CHARACTERISATION OF THE GERM CELL TUMOURS SEEN AT THE RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (1956 - 1995).

Dissertation submitted for Master of Medicine in Pathology - University of Cape Town.

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Contents

GERM CELL TUMOURS OF CHILDHOOD

The aim of the current study is the characterisation (primarily pathological, but with clinical correlation) of the germ cell tumours seen in the Pathology Department of the Red Cross Childrens Hospital since its inception in 1956 (through to the year 1995, date of commencement of the study).

Study population -
Infants and children from birth to 13 years of age (of all population groups, but predominantly those from the disadvantaged black and mixed race communities of the Greater Cape Town metropolitan area).

NOMENCLATURE.

A modification of the W.H.O. classification of ovarian [79] and testicular tumours [80] is employed.

I) Malignant germ cell tumours.

A) Pure:
1. Yolk sac tumour.
2. Embryonal carcinoma.
3. Choriocarcinoma.
4. Germinoma.

B) Mixed: Any of the above tumours mixed with each other, or with a mature/immature teratomatous component.

II) Immature teratomas - Grades I - III.

III) Mature teratomas.

(Although the neoplasms in this study are subsumed under the all embracing term "germ cell", it is acknowledged that the histogenesis of these fascinating tumours is still open to debate. Besides germ cell, other hypotheses of origin have included:

- nongerminal cells of the early conceptus, or "embryonic" cells.
- totipotential "stem cells".
- "included" or conjoined and maldeveloped twins.
- different cell types, and possibly by different pathogenesis, depending on the anatomic site of the neoplasm).

METHODS AND DEFINITIONS.
TUMOUR SPECIFIC HISTOLOGICAL FEATURES EVALUATED.

The study was performed retrospectively by review of archival material. Haematoxylin and eosin stained slides were available for all cases, plus PAS diastase stains for the vast majority of yolk sac tumours. Immunoperoxidase stains where relevant, were available for the more recent cases. The number of sections taken per specimen varied considerably. For the more recent, the protocol of one block per cm. of maximum tumour diameter was invariably followed, whereas for the earlier cases, generally fewer sections were taken.

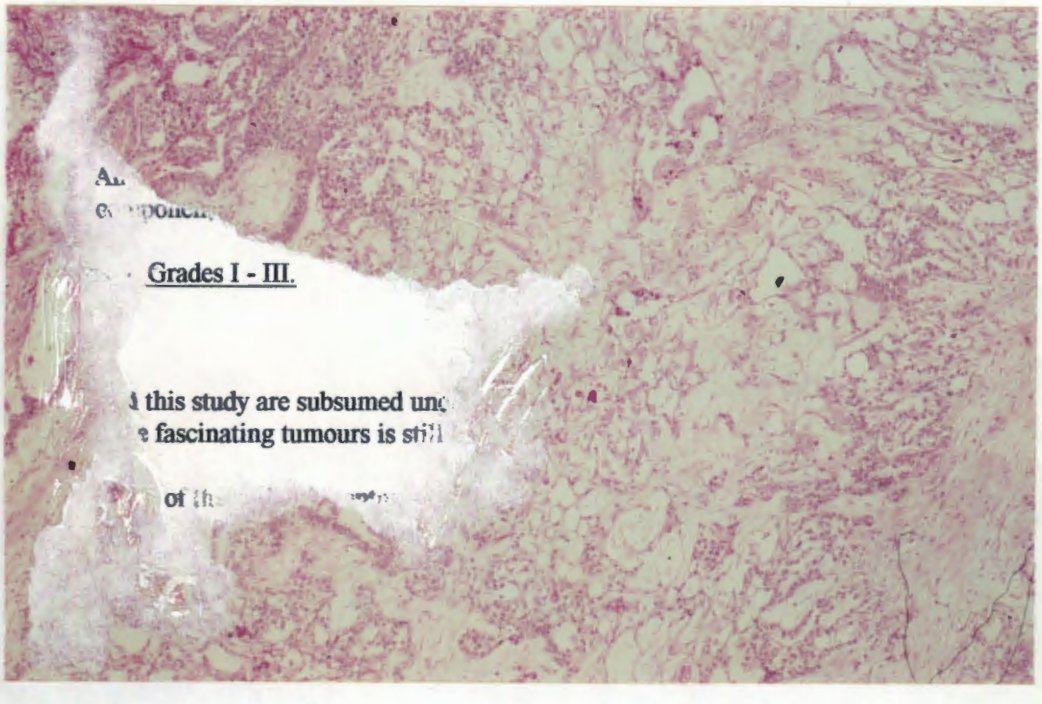
I) Malignant Germ Cell Tumours.

A) Yolk sac tumours

Enumeration of the histological patterns present, and which, if any, predominates [2, 5, 7, 78].

Classical patterns as described by Teilum [109] and elaborated by Kurman & Norris [7].

(i) Reticular/microcystic - Characteristic appearance - Network of variably sized cystic spaces lined by attenuated epithelial cells. Extra- or intracellular PAS positive (diastase resistant) hyaline globules invariably present.



Grades I - III.

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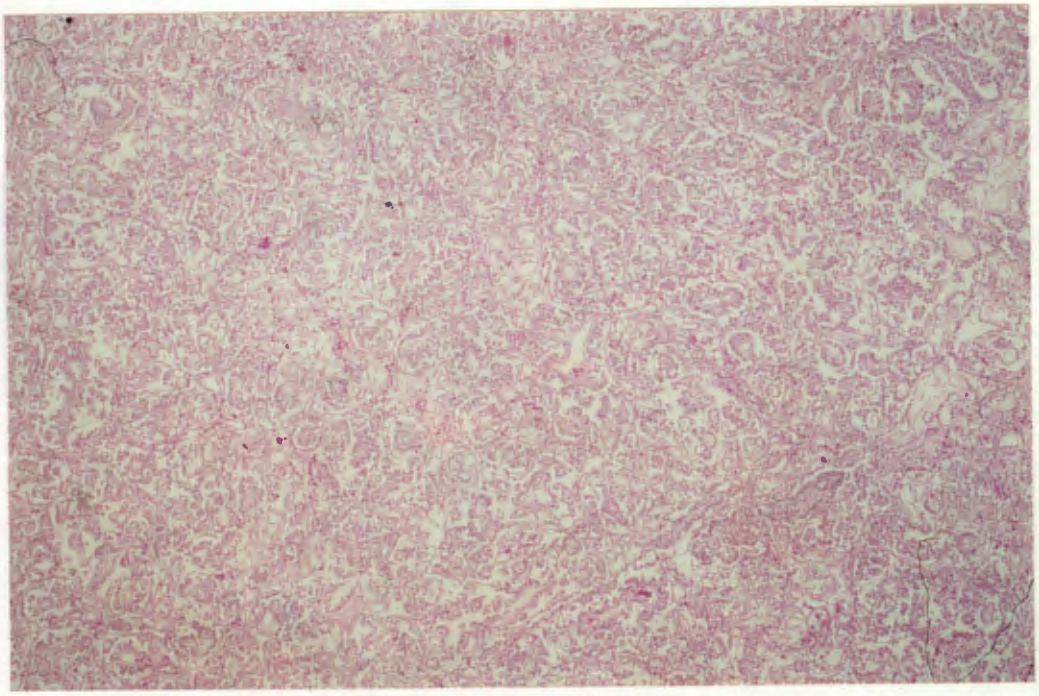
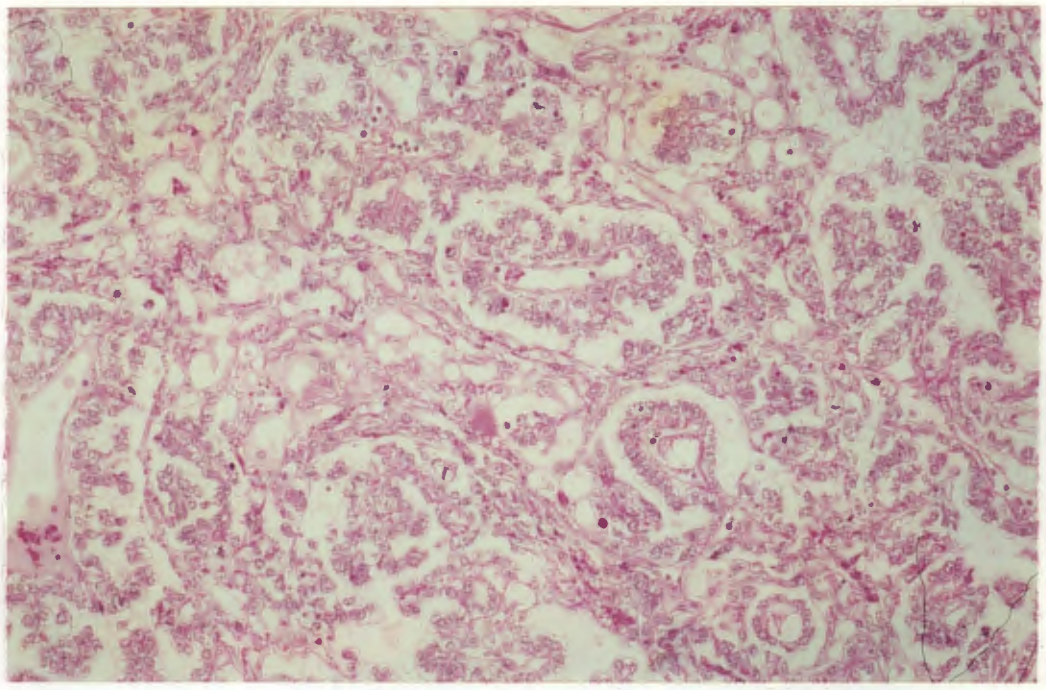
Reticular Y.S.T. pattern with several hyaline globules in field.

(ii) Pseudopapillary/endodermal sinus/festoon - Characteristic appearance - Papillary structures (Schiller-Duval bodies) present, consisting of a loose connective tissue core, penetrated by a central longitudinal capillary, and covered by a monolayer of primitive cuboidal or low columnar mitotically active epithelial cells. The papillary structures, themselves, projecting into a complex labyrinth of inter-anastamosing channels lined by epithelial cells. Hyaline globules are invariably identifiable.

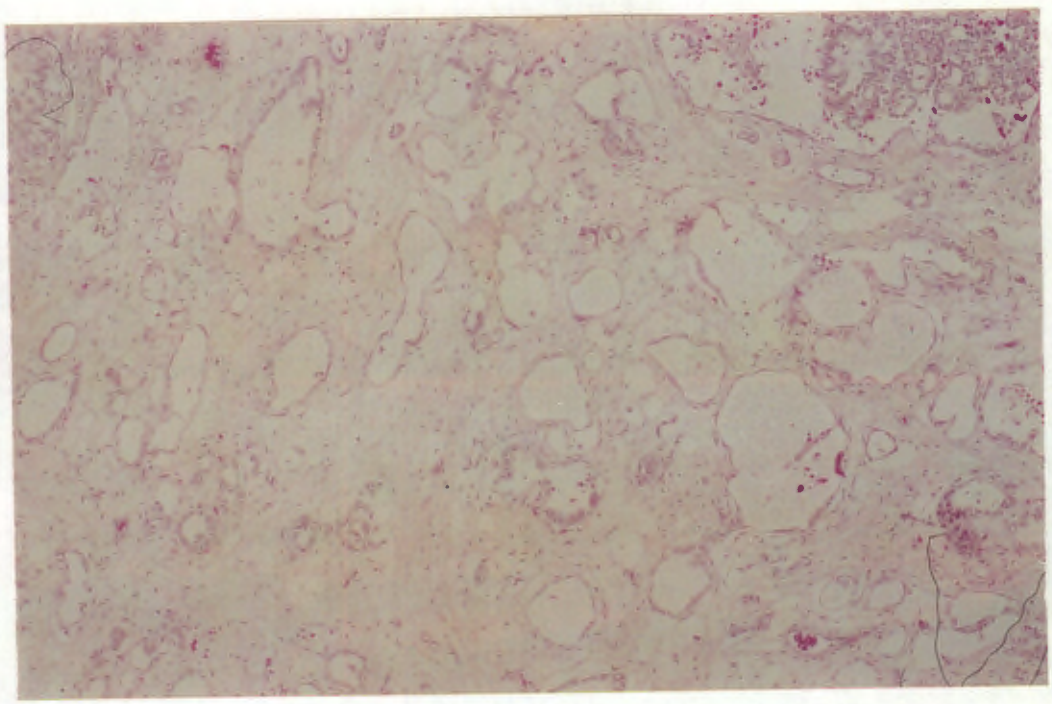


Classical festoon pattern - 5X magnification.



Classical festoon pattern - 10X magnification.

(iii) Polyvesicular-vitelline - Characteristic appearance - Pear shaped "vesicles" lined at their narrow ends by cuboidal epithelium (often with infra- or supranuclear vacuoles) and at their broader ends by flattened mesothelial like cells. (The broad and narrow segments being thought to represent the primary and secondary yolk sac vesicles respectively). A slight luminal constriction is usually present at the interface between the 2 epithelial cell types. A dense spindle cell stroma may encompass the vesicles. Hyaline globules are usually identifiable.



Polyvesicular vitelline pattern.

(iv) Solid - Characteristic appearance - Solid masses or rounded aggregates of small primitive epithelial cells with slightly vacuolated cytoplasm, large vesicular or hyperchromatic nuclei with prominent nucleoli, and accompanying brisk mitotic activity. As with the other histological patterns, hyaline globules are invariably present. This histological subtype needs to be distinguished from:

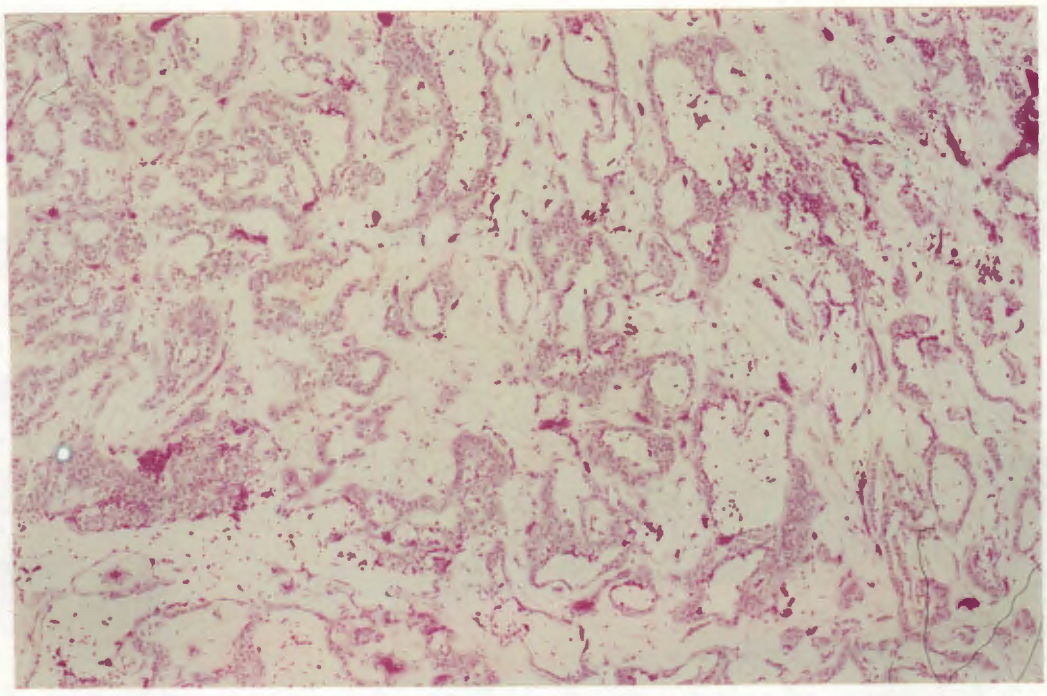
- Embryonal carcinoma - Features of value:
  - Isolated clusters of syncytiotrophobast invariably present in embryonal carcinoma, but extremely rarely seen in Y.S.T.
  - Presence of other Y.S.T. patterns especially - reticular, festoon or polyvesicular.
  - Embryonal carcinoma shows more profound cellular and nuclear pleomorphism, larger cells, and more prominent nucleoli.
    (Profuse numbers of intra- and extracellular hyaline globules plus diffusely positive immunoperoxidase staining for AFP may occur in embryonal carcinoma, as well as Y.S.T. [86]).
- Y.S.T. with hepatoid differentiation (see description below).

Additional subtypes (as described by Talerman [5] and others)

(i) Papillary pattern - Characteristic appearance - Composed of papillary structures consisting of connective tissue cores lined by epithelial like cells showing prominent pleomorphism and mitotic activity. (Differing from the pseudopapillary/festoon type by the lack of a penetrating central longitudinal vessel, plus the lack of projection of the core into an epithelial lined sinusoidal space).

(ii) Macrocystic pattern - Characterised by the presence of large cystic spaces (in contrast to the microcysts of the classical reticular pattern).

(iii) Alveolar-glandular pattern - Composed of gland-like spaces and cavities lined by flattened or cuboidal epithelial cells and surrounded by myxoid stroma.

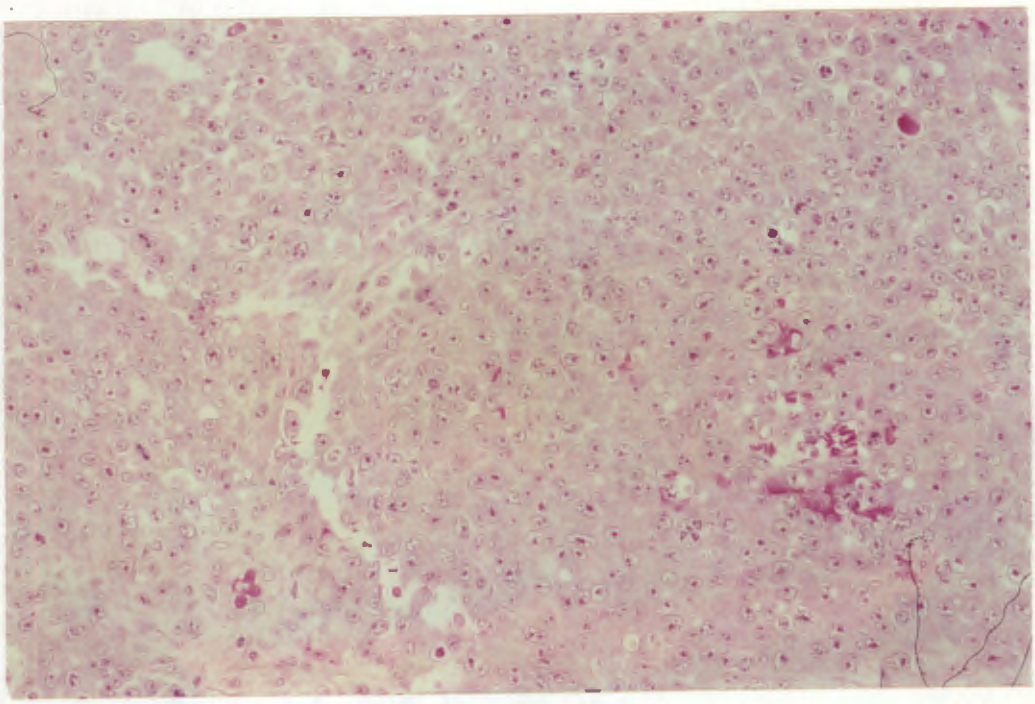


Alveolar-glandular pattern of Y.S.T.

More recently described histological sub-types [81, 82, 83, 84].

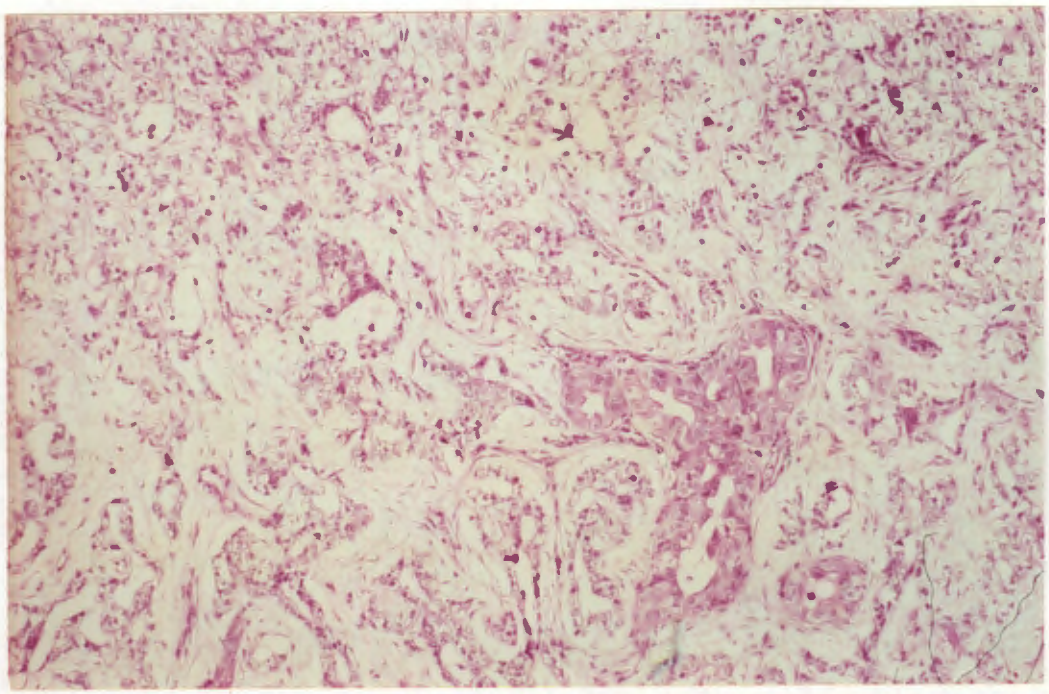
(In early embryonic development the human yolk sac, and the primitive gut, are directly contiguous. These 2 structures being frequently referred to as the primary and secondary yolk sac vesicles respectively. This relationship with primordial gut structures is supported by the ultrastructural demonstration in yolk sac tumours, of cells resembling surface gut epithelium, Paneth cells, gastric cells, and hepatocytes).

(i) Y.S.T. with hepatoid differentiation - Solid growth pattern characterised by sheets and nests of mitotically active polygonal cells, with distinct cell borders, eosinophilic cytoplasm, and a large central nucleus containing a single prominent nucleolus. (The neoplasm bearing considerable resemblance to a hepatocellular carcinoma). As with other yolk sac tumour growth patterns hyaline globules are invariably identifiable. (Differentiation from a Y.S.T. with a solid growth pattern, plus embryonal carcinoma may be difficult).



Photograph demonstrating the grey area between YST with a solid pattern, and that with hepatoid differentiation.

(ii) Y.S.T. with intestinal differentiation - Characteristic appearance - Nests or collections of primitive endodermal glands, showing varying degrees of differentiation - from primitive to well differentiated (resembling a mucin secreting adenocarcinoma).



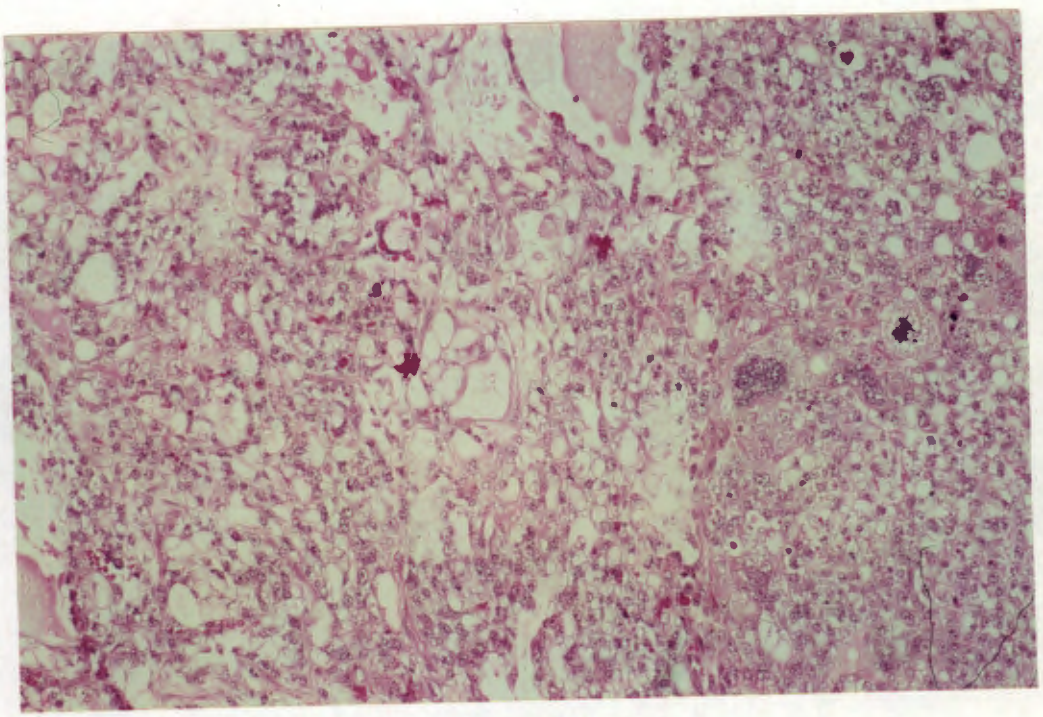
Reticular pattern with foci of glandular spaces - consistent with intestinal differentiation.

(iii) Y.S.T. with endometrioid differentiation - Characteristic appearance - Prominent tubular - glandular structure, epithelial cells hyperchromatic and columnar - shows a striking resemblance to endometrioid adenocarcinoma.

(iv) The parietal yolk sac variant [3] - Characterised by the extracellular accumulation of hyaline eosinophilic basement membrane like material, between adjacent tumour cells. This PAS positive hyaline material occurring most often in the form of bands, and less commonly as globular shapes.

B) Embryonal carcinoma - [5, 86].
Identifying features -

Masses of large primitive pleomorphic cells, demonstrating prominent mitotic activity and not infrequently abnormal mitoses, arranged in solid sheets or less commonly in the form of papillary processes and glandlike clefts. Areas of necrosis and haemorrhage are frequently evident. Clusters of syncytiotrophoblastic cells are invariably present. Differentiation from the solid pattern of yolk sac tumour is necessary, but may be difficult (see features of value above).



Left half of field reticular Y.S.T.
Right half - embryonal carcinoma with marked pleomorphism and numerous syncytiotrophoblastic giant cells.

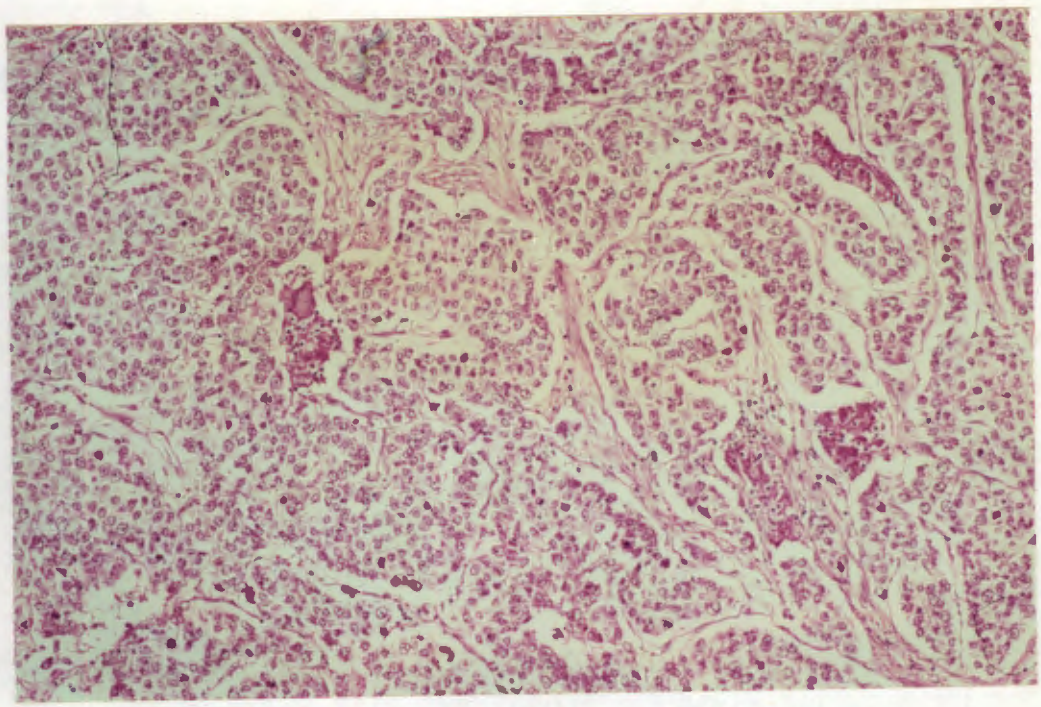
C) Choriocarcinoma -
Identifying features -

Presence of both cyto- and syncytiotrophoblast, plus frequent areas of necrosis, haemorrhage and vascular invasion.

D) Germinoma - [2, 5]

(When this neoplasm arises in the testis the apellation seminoma is used, in the ovary - dysgerminoma, and in extragonadal sites - germinoma).
Characteristic appearance - Monotonous appearing cells, containing a central vesicular nucleus with two or three nucleoli, surrounded by a prominent rim of clear to granular cytoplasm, and arranged usually in agregates separated by fibrous septae containing a variable lymphoid infiltrate (with or without an accompanying granulomatous reaction). The component monotonous cells may at times be arranged in solid sheets or linear profiles, rather than aggregates, and necrosis is occasionally evident.

- Variants - Germinoma with syncytiotrophoblastic giant cells [110]. (The syncytiotrophoblastic giant cells may be distributed in clusters or more diffusely).
- Anaplastic variant - Defined by the presence of increased mitotic activity (three or more mitoses per high power field), nuclear pleomorphism and cellular anaplasia [111].



Classical germinoma with accompanying granulomatous inflammation.

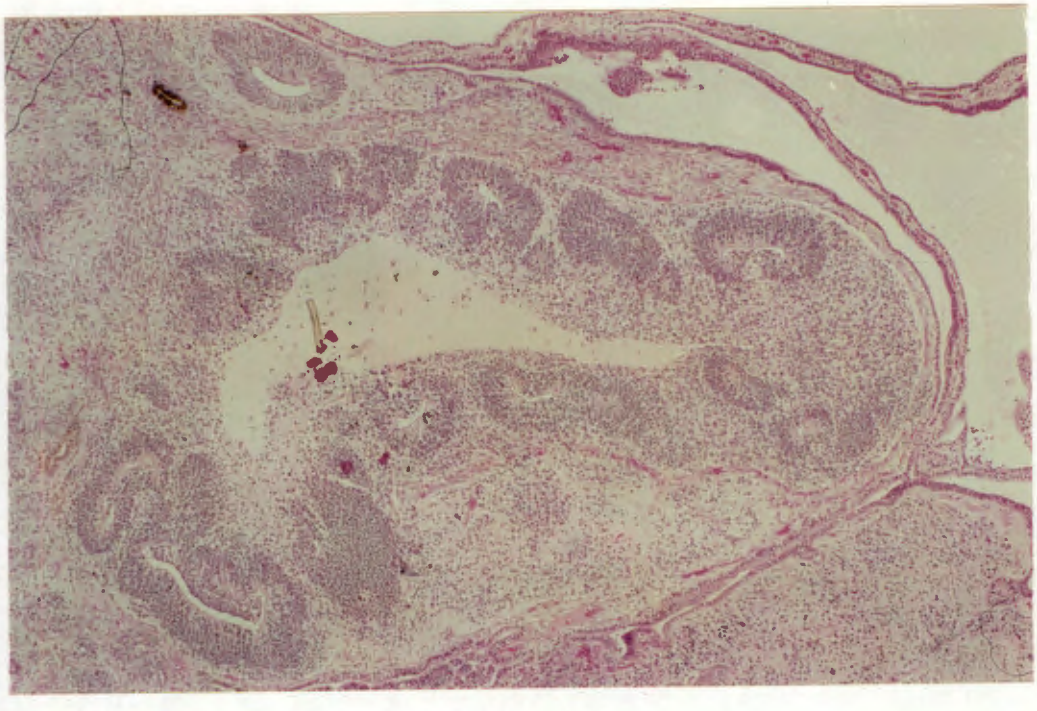
II) Immature Teratomas.

By definition these teratomas contain immature (embryonal) structures, as well as mature tissue, and no malignant germ cell elements. These tumours were graded after the system devised by Thurlbeck & Scully (1960) to indicate the quantity of immature tissue present.

Grade I - Immature tissue limited to a rare low power (x40) field, with no more than one such focus in any slide.

Grade II - Immature tissue comprising more than one but less than four low power (x40) fields, within any individual slide.

Grade III - Immature tissue occupying four or more low power (x40) fields within any individual slide.



Numerous neuroepithelial rosettes.

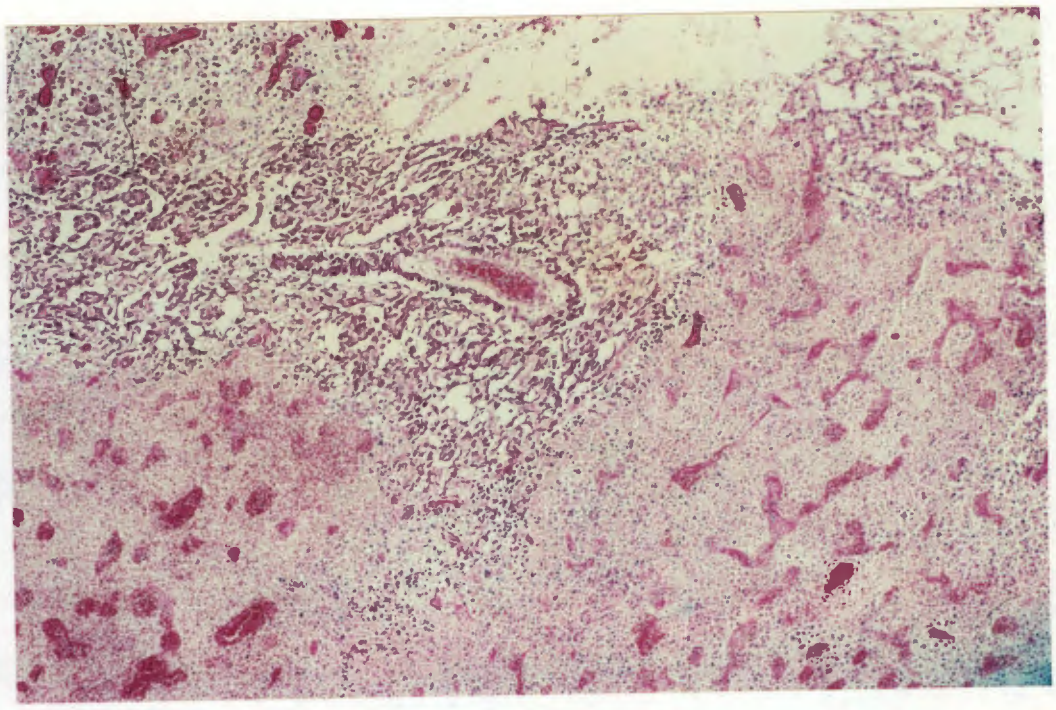
III) Mature Teratomas.

By definition containing no immature or malignant elements.

TUMOUR NON SPECIFIC HISTOLOGICAL FEATURES EVALUATED.

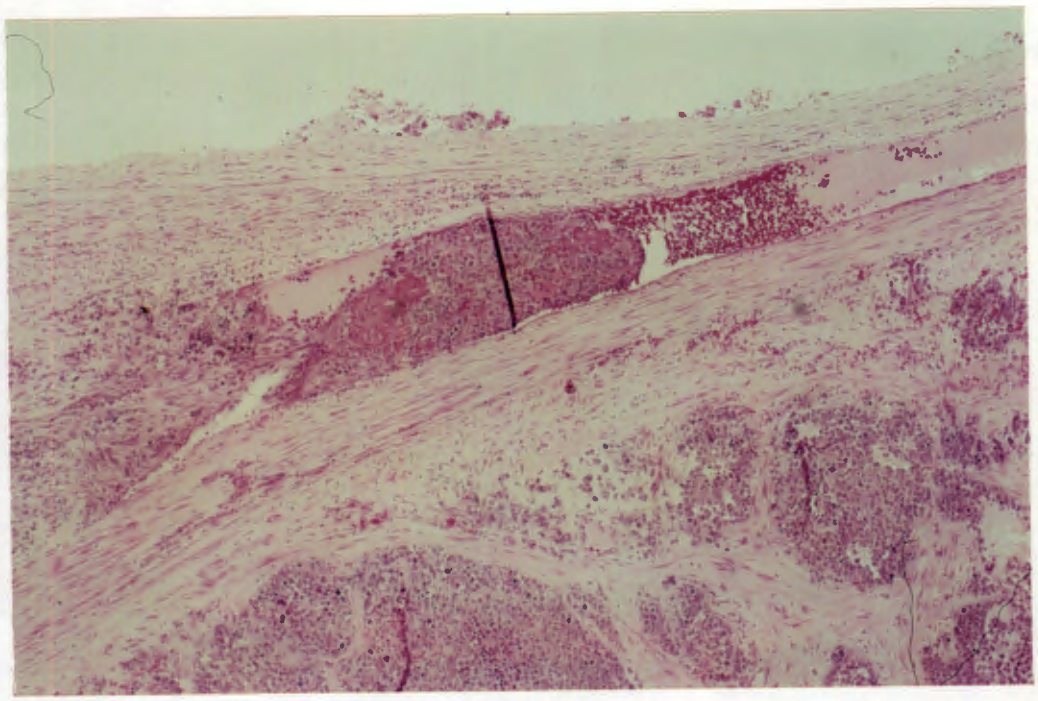
The following histological features were evaluated to assess their prognostic importance:

1. Mitotic rate per 10 high power fields (400 x magnification) - the average count from 30 randomly selected fields being utilized.
2. Presence or absence of microscopic tumour necrosis (where the necrosis occupied more than 3 low power fields, x40 magnification, on any individual slide, it was considered to be extensive).



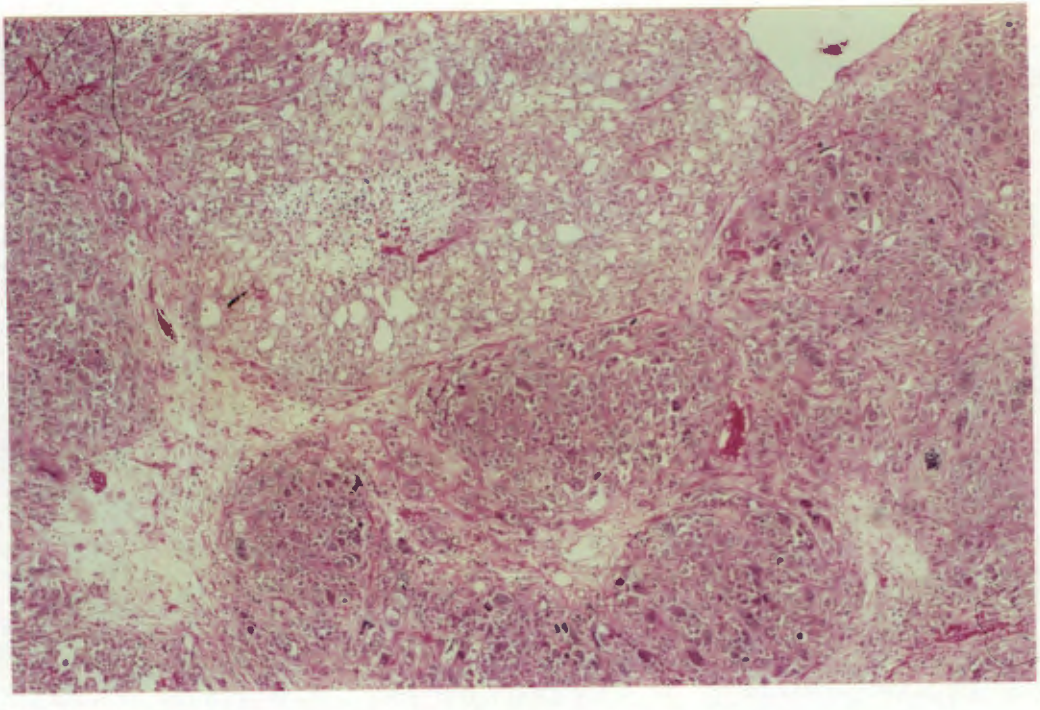
Upper portion of photograph - Viable Y.S.T., reticular pattern, plus Schiller-Duval body in centre of field.
Lower portion - tumour necrosis.

3. Vascular invasion - The criteria applied to distinguish definite vascular invasion from artefact, included one or more of the following:
   - penetration of the vessel wall by tumour
   - adhesion of luminal tumour to the endothelial surface
   - incorporation of luminal tumour within a thrombus



Embryonal carcinoma with vascular space invasion.

4. **Anaplasia - Defined by the presence of marked nuclear and cellular pleomorphism, with at least one nucleus being three times the size of those adjacent to it, with an accompanying very brisk mitotic rate.**

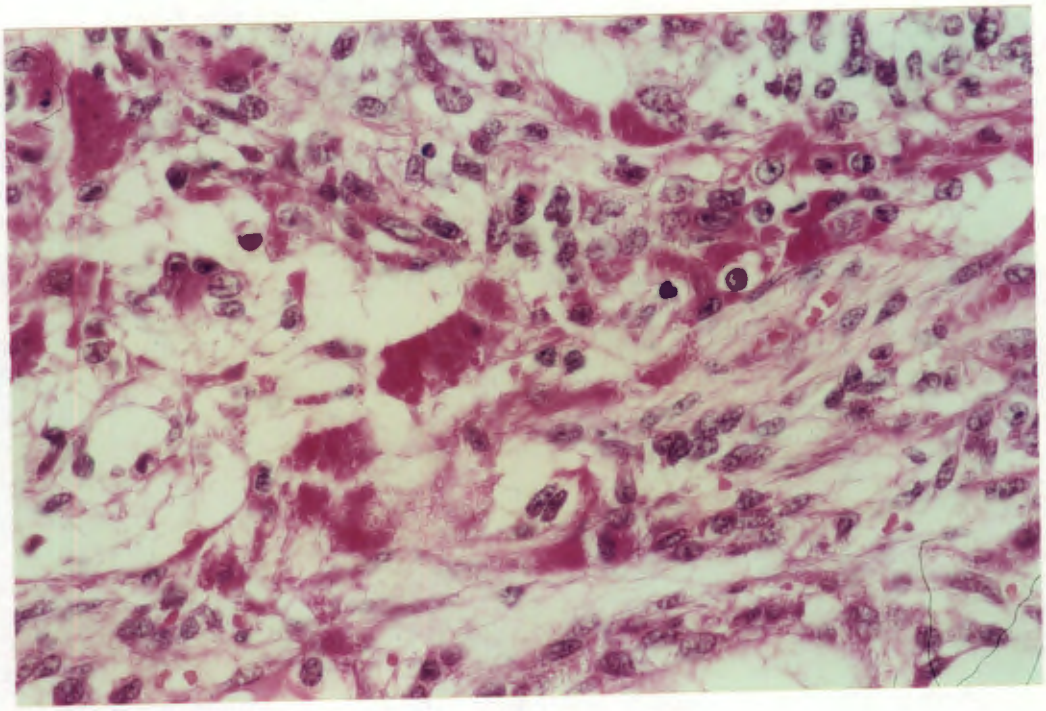


Left half of photograph - reticular Y.S.T.
Right half - embryonal carcinoma with syncytiotrophoblastic giant cell, plus single nucleus at least 3 times the size of the adjacent nuclei - meeting the defined criteria for anaplasia.

Additional histologic features evaluated:

- Presence/absence of intratubular germ cell neoplasia in all malignant testicular neoplasms (immunoperoxiclase staining for placental alkaline phosphatase was, however, unfortunately not employed).

- Presence/absence of hyaline globules in tumours with a yolk sac component.



Intra plus extra cellular hyaline globules - high power veiw.

- Presence/absence of granulomatous inflammation in the germinomatous malignancies.

MACROSCOPIC TUMOUR PATHOLOGY

Information (size, consistency, and description of cut surface) obtained from archival histopathology reports.

CLINICAL PARAMETERS

The clinical data was obtained retrospectively from:

- the folders of the oncology department
- the general hospital medical folders
- data presented at clinico-pathological meetings (involving the patient)
- and biopsy specimen request forms.

Clinical data recorded:

- Year of presentation
- Age
- Sex
- Clinical presentation
- Extent of disease
- Therapy administered
- Response to therapy/clinical course
- Duration of follow up, with clinical status at last examination.

Extent of disease - In general (except in the case of malignant testicular g.c.t.), the extent of the disease has been given in descriptive terms, and numerical staging avoided.

Testicular tumour staging.
Stage I - Tumour confined to the testis.
Stage II - Infradiaphragmatic lymph node involvement.
Stage III - Supradiaphragmatic lymph node involvement or visceral metastases.

BREAKDOWN OF G.C.T. EVALUATED IN STUDY.

A) Malignant	
I) With a YST component (But excluding those with a definite or possible embryonal carcinoma component).	39
II) Y.S.T. with possible embryonal carcinoma component.	3
III) G.C.T. with a definite embryonal carcinoma component.	3
IV) Germinoma.	8
V) Choriocarcinoma.	1
Total number of malignant G.C.T.	54
B) Immature Teratoma	37
C) Mature Teratoma	85
Total number of germ cell tumours	176 (-occurring in 174 patients)

GONADAL GERM CELL TUMOURS.

BREAKDOWN OF OVARIAN G.C.T. EVALUATED IN THE CURRENT STUDY.

	No. Of cases
A) Malignant	
I) With a Y.S.T. component (but excluding those with a definite or possible embryonal carcinoma component).	5
II) With a Y.S.T. component and a possible embryonal carcinoma component.	1
III) With a definite embryonal carcinoma component.	0
IV) Choriocarcinoma.	1
V) Dysgerminoma	6
Total number of malignant ovarian g.c.t.	13
B) Immature teratomas	9
C) Mature teratomas	30
Total number of childhood ovarian g.c.t. included in study	52

FOOTNOTE TO TABLE ON MALIGNANT OVARIAN G.C.T. (EXCLUDING DYSGERMINOMAS).

[1] Solid area noted with multiple syncytiotrophoblastic giant cells.
Differential diagnosis lies between a solid pattern of yolk sac tumour, and a focus of embryonal carcinoma.

FOOTNOTE TO TABLE ON OVARIAN DYSGERMINOMAS.

[1] Superficial resemblance to reticular yolk sac tumour noted in many areas (as a consequence of prominent stromal oedema).

[2] Presented originally with an enlarged supraclavicular lymph node, the histology of which showed a metastatic dysgerminoma. Ovarian biopsies at this stage showed no evidence of tumour.
The patient was lost to follow up, and presented one year later with a large ovarian mass.

MALIGNANT OVARIAN G.C.T (EXCLUDING DYSGERMINOMAS)

Age	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour histology	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Alive with residual disease	Alive No residual disease	Alive, disease status unclear	Follow up duration
8 yrs	1980	?	Both ovaries involved. Left – mass 120mm – capsular peretration. Right – Biopsy only	Pure yolk sac tumour. No predominant pattern	8	Y (Scanty)	N	N	Y	-	-	-	-	Death at 8 months
8 yrs & 7 m	1993	Pelvic mass & abdominal distension	Left ovary – mass 130mm diam.	Yolk sac tumour – pure. Reticular pattern predominant	6	Y (Extensive)	Y	N	-	Y – Pelvic recurrence & omental deposits	-	-	-	Only 7 months – alive with residual disease
12 yrs & 6 m	1973	Abd. Pain – 1 month duration	Left ovary – mass 120mm	Mixed – YST & immature teratoma	6	N	N	N	Y (Extensive pulmonary metastases)	-	-	-	-	Death at 18 months
8 yrs & 8 m	1987	Abdominal distension – 1 week duration	Left ovary – mass – 170mm – capsular penetration	Mixed YST & immature teratoma (YST – predominant-ly reticular)	1	N	N	N	N	N(Glio-matosis peritonei)	-	Y	-	5 months – alive no residual disease
7 yrs & 8 m	1986	Abdominal pain & distension – 1 months duration	Left ovary – mass – 110mm. Capsular penetration	Mixed YST & immature teratoma. YST – No predominant pattern	12	Y(Extensive)	Y	Y	N	N (Free tumor in peritoneal cavity but no peritoneal invasion)	N	Y	N	8 yrs & 9 months alive no residual disease
8 yrs	1986	Abdominal pain & distension x 2 weeks	Left ovary 110mm Predominantl y solid, capsular penetration	YST (No predominant pattern) & possible embryonal carcinoma component[1]	3	Y(Extensive)	Y	N	N	N (Free tumour in peritoneal cavity but no peritoneal invasion)	-	Y	-	7 yrs – alive no residual disease
7 yrs	1983	Precocious puberty, one year later abdominal mass noted	Left ovary 110mm Capsular penetration	Mixed choriocarcin-oma & mature teratoma	17	Y(Extensive)	Y	Y	N	Y Infiltrati-on of colon & abdominal wall	-	Y	-	11 yrs alive no residual disease

OVARIAN DYSGERMINOMAS

Age	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour Histology	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease	Alive with residual disease	Alive no residual disease	Alive, disease status unclear	Follow up duration
7 yrs	1973	Abdominal mass	? Size Solid consistency. Left ovary	Dysgerminoma. No syncytiotrophoblastic giant cells. Granulomatous inflam present.	1	N	N	N	N	Y Pelvic & para aortic lymph nodes	-	Y	-	13 years, alive no residual disease
12 yrs	1982	Abdominal swelling of several weeks duration	Right ovary ? Size ? Macro appearance	Dysgerminoma [1] No. Syn. g.c. Granulomatous inflammation present.	10	N	N	N	N	Y Para-aortic lymph nodes	-	Y	-	5 yrs, alive no residual disease.
7 yrs	1973	Abdominal pain – several days.	Right ovary 90mm. Solid.	Dysgerminoma No syn. g.c. No gran. Inflammation	10	N	N	N	?	Omental involvement	? NO	? FOLLOW	? UP	AVAILABLE
8 yrs	1990	Abdominal swelling – one month duration	Right ovary 150mm	Dysgerminoma No syn. g.c. Gran inflam. Present.	5	N	N	N	N	N	-	Y	-	2 months, alive, no residual disease
12 yrs	1990	Supraclavicular lymph node enlargement[2]	Right ovary. 80mm. Capsule intact. Solid	Dysgerminoma. No syn.g.c. No gran. Inflam	<1	N	N	N	N	Y Supra-clavicular lymph nodes	Y	-	-	5 months, alive with residual disease
14 yrs	1973	?	Right ovary.	Dysgerminoma. No syn. g.c. No gran. Inflam	7	N	N	N	N	Y Pelvic lymph nodes	N	Y	-	5 years, alive, no residual disease

OVARIAN IMMATURE TERATOMAS

Age	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour Histology	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease	Alive with residual disease	Alive, no residual disease	Alive disease status unclear	Follow up duration
9 yrs & 9 m	1995	Abdominal pain & distension – several days duration	Left ovary – mass – 260mm. Solid/cystic. Capsular penetration	Grade III. Immature teratoma. Neuroepith-elial rosettes only	<1	Y (Scanty)	N	N	N	Y Omentum-glial nodules within blood vessels	Y	-	-	3 months – alive with residual disease
9 yrs	1969	?	Right ovary. 150mm Solid – cystic	Grade II. Immature teratoma. Rosettes & solid neuroblast-omatous foci & immature mesenchyme	26 24	Y	N	N	N	N	-	Y	-	17 months alive, well no residual disease
10 yrs	1980	Abdominal pain & vomiting	Side unknown 110mm Multicystic	Grade I. Immature teratoma. Rosettes & immature neuroglial	0	N	N	N	N	No follow up	data			
5 yrs	1970	Progressive abdominal distension	Right ovary 230mm Solid – cystic. Capsular penetration	Grade II. Immature teratoma. Rosettes & solid neuro-blastomatous foci	18	Y (Extensive)	N	N	Y	Extensive peritoneal deposits	-	-	-	Death at 1 year.
8 yrs	1990	Torsion – acute	Right ovary 110mm Cystic	Grade I. Immature teratoma. Only immature neuroglial	1	N	N	N	N	N	-	Y	-	5 yrs – alive, no residual disease
2 yrs & 6m	1981	Abdominal pain – 1 month	Solid – Cystic 130mm side not known	Grade II. Immature teratoma. Rosettes & solid neuroblasto matous foci	3	N	N	N	N	N	-	Y	-	6 yrs – alive, no residual disease

OVARIAN IMMATURE TERATOMAS

12 yrs & 6 m	1986	Acute torsion	Left ovary 140mm	Grade I. Immature teratoma. Rosettes & occasional solid areas.	4	Y (Scanty)	N	N	N	No follow up	Data			
8 yrs & 4 m	1982	Acute torsion	Right ovary 110mm cystic	Grade I. Immature teratoma. Only immature neuroglial	0	N	N	N	N	N	-	Y	-	5 yrs – alive, no residual disease
5 yrs	1970	Abdominal pain & abdominal mass	Left ovary Multicystic 140mm	Grade III. Immature teratoma. Rosettes, solid neuro-blastomatous foci immautre neuroglial, rhabdomyo-blastic focus (confirmed via skeletal muscle actin)	8	Y (Scanty)	N	N	N	N	-	Y	-	12 yrs – alive, no residual disease

MATURE OVARIAN TERATOMAS

Age	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Other	Follow up
3 yrs	1964	?	90mm		
8 yrs	1967	Abdominal pain 2 days duration	125mm Right ovary Multicystic	Spina bifida at L5	
3 yrs	1962	Abdominal swelling	60mm Multicystic		
?	1963	?	35mm		
9 yrs	1965	Acute torsion	40mm Multicystic		
2 yrs	1965	?	100mm Multicystic		
12 yrs	1966	Abdominal mass	Left ovary 120mm		4 yrs later – well
3 yrs	1970	Abdominal mass	Right ovary Cystic 70mm		
8 yrs	1970	Abdominal mass	Left ovary Cystic 100mm		
6 months	1967	Abdominal mass	Left ovary Multiloculated 120mm		Death from postoperative complications
3 weeks	1973	Acute torsion	Left ovary Cystic 50mm		
6 yrs	1974	Abdominal mass	Right ovary Cystic 90mm		
6 yrs	1974	Abdominal mass	Cystic 60mm		
21 months	1981	Acute torsion	120mm Cystic		
7 yrs	1979	Acute torsion	Right ovary Cystic 80mm		
6 yrs	1984	Recurrent urinary tract infections	Left ovary Cystic 30mm		
5 yrs	1991	Abdominal mass	120mm Cystic		
3 yrs	1991	Abdominal mass	Right ovary 120mm Cystic		
8 yrs	1975	Abdominal pain & mass – torsion	Right ovary 60mm Cystic		
10 yrs	1972	Abdominal swelling & acute torsion	Bilateral teratomas 120mm + 22mm respectively Both cystic		
3 yrs	1979	?	Cystic 70mm		

MATURE OVARIAN TERATOMAS

Age	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Other	Follow up
6 yrs & 10 months	1979	Abdominal mass	Left ovary Cystic 130mm		
2 yrs	1965	Abdominal distension	Cystic 100mm		
9 yrs & 6 months	1994	Abdominal pain	Right ovary 50mm		
2 yrs	1994	Acute torsion	Left ovary Cystic 100mm		
10 yrs & 11 months	1991	Abdominal mass & acute torsion	Cystic 120mm		
3 yrs & 8 months	1993	Abdominal mass	Cystic 74mm		
3 yrs	1991	Abdominal mass	Right ovary Cystic 120mm		
7 yrs	1991	Abdominal mass	Right ovary Cystic 110mm		
11 yrs & 10 months	1995	?	Right ovary Cystic		

GONADAL GERM CELL TUMOURS.

OVARIAN GERM CELL TUMOURS OF CHILDHOOD.

A) MALIGNANT.

I) Ovarian germ cell tumours with a yolk sac component.

Incidence

In the current study 6 (11,5%) of 52 childhood ovarian germ cell tumours contained a yolk sac component.

Incidence figures from other childhood studies:

- [9] Harms & Janig - 12 (24%) of 50 ovarian g.c.t. contained a yolk sac component.
- [13] Marsden et al - 7 (15,5%) of 45 neoplasms contained a yolk sac component.

Age

The mean age in the current study was 8 years 10 months - (range: 7 years 8 months to 12 years 6 months).
By comparison, the mean ages for the other ovarian g.c.t. were:

- Mature teratoma - 5 years, 6 months.
- Immature teratoma - 7 years, 9 months.
- Dysgerminoma - 10 years.
- The single patient with a choriocarcinoma was 7 years of age.

Clinical Presentation

Adequate data was available for 5 of the 6 cases. Four presented with abdominal enlargement (2 of these patients had associated pain). In one case abdominal pain alone appeared to have been the symptom precipitating consultation.

[5, 7] Yolk sac tumours of the ovary are almost always unilateral, bilateral involvement being a manifestation of metastatic spread. In the current study only one of the 6 patients had bilateral disease - she subsequently died from disseminated disease.

Macroscopic Pathology

Tumour size

In the large series (71 patients, 29 premenarchal) of Kurman & Norris [7] the median tumour diameter was 15cm, with a range from 7 to 28cm.

In the current childhood study the mean tumour diameter was 12,7cm, with a range from 11 to 17cm.

Tumour consistency

In the present study, the data was unfortunately inadequate in virtually all the 6 cases.

In the literature [2, 5, 7, 6] these tumours are described as being predominantly solid, with a variegated cut surface, showing foci of haemorrhage, necrosis, and cystic degeneration. Capsular rupture, before or during operation occurs in approximately 30% of patients [7].
In the current study capsular penetration was documented to be present in 4 (66%) of the cases.

Microscopic Pathology

In the current study of 6 childhood ovarian neoplasms with a yolk sac component, the histological subtypes were:

- Pure yolk sac tumour - 2 cases (33%). (The one showed no predominant histological pattern, whilst in the others a reticular pattern predominated).
- Mixed yolk sac tumour/immature teratoma - 3 cases (50%).
- Yolk sac tumour with a possible embryonal carcinoma component - 1 case (16%).

Comparison with other childhood series:

Harms & Janig [9] - 12 ovarian tumours with a yolk sac component - 7 (58%) pure, 5 (42%) mixed.
Hawkins et al [15] - 13 ovarian tumours with a yolk sac component - 7 (54%) pure, 5 (38%) mixed YST/teratoma, 1(7%) mixed YST/embryonal carcinoma.

Clinical Outcome

Results from current study compared to other childhood series.

Study	**Total No. Of Cases with a Y.S.T. Component**	**Death**	**Alive with residual Disease**	**Alive, No residual Disease**
Current Study	6	2 (33%)	1 (16.6%)	3 (50%)
Hawkins et al [15]	13	3 (23%)	0	10 (77%)
Harms et al [9]	12	3 (25%)	0	9 (75%)

Prognostic Variables

Pathological

Macroscopic

Kurman & Norris [7] found some correlation, albeit not statistically significant, between tumour size and outcome. In the current study no such tendency was apparent (see detailed table)

Microscopic

In the study of Kurman & Norris [7], as well as that of Hawkins et al [15], no microscopic feature (such as histologic tumour pattern or mitotic activity) correlated with survival. The current study, similarly showed no correlation (other variables, additionally evaluated - microscopic necrosis, vascular invasion, and anaplasia).

Clinical

Type of therapy administered - In the current series the 2 patients who died were diagnosed at an earlier date in the study than the survivors, and neither received multidrug chemotherapy.

II) Ovarian Dysgerminomas of Childhhood.

Incidence

In the current study 6 (11.5%) of 52 childhood ovarian g.c.t. were dysgerminomas.
Comparison with other childhood series:

Study	Total No. Of ovarian G.C.T.	No. Plus percentage of dysgerminomas.
Current Study	52	6 (11.5%)
Marsden et al [13]	45	9 (20%)
Harms et al [9]	50	9 (18%)
Breen et al [66] (literature review)	674	111 (16.4%)

Age

In the current study the mean age was 10 years (range 7 to 14 years) i.e. greater than that for the other ovarian germ cell tumour types.

Clinical presentation

Data was available for 5 of the 6 cases.

- In 3 patients the primary presenting symptom was abdominal enlargement.
- In 1 patient, abdominal pain.
- And 1 patient presented initially with a manifestation of metastatic spread, namely an enlarged supraclavicular lymph node. Ovarian biopsies at this stage showed no evidence of neoplasia, however 12 months later a large ovarian tumour was present.

Macroscopic pathology

In the current study all the tumours were unilateral, the right ovary being involved in five cases and the left in one.

Dysgerminomas are typically large, bossellated tumours, with a homogenous, solid, grey coloured cut surface (often described as having brain- like consistency). [2, 66]

In the current study data was available for only 3 of the 6 cases, all of which were described as being solid. The maximum tumour diameters were - 80, 90, and 150mm respectively.

Microscopic Pathology

Salient findings in current study:

- Granulomatous inflammation could be detected in only 2 of the 6 cases.
- Syncytiotrophoblastic giant cells were not detected in any of the cases.
- None of the neoplasms showed anaplastic foci.
- The stroma of the one tumour showed marked oedema, resulting in a histological appearance strikingly similar to a reticular yolk sac tumour.

Clinical Outcome

Current Study - Follow up data was available on 5 of the 6 patients. Four were alive with no evidence of residual disease (follow up duration ranging from 2 months to 13 years).
One was alive with residual disease.
No deaths were documented, despite metastatic disease being present in 5 of the 6 patients. (Lymph node involvement occurring in 4, and omental disease in one).

III) Choriocarcinoma

Please see detailed tabulated data for information on the single patient with an ovarian choriocarcinoma.

B) IMMATURE OVARIAN TERATOMAS

Incidence

Immature teratomas comprise only 1 - 2 % of all ovarian teratomas, however of those arising during the first two decades of life, they account for 10 - 20%. [2]

In the current series 9 (17%) of the 52 ovarian germ cell tumours were immature teratomas, whilst considering teratomas alone, 23% were immature.

Age

Immature ovarian teratomas occur predominantly in the first two decades of life, with a peak incidence at 14 - 19 years. [2]

In the current study, which included only paediatric patients, the mean age was 7 years 9 months (Range : 2 years 6 months to 12 years 6 months).

Clinical Presentation

Abdominal enlargement (readily palpable tumour), with/without accompanying pain is the usual mode of presentation. [2] In the series of Nogales et al [72] all 20 of the patients presented with abdominal enlargement (40% had accompanying abdominal pain), similarly 80% of the 58 patients in the series of Norris et al [46] (which included all age groups) had abdominal enlargement, 44% accompanying pain.

Current study, abdominal pain was the primary symptom precipitating admission in 7 (87%) of the 8 patients with adequate clinical data. Acute torsion occurred in at least 3 instances. (As the smallest tumour measured 11cm in diameter, it is likely that all the patients had at least some degree of abdominal enlargement, although this was not stated clearly in the clinical notes).

Macroscopic Pathology

Immature ovarian teratomas are almost always unilateral. [2] Only one of the 58 cases reported by Norris et al [46] was bilateral. In the series of Nogales et al [72] none of the 20 cases were bilateral. (No predilection for any one side has been documented).

Current study, all 9 cases were unilateral.

The majority of tumours have both solid and cystic components. [66, 2, 46]
The mean tumour diameter, in various series, ranges from 150mm ([59] Kooijman) to 200mm ([72] Nogales et al).

Current study, 4 of the 8 cases with adequate data were reported as being purely cystic - a finding somewhat at variance with the reported literature (see above). The other 4 cases were of a mixed solid - cystic consistency. The mean tumour diameter in the current study was 153mm (range : 110-260mm) Capsular penetration was documented in 2 (25%) of the cases.

Histopathology

The tumours were graded from 1 - 3, according to the criteria of Thurlbeck & Scully [77] (1960).

Total number of ovarian immature teratomas in current study - 9.

- Grade 1 - 4 (44%) cases.
- Grade 2 - 3 (33%) cases.
- Grade 3 - 2 (22%) cases.

The series of Kooijman [59] (8 patients), which like the present study evaluated only childhood cases, showed similar findings
- grade 1 (50%), grade 2 (25%), grade 3 (25%).
Whereas in the series of Nogales et al [72] plus Norris et al [46] both of which involved predominantly post menarchal patients, grade 2 tumours were the most frequent.

The immature neuroepithelial tissue, which was present in all 9 of the cases, included:

- Neuroepithelial rosettes (Homer-Wright or Flexner Winterstein in type) - seen in 7 cases.
- Solid sheets resembling neuroblastomatous foci - present in 5 cases.
- Immature neuroglial - seen in 4 cases.

Non neuroepithelial immature tissue was noted in only 2 cases, the one having immature mesenchyme and the other a rhabdomyoblastic component.
With regard to the relationship between tumour grade and other histological variables (see also accompanying table):

- A mitotic count of $\leq$ 5/10 H.P.F. occurred in all four grade 1 tumours, however one of the grade 3 cases similarly showed a low mitotic rate (1/10 H.P.F.)
- Microscopic necrosis was present in both grade 3 cases, however one of the grade 1 cases also showed scanty necrosis.
- None of the tumours demonstrated vascular invasion (although intravascular glial nodules were noted in the peritoneal sections of one case - (see discussion later) or anaplasia.

RELATIONSHIP BETWEEN OVARIAN IMMATURE TERATOMA GRADE PLUS HISTOLOGICAL FEATURES (OF MICROSCOPIC NECROSIS, MITOTIC COUNT, VASCULAR INVASION, ANAPLASIA):

	No of cases	Microscopic necrosis	Vascular invasion	Anaplasia	Mitotic count/IOHPF
Grade I	4	1 case (Scanty)	0	0	<5 – 4 cases 6-10 – 0 11-20 – 0 >20 – 0
Grade II	3	2 cases, (1 scanty 1 extensive)	0	0	<5 – 1 case 6-10 – 0 11-20 –1 case >20 – 1 case
Grade III	2	2 cases, (both scanty)	0	0	<5 – 1 case 6-10 – 0 11-20 – 0 >20 – 0 Insufficient data – 1 case

Clinical Outcome

Results from current study:

Tumour Grade	Total Number of cases	Death	Alive with residual disease	Alive, No Disease.
I	2*	0	0	2
II	3	1**	0	2
III	2	0	1***	1

* 4 Grade I teratomas were included in the study, however only 2 of the patients had adequate follow up data.
** Clinical course characterised by extensive peritoneal metastatic deposits.
*** Histology of the peritoneum showed glial nodules, predominantly well differentiated, within blood vessels (see discussion later, under gliomatosis peritoneii) - unfortunately, only 3 months follow up data was available on this patient.

The finding that death occurred in only 1 (14%) of 7 patients, is similar to that of Kooijman's [59] series (which also evaluated only paediatric patients), in which all 8 patients survived.
The mortality figures from series which include predominantly post mernarchal patients are however significantly higher:
- Norris et al [46] - 36% mortality rate.
- Nogales et al [72] - 21% mortality rate.

Prognostic Factors.

Macroscopic Features

Tumour size

Norris et al [56] found a degree of correlation between the maximum diameter of immature ovarian teratomas and prognosis. In their series all patients with tumours less than 10cm in maximum diameter were alive and well, in comparison to 67% with tumours 10 to 19,9cm, and 54% with neoplasms 20cm or greater.

In the current study, the 2 patients with the largest neoplasms (23cm. and 26cm. in diam. respectively) fared worst - see tabulated data. (The small patient sample however precludes the drawing of definite inferences).

Capsular rupture

Nogales et al [72] found capsular rupture to be an important prognostic feature. Seven of 9 patients with rupture developed peritoneal implants of varying histologic grade, two of whom subsequently died.

In the current study the 2 patients whose neoplasms showed capsular penetration fared worst. (See comment above).

Microscopic features

Tumour grade

Tumour grade has been shown in a number of studies (especially those involving post menarchal patients) to be of prognostic significance (see table below):

Correlation between grade of immature ovarian teratoma and mortality rate.

Study	Grade 1	Grade 2	Grade 3
** Norris et al [46] - % Mortality rate - (no. of deaths/total no. of cases).	18 (4/22)	38 (9/24)	70 (7/10)
** Nogales et al [72] - % Mortality rate - (no. of deaths/total no. of cases).	0 (0/6)	11 (1/9)	60 (3/5)
** Ihara et al [103] - % Mortality rate - (no. of deaths/total no. of cases).	0 (0/2)	0 (0/1)	33 (1/3)
* Kooijman [59] - % Mortality rate - (no. of deaths/total no. of cases).	0 (0/4)	0 (0/2)	0 (0/2)#
* Current study - % Mortality rate - (no. Of deaths/total no. Of cases	0 (0/2)	33 (1/3)	0 (0/2)# #

** - Patient population predominantly post menarchal.
* - Exclusively paediatric patient population.
# One of the two grade 3 patients developed tumour recurrence.
# # Residual disease present in one of the two grade 3 cases.

As commented previously, a striking difference is noted in the mortality rate between those studies including predominantly post menarchal patients (22 of 82 patients i.e. 33%) as opposed to those involving exclusively paediatric patients (1 of 15 i.e. 6,6%).

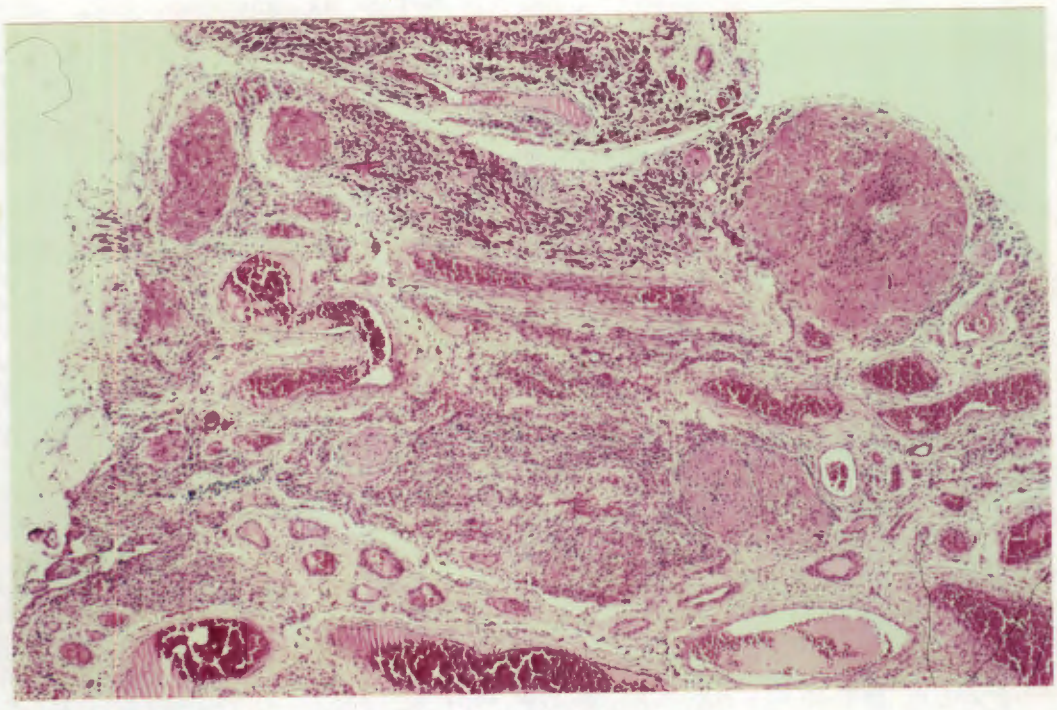
Given the apparent favourable outcome of most paediatric patients with immature ovarian teratomas, tumour grade would appear to be of less prognostic significance in this group. However, as demonstrated in the table, a problem free clinical course can be expected with grade I neoplasms.

Nature of non neural immature tissue

In the current study a rhabdomyoblastic component was present in one neoplasm, and a focus of immature mesenchyme in another. Both patients had uncomplicated clinical courses.

Note on gliomatosis peritoneii and immature ovarian teratomas.

Approximately 10% of patients with immature ovarian teratomas develop peritoneal implants composed exclusively of mature glial tissue - "gliomatosis peritoneii". [2] The biological behaviour of these implants is benign, and additional therapy is not indicated. The lesions are thought to usually result from capsular rupture and consequent implantation of neoplastic tissue (either mature, or immature with subsequent maturation). Some authors (Robboy & Scully 1970, [75], EL Shafie et al 1984, [103]), have suggested that lymphatic spread may also have a role. The finding of well differentiated glial nodules in peritoneal vessels, in one of our cases, would support this hypothesis (See photograph below).



Fragment of omentum showing numerous well differentiated glial nodules, some of which are located within blood vessels.

C) MATURE OVARIAN TERATOMAS

Incidence

In the current study 30 (57,7%) of 52 childhood ovarian g.c.t. were mature teratomas.

Comparison with other childhood series:

Study	Total No. Of Ovarian Germ Cell Tumours.	No. Plus Percentage of Mature Teratomas.
Current Study	52	30 (57,7%)
Marsden et al [13]	45	25 (55,5%)
Harms et al [9]	50	19 (38%)
Breen et al [66] (Literature review)	674	387 (57,4%)

Age

The mean age of the patients in the current study was 5 years 6 months (range 3 weeks to 12 years).
Noteworthy remarks in comparison with:

- Yolk sac tumours + dysgerminomas - in both these groups, the youngest patient was 7 years of age. (18 of the 30 mature teratomas occurred at an earlier age).
- Immature teratomas - youngest patient 2 years 6 months (6 of the 30 mature teratomas occurred at an earlier age).

Clinical Presentation

- No clinical data was available in 5 of the 30 cases.
- Abdominal distension was the primary presenting complaint in 15 (As an embryonic migrant from the area of T10, the ovary in early life is characteristically abdominal in location, descending at puberty into the bony pelvis [66]).
- Abdominal pain as the primary presenting symptom occurred in 9 patients (7 of the 9 having acute torsion - it has been suggested that the abdominal location of these tumours, see above, results in elongation of the ovarian pedicle, and predisposes to adnexal torsion [66]).
- One patient presented with recurrent urinary tract infections.

Macroscopic Pathology

While 25% of mature ovarian teratomas reportedly are bilateral in adults [66], in children most are unilateral - estimates of bilaterality in children ranging from 0-9% [105, 106].

In the current study only 1 (5,5%) of the 18 cases with adequate data was bilateral.

Size - In the current study the mean size was 86mm (range 22mm to 130mm). By way of comparison, the mean diameter of the yolk sac tumours and immature teratomas were 127 and 153mm respectively.

Consistency - All 27 of the cases with adequate data were of a cystic nature (either unilocular or multilocular).

Microscopic Pathology

As in other series a variety of mature tissue types occurred, but with ectodermal and neural tissue being the commonest.

BREAKDOWN OF TESTICULAR G.C.T. EVALUATED IN THE CURRENT STUDY.

	No. Of cases
A) Malignant	
I) With a Y.S.T. component (but excluding those with a definite or possible embryonal carcinoma component)	14
II) With a Y.S.T. component plus a possible embryonal carcinoma component	2
III) With a definite embryonal carcinoma component	1
IV) Seminoma	1
Total no. Malignant testicular g.c.t.	18
B) Immature teratomas	0
C) Mature teratomas	4
Total number childhood testicular g.c.t. included in study	22

Age (Months)	Side involved	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour Histology	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive, no residual disease	Alive, disease status unclear	Follow up duration
14	R	1986	Testicular mass – short duration	8mm, Stage I (& confined within tunica)	Pure YST. No predominant pattern	10	Y (Scanty)	N	N	N	N	N	-	Y	-	10 yrs & 10 months
24	R	1984	Testicular mass – short duration	20mm. Stage I (& confined within tunica)	Pure YST. Reticular & papillary predominant.	21	N	Y	N	N	N	N	-	Y	-	2 yrs & 2 months
36	L	1972	Testicular mass/swelling. 1½ months duration.	?	Pure YST. Reticular & polyvesicular predominant	3	Y (Scanty)	N	N	NO	FOLLOW	UP	DATA	AVAILABLE		
14	R	1981	Torsion	?	Pure YST. No Predominant type.	4	Y (Scanty)	N	N	N	N	N	-	Y	-	3 yrs
11	L	1984	Testicular swelling – 1 month duration	15mm. Stage I (& confined within tunica)	Pure YST. No predominant type.	7	N	N	N	N	N	N	-	Y	-	4 yrs.
24	R	1988	Testicular swelling – 2 weeks duration	25mm. Stage I	Pure YST. Reticular predominant	1	N	N	N	N	N	N	-	Y	-	5 yrs
2	?	1982	Testicular swelling – 1 month duration	30mm Stage I	Pure YST Solid pattern predominant	2	N	N	N	NO	FOLLOW	UP	DATA	AVAILABLE		
6	R	1982	Testicular swelling – 3 months duration	10mm	Pure YST. Reticular predominant	4	N	N	N	N	N	N	-	Y	-	12 months
22	R	1990	Testicular mass	30mm. Stage II. Intra-abd. Nodes. YST	Pure YST. Reticular predominant	<1	Y (Scanty)	N	N	N	Y Intra-abd nodes	N	-	-	Y	5 months
8	?	1972	Testicular mass	?	Pure YST. Reticular predominant	7	N	N	N	NO	FOLLOW	UP	DATA	AVAILABLE		
6	R	1980	Testicular swelling – 2 months duration	Stage I Size ?	Pure YST. Reticular predominant	<1	Y (Scanty)	N	N	N	N	N	-	Y	-	15 yrs
12	R	1970	Testicular swelling ? duration	Stage I 55mm	Pure YST. Reticular predominant	5	Y (Scanty)	N	N	N	N	N	-	Y	-	8 yrs

Age (Months)	Side involved	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour Histology	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive, no residual disease	Alive, disease status unclear	Follow up duration
11 ½	R	1990	Testicular swelling 4 months duration	Size? Stage I	Pure YST. Reticular predominant	10	Y	N	N	N	N	Recurrence in wound 2 months post surgery	-	Y	-	6 months
17	L	1986	Testicular swelling 4 months duration	45mm. Stage I ↓ 6 months later Stage III	Mixed YST & mature teratoma. No predominant pattern	4	N	N	N	N	Hilar lymph nodes	Hilar lymph nodes	-	Y	-	11 yrs & 8 months

OTHER MALIGNANT TESTICULAR GERM CELL TUMOURS

Age (Months)	Side involved	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour Histology	Mitotic count/ 10HPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive no residual disease	Alive disease status unclear	Follow up duration
14	R	1995	Mass in right groin secondary to tomour in undescended testis	55mm Stage III with disseminated disease including pulmonary metastases	YST. With possible embryonal component	8	Y	Y	Y	N	Y Para-aortic lymph nodes & pulmonary metastases	N	-	-	Y	8 months
24	L	1994	?	45mm Stage I	Predominantly YST but possible embryonal component	3	Y	N	N	N	N	NO	FOLLOW	UP		AVAIL-ABLE
60	?	1988	Testicular swelling 1month	75mm Stage II. Intra abd node involvement ↓ 9 months later Stage III	Pure embryonal carcinoma Solid growth pattern, numerous syncytiotrop hoblastic G.C.	30	N	Y	Y	Y	N	Y Dissemina ted with visceral involve-ment	-	-	-	9 months
6	L	1989	Painful swollen testis – 2 weeks duration	20mm	Seminoma	?	?	?	?			NO	FOLLOW		UP	AVAIL-ABLE

TESTICULAR MATURE TERATOMAS

Year	Age (Months)	Side involved	Clinical presentation	Size (max diam in mm)	Tumour histology	Follow up
1985	14	L	Testicular swelling	40mm Multicystic	Mature teratoma	No follow up
1962	48	?	?	?	Mature teratoma	No follow up
1973	36	R	Testicular mass	30mm Encapsulated cystic	Mature teratoma	Alive well at 4½ years
1972	84	R	Testicular swelling	Cystic mass 20mm	Mature teratoma	No follow up

TESTICULAR GERM CELL TUMOURS OF CHILDHOOD.

Incidence

Testicular tumours are said to account for between 3% to 7% of all childhood germ cell tumors [11, 14, 12, 10].
In the current study, 22 (12,5%) of the 176 germ cell tumours were of testicular origin.

Age and relationship to tumour histology

Testicular germ cell tumours may occur at any age, from birth to the 6th decade and beyond. The frequency of the various histological types does however differ markedly in children and adults.
In adults the tumours are more commonly of mixed histological type (approximately 62% mixed and 38% pure) [34], whereas in children the vast majority are pure in type.
In adults seminomas account for approximately 70%, and yolk sac tumours 6% of the pure tumours, [34] whilst in children the converse is seen - yolk sac tumours being by far the most common single histological type, and seminomas extremely rare.

In the current study, of the 22 testicular g.c. tumours:
- 16 (72,7%) contained a Y.S.T. component (13 pure Y.S.T., 2 Y.S.T. with possible embryonal components, and 1 mixed Y.S.T./mature teratoma).
- 4 (18%) were mature teratomas.
- and 1 case each of pure embryonal carcinoma and pure seminoma.

(It is of note that no immature teratomas occurred).

The pathogenesis of adult and childhood testicular g.c.t. would appear to be different. Intratubular germ cell neoplasia being identifiable in 85 - 100% of adult cases, but absent in those occurring in childhood. In the current study no evidence of ITGCN was identifiable in any of the cases. (Immunohistochemistry for placental alkaline phosphatase was however not employed).

Predictors of clinical outcome/prognostic factors in malignant testicular GCT.

A) Y.S.T. - The vast majority of malignant testicular g.c.t. in children are yolk sac tumours. [59].
Where these tumours are localized to the testis and occur in early childhood the prognosis is favourable [9, 2] (unlike the outcome in adults).
Harms et al [9] evaluated 22 children with testicular yolk sac tumors
- 18 with pure YST (mean age 23,7 months; range 0-104 months) and 4 with mixed g.c.t with a Y.S.T. component (mean age 186 months; range 177 - 192). No deaths occurred, 2 of the children from the pure Y.S.T. group were alive with residual disease, all 20 of the remaining children were alive and free of disease.

In the current study the outcome data was as follows:

- Pure Y.S.T. 13 cases (mean age 13,8 months; range 2 - 36 months) - no follow up data was available on 3 patients - all 10 of the remaining children were alive with no evidence of residual disease (follow up duration ranging from 6 months to 15 years). Nine of the ten patients had Stage I disease, and only 1 child with involved intra-abdominal lymph nodes had stage II disease. An additional patient sustained a scrotal recurrence 2 months after the original surgery.

- Mixed mature teratoma/Y.S.T. - Only one case, that of a 17 month infant was included in the study. He presented with stage I disease, however 6 months later developed marked hilar lymphadenopathy. Following chemotherapy, he remains well 11½ years later.

B) Y.S.T. with possible embryonal carcinoma component (occasional solid areas showing prominent nuclear pleomorphism and containing scanty numbers of syncytiotrophoblasts - unclear whether to classify as embryonal carcinoma or solid pattern of a yolk sac tumour) - Two such cases were included. The one, a 14 month infant, presented with disseminated disease, including pulmonary metastases. Follow up notes extended only to 8 months, at which time he was alive and well (disease status unclear). The other a 24 month infant presented with stage I disease - unfortunately no follow up data is available.

C) Pure embryonal carcinoma - Only one case identified, occurring in a 5 year old child who subsequently died from disseminated disease non responsive to chemotherapy. This was the only death amongst the patients with testicular tumours.

D) Pure seminoma - Only a single case, occurring in a 6 month old infant, was identified. Unfortunately, no follow up data was available.

Evaluation of possible histological prognostic indicators.

1. Regarding pure Y.S.T. - Vascular invasion which has been shown in adults with stage I disease to be of prognostic importance, could not be identified in any of our cases.
   - Mitotic count did not appear to be of significance; the only patient with stage II disease having a count of less than 1/10 H.P.F.
   - Of the 6 patients with microscopic necrosis and adequate follow up data, 4 had stage I disease with no tumour recurrence, 1 stage I disease with scrotal tumour recurrence, and 1 stage II disease. The remaining 5 with no microscopic necrosis (and adequate follow up data) all had stage I disease with no recurrence. The significance of these findings requires a larger patient sample for evaluation.
   - Anaplasia was identified in a single patient who had stage I disease and no tumour recurrence.
2. Regarding the 3 patients with a possible/definite embryonal carcinoma component, both vascular invasion and anaplasia were documented in two, one of whom died from disseminated disease, whilst the other developed nodal and pulmonary metastases (final disease status unclear). In both adults [26] and children [113] embryonal carcinoma has been shown to behave in a more aggressive manner (than testicular Y.S.T.).

Concluding remarks regarding the prognosis of childhood malignant testicular g.c.t.

1. The excellent prognosis of stage I pure Y.S.T. in early childhood (less than 2 years of age) was confirmed [9, 112].
2. With regard to pure Y.S.T. - Mitotic count and anaplasia were not found to be of prognostic value, nor was any specific histological tumour pattern.
   - Microscopic tumour necrosis was found to be of possible prognostic significance, and further investigation appears warranted.
   - Vascular invasion could not be identified in any of the cases.
3. Although the number of cases involved were few, a definite/possible embryonal carcinoma component appeared to confer an adverse prognosis.

Other testicular g.c.t.

No cases of immature teratoma were identified ([59] Kooijman, similarly found immature testicular teratomas of childhood to be rare - accounting for 2 (5,5%) of 36 testicular g.c.t.

Four cases of mature teratoma were documented (see tabulated data).

EXTRAGONADAL GERM CELL TUMOURS

BREAKDOWN OF SACROCOCCYGEAL G.C.T. EVALUATED IN THE CURRENT STUDY.

	No. Of Cases
A) Malignant	
I) With a Y.S.T. component	15
II) Embryonal carcinoma (definite or possible)	0
III) Germinoma	0
IV) Choriocarcinoma	0
Total no. Of malignant sacrococcygeal g.c.t.	15
B) Immature Teratomas	15
C) Mature Teratomas	27
Total number of childhood sacrococcygeal g.c.t. included in study.	57

(One immature teratoma, plus one mature teratoma subsequently recurred with a yolk sac tumour component - both the primary and the recurrent malignant tumour are included in the data above).

Age (Months)	Sex	Year of presentation	Pre/Post sacral type presentation	Tumour Type	Predominant Y.S.T. pattern	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Alive with residual disease	Alive with no residual disease	Alive disease status unclear	Duration of follow-up
27 M	F	1977	Post [1]	Pure YST	Reticular	7	Y (Extensive)	N	N	Y	-	-	-	-	Death – 12 months
24 M	F	1965	Post	Pure YST	None	4	N	N	N	Y	-	-	-	-	Death – Prior to therapy
26 M	F	1980	Pre	Pure YST	None	5	Y (Extensive)	N	N	Y	-	-	-	-	Death – 21 months
± 24 M	F	1963	Post [2]	Metastasis[2] Pure YST	Reticular	2	N	N	N	Y	-	-	-	-	Death [2]
43 M	M	1990	Pre	Mixed [3] YST/III I.T.	None	9 [4]	N	Y	N	Y	-	-	-	-	Death – 5 months
36 M	M	1958	?	Pure YST	None	29	N	N	Y	Y	-	-	-	-	Death – 12 months
24 M	M	1986	Pre	Pure YST	Solid	9	N	N	N	N	Y	Y	-	-	5 months
24 M	M	1985	Pre	Mixed MT & YST	Papillary	<1	Y (Scanty)	N	N	N	Y	Y	-	-	26 months
Birth	M	1986	Pre	Original. Mixed YST/IT Recurrence. Pure YST	None Papillary	0 <1	N N	N N	N N	N	N	-	Y	-	89 months
18 M[5]	F	1984	Pre[5]	Mixed [5] YST/MT	Papillary	4	N	N	N	N	Y	-	Y	-	150 months
16 M	F	1989	Pre	Mixed MT/YST	None	2	N	Y	N	N	Y	-	Y	-	36 months
3 M	F	1984	Pre	Mixed MT/YST	None	1	N	N	Y	N	N	-	Y	-	4 months
Birth	F	1957	Post	Pure YST	None	15	Y (Scanty)	N	N	?	?	?	?	?	No Follow up data available
18 M	F	1987	Post	Pure YST[6]	None	1	Y (Scanty)	N	N	?	?	?	?	?	No Follow up data available
60 M	F	1986	Post	Mixed IT/YST	Reticular	<1	Y (Scanty)	N	N	?	?	?	?	?	No follow up data available

Footnotes

1. Postsacral presentation (buttock mass), but tumour also had a presacral component.
2. Original tumour (at birth), grade II immature teratoma – 24 months later disseminated disease, metastic tumour pure YST.
3. Significant proportion of the neoplasm shows nephroblastomatous differentiation.
4. In mixed tumours the mitotic count refers to the Y.S.T component.
5. Original tumour (at birth) mature teratoma, 24 months later disseminated disease – Yolk sac tumour present.
6. Originally thought to be buttock haematoma and incision and drainage attempted.

SACROCOCCYGEAL IMMATURE TERATOMAS:

Age	Sex	Year of presentation	Pre/Post sacral Type of presentation	Tumour Grade & nature of immature tissue	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive with no residual disease	Alive, disease status unclear	Duration of follow-up
Birth	F	1961	Post	Grade II Rosettes Immature glial	1	N	N	N	Y	-	Recurrence 2 yrs later as YST	-	-	-	Death ± 24 months
Birth	F	1987	Post [1]	Grade II Only immature neuroglial	0	N	N	N	Y [2]	-	-	-	-	-	Death 2 months
Birth	F	1993	?	Grade II rosettes, solid neuroblast-omatous foci Immature mesenchyme	6	Y (Extensive)	N	N	N	N	N	N	Y	-	24 months. Alive well no disease
Birth	F	1980	Post	Grade I Only immature neuroglial	0	N	N	N	N	N	N	N	Y	-	Alive well no disease 16 months.
Birth	F	1991	Post	Grade I Only immature neuroglial	0	N	N	N	N	N	N	N	Y	-	Alive well no disease – 48 months.
Birth	F	1990	Post	Grade 3 Rosettes, solid neuro-blastomatous foci	8	Y (Extensive)	N	N	N	N	N	N	Y	-	Alive with no disease 54 months
Birth	F	1957	Post	Grade I Rosettes only	1	N	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE
Birth	M	1984	Pre	Grade III Rosettes & solid neuroblast-omatous foci	43	Y (mild)	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE
Birth	F	1983	Post [1]	Grade I Only immature neuroglial	1	N	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE

SACROCOCCYGEAL IMMATURE TERATOMAS:

Age	Sex	Year of presentation	Pre/Post sacral Type of presentation	Tumour Grade & nature of immature tissue	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive with no residual disease	Alive, disease status unclear	Duration of follow up
Birth	F	1969	Post	Grade I Rosettes & occasional solid neuro-blastom-atous foci	40	N	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE
Birth	M	1983	Post	Grade I Rosettes & immature neuroglial	0	N	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE
Birth	F	1985	Post	Grade I Only immature neuroglial	0	N	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE
Birth	F	1962	Post	Grade I Only immature neuroglial	3	N	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE
Birth	F	1974	Post [1]	Grade II immature neuroglial & solid neuro-blastoma-tous foci	1	N	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE
Birth	F	1989	?	Grade II Immature neuroglial & rosettes	1	Y (Mild)	N	N			NO	FOLLOW	UP	DATA	AVAIL-ABLE

Footnotes (Analysis of immature sacrococcygeal teratomas):

1. **Post sacral type presentation (with buttock mass), but also presacral component at surgery.**
2. **Death unrelated to teratoma (Trisomy 13 with atrial and ventricular septal defects, with death secondary to congestive cardiac failure).**

EXTRAGONADAL GERM CELL TUMOURS

SACROCOCCYGEAL GERM CELL TUMOURS

57 Sacrococcygeal germ cell tumours were included in the study;

- 15 Malignant (having a yolk sac tumour component) 26,3%.
- 15 Immature teratomas 26,3%.
- and 27 Mature teratomas 47,4%.

2 Patients had benign germ cell tumours (mature teratoma and Grade III immature teratoma respectively) which recurred as yolk sac tumours - both the primary and the recurrent malignant tumour are included in the statistical data.

In comparison with the other series, (see below), the percentage of malignant cases is significantly high.

Histologic classification of sacrococcygeal G.C.T. (%).

Series	Benign/Mature	Immature	Malignant
Valdiserri et al [20]	75	11,8	13,2
Berry et al [11]	63,8	24,1	12,1
Mahour et al [92]	66,7	19,4	13,9
Gonzalez-Crussi et al [40]	55	27,5	7,5
Noseworthy et al [47]	66,1	16,2	17,7
Current Study	47,4	26,3	26,3

Analysis of clinical features.

Sex -

In all studies there is a remarkable predilection for females (see below). No satisfactory explanation has been hypothesised.

Classification of sacrococcygeal tumours according to gender (%) - in current study.

Sex	Malignant	Immature	*Mature	Total
Female	(10/15) 66,5	(13/15) 86,6	(18/25) 72	(41/55) 74,5
Male	(5/15) 33,3	(2/15) 13,4	(7/25) 28	(14/55) 25,5

These results are strikingly similar to those found in a number of other studies.

* Insufficient data was available for 2 cases of mature teratoma.

Author	No. Of sacrococcygeal G.C.T.	% Females
Conklin et al (1967) [89]	32	78
Waldenhausen et al (1963) [90]	111	83
Gonzales - Crussi et al (1978) [41]	40	70
Valdiserri et al (1981) [21]	68	73
Noseworthy (1981) [47]	118	83
Berry et al (1969) [11]	58	70
Current Study	53	73,5

Age

All published studies are in agreement that increasing age, beyond the newborn period, increases the risk of malignancy several fold. [46], [89], [90], [41], [13], [49]

Data from other series:

- Valdiserri et al [21] - 89% of their malignant tumours occurred in infants older than 4 months.
  - and 80% of their patients with mature teratomas were less than 4 months of age.
- Noseworthy et al [47] - Average age of malignant tumours - 21 months.
  - Average age of mature + immature teratomas - 2 Days.
- Berry et al [11] - None of 46 tumours detected before 1 year of age was malignant.
  - Whereas 4 of 12 detected after 1 year of age were malignant.
- Harms et al [9] - None of 11 malignant tumours occurred in patients less than 17 months.

Current Study

	Mature Teratoma*	Immature Teratoma	Malignant (Yolk sac tumour) component present
% Of cases present at birth	** (19/24) 79,1%	** (15/15) 100%	*** (2/15) 13%
Mean age of other cases	16½ weeks	-	25,2 months
Range of other cases	3 weeks → 30 weeks	-	3 months → 60 months

* Data was lacking for 3 cases of mature teratoma.
** One tumour from each of these groups recurred 24 months later with a yolk sac component.
*** An additional 2 tumours which had been diagnosed as non malignant (mature and immature teratoma respectively) at birth, recurred at 24 months of age with a yolk sac component.

Comment on the above findings.

1. Mature and immature teratomas - 89% of these were diagnosed at birth, 100% by 7½ months of age - findings consistent with the previously published literature. (Although all the benign/immature neoplasms in this study were diagnosed prior to one year of age, presentation in older infants/children, even up to several years of age, is certainly well described) [2, 1].
2. Yolk sac tumour component present - 13% of these were diagnosed at birth, and 20% by 3 months of age (the remaining 80% beyond 16 months of age). The early onset of 20% of the yolk sac tumours in the current study, is at variance with much of the previously published literature (see above [11, 9]), emphasising the requirement for accurate histological diagnosis in all cases, independent of age.

Clinical Presentation

This is dependent on the tumour growth pattern, 4 major [46] patterns occurring:

Type I.

(Post/retrosacral or extrapelvic) - The tumour grows posterior or superficial to the sacrum and coccyx. This is the most common growth pattern and is usually associated with a benign course. [46]

Type II.

Dumbbell shaped growths with roughly equal presacral (intrapelvic) and post sacral (extra pelvic) components. Approximately 6% of these are said to have metastases when first diagnosed. [46]

Type III.

Assymetrical dumbbell growths with predominance of the presacral (intra pelvic) component. Although far less common than the above preceding types, approximately 20% are said to have metastases at diagnosis. [46].

Type IV.

Entirely presacral (intra pelvic). 8% are said to have metastases at diagnosis. [46]

Tumours with a predominant post sacral growth pattern generally present with an obvious buttock mass, which may be of prodigous proportions (occasionally weighing as much as the attached infant!!).
Whilst those with a predominant presacral growth pattern may present with:

- An abdominopelvic mass.
- Or symptoms related to compressive effects - obstructive uropathy, or bowel (usually rectal) obstruction.

Current Study

			MODE OF PRESEN-TATION			
Tumour Type	**Insufficient data**	**Number evaluated**	**Buttock Mass**	**Abdomino-pelvic mass**	**Urinary tract obstruction**	**Bowel obstruction**
Mature tera-toma	7	19	*17	2	0	0
Immature teratoma	3	11	**10	1	0	0
Malignant ****	1	***14	*8	5	3	1

* One patient had a presacral component, in addition to the presenting postsacral component.
** Four patients had a presacral component, in addition to the presenting postsacral component.
*** The two patients who presented with benign lesions which later recurred as yolk sac tumours have been evaluated here with the malignant group.
**** In the malignant group some patients presented with more than one feature.

Comment on the above findings

- 27 (90%)/30 patients with mature/immature sacrococcygeal teratomas had post sacral presentations - a finding consistent with that of other studies [47, 48].

- With regard to the patients with sacrococcygeal Y.S.T., pre - and post sacral presentations occurred with approximately equal frequency (a finding somewhat at variance with the previously published literature in which a pre sacral mode of presentation is said to be commoner).

Macroscopic Pathological findings

Tumour Size

Results from current study:

			MAXIMUM DIAMETER OF TUMOUR (mm)	
*** Tumour type**	**No. Of cases with insufficient data**	**No. Of cases evaluated**	**Mean**	**Range**
Mature teratoma	2	25	75	30 to 130
Immature teratoma	1	14	106	50 to 160
Malignant (YST)	** 10	3	98	50 to 135

* With regard to the benign tumours which recurred as malignant lesions, the data from the original lesions have been included in their respective benign categories.
** Many of the malignant tumours could not be excised in their entirety.

Comment on the above findings

Considerable overlap exists between the sizes of the mature, immature and malignant lesions. These results are consistent with the findings of Gonzalez - Crussi [41] : "Size of the tumor (sacrococcygeal) had no bearing on prognosis".

Clinical Outcome Synopsis

I) Cases containing a yolk sac tumour component

	Cases
Total No. Of cases	15
Insufficient follow up data	3
No. Evaluated	12
No. Of deaths	6 (50%)
No. Of survivors who developed metastatic disease	4 (66%)
No. Who either died or developed metastatic disease	10 (83%)
No. Alive but with residual disease	2
No. Alive with no evidence of residual disease	4 (33%)

Comment on the above findings.

The highly malignant nature of sacrococcygeal yolk sac tumours was confirmed. The poor outcome being similar to that found in other series (see below).

Series	No. Of sacrococcygeal yolk sac tumours	No. Of deaths
1967 Conklin et al [89]	7	7 (100%)
1978 Gonzalez Crussi et al [41]	7	6 (85,7%)
1981 Valdiserri et al [21]	9	9 (100%)
1986 Hawkins et al [15]	26	10 (38,5%)
Current study	12 (with follow up data)	6 (50%)

II) Immature teratomas

	Cases
Total No.	15
Insufficient follow up data	9
No. Evaluated	6
No. Of tumour related deaths	1*
No. Of recurrences	1*
No. Of non tumour related deaths	1
No. Of patients alive with no disease	4 (out of 5)** 80%
No. Of patients alive with residual disease	0

* Same patient in both instances (recurrence and death secondary to yolk sac tumour).
** Excluding the non tumour related death.

COMPARISON OF RESULTS ABOVE WITH OTHER SERIES (EVALUATING IMMATURE TERATOMAS OF THE SACROCOCCYGEAL REGION).

Tumour Grade plus tumour related complications.

Series	Total No. Immature Teratomas Evaluated	Grade I	Grade II	Grade III
Gonzalez - Crussi et al [41].	10	3 Cases - No complications.	5 Cases Tumour recurrence of same or lower grade - 2 cases.	* 2 cases Tumour recurrence of same or lower grade - 1 case.
Noseworthy et al [47]	18	5 cases Recurrence as malignant g.c.t. - 1 case.	8 cases Recurrence as malignant g.c.t. - 1 case.	5 cases Recurrence as malignant g.c.t. - 1 case. Tumour recurrence of same or lower grade - 1 case.
Valdiserri et al [2]	8 **		2 cases No complications.	4 cases No complications.
Kooijman [59]	6	Recurrence as malignant g.c.t. - 2 cases (Grade I and Grade III immature teratoma respectively). Tumour recurrence of same or lower grade - 1 case (Grade II immature teratoma). Metastatic immature teratoma - 1 case (Grade II tumour with hepatic metastases - themselves of Grade I histological appearance.)		
Berry et al [11]	14	Recurrence as malignant g.c.t. - 4 cases.		
Current Study	6 ***	2 cases - No complications.	3 cases. Recurrence as malignant g.c.t. - 1 case ****	1 case - No complications.

Footnote:

* In this study 10 cases were classified as Grade III immature teratomas - however 7 of these contained yolk sac tumour elements, and one features consistent with an "adenocarcinoma". The latter 8 cases have thus been excluded from the tabulated data.

** In 2 cases the immature tissue was entirely of renal origin (both these cases had uncomplicated clinical courses).

*** Only 6 of the 15 cases of sacrococcygeal immature teratomas had adequate follow up data.

**** Although the recurrence of benign sacrococcygeal teratomas as malignant lesions is well documented, see tabulated data above, plus the study of Hawkins et al [15], this case dates back to 1961, at which time it was not standard protocol to take at least one tissue block per centimetre of the maximum tumour diameter. Inadequate sampling of the original tumour specimen can thus not be excluded.

Comment regarding the data on the 60 cases of sacrococcygeal immature teratoma reviewed above.

1. Recurrence as a malignant g.c.t. was documented in 10 (16,6%) of the 60 immature teratomas. The question whether some (or even all) of these could have been malignant de novo is purely conjectural, and cannot be answered with any forthrightness. In any event, the need for early, complete excision (including coccygectomy) of all sacrococcygeal g.c.t. cannot be overemphasised. Similarly, adequate sampling by the pathologist, of all such excised lesions, is mandatory.
2. Tumour recurrence, as a teratoma of the same/lower grade occurred in 5 (8,3%) of the 60 cases.
3. Only a single case, of a sacrococcygeal immature teratoma, without malignant elements, giving rise to metastases is documented.

Mature Teratomas

	Cases
Total No.	27
Absent follow up data	20
No. Evaluated	7
No. Of tumour related deaths	0
No. Of recurrences*	1
No. Of non tumour related deaths**	1
No. Alive with no residual disease	6 (out of 6***)
No. Alive with residual disease	0

* Recurrence as yolk sac tumour.
** Death secondary to septicaemia.
*** Non tumour related death excluded.

COMPARISON OF RESULTS (MATURE SACROCOCCYGEAL TERATOMAS) WITH OTHER SERIES.

Series	No. of mature sacrococcygeal teratomas evaluated	No. of recurrence - as mature teratomas.	No. of recurrences - with malignant g.c.t. elements
Gonzalez - Crussi [41]	22	4	0
Conklin et al [89]	19	1	0
Berry et al [11]	41	1	3
Current Study	7*	0	1

* Additional 20 cases identified but follow up data inadequate.

BREAKDOWN OF RETROPERITONEAL G.C.T. EVALUATED.

	No. Of cases
A) Malignant	
I) With a yolk sac tumour component	2
II) Embryonal carcinoma	1
Total no. Of malignant retroperitoneal g.c.t.	3
B) Immature Teratomas	6
C) Mature Teratomas	3
Total no. Of childhood retroperitoneal g.c.t. included in study	12

RETROPERITONEAL GERM CELL TUMOURS – IMMATURE & MALIGNANT

Age (Months)	Sex	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour histology	Mitotic count/ 10HPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive, no residual disease	Alive, disease status unkcear	Follow up duration
144	F	1966	?	110mm. Solid, hemorrhagic, partly encapsulated	Pure YST. No predominant pattern	2	Y (Scanty)	N	N	Y	-	-	-	-	-	
22	F	1981	Abdominal mass	Biopsy only	Pure YST. No predominant pattern	10	Y (Extensive)	N	N	Y	-	-	-	-	-	2 years
41	M	1993	Abdominal pain of 5 days duration.	Massive multi loculated tumour at laparotomy	Embryonal carcinoma (pure)	13	N	N	N	N	Y [1]	-	Y	-	-	11 months still residual disease
3	F	1986	Abdominal distension – 1 month	150mm Multilocular cystic	Grade II. I.T. Rosettes & solid neuroblasto-matous foci & immature renal elements	12	N	N	N	N	N0	-	-	Y	-	Alive, no disease – 5 years. 2 months
4	F	1984	Abdominal distension	140mm Multicystic mass	Grade III. I.T. Rosettes & neuroblas-tomatous solid foci	33	N	N	N	N	N	-	-	Y	-	Alive, no diesease – 9 years.
1	F	1993	Left flank mass noted at birth	Mixed solid/cystic 110mm	Grade III. I.T. rosettes & solid neuroblasto-matous foci	7	Y(Scanty)	N	N	?	?	?	?	?	?	?
2	M	1993	Abdominal mass detected during routine postnatal follow up	100mm. Mixed solid/cystic	Grade II. I.T. Immature neuroglial & rosettes & renal blastema	?	N	N	N	N	N	-	-	Y	-	Alive no disease – 15 months.

RETROPERITONEAL GERM CELL TUMOURS IMMATURE & MALIGNANT

Age (Months)	Sex	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour Histology	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive, no residual disease	Alive, disease status unclear	Follow up duration
8	F	1994	?	160mm Mixed solid/cystic	Grade I. I.T. rosettes & occasional solid neuroblas-tomatous foci	1	N	N	N	N	N	-	-	Y	-	Alive no disease – 18 months
54	F	1987	Abdominal mass detected during routine follow up	80mm. Lobulated mass, cut surface showing areas of hemorrhage & necrosis	Grade II. I.T. Typical Wilms tumour but neuro-epithelial rosettes & neuroglial in capsule					N	N	N	-	Y	-	Alive, no disease at 3 years.

Footnotes: [1] Intra abdominal lymph node involvement. (The tumour also showed marked invasiveness, including involvement of the inferior vena cava)

MATURE RETROPERITONEAL TERATOMAS

Age (Months)	Sex	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Clinical follow up
8	F	1992	?	105mm Multicystic	None
Birth	F	1968	Abdominal mass noted at birth	100mm Multicystic	Unrelated death from gastroenteritis 7 months later
8	M	1960	Abdominal mass	Multicystic with solid areas	None

RETROPERITONEAL GERM CELL TUMOURS OF CHILDHOOD..

Incidence

These uncommon tumours account for approximately 4% of all childhood g.c.t. [11, 12, 10, 13].
In the present study 12 retroperitoneal neoplasms were included, out of a total of 176 gonadal and extra gonadal g.c.t. ie 6,7% of the total.

Clinical features

1. Age

In previously published studies the patients have ranged in age from newborns to those in the 6th decade of life [93, 63, 48]. The average age in the series of Engel et al [96] (30 cases) was 16 years (with 43% being children less than 10 years of age), while that in the series of Lack et al [63] (11 cases), 18 months.

In the current study the average age for all the cases was 23, 2 months (range birth to 12 years). Subdividing the patients according to tumour type, the average ages were:

- malignant g.c.t. - 69 months (range 22 months to 144 months)
- immature teratomas - 12 months (range 1 month to 54 months)
- mature teratomas - 5,3 months (range birth to 8 months)

The increasing risk of malignancy with increasing age, seen in the current study, was not evident in those of Engel [96] and Lack et al [63].

2. Sex

Engel and associates [96] in their review of previously published cases found a slightly higher incidence in males (M:F = 3:2), whereas Lack et al [63] found a strikingly higher occurrence rate in females, 10:1.

Current study F : M = 3:1.

3. Clinical presentation [96, 63, 48]

- Not infrequently the presenting manifestation is an asymptomatic increase in abdominal girth (noted during routine post natal follow up, or by the mother herself).
- More commonly however, abdominal pain, nausea, vomiting and weight loss accompany the abdominal distension (thus raising the suspicion of gastrointestinal pathology).
- Urinary tract symptoms appear to be surprisingly uncommon, given the close proximity of these tumours to the kidneys.

- Constitutional symptoms related directly to the tumour are rare (low grade fever being occasionally reported).

In the current study the vast majority of patients presented with an abdominal mass/ distension (see tabulated data).

Pathology

A) Macroscopic pathology [46, 63]

The tumours are usually of prodigous proportions - the average diameter in the series of Lack et al being 98mm. As with g.c.t. at other sites, the benign lesions are usually multicystic with a variable proportion of solid areas, whilst the malignant ones are predominantly solid, and apt to show foci of haemorrhage and necrosis.

The findings in the current study conformed with the above (see tabulated data).

B) Microscopic pathology

Retroperitoneal g.c.t. are usually benign [2]. Review of the 11 g.c.t. in the series of Lack et al [63] shows 5 to be mature, 3 immature and 3 malignant (2 pure yolk sac tumours and 1 mixed immature teratoma/yolk sac tumour). Of the 30 cases studied by Engel and associates [96], 27 were benign and 3 malignant. Combining the 2 studies 14,6% were malignant. The results from the current study (for details see tabulated data) show 3 mature, 6 immature, and 3 malignant retroperitoneal g.c.t. (2 yolk sac tumors and 1 embryonal carcinoma).
Of remarkable note in the present study, was the one immature teratoma which completely resembled a Wilms tumour, except for the immature neuroepithelial tissue at its periphery. (Of additional interest, 2 other immature teratomas contained small amounts of immature renal tissue).

Prognosis

Considering the 2 previously cited studies (Engel and Lack et al) 5 of the 6 patients with malignant g.c.t. died.
In the current study the outcome for the 3 children with malignant neoplasms was similarly poor - 2 deaths plus 1 patient alive with residual disease at 11 months (further follow up not available).
Thus malignant retroperitoneal g.c.t., like their counterparts in the sacrococcygeal region have an extremely poor prognosis.

With regard to the 6 children with immature teratomas in the current study, none had metastatic disease on presentation. And of the 5 with adequate follow up data, all were alive with no evidence of residual disease (including the infant whose neoplasm resembled a Wilms tumour).

RENAL GERM CELL TUMOURS OF CHILDHOOD.

Breakdown of Renal G.C.T. evaluated in the current study.

	No. Of cases
A) Malignant	0
B) Immature Teratomas	0
C) Mature Teratomas	2
Total no. Of childhood renal g.c.t. included in study	2

GERM CELL TUMOURS OF THE KIDNEY (IN CHILDHOOD).

Germ cell tumours arise very rarely within the kidney [48]. Dehner reviewed the available literature up to 1973, only 2 cases had previously been described [107]. In 1978, Albert & Casamayou reported one case and reviewed six others [108]. The few cases thus far described in children have had benign clinical courses (whereas in adults, there have been occasional case reports of malignant renal g.c.t. [48]).

Two cases of mature teratoma arising from the kidney are included in the present study - see tabulated data below:

Age	Sex	Site	Clinical presentation	Gross pathology	Microscopic pathology	Follow up
4 months	F	Left kidney	Abdominal distension	Multicystic with scattered solid areas. 11cm-max. diam.	Mature teratoma-wide range mature tissues - neural, keratinizing squamous, respiratory, gastrointestinal, renal, cartilage, skeletal, muscle etc.	No data available
13 months	F	Left kidney	Abdominal distension	Multicystic. 12cm-max. diam.	Mature teratoma-predominantly neural + squamous epith. With adnexal structures	Well at 2 years.

BREAKDOWN OF MEDIASTINAL G.C.T. EVALUATED IN THE CURRENT STUDY.

	No. Of Cases
A) Malignant	
I) With a yolk sac tumour component	1
Total no. Of malignant mediastinal g.c.t.	1
B) Immature Teratomas	2
C) Mature Teratomas	8
Total no. Of childhood mediastinal g.c.t. included in study.	11

MEDIASTINAL GERM CELL TUMOURS

Age (Months)	Sex	Year	Clinical presentation	Size (max diam in mm) & macroscopic appearance	Tumour Histology	Mitotic count/ 10HPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive, with residual disease	Alive no residual disease	Alive disease status unclear	Follow up duration
24	M	1986	Cough, recurrent chest infections, stridor.	[1] Post chemotherapy – 65mm Necrotic tumour	Mixed – Mature teratoma/ YST. (YST. No predominant pattern)	18	Y(Extensive)	N	N	N	N	N	-	Y	-	Alive, no residual disease – 8 years later
5	M	1992	2 weeks history of cough	75mm. Mixed multicystic/ solid encpasulated	Grade II. I.T. Rosettes only	15	N	N	N	N	N	N	-	Y	-	Alive, no residual disease - 3½ years
Birth	F	1984	Stridor since birth	65mm. Mixed solid/ cystic, adherent to thymus	Grade I. I.T. Rosettes only	1	N	N	N	N	N	N	-	Y	-	Alive, no residual disease – 5 years later.
72	F	1989	?	Multicystic 90mm	Mature teratoma	-	-	-	No		FOLLOW	UP	AVAIL-ABLE			
Birth	M	1984	?	Cystic mass 75mm	Mature teratoma	-	-	-	NO		FOLLOW	UP	AVAIL-ABLE			
24	M	1974	?	Multicystic 40mm	Mature teratoma	-	-	-	NO		FOLLOW	UP	AVAIL-ABLE			
24	M	1983	Recurrent chest infection	Multicystic 80mm	Mature teratoma	-	-	-	NO		FOLLOW	UP	AVAIL-ABLE			
36	F	1967	?	Multicystic 85mm	Mature teratoma	-	-	-	NO		FOLLOW	UP	AVAIL-ABLE			
12	F	1967	?	Mixed solid/cystic 100mm	Mature teratoma	-	-	-	NO		FOLLOW	UP	AVAIL-ABLE			
8	F	1967	Stridor	Multicystic 90mm	Mature teratoma	-	-	-	NO		FOLLOW	UP	AVAIL-ABLE			
156	F	1964	?	Multicystic 200mm	Mature teratoma	Well	at 6½ years	follow	up							

Footnotes on tabulated data for mediastinal germ cell tumours.

1. At the inital thoracotomy, the tumour appeared as a non resectable necrotic mass, anterior to & surrounding the heart, plus infiltrating the middle lobe of the right lung. A repeat thoracotomy, with tumour resection, was performed following 4 courses of chemotherapy.

MEDIASTINAL GERM CELL TUMOURS OF CHILDHOOD.

Clinical Features

Incidence

Approximately 7% of childhood g.c.t. are said to occur in the mediastinum [2].
11 Cases of mediastinal g.c.t. are included in the current study - representing 6,2% of the total (176 cases).

Age

Mediastinal g.c.t. have been detected from birth to the 6th decade (and possibly even beyond!). The mean age of the patients, in various series, depending entirely on the nature (adult-/childhood) of the population being studied [96, 97, 11].
In the current study the average age was 32 months (range: birth to 13 years).

Sex

There does not appear to be any sex predilection [2, 46, 9].
Current study F : M = 6:5.

Clinical presentation

- Up to 50% of children are asymptomatic - a mass lesion being discovered incidentally on Chest x ray. [2].
- Respiratory distress, cough and chest pain appear to be the most common presenting features. [2, 46]
- Compression of structures other than the tracheobronchial tree may occur:
    - Oesophagus → dysphagia
    - Spinal cord → paraplegia
    - Superior vena cava → SVC obstruction
    - Sympathetic trunk → Horner's syndrome
    - Major vessel, especially pulmonary artery → acquired stenosis

  (As most tumours arise in the anterior mediastinum, the above features are far less common than those related to the tracheobronchial tree).

- Rarely expectoration of hair and Keratinous material, or endocrinologic manifestations (hypoglycemia and precocious puberty, secondary to insulin and B HCG secretion respectively) may occur.

In the current study, no data unfortunately was available for 6 of the 11 cases. The other 5 presenting with respiratory symptomatology - cough, stridor, recurrent chest infections; and/or chest pain.

A) Gross Pathology

As with g.c.t. at other sites, the benign lesions are predominantly cystic and encapulated; with the malignant being largely solid, non encapulated/infiltrative, and apt to show areas of haemorrhage and necrosis.

The g.c.t. in the current study conformed to the above generalizations. There was no significant difference in size between the mature and immature tumours (only one malignant neoplasm, which was treated with chemotherapy prior to surgery, was included in the study).

B) Microscopic pathology

The histological finding in several studies are tabulated below:

STUDY	TOTAL NO. MEDIASTINAL G.C.T.	NO. MATURE	NO. IMMATURE	NO. MALIGNANT
Harms et al [9]	7	1 (14%)	4 (57%)	2 (one Y.S.T. + one germinoma) (28%)
Berry [10]	5	3 (60%)	2 (40%)	0 (0%)
Kooijman [59]	16	10 (62,5%)	1 (6,2%)	5 (31%)
Current Study	11	8 (72,7%)	2 (18%)	1 (9%) (Mixed mature teratoma /Y.S.T.

With regard to malignant germ cell tumours, all histological types (germinoma, yolk sac tumour, embryonal carcinoma, choriocarcinoma, plus combinations of these with each other, and with mature/immature teratomas) have been described as occurring in the mediastinum. Germinoma appears to be the most frequent malignant histological type [48, 97]. Yolk sac tumour, by contrast, rarely occurrs at this anatomical site - up until 1979 only 12 mediastinal cases had been reported [100].

Prognosis.

1) Immature teratomas

Carter et al [98] in 1980 reviewed the previously published literature on mediastinal immature teratomas. They found a striking relationship between age and prognosis. All 13 patients who were 15 years of age or older had died as a direct result of their tumours (which were locally infiltrative in 9, and gave rise to metastatic disease in 4). By contrast the 11 patients younger than fifteen, all survived, and were free of disease.
In the current study the 2 infants with immature teratomas were likewise both well, with no evidence of residual disease.

2) Malignant g.c.t.

There is scanty literature on the prognosis of malignant mediastinal g.c.t. in children. In the 6 childhood cases reviewed by Hawkins et al [15], there were 3 tumour related deaths, 2 children were alive with no evidence of disease, and 1 child was lost to follow up. The only child included in the current study (mixed mature teratoma/Y.S.T) is alive and well with no evidence of disease at 8 years follow up.

(In adults, the prognosis appears abysmal for non germinomatous malignancies - the 12 such patients in the series of Recondo et al [97] all died).

3. Mature Teratomas

The prognosis here largely being dependent on the skill of the surgeon and the quality of peri-operative care.

BREAKDOWN OF PARAVERTEBRAL G.C.T. EVALUATED IN THE CURRENT STUDY.

	No of Cases.
A) Malignant	0
B) Immature Teratomas	1
C) Mature Teratomas	3
Total no. Of childhood paravertebral g.c.t. included in study	4

PARAVERTEBRAL GERM CELL TUMOURS.

Included in the study are 4 paravertebral g.c.t. (3 mature, and 1 immature teratoma).
- See tabulated data below.

Year	Sex	Age	Site	Associated cong. anomalies.	Gross pathology	Histology
1989	F	Birth	Paravertebral	Spina bifida with teratoma overlying site of vertebral defect	2,5cm max. diam.	Immature teratoma Grade I.
1981	F	Birth	Paravertebral T2 - 8 area.	Nil	6cm. max. diam.	Mature teratoma.
1988	M	Several months	Paravertebral	Associated meningocoele	2,5cm max. diam.	Mature teratoma.
1989	?	?	Paravertebral	Associated meningocoele	?	Mature teratoma

Unfortunately no follow up data is available.

BREAKDOWN OF HEAD AND NECK G.C.T. EVALUATED IN THE CURRENT STUDY.

	No. Of Cases
A) Malignant	
I) With a yolk sac tumour component	2
II) With an embryonal carcinoma component	1
Total no. Of malignant head and neck g.c.t.	3
B) Immature Teratomas	4
C) Mature Teratomas	8
Total no. Of childhood head and neck g.c.t. included in study	15

Footnote for table analysing G.C.T. of the head and neck.

1. No metastatic spread, however extensive local infiltration occurred - through the mastoid sinus to reach the cerebellopontine angle.
2. No metastatic spread, but extensive local infiltration, including into floor of mouth.
3. The tumour was resected shortly after birth. At post mortem no obvious cause of death could be found. Nor was there evidence of disseminated disease.
4. Cervical lymph node involvement - histology Grade III immature teratoma with neuroepithelial rosettes plus large neuroblastomatous areas.
5. Recurrence of tumour 9 months after original excision (all tissue of recurrence, histologically mature).

GERM CELL TUMOURS (MALIGNANT AND IMMATURE TERATOMAS) OF THE HEAD (EXCLUDING THE C.N.S.) AND NECK

Age (Months)	Sex	Year	Site and clinical presentation	Tumour histology	Mitotic count/ IOHPF	Microscopic necrosis	Anaplasia	Vascular invasion	Death	Metastatic disease but alive	Tumour recurrence	Alive with residual disease	Alive with no residual disease	Alive, disease status unclear	Duration of follow up
21	F	1985	Enlarging mass Right side of neck, present for 1 month	Mixed embryonal carinoma and yolk sac tumour (no predominant, pattern)	19 3	Y (Extensive) Y (Extensive)	N	N	N	N [1]	-	N	Y	-	Alive with no evidence of disease – 6 years
24	M	1990	Enlarging mass submandibular region – accompanying stridor, tracheostomy required	Pure yolk sac tumour (no predominant pattern)	6	Y (Mild)	N	N	N	N [2]	-	-	-	Y	Alive but disease status unclear – 4 months
5	F	1985	Scalp mass, otherwise asymptomatic	Pure YST (predominant pattern reticular)	3	N	N	N	?	?	Recurrence after 4 months	?	?	?	
Birth	M	1968	Anterior neck mass at birth	Grade II I.T. Rosettes & occasional solid neuro-blastomatous foci	15	Y (Scanty)	N	N	?	?	?	?	?	?	
Birth	F	1975	Neck mass (? Precise location, stridor present)	Grade I. I.T Occasional neuroblast-omatous foci	?	?	?	?	Y [3]	-	-	-	-	-	Death at 4 days of age
Birth	M	1984	Anterior neck mass associated with the thyroid gland. No stridor	Grade III. I.T. rosettes & solid neuroblasto-matous foci	<1	N	N	N	N	Y [4]	N	N	Y	N	Alive, well no disease at 4 years and 10 months
Birth	F	1990	Nasopharynx. Feeding difficulties. Large pharyngeal mass. Associated cleft palate.	Grade II. I.T. Only immature neuroglial	0	N	N	N	N	N	Y [5]	N	N	Y	Alive well no disease at 6 years

MATURE TERATOMAS OF THE HEAD (EXCLUDING CNS) AND NECK:

Age	Sex	Year	Site and clinical presentation	Tumour Histology
Birth	Female	1991	Left neck mass	Mature teratoma.
Birth	Male	1985	Anterior neck mass	Mature teratoma.
Birth	Female	1958	Posterior neck mass	Mature teratoma (possible abortive attempt at twinning)
Birth	Male	1970	Anterior neck mass. Associated respiratory distress	Mature teratoma.
Birth	Female	1975	Post auricular neck mass (left)	Mature teratoma.
Birth	Female	1982	Cervico facial region	Mature teratoma.
Birth	Female	1984	Orbit of left eye.	Mature teratoma.
4 yrs *	Female	1991	Swelling left cheek.	Mature teratoma.

* Possibly present since birth.

TABULATED COMPARISON OF FINDINGS IN CURRENT STUDY WITH THAT OF OTHER SERIES:

I) Mature Teratomas

II) Immature Teratomas

III) Malignant G.C.T.

I) Mature Teratomas

SERIES	LOCATION	NO. OF CASES	*AGE/SEX	OUTCOME
Lack [50]	Neck	1	B/M	N.E.D.
	Facial	3	B/2F/1M	N.E.D.
	Orbital	2	B/1F/1M	N.E.D.
	Nasopharyngeal	1	B/F	N.E.D.
	Oropharyngeal	1	B/M	D.O.D. [1]
Berry [10]	Neck	2	B/2F	N.E.D.
	Palate	1	B/1F	No data
Current Study	Neck	5	B/3F/2M	All patients well post-operatively, but no further follow up data available.
	Cervico-Facial	1	B/F	
	Orbit	1	B/F	
	Cheek	1	B/F	Local recurrence at 4 years of age.

* Age - Refers to age at which the tumour was first noted.
[1] - Teratoma irresectable, death from inanition.
Abbreviations - N.E.D. - No evidence of disease.
- D.O.D. - Death of disease.
- B - Birth.

Summary of information from tabulated data on childhood mature teratomas of the head and neck region (excluding the CNS).

Total No. 19 - All first noted at time of birth.
- F : M = 2,1 : 1.
- Location - Neck - 42%.
  - Facial - 22%.
  - Cervico-facial - 5,5%.
  - Orbit - 16,6%.
  - Oropharyngeal - 10,5%.
  - Nasopharyngeal - 5,5%.
- Outcome - Follow up data available on 11, nine (81,8%) uncomplicated clinical courses, one death from irresectable oropharyngeal tumour, one local recurrence (4 years later) of facial (cheek) teratoma.

II) Immature Teratomas

SERIES	LOCATION	NO. OF CASES	AGE/SEX	OUTCOME
Lack [50]	Neck	5	B/3F/2M	N.E.D.
Dehner [53]	Neck	2	B/1F*/1M	N.E.D.
Berry [11]	Neck	1	B/F	Died post-operatively.
	Palate	1	B/M	Recurrence at 6 months, currently N.E.D.
Current Study	Neck	3	B/2M/1F*	1 case - No follow up data. 1 case - Death post operatively. 1 case - Alive and well 4 years and 10 months later.
	Nasopharynx	1	B/F	N.E.D. (6 years follow up).

* The same patient (included in both studies).

Summary of information from tabulated data on childhood immature teratomas of the head and neck region (excluding the CNS).

Total no. 12 - All first noted at birth.
- F : M = 1 : 1.
- Locations - Neck - 83,3%.
  - Palate - 8,3%.
  - Nasopharynx 8,3%.
- Outcome (data available on 11 cases) - Eight (72,7%) uncomplicated clinical courses, two (18,1%) post operative deaths, one (9%) local recurrence.

III) Malignant Germ cell Tumours

SERIES	LOCATION	NO. OF CASES	AGE/SEX	HISTOLOGY + OUTCOME
Lack [50]	Oropharynx	1	B/F	Yolk sac tumour - death at 15 months.
	Floor of mouth	1	6 months/F	Y.S.T. - death, 1 month later.
	Nasopharynx	1	10 months/F	Y.S.T. - death, 9 months later.
Dehner [53]	Forehead	1	6 weeks/F	Y.S.T. - death from disease.
	Retro-auricular	1	2 years, 6 months/F	Y.S.T. - Alive, no residual disease.
	Facial	1	4½ months/F	Y.S.T. - Alive, free of disease.
	Neck	1	B/M	Y.S.T. - Two local recurrences, currently free of residual disease.
Current Study	Neck	1	21 months/F	Mixed embryonal carcinoma/Y.S.T. - alive, no residual disease 4 years later.
	Submandibular region	1	2 years/M	Y.S.T. - Alive 4 months later, but disease status unclear.
	Scalp	1	5 months/F	Y.S.T. - Local recurrence at 4 months, further follow up not available.

Abbreviations - B - Birth
- Y.S.T. - Yolk sac tumour.

Summary of information from tabulated data on childhood malignant g.c.t. of the head and neck region (excluding the CNS).

Total No. 10 - Age (when first noted) - Range from birth to 2½ years.
- Sex - F : M = 4 : 1.
- Location - Oro/nasopharynx + mouth - 30%.
- Neck - 20%.
- Head - 20%.
- Facial, submandibular, retro-auricular - 10% each.

GERM CELL TUMOURS OF THE HEAD AND NECK REGION (EXCLUDING THE C.N.S).

I) Incidence

Germ cell tumours in this region are uncommon. According to most authorities [48, 50, 53] they account for approximately 5% of all childhood g.c.t.

Current study, 15 g.c.t. occurred in this region (head and neck excluding the CNS) representing 8.4% of the total number of cases.

II) Sex

Current study F : M = 2:1. Using the data obtained from 3 additional studies [11, 50, 53] (see comparative tabulated data), the ratio was similarly 2 : 1 (F : M).

III) Clinical Presentation

Age - Current Study: Mature teratomas - 8 cases - 6 from neck or cervico-facial region.
- 1 from the cheek.
- 1 orbital lesion.
All present since birth.

Immature teratomas - 4 cases - (3 cervical and 1 nasopharyngeal) - all present since birth.

Malignant tumours - 3 cases, respective location and age of presentation :
Lateral neck mass - 21 months.
Submandibular mass - 24 months.
Scalp - 5 months.

Additional data, obtained from 3 other studies, similarly showed all the mature and immature teratomas to have been first noted at birth. The malignant lesions however tended to occur at a slightly older age - range from birth to 2½ years.

The Clinical signs/symptoms are dependent on the location and size (the majority having already attained large to massive proportions by the time of birth).
Foetal + perinatal [50, 53, 48] problems include:
- Polyhydramnios due to interference with foetal swallowing of amniotic fluid.
- Non immune hydrops foetalis.
- Dystocia (large neck masses causing hyperextension of the head).

Problems during infancy:
- Neck + pharyngeal lesions - Upper airways obstruction and consequent respiratory distress.
  - Dysphagia, leading to feeding difficulties + aspiration pneumonia.
- Orbital lesions - External opthalmoplegia + blindness secondary to optic nerve compression.
- Facial lesions - May cause distortion of facial bones.

Current Study - For presenting symptoms/signs - see tabulated charts.

Histology, location, outcome.

Evaluation of the data from the current study, plus three others [11, 50, 53], ie. a total of 41 g.c.t. of the head and neck region, showed:

- Mature teratomas to be the most frequent histological type (46% of cases), followed by immature teratomas (29%), and malignant g.c.t. (25%).

- With regard to mature and immature teratomas the neck was the most common location, 42% and 84,5% of these tumours, respectively, occurring at this site.

- Malignant g.c.t. by contrast occurred with similar frequency in the oro/nasopharynx, neck and head.

- The outcome of the mature and immature teratomas was excellent with only a single tumour related death documented.

- By contrast 4 (50%) of the 8 infants with malignant tumours (and adequate follow up data) died as a direct result of their neoplasms.

Case of note included in the present study (- data regarding this patient was published earlier by Dehner et al [53]) - Of particular interest is the patient with a grade III immature teratoma of the neck who developed cervical lymph node metastases (mixture of mature and immature neural tissue). This gave rise to no long term consequences and the patient was well (free of disease) 4 years and 10 months later, following surgical management alone.

SUMMARY OF DATA COLLECTED ON IMMATURE TERATOMAS OCCURRING IN CHILDHOOD.

Location

37 cases of immature teratomas were included in the present study. The table below reflects the sites of occurrence of these tumours, and draws a comparison with other childhood studies.

No. Of cases of immature teratoma at specific anatomical sites.

	Present Study Cape Town, S.A.	**Harms and Janig [9] Kiel, Germany**	**Kooijman [59] Utrecht, Holland**
Sacrococcygeal	15 (40,5%)	8 (26,6%)	6 (22,2%)
Ovarian	9 (24,3%)	8 (26,6%)	8 (29,6%)
Retroperitoneal	6 (16,2%)	3 (10%)	5 (18,5%)
Neck (including nasopharynx)	4 (10,8%)	2 (6,6%)	2 (7,4%)
Mediastinum	2 (5,4%)	4 (13,3%)	1 (3,7%)
Paravertebral soft tissue	1 (2,7%)	0 (0%)	0 (0%)
Testicular	0 (0%)	4 (13,3%)	2 (7,4%)
Other (unspecified)	0 (0%)	1 (3,3%)	0 (0%)
Intracranial	0 (0%)	0 (0%)	2 (7,4%)
Gastric	0 (0%)	0 (0%)	1 (3,7%)
Total	37	30	27

Comment

The sacrococcygeal region, plus the ovary, are the commonest sites of occurrence of immature childhood teratomas, followed by the retroperitoneum, mediastinum, neck and testis (in the current study however, no immature teratomas of testicular origin were documented). Less common locations include - central nervous system, stomach plus paravertebral soft tissue.

Sex

Current Study - 37 immature teratomas - male - 6 (16,2%).
- female - 31 (83,8%).

The increased incidence in females was especially evident in the sacrococcygeal plus retroperitoneal locations (in addition no immature teratomas of testicular origin were documented, whereas ovarian neoplasms accounted for 24% of the total).

In the study of Harms & Janig, 66% of the immature teratomas occurred in females.

Age

The ovarian neoplasms presented at a considerably older age than those at other sites (see tabulated data).

Clinical Outcome

Follow up data was unfortunately available for only 23 (62%) of the cases. With regard to these 23 cases:

- 2 Tumour related deaths occurred.
- And an additional 2 patients developed metastatic disease.
  (For details of the above please see tabulated data).

Thus only 4 (17%) of the 23 patients with follow up data had complicated clinical courses. (An additional single patient developed tumour recurrence, 9 months after the original excision). The other 18 patients had uneventful courses following complete surgical excision alone.

Comparison of the clinical outcome of the current study with that of Kooijman [59].

Study	No. Of Cases with follow up data	No. Of cases recurring with a Y.S.T. component.	No. Of cases developing metastatic dis. (Excluding those recurring with a Y.S.T. component)	No. Of cases recurring (Excluding those developing a Y.S.T. component)	No. Of tumour related deaths
Kooijman	27	2 (Both sacrococcygeal, Grade I and Grade III respectively)	1 (Sacrococcygeal, Grade II, single liver metastasis)	2 (Grade II, sacrococcygeal + Grade III, ovarian)	2 (- Grade I, sacrococcygeal, recurring with a YST component. - Intracranial imm. Teratoma, death from raised I.C.P.)
Current Study	23	1 (Grade II, sacrococcygeal)	3 (- Grade II, ovarian, extensive peritoneal metastases. - Grade III, ovarian, glial nodules in peritoneal vessels. - Grade III, neck, metastases to local cervical lymph nodes)	1 (- Grade II, pharyngeal)	2 (- Grade II ovarian-extensive peritoneal deposits. -Grade II sacrococcygeal recurring with Y.S.T. component)
Combination of present study and that of Kooijman	50	3 (6%)	4 (8%)	3 (6%)	4 (8%)

On combining the results of the current study with those of Kooijman, it becomes apparent, with regard to immature teratomas of childhood, that:

1. The outcome is usually favourable (mortality rate less than 10%).
2. Metastatic disease is uncommon (less than 10% of cases).
3. Recurrence with a Y.S.T. component is rare (6% of cases) - in these 2 studies occurring only in sacrococcygeal tumours, and with all tumour grades.
4. Recurrence of tumour following complete surgical excision is rare (6% of cases).

Relationship between tumour grade plus other histological factors, and outcome.

As the majority of childhood immature teratomas appear to have an uncomplicated clinical course following complete surgical excision, it is difficult to establish definite prognostic factors.

1. Tumour grade - In the current study complications were confined to grade II and III tumours. (Kooijman does however document a grade I sacrococcygeal tumour which recurred with a Y.S.T. component).
2. Mitotic count, microscopic necrosis, anaplasia, vascular invasion - there was no correlation between these variables and clinical outcome (anaplasia, and vascular invasion, could in fact not be identified in any of the cases examined) - see tabulated data below.

Relationship (or lack thereof) between immature teratomas with a complicated clinical course (in the current study) and mitotic rate plus microscopic necrosis :

Site	Complication	Mitotic count/10HPF	Microscopic necrosis
Sacrococcygeal	Recurrence of grd II tumour with a Y.S.T. component.	1/10HPF	Absent
Ovary	Grd II tumour with extensive metastatic peritoneal deposits, resulting in death of patient.	18/10HPF	Present (extensive)
	Grd III tumour with glial nodules demonstrated in peritoneal blood vessels.	<1/10HPF	Present (scanty)
Neck	Grd III tumour with metastases to adjacent cervical lymph nodes.	<1/10HPF	Absent
Pharynx	Grd II tumour, recurrence 9 months after original excision.	0/10HPF	Absent

3. Presence of non neural immature tissue (rhabdomyoblastic, renal, and mesenchymal) - These had no adverse effect on the clinical outcome.

Relationship between tumour grade and other histological variables.

1. Mitotic rate - In the current study the mitotic rate correlated with the nature of the immature neural tissue present (low with neuroglial and high with neuroepithelial tubules) rather than the tumour grade. Thus addition of mitotic rate to the grading system is unlikely to be of benefit.
2. Microscopic necrosis - The presence of microscopic necrosis did correlate with tumour grade - of the 10 cases with microscopic necrosis only one (with scanty necrosis) occurred in a Grade I tumour (the other 9 cases all being associated with Grade II/III tumours). However, as this variable when evaluated alone, did not correlate with prognosis, its addition to the current grading system is unlikely to be of benefit.

SUMMARY OF DATA ON IMMATURE TERATOMAS OCCURRING IN CHILDHOOD

Site	Total No. of cases	Grade I	Grade II	Grade III	Sex F	Sex M	Ave. Age.	No. of cases with follow up data	No. of tumour related deaths	No. with metastatic disease (Excluding those who died)	No. of recurrences (Excluding those who died or developed metastases)
Sacrococcygeal	15	8	5	2	2	13	All present at birth	6	1 (Grade II tumour, recurred with yolk sac component)	0	0
Ovarian	9	4	3	2	0	9	7 years 9 months	7	1 (Grade II tumour, with extensive peritoneal deposits)	1 (Grade III tumor- glial nodules in peritoneal vessels- see discussion in relevant section)	0
Retroperitoneal	6	1	2	3	1	5	12 months	5	0	0	0
Neck (Soft tissue)	3	1	1	1	2	1	All present at birth	2	0	1 (Grade III tumour, associated cervical lymph node involvement)	0
Neck – Nasopharynx	1	0	1	0	0	1	Present at birth	1	0	0	1 (Recurrence 9 months after original excision)
Anterior mediastinum	2	1	1	0	1	1	2 ½ months	2	0	0	0
Paravertebral soft tissue	1	1	0	0	0	1	Present at birth	0	-	-	-
Total	37	16	13	8	6	31		23	2	1	0

RELATIONSHIP BETWEEN HISTOLOGICAL FINDINGS – NECROSIS, MITOTIC COUNT, VASCULAR INVASION, ANAPLASIA, NON NEURAL IMMATURE TISSUE – AND IMMATURE TERATOMA GRADE PLUS OUTCOME

Site	Tumour Grade	Ave. mitotic count/ IOHPF (Range)	No. of cases with microscopic necrosis	No. of cases with Anaplasia	No. of cases with vascular invasion	No. cases with immature tissue other than neural	No. cases with Death/Metastases/ Recurrence
Sacrococcygeal	Grade I (8 cases)	5,6/IOHPF (0 → 40/IOHPF)	0	0	0	0	0
	Grade II (5 cases)	1,5/IOHPF (0 → 6/IOHPF)	2 (1 – Extensive, 1 – Scanty)	0	0	1 (Immature mesenchyme)	1 (Recurrence with yolk sac component & ultimately death)
	Grade III (2 cases)	25,5/IOHPF (8 → 43/IOHPF)	2 (1 – Extensive, 1 – Scanty)	0	0	0	0
Ovarian	Grade I (4 cases)	0,66/IOHPF (0 → 4/IOHPF)	1 (Scanty)	0	0	0	0
	Grade II (3 cases)	15,6/IOHPF (3 → 26/IOHPF)	2 (1 – Extensive, 1 – Scanty)	0	0	1 (Immature mesenchyme)	1 (Extensive peritoneal deposits, with death at one year)
	Grade III (2 cases)	4,5/IOHPF (1 → 8/IOHPF)	2 (Both Scanty)	0	0	1 (Rhabdomyoblastic focus)	1 (Omentum – glial nodules within blood vessels – see relevant section for further details)
Retroperitoneal	Grade I (1 case)	0/IOHPF	0	0	0	0	0
	Grade II (2 cases)	12/IOHPF	0	0	0	2 (Both cases contained immature renal elements)	0
	Grade III (3 cases)	20/IOHPF (7 → 33/IOHPF)	1 (Scanty)	0	0	1 – Typical appearance of a Wilms tumour except for neuroepithelial rosettes & neuroglial in capsule	0
Neck (Soft tissue)	Grade I (1 case)	DATA	NOT	AVAILABLE			
	Grade II (1 case)	15/IOHPF	0	0	0	0	0
	Grade III (1 case)	<1/IOHPF	0	0	0	0	1 (Cervical lymph node metastases)

RELATIONSHIP BETWEEN HISTOLOGICAL FINDINGS – NECROSIS, MITOTIC COUNT, VASCULAR INVASION, ANAPLASIA, NON NEURAL IMMATURE TISSUE – AND IMMATURE TERATOMA GRADE PLUS OUTCOME:

Site	Tumour Grade	Ave. mitotic count/IOHPF (Range)	No. of cases with microscopic necrosis	No. of cases with Anaplasia	No. of cases with vascular invasion	No. of cases with immature tissue other than neural	No. cases with death/Metastases/ Recurrence
Nasopharynx	Only 1 case Grade II tumour	0/IOHPF	0	0	0	0	1 Recurrence 9 months later
Anterior mediastinum	Grade I (1 case) Grade II (1 case) No Grade III cases	1/IOHPF 15/IOHPF	0 0	0 0	0 0	0 0	0 0
Paravertebral Soft tissue	Only 1 case Grade I tumour	1/IOHPF	0	0	0	0	0

Footnote to table summarising data on yolk sac tumours

1. Sacrococcygeal Y.S.T.
   - In two of the cases, the primary tumours were a mature and an immature teratoma respectively, with only the recurrence/metastatic deposit showing a Y.S.T. component.
   - The histological data, from one of the cases, refers to metastatic tumour (the original primary sacrococcygeal tumour being a mature teratoma - see above).
   - The mean maximum tumour diam. given, is from data on only 3 cases (the majority of tumours could either not be fully excised or were removed piecemeal).

2. Testicular Y.S.T.
   - The mean max. tumour diam. is from data on 9 cases only.

3. Retroperitoneal Y.S.T.
   - The mean max. tumour diam. is from data on one case only.

4. Mediastinal Y.S.T.
   - The tumour diam. given is following initial chemotherapy, prior to surgery.

SUMMARY OF DATA ON YOLK SAC TUMOURS – PURE OR IN COMBINATION WITH A MATURE/IMMATURE TERATOMA (BUT EXCLUDING THOSE CASES WITH A DEFINITE/POSSIBLE ASSOCIATED EMBRYONAL CARCINOMA COMPONENT):

Location	Total no. of cases	Pure	Mixed	Sex F M	Ave. age (Range) (Months)	Ave. Max Tumour Diam (Range) (mm.)	Ave. Mitotic count/ 10HPF	No with microscopic necrosis	No. with vascular invasion	No. with Anaplasia	No. with Follow up data	No. tumour related deaths	No. with Metastatic disease (Excluding those who died)	No. with Local recurrence (Excluding those who died or developed metastases)	No. Alive with residual disease	No. Alive free of disease	No. Alive disease status unclear
Sacroco-ocygeal	15 (38,5%)	8	7	10 5	22,8 (Birth to 60)	98 (50 – 135)	6	6 (40%)	2 (13,3%)	2 (13,3%)	12 (80%)	6 (50%)	4 (33%)	1 (8,3%)	2 (16,6%)	4 (33%)	-
Testicular	14 (35,9%)	13	1	0 14	14 (2 to 36)	26 (8 to 55)	5,7	7 (50%)	0	1 (7%)	11 (78,5)	0	2 (18,2%)	1 (9%)	0	11 (100%)	-
Ovarian	5 (12,5%)	2	3	5 0	109 (91 to 150)	130 (110 to 170)	7	3 (60%)	1 (20%)	2 (40%)	5 (100%)	2 (40%)	1 (20%)	1 (20%)	1 (20%)	2 (40%)	-
Retroperi-toneal	2 (5,1%)	2	0	2 0	83 (22 and 144)	110	6	2 (100%)	0	0	2 (100%)	2 (100%)	-	-	-	O	-
Mediasti-nal	1 (2,5%)	0	1	0 1	24	65	18	1 (100%)	0	0	1	0	0	0	0	1 (100%)	-
Neck	1 (2,5%)	1	0	0 1	24	90	6	1 (100%)	0	0	1	0	0	-	-	-	1
Scalp	1 (2,5%)	1	0	1 0	5	15	3	0	0	0	0	0	-	1 (100%)	-	-	-
Total	39	27 (69%)	12 (31%)	18 (46%) 21 (54%)				20 (51%)	3 (7,6%)	5 (12,8%)	32 (82%)	10 (31%)	7 (21,8%)	4 (12,5%)	3 (9,5%)	18 (56%)	

SUMMARY OF DATA ON G.C.T. WITH DEFINITE OR POSSIBLE EMBRYONAL CARCINOMA COMPONENT

Location	Total No. of cases	Histopathology	Sex F	Sex M	Ave. Age. (Months) (Range)	Mean max. tumor diam (mm) (Range)	Avg. Mitotic count/ IOHPF	No. with Microscopic necrosis	No. with vascular invasion	No. with Anaplasia	No. with Follow up data	No. tumour related deaths	No. with Metastatic disease (Excluding those who died)	No. with local recurrence (Excluding those who died or developed metastases)	No. alive with residual disease	No. alive free of disease	No. alive disease status unclear
TUMOURS WITH DEFINITE EMBRYONAL CARCINOMA COMPONENT																	
Testicular	1	Pure embryonal carcinoma	1	0	60	75	30	0	1	1	1	1	-	-	-	-	-
Retroperi-toneal	1	Pure embryonal carcinoma	1	0	41		13	0	0	0	1	0	1	-	1	-	-
Neck	1	Mixed YST & embryonal carcinoma	0	1	21	100	19	1	0	0	1	0	0	-	-	1	-
YOLK SAC TUMOURS WITH POSSIBLE EMBRYONAL CARCINOMA COMPONENT																	
Testicular	2	YST with posaible embryonal carcinoma component	2	0	18 (14 & 24)	50 (45 & 55)	5,5	2	1	1	1	0	1	-	-	-	1
Ovarian	1	YST with posaible embryonal carinoma component	0	1	96	110	3	1	0	1	1	0	0	0	0	1	-

SUMMARY OF FACTORS CLINICAL AND PATHOLOGICAL, INFLUENCING THE CLINICAL OUTCOME OF MALIGNANT GERM CELL TUMOURS OF CHILDHOOD.

I) Clinical

A) Site

The significance of anatomical location is exemplified by the outcome of those with testicular Y.S.T. (100% alive and free of disease), as opposed to the sacrococcygeal-retroperitoneal group (57% mortality rate, with overall 86% either dying or developing disseminated disease) plus the ovarian group (40% mortality rate). The cause of this discrepancy in prognosis between tumours which are histologically identical is unclear. Tumour longevity prior to diagnosis may be of significance. The testicular lesions occurring in a superficial/"exposed" location will be diagnosed at an earlier stage in their development (see tabulated data on size of neoplasms), and theoretically have had less time to form cell clones with metastasizing capability, than those tumours in cryptic locations (ovarian, sacrococcygeal, retroperitoneal).

B) Age

[This factor is of most importance as a potential predictor of biological behaviour of sacrococcygeal tumours - with only 2 (15%)/36 neoplasms present at birth showing malignant histology, as opposed to 13 (72%) of 18 diagnosed later in infancy].

As a group the testicular Y.S.T. occurred at a significantly younger age than those in the poor prognosis locations (ovary, retroperitoneum, sacrococcygeal region) - see comment on tumour longevity above.

In addition, with regard to testicular Y.S.T., infants less than 24 months of age are generally held to have a better prognosis [2, 12, 13] (It should however be noted, that in the childhood series of Hawkins et al [15], advanced age beyond 24 months did not adversely affect the prognosis. In the current study only one child was older than 24 months, precluding personal comment).

C) Therapy administered

Modern day multi drug chemotherapy has dramatically altered the prognosis for malignant g.c.t. All 8 of the patients (with available data) diagnosed prior to 1981 as having Y.S.T. of the ovary, retroperitoneum or sacrococcygeal region died. By contrast, in only 1 of 10 patients diagnosed since 1981 was death documented.

II) Pathological

A) Tumour size

As a group the testicular Y.S.T. were of a significantly smaller size than those in the poor prognosis locations - see comment above on tumour longevity.

B) Histological malignant G.C.T. type

1. Embryonal carcinoma - With regard to the malignant testicular g.c.t., the only death, as well as the only 2 cases of visceral metastases, occurred amongst the 3 patients with a definite or possible embryonal carcinoma component.
2. Germinomas - All 5 patients with ovarian dysgerminomas were alive at documentation (4 free of disease) - consistent with the excellent prognosis of this radiosensitive neoplasm.

C) Y.S.T. Histological subtype

Review of the Y.S.Ts with clinical follow up revealed 7 (30%) deaths amongst 23 patients with histologically pure tumours, and 2 (18%) deaths amongst 11 with mixed (Y.S.T. + mature/immature teratoma). These findings are of doubtful significance. [15] Hawkins et al in their review of 89 childhood Y.S.T. found no statistically significant difference in behaviour between pure and mixed tumours.

D) Predominant Y.S.T. Histological pattern

Review of the data for the 37 primary yolk sac tumours shows:

- No predominant histological pattern - 21 cases.
- Reticular pattern predominant - 11 cases.
- Papillary pattern predominant - 2 cases.
- Trabecular pattern predominant - 1 case.
- Mixed trabecular - polyvesicular - vitelline pattern - 1 case.
- Solid pattern predominant - 1 case.

No correlation could be demonstrated between predominant histological pattern and outcome.

E) Mitotic rate plus microscopic necrosis

There was no statistically significant difference in mitotic rate, or incidence of microscopic necrosis, between the excellent prognosis group (testicular) and the poor prognosis group (sacrococcygeal - ovarian - retroperitoneal).

F) Vascular invasion + anaplasia.

1. With regard to non testicular malignant g.c.t. these variables were not shown to be of prognostic importance (see data below).

	Percentage patients dying or developing metastatic disease (non testicular malignant g.c.t.).
Anaplasia present	80%
Anaplasia absent	62,5%
Vascular invasion present	50%
Vascular invasion absent	72%

2. Two of the 3 cases with a possible/definite testicular embryonal carcinoma component showed both anaplasia and vascular invasion. Visceral metastases developed in both these patients.

SUMMARY OF DATA ON MATURE TERATOMAS

Location	Total No. Of cases (% of total no. of mature teratomas)	Mean age. (Range)	Sex F	Sex M	Mean Max tumour diam (mm). (Range)	No. of cases recurring as malignant tumours or as immature teratomas
Ovarian	30 (35,3%)	66 months (3 weeks to 12 years)	30	0	86 (22 to 130)	0
Sacrococcygeal	27 (31,7%)	3½ weeks (Birth to 30 weeks)	18	7	75 (30 to 130)	1 – Recurrence with YST component
Mediastinal	8 (9,4%)	41,5 months (Birth to 13 years)	5	3	95 (40 to 200)	0
Neck	6 (7%)	All present at birth	4	2	77 (40 to 100)	0
Testicular	4 (4,7%)	45,5 months (14 months to 84 months)	0	4	30 (20 to 40)	0
Retroperitoneal	3 (3,5%)	5,3 months (Birth to 8 months)	2	1	102,5 (100 to 105)	0
Paravertebral	3 (3,5%)	(Birth to several months)	1	1	(25 to 60)	0
Renal	2 (2,3%)	(4 months and 13 months)	2	0	(110 to 120)	0
Face (cheek)	1 (1,2%)	4 years	1	0		
Orbit	1 (1,2%)	Birth	1	0	Piecemeal resection	0
Total	85		64 (78,1%)	18 (21%)		1 (1,2%)

Footnote: In some instances data was not available for all the cases (see relevant specific organ systems).

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