Testis Tumors

78

Jonathan H. Ross

Contents

78.1 Introduction

There is a bimodal age distribution for testis tumors with one peak occurring in the first 2 years of life, and a second, much larger peak occurring in young adulthood. Therefore pediatric testis tumors occur in two distinct groups—prepubertal patients and adolescents. Testicular tumors in adolescents and children do have some similarities. Both usually present with a testicular mass and are treated initially with excision of the primary tumor. In both children and adolescents, malignant testis tumors are particularly sensitive to platinum-based chemotherapy, which has revolutionized the management of testicular cancer throughout the age spectrum. However, there are important differences between testis tumors occurring in children and adolescents. These differences occur in the tumor histopathology, malignant potential, and pattern of metastatic spread. The patients themselves are also dissimilar with different concerns regarding surgical morbidity and preservation of testicular function. These differences have resulted in a significantly different approach to testicular tumors in the two age groups.

78.2 Epidemiology

The incidence of pediatric testis tumors is 0.5–2.0 per 100,000 children accounting for 1–2% of all pediatric tumors. Testis tumors are categorized based on the presumed cell of origin into stromal tumors and germ cell tumors. The frequency and behavior of the various tumor types in prepubertal patients and adolescents is summarized in Table 78.1. Teratoma is the most common prepubertal tumor, followed by yolk sac whereas mixed germ cell tumors, which are malignant, account

P. Puri and M. Höllwarth (eds.), *Pediatric Surgery: Diagnosis and Management*,
DOI: 10.1007/978-3-540-69560-8_78, © Springer-Verlag Berlin Heidelberg 2009

Table 78.1 Tumor types and behavior in prepubertal patients and adolescents

Tumor type		Frequency of occurrence in prepubertal children	Frequency of occurrence in adolescents	Malignant potential
Germ Cell	Pure yolk sac	+++	0	Malignant
	Mixed germ cell tumor	0	+++	Malignant
	Pure seminoma	0	+	Malignant
	Teratoma	+++	++	Benign in children/Potentially malignant in adolescents
	Epidermoid cyst	++	++	Benign
Stromal	Leydig cell	+	+	Benign
	Sertoli cell	+	+	Occasionally malignant in patient over 5 years old
	Juvenile granulosa cell	+	0	Benign
	Undifferentiated stromal	+	0	Occasionally malignant
Gonadoblastoma		+	+	Benign (but can give rise to seminoma)

0 – virtually never, + – rare, ++ – uncommon, +++ – common

for the large majority of tumors in adolescents. Because teratomas (and most stromal tumors) are benign in children, the percentage of prepubertal testis tumors that have malignant potential is much lower than the 90% of tumors in adolescents.

78.3 Evaluation

The majority of patients with a testicular tumor will present with a testicular mass noted by the patient, a parent, or a health care provider. These masses are usually hard and painless. Occasionally patients may present with a hydrocele or pain due to torsion or bleeding into the tumor. Physical examination can usually distinguish testicular tumors from other scrotal masses such as hydroceles, hernias or epididymal cysts. When the physical exam is equivocal, an ultrasound of the testicles can resolve the issue. An ultrasound should always be obtained in a patient with a large or tense hydrocele that precludes palpation of the testis. Ultrasound can also assist in characterizing the lesion. While ultrasound cannot reliably distinguish malignant from benign testicular tumors, cystic tumors are more likely to be benign.

Tumor markers typically utilized in the evaluation and management of adolescent testis tumors include human chorionic gonadotropin (HCG) and alphafetoprotein (AFP). While HCG is elaborated in a significant number of mixed germ cell tumors, this tumor type is vanishingly rare in prepubertal patients. It is therefore not a helpful marker for the prepubertal population. On the other hand, AFP is elevated in 90% of patients with yolk sac tumor and can be very helpful in the preoperative distinction between yolk sac and other tumors (almost all of which are benign in children). One caveat is that AFP is quite high in normal infants. Though AFP levels are highly variable in infants; typical levels range from approximately 50,000 ng/ml in newborns, to 10,000 ng/ml by 2 weeks of age, 300 ng/ml by 2 months, and 12 ng/ml by 6 months of age. Therefore AFP levels among patients with yolk sac tumor and benign tumors overlap in the first 6 months of life making AFP less helpful in distinguishing tumor types in young infants.

The timing of a metastatic evaluation depends on the likelihood that a testis tumor is malignant. Delaying radiographic studies until pathology is available on the primary tumor avoids the unnecessary expense and radiation exposure for patients with benign tumors. However, changes related to orchiectomy, such as reactive lymphadenopathy or retroperitoneal bleeding, may confuse interpretation of post-operative radiographic studies. Since many, if not most prepubertal patients will have a benign tumor, the metastatic evaluation may be deferred until a histological diagnosis of the primary tumor is obtained for these patients. A preoperative metastatic evaluation may be undertaken in patients over 6 months of age with an elevated AFP level, who likely harbor a yolk sac tumor. A pre-operative evaluation is also appropriate in adolescents, particularly if

tumor markers are elevated. Metastases from malignant testis tumors occur primarily in the retroperitoneal lymph nodes and lungs. A chest x-ray or chest computerized tomography scan (CT) and abdominal CT are obtained. For patients with very high tumor markers following chemotherapy or wide-spread pulmonary metastases, MRI of the brain should also be considered. Tumor markers are also followed post-operatively. The half-lives of AFP and beta-HCG are approximately 5 days and 48 h respectively. Failure of tumor markers to decline as expected after removal of the primary tumor is evidence of persistent metastatic disease.

78.4 Surgical Management

The standard initial treatment for a malignant testicular tumor in an adult or adolescent is an inguinal orchiectomy with early control of the vessels. In prepubertal patients, this approach should be applied only to patients greater than 6 months of age with an elevated AFP. In all other prepubertal patients a benign tumor is likely to be present, and the initial surgical management should be an excisional biopsy with frozen section analysis (Fig. 78.1). The exploration

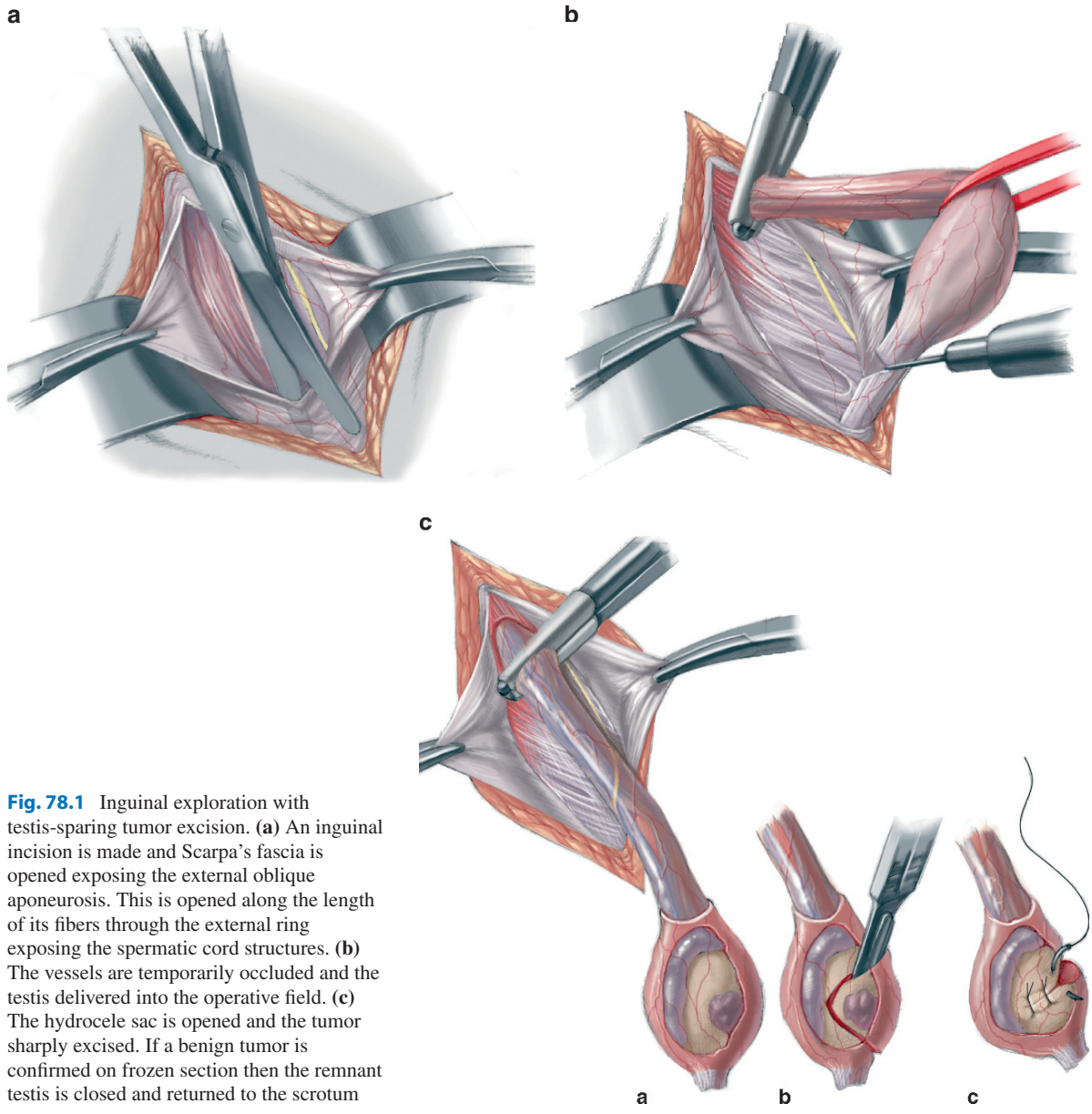

Fig. 78.1 Inguinal exploration with testis-sparing tumor excision. **(a)** An inguinal incision is made and Scarpa's fascia is opened exposing the external oblique aponeurosis. This is opened along the length of its fibers through the external ring exposing the spermatic cord structures. **(b)** The vessels are temporarily occluded and the testis delivered into the operative field. **(c)** The hydrocele sac is opened and the tumor sharply excised. If a benign tumor is confirmed on frozen section then the remnant testis is closed and returned to the scrotum

is accomplished through an inguinal incision with occlusion of the testicular vessels. Failure to follow these guidelines, particularly scrotal violations, may increase the recurrence rate if the tumor proves to be a yolk sac tumor. If the frozen section reveals a likely malignancy, then the entire testis is removed. If a benign histology is confirmed (usually teratoma), the remaining testis is closed with chromic suture and returned to the scrotum. Even large tumors can be enucleated with preservation of significant testicular tissue (Fig. 78.2).

One concern with this approach is the malignant potential of the remnant testicular tissue. In adults, 88% of testicles with teratoma harbor carcinoma in situ (CIS) elsewhere in the testis, and so orchiectomy is still an appropriate management in postpubertal patients. However, CIS is extremely rare in testicles of prepubertal patients harboring a teratoma. Testis-sparing surgery in this population appears to be safe and effective in preserving testicular tissue.

For some patients a retroperitoneal lymph node dissection is undertaken (see later discussion). Historically, this involved removing all lymphatic tissue from a template defined by the renal hila superiorly, the ureters laterally and the iliac bifurcations inferiorly. The classic complication of a standard RPLND is anejaculation due to disruption of the lumbar sympathetic nerves and hypogastric plexus. It was recognized that testis tumors tend to metastasize initially ipsilaterally in the retroperitoneum and so modified templates for right and left-sided tumors were developed which preserved the hypogastric complex and ejaculation (see Fig. 78.3). These modified templates became the standard approach for staging RPLND in stage 1 disease. Patients with positive nodes detected at the time of modified RPLND then underwent conversion to a full bilateral dissection. Recent advances have lead to intraoperative identification and preservation of the lumbar nerve roots. This allows preservation of ejaculation even when a full bilateral dissection is undertaken. Some centers have moved to a full bilateral nerve-sparing approach for all patients, while many still perform a modified template for staging RPLND's in low-risk patients.

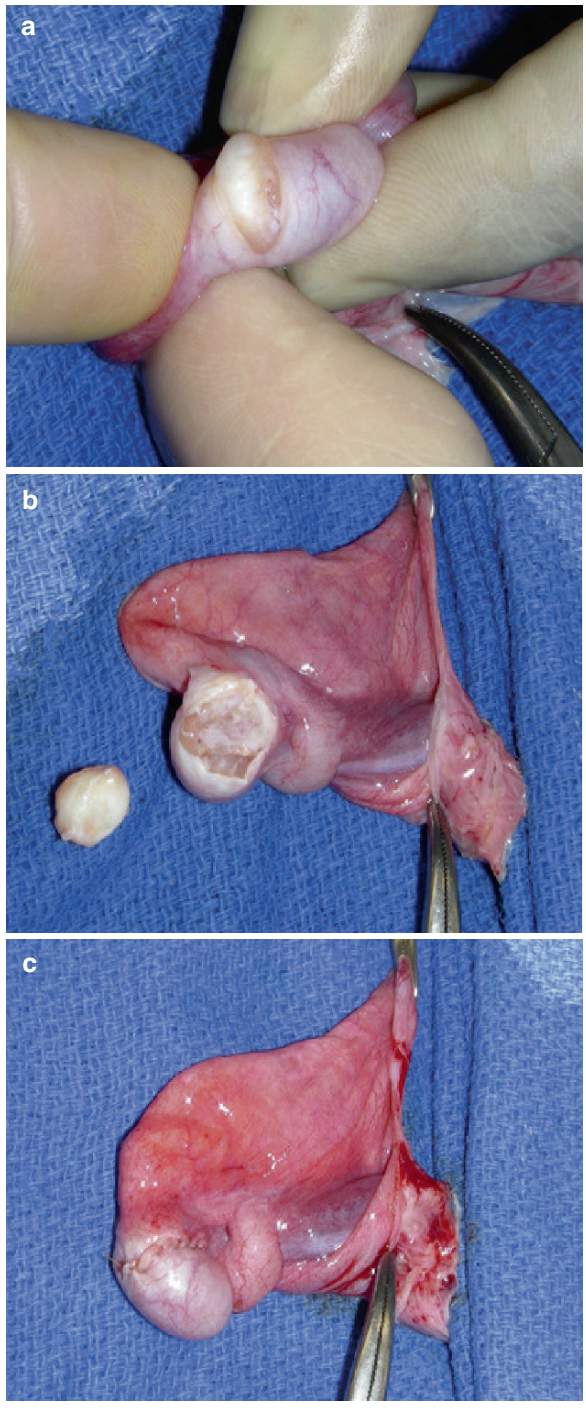

Fig. 78.2 Enucleation of a benign tumor (epidermoid cyst). **a** Through an inguinal approach, with the vessels occluded an incision is made in the testicular tunix exposing the tumor. **b** The tumor is enucleated from the testis. **c** The testis is closed with interrupted chromic suture

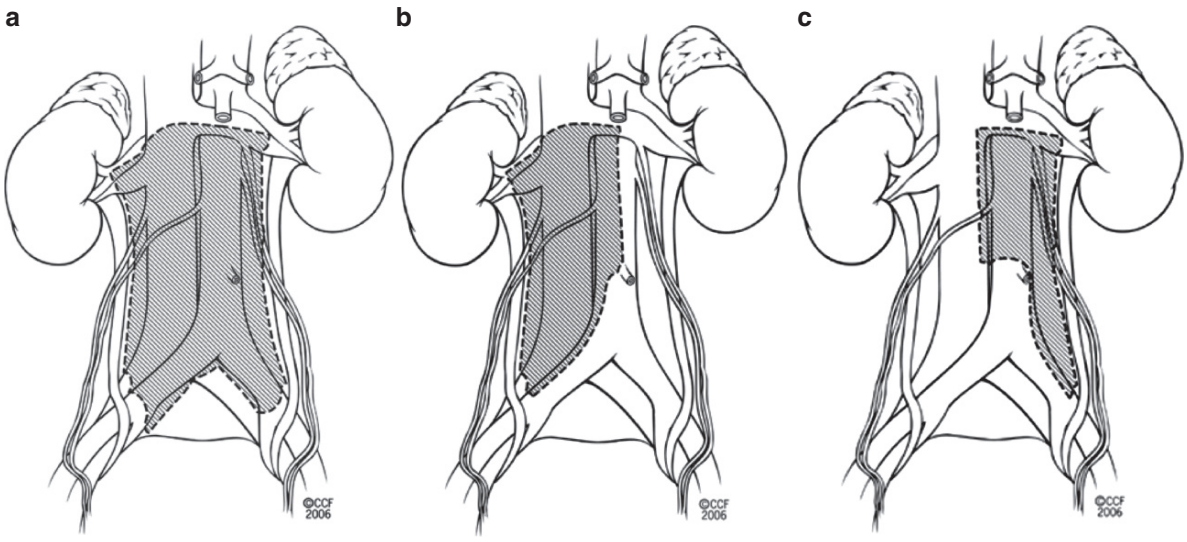

Fig. 78.3 Templates for a retroperitoneal lymph node dissection—**a** Standard bilateral template. **b** Modified template for a right-sided tumor. **c** Modified template for a left-sided tumor

78.5 Adjuvant Therapy for Malignant Adolescent Testicular Tumors

The typical mixed germ cell tumors (MGCT) seen in adults occur only after puberty. There is little data regarding the behavior of mixed germ cell tumors in adolescents, though they appear to exhibit behavior similar to that seen in adults. It is therefore assumed that they should be managed as adults with observation, retroperitoneal lymph node dissection, radiotherapy and/or chemotherapy depending on the specific histology and stage of the disease. This seems a reasonable approach until further studies in adolescents with testicular malignancies are undertaken.

Patients with MGCT limited to the testis and normalization of markers post-operatively may be managed with observation, retroperitoneal lymph node dissection (RPLND) or chemotherapy. The recurrence rate on observation is 25–30%. Recurrence may be prevented with a modified nerve-sparing RPLND or two cycles of platinum-based chemotherapy, but this "over-treats" the 70–75% of patients who do not have occult metastatic disease. On the other hand, when recurrence occurs on observation a longer course of chemotherapy is required and so patients may prefer an RPLND or short course of chemotherapy up front. Generally this dilemma is resolved by stratifying patients based on the local stage and histology of the primary tumor. Patients with low risk disease are usually observed with frequent chest x-rays, tumor marker measurements and abdominal CT scans. Nearly all recurrences occur within 2 years of orchiectomy and are treated with chemotherapy. Patients at higher risk for recurrence (such as those with vascular invasion, largely embryonal cell histology, or those who are poorly compliant with therapy) generally undergo a modified nerve-sparing RPLND. In Europe, some centers offer two courses of chemotherapy as an alternative. If microscopically positive nodes are found at the time of RPLND patients may elect a brief course of chemotherapy, although many with microscopic disease will be cured by the RPLND.

Patients with radiographic evidence of metastatic disease or persistently elevated tumor markers are treated with 3–4 cycles of BEP chemotherapy (bleomycin, etoposide and cis-platinum). RPLND may be considered for patients with very limited retroperitoneal lymph node disease and normalization of tumor markers as 70–80% of these patients are cured with RPLND alone. The relapse rate following chemotherapy for metastatic disease is approximately 15%.

Roughly one third of patients treated with chemotherapy for metastatic disease will have a residual retroperitoneal mass following therapy. These residual masses should be resected. 40–50% will contain only necrotic tissue and fibrosis, but 10–20% will have persistent malignancy and 40–45% will have mature teratoma in the mass.

78.6 Adjuvant Therapy for Prepubertal Malignant Germ Cell Tumors

Virtually all malignant germ cell tumors in children are yolk sac tumors. As with most malignancies, adjuvant therapy for yolk sac tumor is based on tumor stage. 85% of patients present with localized (Stage 1) disease. Recent studies suggest that these patients can be safely managed with observation. Observation should include frequent chest and abdominal imaging and measurement of AFP levels. The recurrence rate on observation is 17% and virtually all patients with recurrence can be salvaged with four courses of platinum-based chemotherapy. The overall survival of all patients receiving chemotherapy for recurrent or metastatic disease is 98%. The potential toxicities of the chemotherapy regimens employed include myelosuppression, ototoxicity and renal toxicity from platinum-based agents and pulmonary toxicity from bleomycin. High-grade ototoxicity is rare when carboplatinum is employed instead of cis-platinum. However, carboplatin is more myelotoxic.

RPLND plays very little role in the management of prepubertal testis tumors. The rationale for this dissection in select adolescent patients is the likelihood of retroperitoneal disease and the ability to avoid the morbidity of chemotherapy in some patients. Several characteristics of prepubertal tumors argue against its use in children. Most prepubertal patients have clinical stage 1 disease and the recurrence rate for these patients with observation alone is only 17%. Nearly all the recurrences can be salvaged with chemotherapy. For those with metastatic disease, it appears that only a minority of prepubertal patients have disease limited to the retroperitoneum. The majority have disease in the chest (with or without retroperitoneal disease). Finally, the morbidity of abdominal surgery is greater for children than for adults. Children have a particularly high rate of post-operative bowel obstruction. It is also unclear that a nerve-sparing approach is technically feasible in small children. For prepubertal testis tumors, RPLND is limited to patients with persistent retroperitoneal masses following chemotherapy—an extremely rare occurrence.

78.7 Teratoma and Epidermoid Cyst

Teratoma is the most common benign tumor in prepubertal patients. The median age of presentation is 13 months, with several patients presenting in the neonatal period. Histologically, teratomas consist of tissues representing the three germinal layers—endoderm, mesoderm and ectoderm. Epidermoid cysts are benign tumors composed entirely of keratin producing epithelium. They are distinguished from dermoid cysts, which contain skin and skin appendages, and from teratomas, which contain derivatives of other germ cell layers. Teratomas and epidermoid cysts are universally benign in prepubertal children. However, a small minority of teratomas in adolescents will behave in a malignant fashion.

For adolescents an inguinal orchiectomy is still the standard management for teratoma. However, in prepubertal patients a more conservative approach is undertaken. At the time of inguinal exploration, an excisional biopsy with frozen section is performed to confirm the diagnosis. In older children with teratoma, surrounding testicular parenchyma must be carefully evaluated. If there is histological evidence of pubertal changes then an orchiectomy should be performed. Biopsies of surrounding testicular parenchyma are probably unnecessary in prepubertal patients.

For all patients with epidermoid cyst and prepubertal patients with teratoma, no radiographic studies or follow-up for the development of metastatic disease are required. Because of the potential for malignancy, post-pubertal patients with teratoma should be evaluated and followed on the same protocol as adults with potentially malignant germ cell tumors.

78.8 Gonadal Stromal Tumors

Stromal tumors include Leydig cell, Sertoli cell, juvenile granulosa and mixed or undifferentiated tumors. Stromal testis tumors are rare in children,

and there are no large series to guide their management. However, anecdotal reports and small series in the literature offer some experience on which to base therapy.

Leydig cell tumors are universally benign in children. They usually present between 5 and 10 years of age with precocious puberty. Congenital adrenal hyperplasia (CAH) can also lead to precocious puberty and testicular masses. Patients with Leydig cell tumors typically have elevated testosterone levels with low or normal gonadotropin levels, whereas patients with CAH will usually have elevated levels of 17-hydroxyprogesterone. Leydig cell tumors may be treated by testis-sparing excision. Persistence of androgenic effects may be due to a contralateral tumor, but this is rare in children. Because Leydig cell tumors are sometimes difficult to detect on physical exam, an ultrasound may be necessary to rule out a contralateral tumor. However, even after successful removal of a solitary tumor, androgenic changes are not completely reversible, and some children may proceed through premature puberty due to activation of the hypothalamic-pituitary-gonadal axis.

Sertoli-cell tumors are rare in children. Sertoli cell tumors are usually hormonally inactive in children, although they may occasionally cause gynecomastia or isosexual precocious puberty. While all reported cases to date have been benign in children under 5 years of age, there have been a few cases of malignant Sertoli cell tumors in older children and adults. Orchiectomy is usually sufficient treatment in infants and young children. A metastatic evaluation should be considered in older children and in patients with worrisome histological findings. When metastatic disease is present, aggressive combination treatment including RPLND, chemotherapy, and radiation therapy should be considered.

The large-cell calcifying Sertoli cell tumor is a clinically and histologically distinct entity with a higher incidence of multifocality and hormonal activity. These tumors are composed of large cells with abundant cytoplasm and varying degrees of calcification ranging from minimal amounts to massive deposits. While standard Sertoli cell tumors are more common in adults, large-cell calcifying Sertoli cell tumors are found predominantly in children and adolescents. Most present with a testicular mass. Approximately 1/4 of patients have bilateral and multifocal tumors. The presence of calcifications results in a characteristic ultrasound appearance including multiple hyperechoic areas.

Approximately one third of patients with large-cell calcifying Sertoli cell tumor have an associated genetic syndrome and/or endocrine abnormality. The two most common associated syndromes are Peutz-Jegher's syndrome and Carney's syndrome. Screening for these syndromes in patients with large cell calcifying Sertoli cell tumors is important since the patients and their first-degree relatives are at risk for the potentially lethal associated anomalies. While occasionally malignant in adults, large-cell calcifying Sertoli cell tumors have been universally benign in patients under 25 years of age and inguinal orchiectomy is sufficient treatment for children.

Juvenile granulosa cell tumor is a stromal tumor bearing a light microscopic resemblance to ovarian juvenile granulosa cell tumor. Granulosa-cell tumors occur almost exclusively in the 1st year of life, most in the first 6 months. Structural abnormalities of the Y chromosome and mosaicism are common in boys with juvenile granulosa cell tumor. Several cases have been described in association with ambiguous genitalia. These tumors are hormonally inactive and benign. Although these children should undergo chromosomal analysis, no treatment or metastatic evaluation is required beyond testis-sparing excision.

78.9 Gonadoblastoma

Gonadoblastomas are benign tumors that typically arise in dysgenetic gonads. They contain both germ cell and stromal elements. Gonadoblastoma arises almost exclusively in the dysgenetic gonads of patients with a Y chromosome or evidence of some Y chromatin in their karyotype. Dysgenetic gonads in patients without Y chromatin, such as patients with Turner's syndrome or XX gonadal dysgenesis, seem to be at little risk. Gonadoblastomas have been reported in 3% of true hermaphrodites, and 10–30% of patients with mixed gonadal dysgenesis or pure gonadal dysgenesis in the presence of Y chromatin. While gonadoblastomas are benign, they are prone to the development of malignant degeneration and overt malignant behavior is seen in 10% of cases. While most cases of malignancy occur after puberty, there have been cases reported in children as well. Therefore, early prophylactic removal of dysgenetic gonads should be performed. If malignant

elements are present, a metastatic evaluation should be undertaken. Dysgerminoma (or seminoma) is the most common malignancy to occur in association with gonadoblastoma. Like their counterpart in normal testicles, these tumors are very radiosensitive, and the outlook for these patients is generally favorable.

78.10 Leukemia

The role of testis biopsy for patients with acute lymphoblastic leukemia (ALL) has decreased markedly with modern chemotherapy. Approximately 20% of ALL patients have microscopic involvement at the time of diagnosis. However, with current chemotherapy, most patients with microscopic testicular involvement achieve a complete remission. Conversely, some patients without histological evidence of testicular involvement at diagnosis will ultimately relapse in the testicles. Therefore, pre-treatment testicular biopsy is not recommended since it does not predict those at risk for persistent or relapsing disease. Modern treatment has reduced the post-treatment relapse rate to less than 1%. Therefore, post-treatment biopsy in the absence of clinical evidence of persistent disease is also unnecessary. Rare patients with persistent or recurrent testicular enlargement following chemotherapy should undergo testicular biopsy to confirm the presence of ALL. In most cases the patient will have relapsed at other sites and further systemic treatment will be required. Typically the testicles are also treated with radiation.

Further Reading

Horwich A, Shipley J, Huddart R (2006) Testicular germ-cell cancer. Lancet 367:754–765

Klein E (2006) Nerve-sparing retroperitoneal lymphadenectomy. In AC Novick, JS Jones (eds) Operative Urology at the Cleveland Clinic. Humana Press, Totowas, NJ, pp 139–148

Ross J (2006) Testicular tumours. In P Puri, ME Höllwarth (eds) Pediatric Surgery, Springer Surgery Atlas Series. Springer-Verlag, Berlin, Heidelberg, New York, pp 477–482

Ross JH, Rybicki L, Kay R (2002) Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: A summary of the Prepubertal Testis Tumor Registry. J Urol 168:1675–1679

Schlatter M, Rescorla F, Giller R et al (2003) Excellent outcome in patients with stage I germ cell tumors of the testes: A study of the Children's Cancer Group/Pediatric Oncology Group. J Pediatr Surg 38:319–324

Thomas JC, Ross JH, Kay R (2001) Stromal testis tumors in children: A report from the prepubertal testis tumor registry. J Urol 166:2338–2340