*Philip Corbett, MD and Feilim Liam Murphy, FRSCI**

Testicular Tumours in Children and Adolescents

**Department of Paediatric Surgery and Urology, St Georges's Hospital, Blackshaw Road, London, SW17 0QT*

Prepubertal testicular tumours account for 2% of all childhood malignancies with an incidence of 0.3-2 per100,000 children. Overall they account for 2% of all childhood malignancies with an incidence of 0.3-2 per100,000 children. Until the creation of tumour registries the majority of the data on these lesions was based on case reports or small personal series. Although the national and regional tumour registries have dramatically increased our knowledge they are not perfect as demonstrated by the significant variation in tumour types between and within the registries. The relative infrequency of some of the tumours means that we are still dependent on relatively small series for data. The purpose of this review is to identify the key points of difference in pre pubertal testicular tumours relative to their diagnosis, treatment and outcome and to describe all the common and less common testicular neoplasms in order for the surgeon to al develop a clear management for every testicular tumour prior to surgery. Prepubertal testicular tumours are classified from their cells of origin. Hence there are germ cell tumours arising from germ cells which include yolk sac tumours and teratomas. Stromal cell tumours arise from and include Leydig cell, Sertoli cell and Juvenile Granulosa cell tumours. Gonadoblastoma contain both stromal elements and germ cell. Rarer benign lesions such as multicystic dysplastic testis and secondary malignancies such as leukaemia are discussed.

Epidemiology

Epidemiological data on the pre pubertal testis tumour group is scant and relatively infrequently studied which is in part due to the relative infrequency of the tumours themselves. Adult testicular tumour risk factors have been very well studied and debated within in the overall framework of the male testicular malignancy. Knowledge of the adult epidemiology allows improved counselling to the parent and child particularly after the successful treatment off the child's testicular malignancy.

Data from the Swedish Family-Cancer Database which assessed the familial risk of malignancy in the offspring of people who had suffered a malignancy revealed that testicular cancer had the highest relative risk of 4.52 of the all the twenty five site specific cancers assessed. The relative risk with an effected sibling was 6.63, the second highest within the studied population of 3.5 million families consisting of 11.5 million individuals[1]. In adults high quality evidence has demonstrated increased risk caused by cryptorchidism, late or delayed orchidopexy (after five years of age), the presence or previous existence of a contralateral testicular tumour and familial testis cancer or familial cancer history[2,3]. Overall the issues of testicular atrophy and exposure to maternal oestrogens are probably important but the evidence is still unproven[3,4]. Overall the majority of cases will be spontaneously arise however there is be a higher incidence in boys with a strong family cancer history, ambiguous genitial and chromosomal abnormalities.

Presentation

The vast majority of testicular tumours present as a painless mass noticed either by the parents or by the older child themselves. A common clinical trap for the unwary is a recent onset hydrocoele in which the testis is either impalpable or palpably abnormal which requires an early ultrasound. Painful swelling and acute scrotal pain are less frequently reported. Physical examination usually reveals a distinct abnormality within the testis although localized distinct lesions within the testis itself can be detected. A key step is to determine where the pathology is testicular, epididymal or paratesticular in origin. However this can be difficult clinically. Rarely the tumour is detected only due to either precocious puberty or syndromal conditions in which no mass is palpable in the testes. Once a testicular mass is discovered a full physical examination is undertaken with particular focus on signs of precocious puberty, central nervous system and evidence of bony metastases. Ultrasound of the scrotum (USS) is very sensitive at distinguishing between testicular and paratesticular pathology such as epididymal cysts, true hydrocoeles with a normal testis and paratesticular rhabdomyosacroma. It enables mapping of the extent of the lesion and it differentiates between those who may be localized and hence suitable for enucleation and testis sparing surgery. Ultrasound does not have a high specificity in determining the definitive testicular tumour type. Further imaging such as bony x rays and computerized axial tomogram of brain, abdomen and pelvis maybe useful on a case to case basis but are dependent on clinical signs, tumour markers and the histological diagnosis. Alpha fetoprotein (AFP) is the key tumour marker for testicular tumours in prepubertal boys. AFP is a single polypeptide chain produced by the foetal yolk sac, liver and gastrointestinal tract. It has a half life of about 5 days, making it invaluable in assessing the efficacy of initial treatment as a persistently high level indicates the presence of residual disease. It is important to note that as AFP is a normal

product of foetal development and levels in neonates are vastly higher than standard reference ranges. For this reason, most authors do not regard elevated serum AFP levels in children less than 1 year of age as being diagnostic. Similiarly a raised level (>5IU/L) of Human Chorionic Gonadotrophin, â subunit (âHCG) is detected in up to 45% of yolk sac tumours but the majority of centres do not measure it, arguing that it is of little clinical value except to note a decrease in the initial measured value.

Staging

There are a number of staging systems using the TNM system and classical clinico-pathological systems. As the majority of these are individual tumour type specific and routine retroperitoneal lymph node dissection does not occur, these classification systems can be incomplete and can lead to unnecessary confusion. The authors have used the modified classification system without complication.[5] (Fig. 1)

Fig. 1. Staging for prepubertal testis tumours

Stage	Findings following Orchidectomy
I	Local disease with complete resection, markers normalize
II	Microscopic disease in scrotum or high cord (<5 cm from proximal end)
	Trans-scrotal orchidectomy
	<2 cm retroperitoneal lymph node
	Persistently elevated markers
III	>2 cm retroperitoneal lymph node
IV	Distant metastases

Adapted from Wu and Snyder[5]

Yolk Sac Tumours

Yolk sac tumours are reported as being the most common pre-pubertal tumour by the American Academy of Pediatric's Prepubertal Testis Tumor Registry, comprising 59%-62% of all primary tumours of the testis[6,7]. Other large series report a higher percentage of other lesions such as teratoma and it is postulated that benign teratomas are not regularly reported to tumour registers hence the possibility of underreporting in some series[8]. Overall the data suggests that incidence of yolk sac tumours may be less than 50%.(Fig. 2)

Further confusion is caused by the multitude of names given to yolk sac tumours such as endodermal sinus tumours, orchidoblastoma, juvenile embryonal carcinoma, mesoblastoma vitellinum, clear cell adenocarcinoma, extraembryonal mesoblastoma, archenteronoma and Teillum's tumour. The median age of presentation is 16 months almost always with painless testicular mass[6]. Yolk sac tumours are malignant germ cell tumours, which metastasise to retroperitoneal lymph nodes (RPLN) in up to 13% of cases and to distant sites such as lung and liver. 90% of tumours are confined to the testis at the time of presentation. Initial investigations should include serum AFP, which is significantly raised at presentation in up to 90% of yolk sac tumours. Histologically, they can appear similar in appearance to adult embryonal carcinoma although various patterns have been described. They are solid homogenous lesions which are yellow to pale grey in colour with prominent intra and extra cellular hyaline bodies and glomerular bodies. Specialist staining for AFP is probably the most specific discriminator available when there is diagnostic uncertainty. They have a characteristic diploid or even tetraploid appearance, with a deletion from of chromosome 1(1p36)[12].

The standard first line management for yolk sac tumour is inguinal orchidectomy. Metastatic evaluation of yolk sac tumours should include computerised tomography (CT) of the abdomen and pelvis to rule out RPLN and hepatic metastases and a chest x-ray (or CT) to exclude pulmonary spread. Historically, RPLN dissection was undertaken as part of the initial surgery as this has been shown to have value in adults both as a staging tool and in preventing recurrence. However, as previously stated, the majority (90%) of these tumours are stage I at presentation and only around 20% show signs of recurrence when managed by orchidectomy and observation[13]. The vast majority with recurrent disease can be salvaged by appropriate chemotherapy. The morbidity associated with the surgery (*e.g.* retrograde ejaculation, lymphoedema) is significant and can occur in up to 40%

of cases hence, RPLN dissection is not recommended to stage yolk sac tumours or to clear suspected or apparent lymph node spread.

Follow up for patients with stage I disease should include clinical examination, CT of abdomen and pelvis, chest x-ray, and serum AFP level one month after surgery. Subsequently, Serum AFP and chest x-ray should be repeated 6 weekly for a period of not less than two years. Over this period, 3 monthly CT scans are also advised if available. For those with metastatic disease evident at the time of initial surgery or with subsequent evidence (*e.g.* persistently raised serum AFP following orchidectomy), the mainstay of treatment is platinum based chemotherapy which has demonstrated a 91% 5 year survival rate in boys. Persistently raised AFP or recurrence on imaging following standard chemotherapy is uncommon and should prompt the use of second line agents. A persistent mass either in the retroperitoneum or at distal sites necessitates surgery and or radiotherapy.

Teratoma

As discussed in Fig. 2 there may be a significant variation in the incidence of testicular teratomas ranging from 23%-60%. In the under sixteen year-olds, teratomas exhibit a bimodal distribution, presenting either at puberty (classically at older than twelve years) or at a median age of around 13 months ranging from 1-18 months, with occasional antenatal diagnoses.[7] Whereas teratomas in pubertal children can exhibit clinical and pathological similarities to adult lesions, true pre-pubertal tumours behave in a benign fashion. As with other testicular tumours, teratomas most commonly (83%) present with a palpable mass although hydrocele is the first symptom in 8% of cases, higher than for testicular tumours as a whole (2%).[7]

Teratomas are germ cell tumours which classically contain all three cell layers: endoderm, mesoderm and ectoderm. These can be subdivided into mature (~90% of cases) and immature teratomas with more primitive cells. On gross examination, all teratomas are cystic with variable consistency, often surrounded by a pseudo-capsule. The pre-pubertal teratoma lacks cytological atypi and widespread mitosis. Mature pre-pubertal teratomas are universally benign although historically, immature tumours are treated with a greater degree of caution, being regarded as a higher grade. In the very rare instances of metastatic disease encountered with immature teratoma, the distant deposits are yolk sac tumour and are thought to result from microscopic foci within the original tumour.[14,15] Epidermoid cysts are described as teratomas which are composed of epithelium which produces keratin hence are described as monophasic teratomas. Numerous authors have sub-grouped them within the teratoma family however there is no diagnostic or significant management issue relating to them and hence we include them within the teratoma discussion to avoid any confusing subdivision.

Initial investigations most often include an ultrasound which typically reveals a cystic, intra-testicular lesion. Many series report mildly elevated (~100ng/ml) serum AFP levels in a small proportion of teratomas although the majority of these cases are presentations in infancy when AFP levels are naturally raised. âHCG is never raised. Management of pre-pubertal teratoma is dictated by the fact that biochemical studies and imaging cannot reliably differentiate benign teratoma from malignant tumours. The gold standard remains inguinal orchidectomy with the testis being sent for histology to confirm the diagnosis. However, if facilities are available, frozen section biopsy may be taken from the affected testis. If the diagnosis of teratoma can be confirmed on the operating table, some authors advocate testis sparing enucleation of the tumour to reduce functional, cosmetic and psychological morbidity and it has been demonstrated to be safe with no recurrence detected and reasonable testicular growth.[16] Management of testicular teratoma in older boys is orchidectomy. However, Ross suggests that in boys close to the age of puberty, a sample of the surrounding testicular parenchyma should be taken and sent for frozen section at the time of tumour biopsy.[6] If the testicular tissue is pubertal, a complete orchidectomy to the level of the internal inguinal ring should be performed. A persistently raised serum AFP postoperatively or histology showing an immature tumour with or without yolk sac tumour seeding demands the same careful monitoring as an excised stage I yolk sac tumour. Pubertal boys should be evaluated as for adults with malignant germ cell tumours.

Leydig cell tumours

Leydig cell tumours (LCT's) constitute between 1-4% of testicular tumours in pre-pubescent boys and are universally benign.[6,9] Median age of presentation is 6.5 years, ranging from 2 to 10.5years.[6] Clinically, the boys present with accelerated somatic growth and progressive virilisation. Increasing height and muscle mass are almost always present along with pubic hair and penis enlargement. Facial hair and deepening of the voice are later signs. This unusual presentation is due to the fact that LCT's secrete testosterone, triggering precocious puberty. These changes usually reverse when the tumour, the source of the excess testosterone, is removed. However, when presentation is delayed (>3 years), pubertal changes may continue due to inappropriate gonadotrophin secretion from the pituitary, causing the healthy testicle to be stimulated into producing

testosterone.[17] LCT's account for only 10% of cases of precocious puberty, the other common causes being: pituitary tumours, CAH, and idiopathic or 'true' precocious puberty.

Testicular examination may be entirely unremarkable in patients with a short history. As the condition progresses, a diffuse enlargement of one testis may become apparent, thought to be due to a local androgenic effect caused by the tumour.[18] A discrete mass may not be palpable or even detectable on ultrasound scan. When USS is successful, the typical findings are of a small (<10mm), single, homogenous, hypo-echogenic nodule located within the testicular parenchyma. If specialised imaging and biochemical tests are not available and the other causes of precious puberty have been out ruled it is acceptable to observe the child regularly for a period of up to 18 months for unilateral testicular enlargement to present itself (longer delay increases the risk of permanent abnormal sexual development to an unacceptable level). If no enlargement occurs or both testes are affected, a clear diagnosis must be sought before surgery is contemplated. Orchidectomy via an inguinal incision is still the gold standard of management but due to its benign nature, authors support testis sparing enucleation.[6,14] The numbers of patients treated are low but no cases of recurrence in paediatric cases have been reported.

Juvenile Granulosa Cell Tumours

Juvenile Granulosa cell tumours (JGCT) account for 2%-5% of testicular tumours classically presenting as a mass in the first 6 months of life. They are a stromal tumour which are supposed to originate from the granulosa cells however significant confusion remains as to their primary cell type.[6,10] JGCT are associated with chromosomal abnormalities and can be seen in boys with ambiguous genitalia or boys being managed for disorders of sexual development. Importantly they are benign inactive lesions and thus following orchidopexy and histological diagnosis patients require no follow up other than chromosomal analysis.

Sertoli Cell Tumours

Sertoli cell tumours are responsible for about 3% of testicular tumours in prepubescent boys.[6,9,10] This neoplasm is commonly subdivided into two main categories; Sertoli Cell Tumours (SCT's) and Large Cell Calcifying Sertoli Cell Tumours (LCCSCT's). These two lesions are sufficiently different in their histology, presentation and behaviour that it is useful to address them as two distinct entities.

Pure Sertoli Cell Tumours (SCT's)

The characteristic histological appearance of SCT's are polygonal cells with eosinophilic cytoplasm arranged in rosettes, reminiscent of seminiferous tubules. However, accurate histological diagnosis of SCT's is extremely difficult. A fact demonstrated by 38% of gonadal stromal tumours being listed as 'unspecified' by Ross *et al*.[6] Prepubertal SCT's present as painless masses in newborns and infants with normal biochemical markers. In practice, Sertoli Cell Tumours are diagnosed histologically after radical orchidectomy in boys less than six months of age with painless, unilateral testicular swelling, normal tumour markers and no hormonal irregularity. As metastatic spread to retroperitoneal lymph nodes is possible, an extended period of observation (10yrs) with serial ultrasound scans following orchidectomy is advised.

Large Cell Calcifying Sertoli Cell Tumour

This rare subtype is characterized by fairly regular cells with eosinophilic cytoplasm arranged within a fibromyxomatous stroma, and calcifications varying from large, centrally located islands to microscopic, psammoma-like bodies. In the absence of associated syndromes (see below) they are almost always unilateral with no gynaecomastia or precocious puberty and normal AFP and bHCG. Radical orchidectomy is advised but unless abdominal ultrasound scan or histology indicates malignancy, retroperitoneal lymph node dissection is not indicated and long term follow up is of little value. Bilateral LCCSCT's are classically associated with Carney complex and Peutz-Jegher's Syndrome. These tumours are hormonally active with high levels of oestradiol and testosterone, resulting in gynecomastia and precocious puberty.

Gonadoblastomas

Gonadoblastomas account for less than 2% of all primary testicular tumours and are almost exclusively found in the gonads of patients with disorders of sexual development with dysgenetic gonads also called streak gonads.[6,9,10] Typically they occur in dysgenetic gonads which contain evidence of the Y chromosome. Evidence now points towards the Testis-Specific Protein Y-encoded gene (TSPY) being the gonadoblastoma locus on the Y chromosome which could be used as a marker for the tumour. Classically they are defined histologically by

the presence of discrete aggregates of intimately mixed large, round germ cells and smaller epithelial cells resembling immature Sertoli-granulosa cells.

Gonadoblastomas are usually asymptomatic and are usually detected on the removal of the dysgenetic gonad. They have been universally reported as benign but the dysgenetic gonads from which they grow are also prone to developing malignant tumours occurring in 17%-50%. Patients present with disorders of sexual development at varying ages. However once a dysgenetic gonad in a child with Y chromosomes is identified, they should undergo elective gonadectomy as soon as possible as cases of bilateral gonadoblastoma and seminoma/dysgerminoma have been reported in infancy.[19]

Multicystic Dysplastic Testes

Multicystic dysplastic testis (cystic dysplasia of the rete testis or cystic dysplasia of the testes) is an extremely rare lesion which is associated with ipsilateral multicystic dysplastic kidneys (MCDK) and seminal vesicle cysts. Invariably unilateral in nature it presents in the first year of life in patients usually in boys already been followed for an antenatal diagnoses of MCDK with a painless testicular swelling. Although benign in nature orchidectomy is required for diagnoses and is curative.

Secondary Malignancies and Leukaemia

Secondary malignancies rarely occur in the testes. The most common secondary malignancy is leukaemia which can develop testicular involvement in up to 25% of boys especially those with acute lymphoblastic leukaemia (ALL). The majority of the involvement is sub clinical and only 1%-2% of boys with ALL will have a palpable abnormality. Historically it was believed that the testicular involvement allowed a reservoir of tumour to remain untreated behind the blood testis barrier that could allow relapse. However high biopsy rates did not detect high occult testicular involvement and negative biopsies did not out rule relapsed with testicular involvement hence ALL patients are no longer routinely biopsied.[20] If the boy does relapse with testicular enlargement then orchidectomy followed by chemotherapy and radiotherapy maybe required.

Summary

Prepubertal testicular tumours are dramatically different from their adult counterparts. The epidemiology is unclear except for a strong familial cancer risk. Clinically the vast majority of the tumours present in the preschool child with a painless testicular mass and occasionally, as a trap for the unwary, with a hydrocoele. In the first 6 months of life juvenile granulosa cell tumours, sertoli cell tumours and teratomas commonly present as painless benign enlarged testes. In the first year multicystic dysplastic testes and excised Gonadoblastomas present. Between six and thirty six months of life yolk sac tumours, then teratomas peak in incidence. Clinical differentiations of the tumours can challenging as AFP can be physiologically raised and ultrasound of the scrotum can lack in specificity. However the tumours are can easily be identified on histology and the prognosis is excellent with teratomas being benign and yolk sac tumours presenting in clinical stage I. Between five and twelve years Leydig cells occur associated with precious puberty while the incidence of yolk sac tumours dramatically falls after age of four. In boys older than twelve the incidence of teratoma and the key issue at this age is to identify the onset of puberty as they should be evaluated and managed as for adults with malignant germ cell tumours. In order that we can improve our data on the incidence and demographics of testicular tumours all testicular tumours benign or malignant, enucleated or excised should be centrally reported to the appropriate tumour registry. If no suitable registry exists in your region we hope that this review prompts its creation.

Fig. 2. Relative incidence of tumour types.

	Yolk Sac	Teratoma	Leydig Cell	Sertoli Cell	Granulosa Cell	Gonado-blastoma	Epidermoid Cyst	Other
Ross[8] (n=395)	62%	23%	1%	3%	3%	1%	3%	4%
Pohl[9] (n=98)	23%	46%	4%	3%	5%	2%	14%	8%
Sugita[10] (n=59*)	31%	49%	5%	3%	2%	2%	0%	3.5%
Tasman[11] (n=34)	17%	47%	6%	3%	0%	0%	6%	6%

*13 Paratesticular Rhabdomyosarcoma excluded from this table

Reference:

1. Hemminki KA,, Sundquist J, Bermejo JL. Familial Risks for Cancer as the Basis for Evidence-Based Clinical Referral and Counselling. *The Oncologist,* 13(3): 239-247, 2008.
2. Dusek L, Abrahamova J, Lakomy R *et al*. Multivariate analysis of risk factors for testicular cancer: a hospital-based case-control study in the Czech Republic. *Neoplasma,* 55(4): 356-368, 2008.
3. Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumours. World J Urol 2004;22(1):2-14.
4. Weir HK, Marrett LD, Kreiger N *et al*. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. *Int J Cancer,* 87(3): 438-443, 2000.
5. Wu H, Snyder HM. Pediatric urologic oncology: bladder, prostate, testis. *Urol Clin North Am,* 31: 619-627, 2004.
6. Ross JH, Rybicki L, Kay R. Clinical behaviour and contemporary management algorithm for pre-pubertal testis tumours: a summary of the prepubertal testis tumor registry. *J Urol,* 168: 1675-1678, 2002.
7. Grady RW, Ross JH, Kay R. pidemiological features of testicular teratoma in a prepubertal population. *J Urol,* 158: 1191-1192, 1997.
8. Shukla A , Huff D, Canning D *et al*. Juvenile Granulosa Cell Tumor of the Testis: Contemporary Clinical Management and Pathological Diagnosis. *The Journal of Urology,* 171(5): 1900-1902, 2004.
9. Pohl HG, Shukla AR, Metcalf PD *et al*. Prepubertal testis tumours: actual prevalence of historical types. *J Urol,* 172: 2370-2372, 2004.
10. Sugita Y, Clarnette TD, Cooke-Yarborough C *et al*. Testicular and paratesticular tumours in children: 30 year's experience. *Aust NZ J Surg,* 69: 505-508, 1999.
11. Taskinen S, Fagerholm R, Aronniemi J *et al*. Testicular tumours in children and adolescents. *J Ped Urol,* 4(2): 134-137, 2008.
12. Perlman EJ, Valentine MB, Griffin CA, *et al*. Deletion of Ip36 in childhood endodermal sinus tumours by two-color fluorescence in situ hybridization: A pediatric oncology group study. *Genes, Chromosomes and Cancer* 16(1): 15-20, 1998.
13. Liu HC, Liang DC, Chen SH *et al*. The stage I yolk sac tumor of testis in children younger than 2 years, chemotherapy or not? *Pediatr Hematol Oncol,* 15(3): 223-228, 1998.
14. Metcalfe PD, Farivar-Mohseni H, Farhat W *et al*. Pediatric testicular tumours: contemporary incidence and efficacy of testicular preserving surgery. *J Urol,*170: 2412-2415, 2003.
15. Heifetz SA, Cushing B, Giller R *et al*. Immature Teratomas in Children: Pathologic Considerations: A Report From the Combined Pediatric Oncology Group/Children's Cancer Group. *American Journal of Surgical Pathology,* 22(9): 1115-1124, 1998.
16. Valla JS for the Group D'Etude en Urologie Pediatrique. Testis sparing surgery for benign testicular tumours in children. *J Urol,* 165: 2280-2283, 2001.
17. Mengel W, Knorr D. Leydig cell tumours in childhood. *Prog Pediatr Surg,* 16: 133-138, 1983.
18. Gittes R, Smith G, Conn C *et al*. Local androgenic effect of interstitial cell tumor of the testis. *J Urol,* 104: 774, 1970.
19. Dumic M, Jukic S, Batinica S *et al*. Bilateral gonadoblastoma in a 9-month-old infant with 46XY gonadal dysgenesis. *J Endocrinol Invest,* 16(4): 291, 1993.
20. Murphy FL, Law H, Mushtaq I, Sebire NJ Testicular and paratesticular pathology in infants and children: the histopathological experience of a tertiary paediatric unit over a 17 year period. *Pediatr Surg Int.,* 23: 867-872, 2007.