:407–429

Teilum G (1976) Special tumors of the ovary and testis and related extragonadal lesions, 2nd edn. Munksgaard, Copenhagen

Teilum G, Albrechtsen R, Nøgaard-Pedersen B (1974) Immunofluorescent localization of alpha-fetoprotein synthesis in endodermal sinus tumor (yolk sac tumor). Acta Pathol Microbiol Scand Sect A 82:586–588

Valdiserri RO, Yunis EJ (1981) Sacrococcygeal teratomas: A review of 68 cases. Cancer 48:217–221

Viprakasit D, Navarro C, Guarin UK, Garnes HA (1977) Seminoma in children. Urology 9:568–570

Weißbach L, Böttcher K, Sommerhoff CH (1982) Kindliche Hodentumoren aus klinischer Sicht. In: Weißbach L, Hildenbrand G (Hrsg) Register und Verbundstudie für Hodentumoren, Bonn. Ergebnisse einer prospektiven Untersuchung. Zuckschwerdt, München, S 215–264

Wilke H, Harms D (1979) Alpha-1-Fetoprotein im Tumorgewebe. Lichtmikroskopischer Nachweis in malignen Teratomen, endodermalen Sinustumoren, Hepatoblastomen und primären Leberzellkarzinomen. Dtsch Med Wochenschr 104:1527–1529

Wold LE, Kramer SA, Farrow GM (1984) Testicular yolk-sac and embryonal carcinomas in pediatric patients. Comparative immunohistochemical and clinicopathologic study. Am J Clin Pathol 81:427–435

Woodtli W, Hedinger Chr (1974) Endodermal sinus tumor or orchioblastoma in children and adults. Virchows Arch [Pathol Anat] 364:93–110

Accepted February 3, 1986