An Overview of Testicular Germ Cell Tumors

Armita Bahrami, MD; Jae Y. Ro, MD, PhD; Alberto G. Ayala, MD

● ***Context.*—More than 90% of testicular neoplasms originate from germ cells. Testicular germ cell tumors (GCTs) are a heterogeneous group of neoplasms with diverse histopathology and clinical behavior.**

***Objective.*—To help the readers distinguish various subtypes of GCTs, to highlight the clinical manifestations and pathologic features of these tumors, and to review several newly developed immunohistochemical markers for GCTs.**

***Data Sources.*—Review of the pertinent literature and our experience.**

***Conclusions.*—The etiology of GCTs is largely unknown. Cytogenetic studies suggest a different pathogenesis for each group of infantile/prepubertal GCTs, postpubertal GCTs, and spermatocytic seminoma. Unclassified intratubular germ cell neoplasia is the precursor of all GCTs, excluding spermatocytic seminoma and infantile/prepubertal GCTs. Seminoma, the most common GCT in adults, does not occur before 5 years of age. Spermatocytic seminoma, a tumor of elderly men, typically has an indolent clinical behavior, but rarely it undergoes sarcomatous transformation associated with an aggressive behavior. Embryonal carcinoma is the most common component in mixed GCTs. Eighty percent or more of embryonal carcinoma component and vascular invasion are recognized predictors of occult metastasis for clinical stage I mixed GCTs. Most patients with prepubertal yolk sac tumor, the most common pediatric GCT, have stage I disease at presentation. Most choriocarcinomas present with metastatic symptoms because of the propensity for rapid hematogenous dissemination. Teratomas in children regardless of maturity and dermoid cysts in adults are benign; in contrast, teratomas in adults have a malignant behavior. With appropriate therapy, the majority of testicular GCTs are curable.**

(*Arch Pathol Lab Med.* 2007;131:1267–1280)

Testicular tumors are the most common malignancies among American men between the ages of 20 and 39 years.[1,2] The American Cancer Society has estimated that in the year 2006, 8250 men will develop testicular cancers and 370 men will die of these tumors in the United States.[3] Testis tumors comprise approximately 1% of all cancers in men,[3,4] but only about 0.1% of cancer deaths in males[3] because the majority of these tumors are curable.[5]

More than 90% of testicular neoplasms originate from germ cells.[6] The incidence of testicular germ cell tumors (GCTs) increases shortly after the onset of puberty and peaks in the fourth decade of life with a median age of 34 years at diagnosis.[7] The incidence varies among different races and various geographic locations. It is 5 times more frequent in white men compared with African American men.[8] Among nations with the highest reported incidence are Scandinavia, Germany, and New Zealand.[9]

Despite several recognized risk factors in the development of GCTs (eg, cryptorchidism or a prior history of GCT), the pathogenesis of germ cell neoplasms including the contributing role of environmental factors or genetic susceptibility remains unknown. Reports from the epidemiologic studies in the United States and Europe have revealed an increase in the incidence of GCTs during the past several decades,[10,11] but the reason for such a trend is unclear.

Testicular GCTs are a heterogeneous group of neoplasms with diverse histopathology and variable clinical course and prognosis. This diversity is best reflected in various systems offered to classify these tumors.[12–17] Currently the most comprehensive and widely accepted system of classification is the one proposed by the World Health Organization,[18] which is summarized in Table 1.

There is some evidence that the origin and biology of prepubertal and postpubertal testicular GCTs are distinct from each other. First, the distribution pattern of GCTs in adults and children is different. Testicular neoplasms in adult patients often consist of seminoma, embryonal carcinoma, or mixed testicular GCTs. In the pediatric population, yolk sac tumor and teratoma are the most frequent tumors; on the contrary, seminoma and embryonal carcinoma are rare.[19] Non-GCTs, which account for less than 10% of testicular neoplasms in adults, comprise as high as one third of testis tumors in children. Furthermore, although there is a strong association between postpubertal testicular tumors and intratubular germ cell neoplasia, such association has not been observed in prepubertal GCTs.

Genetic studies have shown that postpubertal testis tumors are often aneuploid with a consistent chromosomal abnormality composed of a gain of short arm of chromosome 12, usually in the form of an isochromosome, i(12p).[20] In contrast tumors arising in prepubertal gonads are typically unassociated with 12p amplification and tend to be diploid. For these reasons, testicular GCTs have been

Accepted for publication November 20, 2006.

From the Departments of Pathology, Baylor College of Medicine (Dr Bahrami), and Weill Medical College of Cornell University, The Methodist Hospital (Drs Ro and Ayala), Houston, Tex.

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: Alberto G. Ayala, MD, Department of Pathology, The Methodist Hospital, Weill Medical College of Cornell University, 6565 Fannin St, Houston, TX 77030 (e-mail: aayala@tmh.tmc.edu).

Table 1. 2004 World Health Organization Histologic Classification of Germ Cell Testis Tumors

- Intratubular germ cell neoplasia, unclassified
- Tumors of 1 histologic type (pure forms)
  - Seminoma
    - Seminoma with syncytiotrophoblastic cells
  - Spermatocytic seminoma
    - Spermatocytic seminoma with sarcoma
  - Embryonal carcinoma
  - Yolk sac tumor
  - Trophoblastic tumors
    - Choriocarcinoma
    - Trophoblastic neoplasms other than choriocarcinoma
      - Monophasic choriocarcinoma
      - Placental site trophoblastic tumor
  - Teratoma
    - Dermoid cyst
    - Monodermal teratoma
    - Teratoma with somatic type malignancies
- Tumors of more than 1 histologic type (mixed forms)
  - Mixed embryonal carcinoma and teratoma
  - Mixed teratoma and seminoma
  - Choriocarcinoma and teratoma/embryonal carcinoma
  - Others

also divided into 3 biologically distinct categories of infantile/prepubertal GCTs, postpubertal GCTs, and spermatocytic seminoma. Spermatocytic seminoma is a disease of elderly men and appears to have a different pathogenesis than seminoma.

Germ cell tumors have been traditionally separated into seminomatous and nonseminomatous tumors. This division, however, is essentially for clinical purposes because of some differences in the management approach and prognosis of these 2 groups of tumors.

INTRATUBULAR GERM CELL NEOPLASIA, UNCLASSIFIED

There is convincing evidence that intratubular germ cell neoplasia, unclassified (IGCNU), is the precursor of all invasive GCTs with the exception of spermatocytic seminoma and infantile/prepubertal GCTs.[21,22] Intratubular germ cell neoplasia, unclassified, has been identified in the vicinity of GCTs in about 90% of cases.[23,24] Additionally, there is an increased prevalence of IGCNU in clinical conditions at risk for testicular cancer, including cryptorchidism (2%–4%),[25,26] oligospermic infertility (0–1.1%),[27,28] and contralateral testis of patients with testicular cancer (4.9%–5.4%).[29–31] The prevalence of IGCNU in healthy males, in contrast, is only 0.43%.[32]

The IGCNU cells are both morphologically and immunohistochemically similar to seminoma cells. This observation has led to the hypothesis that seminoma is the direct derivative of IGCNU and a common pathway in the development of all other GCTs.[33] Cytogenetic studies have supported a similar chromosomal constitution in IGCNU cells and the adjacent invasive component, with the major difference being the gain of 12p in the invasive part.[34–36] It is therefore hypothesized that the critical genetic event leading to invasion is acquisition of excess genetic material on the short arm of chromosome 12.

The term *unclassified* implies the presence of an uncommitted undifferentiated cell that is capable of progressing toward an invasive GCT. Furthermore, it is used to distinguish this lesion from other types of intratubular germ cell neoplasia (eg, intratubular embryonal carcinoma or intratubular yolk sac tumor). Intratubular germ cell neoplasia, unclassified, is known to be the precursor of most adult GCTs; on the other hand, other types of intratubular germ cell neoplasia are developed as an outcome of pagetoid intratubular spread of their invasive counterpart in the testicular parenchyma adjacent to a preexisting GCT.

Pathologic Features

Testes with IGCNU are usually normal in size but can be smaller than normal. Histologically, IGCNU is characterized by large primitive atypical cells that are usually twice the size of normal germ cells. These cells lie along the thickened basement membrane of atrophic seminiferous tubules (Figure 1) or may replace the entire tubules. The malignant germ cells have large nuclei with prominent nucleoli and abundant clear cytoplasm that is rich in glycogen, demonstrable by a periodic acid–Schiff (PAS) stain. Because normal germ cells are not stained with PAS, this stain may help to distinguish IGCNU cells from normal cells.

Immunoprofile

Most IGCNU cells stain for placental-like alkaline phosphatase (PLAP)[37–40] usually with a membranous and cytoplasmic pattern. Placental-like alkaline phosphatase is an enzyme that in addition to IGCNU is present in embryonal carcinoma, seminoma, and several other GCTs but is usually absent in normal germ cells. The IGCNU cells are also positive for c-Kit (CD117)[41,42] and p53 but are negative for cytokeratins, human chorionic gonadotropin (hCG), or α-fetoprotein (AFP). OCT3/4, also known as POU5F1, is a recently recognized marker for GCTs.[43] In adult testis, positive immunostaining for OCT3/4 is an indicator for the presence of IGCNU, seminoma, and/or embryonal carcinoma.[44] OCT3/4 immunostain highlights IGCNU with a nuclear staining pattern and has proved to be a sensitive and specific marker for detection of IGCNU in biopsy specimens.[44,45] D2-40, an antibody raised against a transmembrane mucoprotein called podoplanin, stains IGCNU cells[46–48] (Figure 2) as well as lymphatics. Therefore, this antibody can be used to confirm the presence or absence of IGCNU adjacent to invasive GCTs and also to highlight lymphatic invasion.

Clinical Course and Management

Spontaneous regression of IGCNU generally does not occur. Without intervention, about 50% of IGCNU cases will progress to an invasive GCT within 5 years of the diagnosis of IGCNU,[31] but on long-term follow-up almost all patients will develop an invasive GCT.[49]

There is controversy in regard to the management of IGCNU. Orchiectomy clearly provides the highest success rate and perhaps is the therapy of choice in unilateral IGCNU.[49,50] Several studies have shown the effectiveness of localized low-dose radiotherapy as compared with chemotherapy in eradication of IGCNU.[51,52] Radiation therapy has been considered by some authorities as the treatment of choice in bilateral IGCNU. Although radiotherapy leads to permanent infertility, it has the benefit of preserving hormonal function of the testis. Yet others have advocated surveillance on the basis that if an invasive GCT develops, it will be easy to detect and manage with available effective treatments.

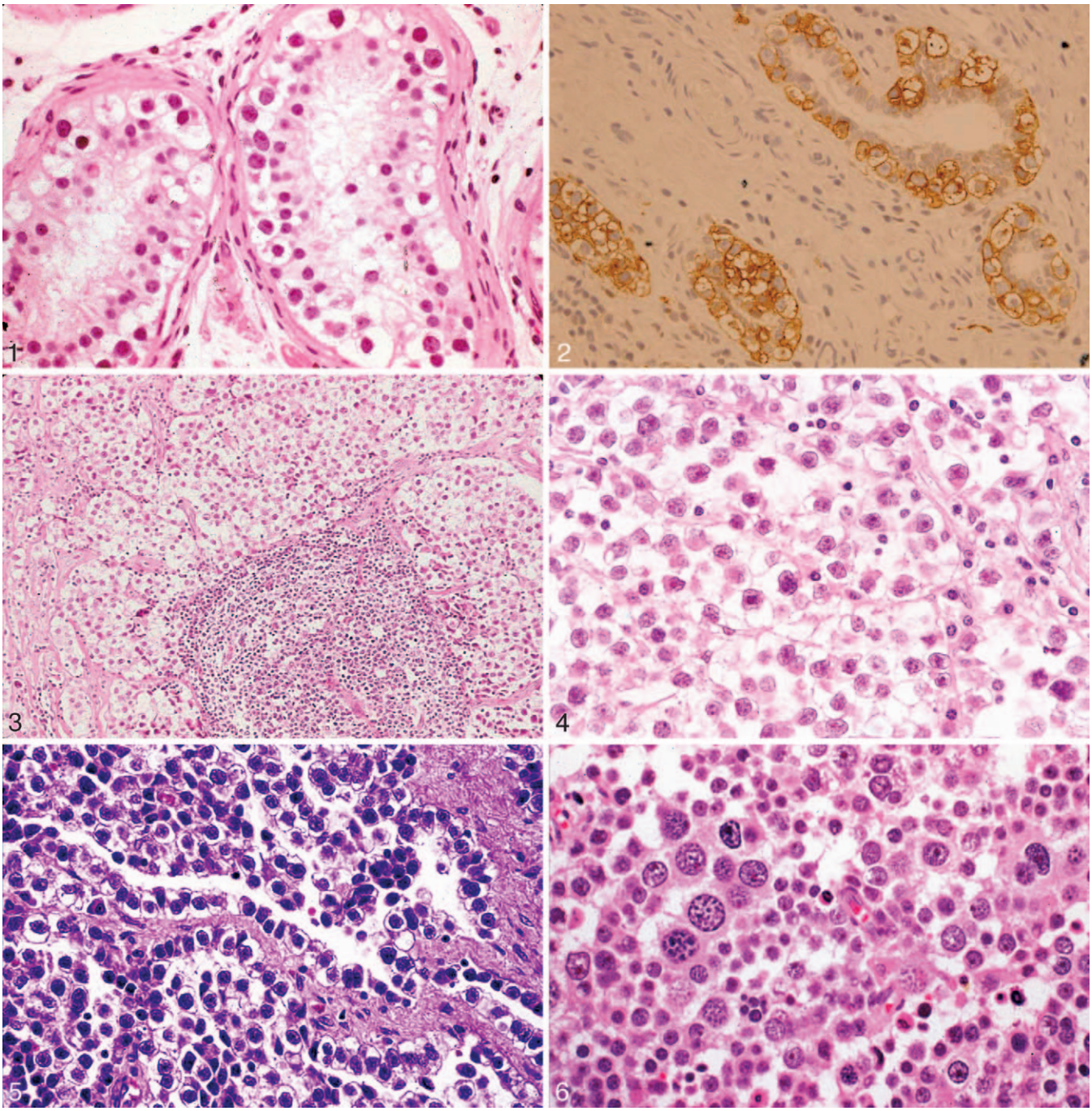

Figure 1. *Intratubular germ cell neoplasia, unclassified, showing large atypical germ cells lying along the basement membrane of atrophic seminiferous tubules (hematoxylin-eosin, original magnification ×400).*

Figure 2. *Intratubular germ cell neoplasia, unclassified, showing strong immunoreactivity for D2-40 with a membranous pattern in atypical intratubular germ cells (immunoperoxidase, original magnification ×200).*

Figure 3. *Seminoma with a nested growth pattern separated by lymphocyte-rich fibrovascular trabeculae (hematoxylin-eosin, original magnification ×100).*

Figure 4. *Seminoma characterized by large uniform evenly dispersed tumor cells displaying clear cytoplasm and distinct cell membrane (hematoxylin-eosin, original magnification ×400).*

Figure 5. *Tubular variant of seminoma composed of hollow tubular structures lined by characteristic seminoma cells with clear cytoplasm and distinct cytoplasmic border (hematoxylin-eosin, original magnification ×200).*

Figure 6. *Spermatocytic seminoma characterized by a diffuse proliferation of polymorphous tumor cells, composed of small (lymphocyte-like), intermediate, and large cells with characteristic spireme-type chromatin pattern (hematoxylin-eosin, original magnification ×400).*

SEMINOMATOUS GCT

There are 2 types of seminomatous tumors: (1) classic seminoma and its variants and (2) spermatocytic seminoma.

Classic Seminoma and Its Variants

Seminoma is the most common testicular germ cell neoplasm, accounting for approximately 50% of these tumors.[53–55] In addition, seminoma is a recognizable component in a large proportion of mixed GCTs.[54]

Clinical Features.—The peak incidence is between 34 to 45 years, which is about 1 decade later than that of most other GCTs.[54] Before puberty, seminoma is extremely rare; in fact, it does not occur in the first decade of life especially in children younger than 5 years. Most patients present with a typically painless testicular enlargement. Gynecomastia and infertility are rare presenting symptoms. A fraction of cases may present with symptoms of metastases.[56] Extension to the spermatic cord or epididymis is seen in less than 10% of patients,[54,56] and in 2% of cases both testes are involved.

Pathologic Features.—Grossly, seminomas are firm when intact, but after sectioning they are soft at palpation with a light tan, moist, homogenous appearance. They may form a single nodule or may be multinodular separated by thick connective tissue septae. Small areas of necrosis or petechial hemorrhage are frequently present, but extensive necrosis, hemorrhage, and cyst formation are uncommon. Gross appearance of seminoma is rather typical and relatively easy to recognize, but similar gross features can be seen in spermatocytic seminoma and testicular lymphoma.

In histologic examination, seminoma cells typically have a solid or nested growth pattern separated by thin fibrovascular trabeculae rich in T-cell lymphocytes (Figure 3). Only 1% of seminomas are devoid of lymphoid infiltration.[57] The individual tumor cells are large, uniform, round to polygonal, and evenly spaced without nuclear overlapping (Figure 4). Seminoma cells display a distinct cell membrane and usually a lightly eosinophilic to clear cytoplasm because of the presence of glycogen, demonstrable by a PAS stain. The nuclei contain 1 or more prominent nucleoli. Mitoses are variable but usually readily identifiable.

Ill-defined granulomatous reactions are frequently seen in seminomas. These reactions at times are so intense that they obscure the seminoma cells.[56] Under these circumstances, the presence of IGCNU in the peritumoral testicular parenchyma is a helpful observation in resolving the diagnostic difficulty. Such reactions, however, more commonly occur in metastatic than in primary locations. In such cases, immunohistochemical staining may contribute to the identification of the nature of lesion.

Histologic Variants of Seminoma.—Seminoma with syncytiotrophoblastic giant cells is a recognized variant of seminoma by the World Health Organization classification system.[18] Syncytiotrophoblasts, which stain positively for hCG and cytokeratin, are seen in approximately 20% of seminomas.[58,59] The presence of these cells does not impart an adverse prognosis[60] but does correlate with mild elevation of serum hCG, which is generally normalized after orchiectomy. A persistent elevation of serum hCG level following orchiectomy or a high level of serum hCG, in contrast, may indicate a hidden focus of choriocarcinoma.

There are a variety of histologic variants of seminoma characterized by different growth patterns. These histologic profiles, including cribriform/microcystic,[61] tubular,[62–65] and intertubular,[66] may mimic other pathologic entities[67] and create diagnostic confusion. When cribriform/microcystic pattern is the dominant picture, seminoma may superficially resemble yolk sac tumor. The tubular variant (Figure 5) can simulate Sertoli cell tumor. The intertubular variant exhibits a diffuse intertubular growth of seminoma cells similar to the pattern of testicular involvement by hematopoietic neoplasms. Despite these variable growth patterns, seminoma cells retain their cytologic features; therefore, the key to the differential diagnosis is attention to cytologic details of tumors cells. In questionable circumstances, immunohistochemical staining can help to make an accurate diagnosis.

On rare occasions, seminomas may be entirely infarcted and seen as a mass of ''ghost'' cells suspicious for neoplasm. Florentine et al[68] reported a case of necrotic seminoma in which a Masson trichrome stain plus PLAP immunostain improved the histology and helped to establish the diagnosis. The authors concluded that, in the presence of architectural distortion in a tumor suspicious for seminoma, selected immunostains might aid in arriving at the right diagnosis.

Seminoma with high mitotic rate, also known as anaplastic or atypical seminoma, constitutes 5% to 15% of seminomas.[69,70] Histologically, it is characterized by increased mitotic activity (3 or more mitoses per 1 high-power field),[69] a greater nuclear pleomorphism, and a paucity of the lymphocytic infiltrate. The prognostic significant of this entity, however, is controversial. Although some studies reported a more aggressive behavior and a lower survival rate in anaplastic seminomas compared with classic seminomas,[69,71] several other studies failed to demonstrate such differences when the 2 groups were compared stage by stage.[72–74] One possible explanation is the confounding effect of a higher stage at clinical presentation in anaplastic seminoma compared with classic seminoma.

Immunoprofile.—Immunohistochemically, seminomas are positive for PLAP[75] and c-Kit (CD117)[76,77] but are negative for epithelial membrane antigen, Ki-1 (CD30),[78] AFP, and hCG.[79] The transcription factor OCT3/4 is a robust diagnostic marker for seminoma as well as for embryonal carcinoma.[80] OCT3/4 has been shown to be a highly sensitive and specific marker for the diagnosis of both tumors in metastatic sites as well.[81] Recent studies have reported that podoplanin, recognized by the commercially available D2-40 monoclonal antibody,[47,48] is a specific marker for seminoma because unlike OCT3/4, it is not expressed by embryonal carcinoma. Cytokeratin is usually negative but may be focally positive in up to 40% of seminomas.[82]

Treatment of Seminomatous Tumors

Because the management of seminoma and other GCTs following radical inguinal orchiectomy largely depends on the stage of the lesions, before discussion on the management, we shortly review the staging system of testis tumors.

Staging of Testicular Tumors

In 1997, an internationally agreed-on prognostic factor–based staging classification, applicable to both seminoma and nonseminomatous tumors, was published.[83] This well-

Table 2. TNM System in Testis Tumors*

	Primary Tumor (pT)
pTx	Primary tumor cannot be assessed
pT0	No evidence of tumor (eg, scar)
pTis	IGCNU
pT1	Limited to testis and epididymis No vascular/lymphatic invasion, may invade tunica albuginea but not tunica vaginalis
pT2	pT1 with vascular/lymphatic or tunica vaginalis invasion
pT3	Invades spermatic cord with or without vascular/lymphatic invasion
pT4	Invades scrotum with or without vascular/lymphatic invasion
	Regional Lymph Nodes (pN)
pNx	Regional lymph nodes cannot be assessed
pN0	No lymph node metastasis
pN1	Metastasis to ≤5 lymph nodes, none > 2 cm; or lymph node mass ≤ 2 cm
pN2	Metastasis to >5 lymph nodes, none > 5 cm; or lymph node mass >2 cm but ≤5 cm; or extranodal extension
pN3	Lymph node mass > 5 cm
	Distant Metastasis (M)
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional nodal and lungs
	Serum Tumor Markers (S)
Sx	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 × N† AND hCG < 5000‡ AND AFP < 1000§
S2	LDH 1.5–10 × N OR hCG 5000–50 000‡ OR AFP 1000–10 000§
S3	LDH > 10 × N OR hCG > 50 000‡ OR AFP > 10 000§

* TNM indicates tumor-node-metastasis; IGCNU, intratubular germ cell neoplasia, unclassified; LDH, lactate dehydrogenase; hCG, human chorionic gonadotropin; and AFP, α-fetoprotein.

† N, the upper limit of normal for the LDH assay.

‡ hCG unit: mIU/mL.

§ AFP unit: ng/mL.

Table 3. Stage Grouping of Testis Tumors*

Stage	pT	N	M	S
0	pTis	N0	M0	S0
I	pT1–4	N0	M0	Sx
IA	pT1	N0	M0	S0
IB	pT2–4	N0	M0	S0
IS	Any pT/Tx	N0	M0	S1–3
II	Any pT/Tx	N1–3	M0	Sx
IIA	Any pT/Tx	N1	M0	S0–1
IIB	Any pT/Tx	N2	M0	S0–1
IIC	Any pT/Tx	N3	M0	S0–1
III	Any pT/Tx	Any N	M1	Sx
IIIA	Any pT/Tx	Any N	M1a	S0–1
IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1a	S2
IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

* pT indicates primary tumor; N, nodes; M, metastasis; and S, serum tumor markers.

validated classification has now been incorporated into the tumor-node-metastasis (TNM) (Table 2) and the American Joint Committee on Cancer staging systems (Table 3).[84] Staging of testis tumors considers the TNM system of classification plus levels of prognostically important tumor-specific serum markers including hCG, AFP, and lactate dehydrogenase. Serum levels of the liver enzyme lactate dehydrogenase reflect tumor turnover.

In summary, stage I is a localized disease in which the tumor is limited to the testis and paratesticular tissues; stage II is defined by the involvement of regional (retroperitoneal) lymph nodes, which is further divided into 2 major groups of nonbulky or low-volume (lymph node mass ≤ 5 cm) and bulky or high-volume (lymph node mass > 5 cm) disease; stage III includes metastasis to nonregional lymph nodes or disseminated disease. Although pathologic staging based on the TNM system is largely applicable to localized disease, and to retroperitoneal lymph node dissections, it really cannot be applied to nonsurgical metastatic disease. Metastatic disease in patients with seminoma is usually assessed radiographically in terms of computed tomography/magnetic resonance imaging size of the metastatic lymph nodes in the retroperitoneum. Thus, the decision to give radiation or chemotherapy is made according to the clinical staging based on the radiographic findings.

Management of Seminomatous Tumors.—Following radical inguinal orchiectomy, the traditional treatment of classic seminoma with clinical stage I (localized disease) is low-dose radiation to the regional lymph nodes that achieves a cure rate of more than 90%.[9] Other management options available to patients with stage I seminoma include surveillance and adjuvant chemotherapy. However, with surveillance alone, 15% to 20% of such cases may relapse.[85] In a pooled analysis of 638 patients with stage I seminoma from 4 large surveillance studies, the primary tumor size (cutoff of 4 cm) and the rete testis invasion were 2 important prognostic factors for relapse.[86] A nationwide Danish surveillance study for stage I testicular seminoma similarly showed the tumor size as a significant independent prognostic factor for relapse. In that series, the 4-year survival rates were 94%, 82%, and 64% for tumors measuring less than 3 cm, 3 to 6 cm, and more than 6 cm, respectively.[87] Chemotherapy is the treatment of choice for patients with bulky retroperitoneal involvement and all stage III cases, which results in a complete response rate of approximately 90% in these patients.[88,89]

Spermatocytic Seminoma

Spermatocytic seminoma is an uncommon germ cell neoplasm that accounts for 1% to 2% of all testis tumors.[90] Spermatocytic seminoma exclusively develops in the testis and has no ovarian or extragonadal counterpart.[56] Classic seminoma and spermatocytic seminoma are believed to have a different pathogenesis and separate cell of origin. The cell origin of spermatocytic seminoma appears to be more differentiated than that of seminoma and capable of spermatogenesis.[91] Cytogenetic studies have shown that spermatocytic seminoma is either diploid or aneuploid with loss of chromosome 9 rather than isochromosome 12p, which is seen in other postpubertal GCTs.[92]

Clinical Features.—Spermatocytic seminoma typically occurs in men older than 50 years of age (median, 55 years), although it may be occasionally seen in younger patients.[93] This tumor classically presents as a painlessly

enlarging testicular mass. Although most textbooks have reported the incidence of bilaterality in spermatocytic seminoma to be as high as 10%,[90] compared with only 1.6% in all other GCTs,[94,95] our personal experience has shown a more or less similar frequency to that of other GCTs including classic seminoma. Spermatocytic seminoma is not associated with cryptorchidism, IGCNU, or other germ cell neoplasia[90,96]; therefore, it is not seen as a component in mixed GCTs.

Spermatocytic seminoma often has an indolent natural history. The risk of metastasis is extremely rare.[96,97] However, in a small fraction of cases (approximately 6%), the tumor may undergo sarcomatous dedifferentiation, which is associated with an aggressive behavior.[98–101] Of significance, in cases with sarcomatous dedifferentiation and distant metastasis, the metastases were exclusive to the sarcomatous components.[100]

Pathologic Features.—Grossly, spermatocytic seminomas are well circumscribed, yellow-gray, soft, gelatinous, and sometimes mucoid. The gross appearance may be similar to that of classic seminoma or testicular lymphoma.[102] Foci of cystic change, hemorrhage, and necrosis may be evident. In cases with sarcomatous transformation, the tumor may appear dull gray, fleshy, and more solid.[56]

Histologically, spermatocytic seminoma consists of a diffuse proliferation of polymorphic cells supported by a scanty or edematous stroma. The tumor cells are classically of 3 types (Figure 6): small (lymphocyte-like), intermediate (10–30 μm), and large or giant (50–100 μm), which are usually uninucleated but rarely multinucleated. Intermediate cells are often the predominant cell type and comprise the bulk of the tumor. The nuclei of large and intermediate cells often display a typical spiral deposition of chromatin similar to that seen in spermatocytes. The nuclei of small cells are rather dense. The cytoplasm of tumor cells is eosinophilic to amphophilic and does not contain glycogen. A high mitotic activity is often appreciated. Intratubular spread of spermatocytic seminoma in the adjacent seminiferous tubules may be present.

The sarcomatous component of spermatocytic seminoma is usually composed of undifferentiated spindle cells, but differentiated patterns such as rhabdomyosarcoma and chondrosarcoma have also been reported.[98–101] An ''anaplastic'' variant of spermatocytic seminoma, characterized by a predominance of anaplastic cells with prominent nucleoli, extensive necrosis, and vascular or tunical invasion without sarcomatous elements, has been described in a small series.[103] In all cases, foci of classic spermatocytic seminoma within the tumor were present. Although the clinical course of patients in that series was indolent and essentially similar to that of typical spermatocytic seminoma, the prognostic significance of this variant needs to be determined in larger series with long-term follow-up.

Immunoprofile.—Many of the markers including OCT3/4 and PLAP, which are demonstrated in other types of GCTs, have not been detected in spermatocytic seminoma.[84,104–106] Spermatocytic seminoma cells do not react with hCG, AFP, leukocyte common antigen,[104] or CD30. However, consistent expression of c-Kit[106] and germ cell marker VASA[107] as well as focal cytoplasmic staining for CAM 5.2 in some cases have been described.[105]

Differential Diagnosis.—The differential diagnoses of spermatocytic seminoma mainly include classic seminoma and malignant lymphoma. The presence of lymphocyte-rich fibrovascular trabeculae, granulomas, and the uniformity of a single-cell population distinguish classic seminoma from spermatocytic seminoma. Large cell lymphoma, the most common testicular malignancy in the same age group, is characterized by an interstitial growth pattern. Cytologically, lymphoma cells displays a fine nuclear chromatin pattern as compared with the typical spiremelike chromatin distribution of spermatocytic seminoma.[102] In difficult cases, immunohistochemical staining for lymphoid markers can aid to differentiate the 2 entities.

Clinical Course and Management.—The prognosis of spermatocytic seminoma is remarkably good with a very low tendency for metastasis. Although low-dose radiation to the abdomen following orchiectomy has been traditionally the treatment of choice, surveillance is currently becoming the preferred management option by most authorities.[93,108] Spermatocytic seminoma with sarcomatous transformation necessitates aggressive treatment with chemotherapy although the prognosis remains very poor despite chemotherapy.[98,100]

NONSEMINOMATOUS GCT

Nonseminomatous GCTs are composed of embryonal carcinoma, yolk sac tumor, immature or mature teratoma, choriocarcinoma, and other rare trophoblastic tumors. These tumor types are often seen together in various combinations, referred to as mixed GCTs, which may also include seminoma. The words nonseminomatous and mixed GCTs are usually used interchangeably in daily clinical practice.

Embryonal Carcinoma

Pure embryonal carcinoma, although relatively uncommon, is the second most common single-cell–type GCT after seminoma. Embryonal carcinoma as a component, however, is present in more than 80% of mixed GCTs.[54,109]

Clinical Features.—Pure embryonal carcinoma occurs most frequently between 25 and 35 years of age, which is 10 years earlier than the age range for seminoma. Embryonal carcinoma is rare after the age of 50 years and does not occur in infancy. Most patients present with a painless unilateral enlarging testicular mass. Approximately two thirds of cases have retroperitoneal lymph node or distant metastases at the time of diagnosis.[110]

Pathologic Features.—Grossly, embryonal carcinoma often presents as a poorly demarcated mass with a soft gray-tan cut surface, frequently associated with large foci of hemorrhage and necrosis.[56] Extension into the cord and epididymis is not uncommon.

On microscopic examination, embryonal carcinoma displays variable growth patterns, including solid, syncytial, acinar, tubular, or papillary arrangement (Figure 7, A).[56] Marked anaplasia, numerous mitoses including abnormal forms, and cellular overlapping characterize this tumor (Figure 7, B). The neoplastic cells are polygonal, undifferentiated, and epithelial looking with large vesicular and empty-looking nuclei and thick, distinct nuclear membrane. The cytoplasm is usually abundant and finely granular with a nondistinct cell border.

Intratubular germ cell neoplasia, unclassified, and less commonly intratubular embryonal carcinoma,[111] may be seen in the adjacent testicular parenchyma. Vascular/lymphatic invasion in the peritumoral tissue is an important feature to document. True vascular/lymphatic invasion, however, should be distinguished from the artifactual in-

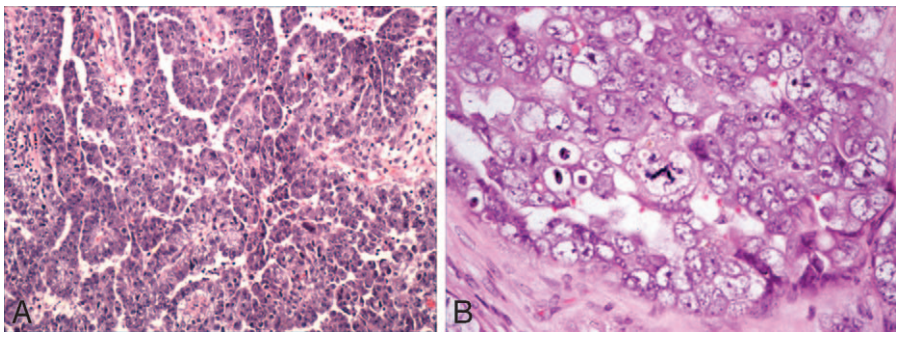

Figure 7. *A, Embryonal carcinoma displaying a papillary pattern of growth (hematoxylin-eosin, original magnification ×100). B, Embryonal carcinoma cells characterized by marked anaplasia and abnormal mitotic figures (hematoxylin-eosin, original magnification ×400).*

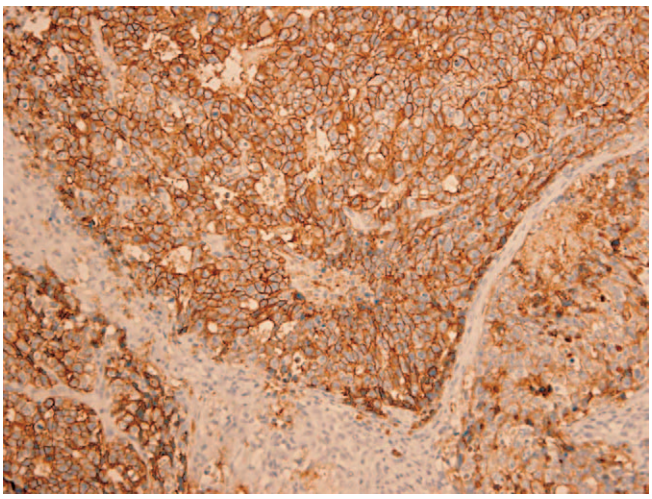

Figure 8. *Embryonal carcinoma showing strong membranous immunoreactivity for CD30 (immunoperoxidase, original magnification ×200).*

travascular implants, which easily happen during tissue sectioning because of the cellular and friable nature of the tumor.

Immunoprofile.—Embryonal carcinomas are commonly positive for cytokeratin[112,113] but negative for epithelial membrane antigen, which can help distinguish a metastatic embryonal carcinoma from a somatic carcinoma. Placental-like alkaline phosphatase[40,113] and OCT3/4[80] are both sensitive markers for embryonal carcinoma but do not discriminate against seminoma. D2-40, which stains seminoma, in contrast, does not label embryonal carcinoma.[47,48] Ki-1 (CD30), which is also a sensitive marker for embryonal carcinoma[40,78] (Figure 8), stains no other GCTs including seminoma or yolk sac tumor. CD30 expression, however, is frequently lost in metastatic embryonal carcinoma after chemotherapy.[111] The embryonal carcinoma cells are usually negative for carcinoembryonic antigen, hCG, and CD117 (c-Kit).[76] When distinction of seminoma from the solid pattern of embryonal carcinoma is a diagnostic consideration, a cytokeratin cocktail, CD30, D2-40, and CD117 immunostaining used in combination may help the differential diagnosis.[76] Although AFP may occasionally stain scattered tumor cells,[59,113] the presence of AFP, either immunohistochemically or in the serum, is generally regarded as an evidence of yolk sac differentiation.

Yolk Sac Tumor

Yolk sac tumor is a germ cell neoplasm that differentiates in the direction of the embryonic yolk sac, allantois, and extraembryonic mesenchyme. It is the most common testicular neoplasm in the pediatric population, accounting for approximately half of the prepubertal testis tumors.[19,114,115] Childhood yolk sac tumor does not appear to be associated with cryptorchidism[56] or IGCNU. Yolk sac tumor in children is almost always seen in the pure form. On the contrary, in adults it is seen only admixed with other neoplastic germ cell elements, and the pure form is extremely rare.[116] Foci of yolk sac tumor are found in 40% of mixed GCTs in adults.

Clinical Features.—In children, the median age at presentation is 16 months (range, newborn to 11 years). Patients usually present with a rapid painless testicular enlargement. About 80% of pediatric yolk sac tumor present with stage I disease.[115]

Elevated serum AFP, which is seen in 95% to 100% of patients with testis tumors containing yolk sac elements, is a useful indicator for the presence of this tumor.[117] In addition, serial measurement of serum AFP provides a mean for monitoring therapy and for early detection of metastases and recurrences.[117] However, caution should be exercised in interpretation of AFP values in children younger than 6 months in whom serum AFP may be physiologically elevated.[115,118]

Pathologic Features.—On gross examination, yolk sac tumor presents as a solid, lobulated, gray-white, soft ill-defined mass with a gelatinous to mucinous cut surface. Hemorrhage, necrosis, and cystic change may be present.[56]

Microscopically, the key to the recognition of yolk sac tumor is the presence of a spectrum of histologic patterns, including reticular (microcystic, vacuolated, honeycomb), macrocystic, endodermal sinus (perivascular, festoon), papillary, solid, glandular-alveolar, myxoid, sarcomatoid (spindle cell), hepatoid, and parietal patterns.[56,119] Several of these histologic appearances are usually admixed in a tumor. The reticular-microcystic pattern is the most common feature, occurring in 80% of patients (Figure 9, A).[56] The anastomosing thin cords and irregular loose spaces are lined by deceptively benign-appearing flat or cuboidal tumor cells. The cytoplasmic vacuoles within the tumor cells form a meshwork of vacuolated lipoblast-like cells imparting a honeycomb appearance.

The most distinctive histologic feature is the one forming Schiller-Duval bodies in which a central fibrovascular core is surrounded by malignant cuboidal to columnar cells (Figure 9, B). Another helpful histologic finding is the presence of round, homogeneous diastase-resistant PAS-positive hyaline globules (Figure 10), which contain AFP or α_1-antitrypsin. These globules are seen in 85% of cases and represent visceral yolk sac differentiation. Parietal yolk sac differentiation in contrast is characterized by

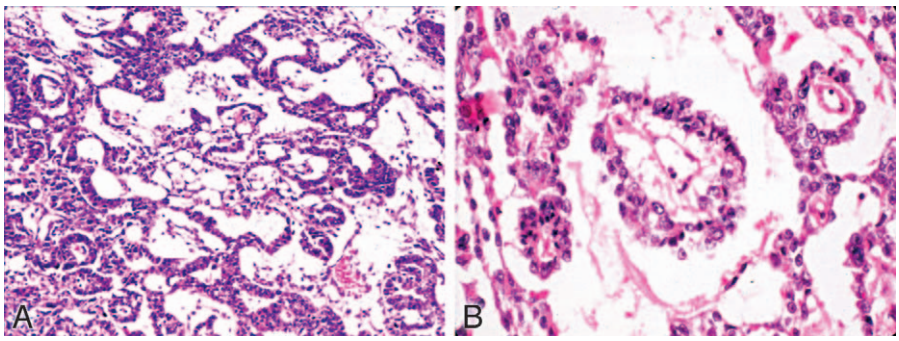

Figure 9. *A, Yolk sac tumor with a reticular, microcystic pattern characterized by thin anastomosing cords and loose spaces (hematoxylin-eosin, original magnification ×100). B, Yolk sac tumor showing classic Schiller-Duval bodies with a central fibrovascular core surrounded by malignant cuboidal to columnar cells (hematoxylin-eosin, original magnification ×400).*

the presence of irregular thick linear eosinophilic basement membrane deposits that are PAS positive but usually negative with AFP.[56,120]

Rarely, yolk sac tumors may be entirely composed of 1 single histologic pattern. These histologic variants at times may cause diagnostic challenges; for example, a solid yolk sac tumor can be confused with seminoma or embryonal carcinoma. Immunohistochemical staining in such cases can help to make an accurate diagnosis.

Immunoprofile.—Most yolk sac tumors are positive for AFP, but staining is variable and often patchy.[38,59,121] Therefore, a negative staining for AFP does not completely exclude a diagnosis of yolk sac tumor. In addition in rare circumstances, a viable yolk sac tumor in the metastatic site may lose its staining for AFP even though the primary tumor is positive for it.[122] Staining for cytokeratin, in contrast, is usually diffuse and intensely positive.[59,121] Yolk sac tumors are often positive for PLAP and α_1-antitrypsin[59] but negative for Ki-1,[78] hCG, and OCT3/4.[45] In a recent report, Glypican 3, a membrane-bound heparin sulfate proteoglycan, has been found to be a very sensitive and relatively specific marker for yolk sac tumor and choriocarcinoma against seminoma, embryonal carcinoma, and teratoma.[123]

Treatment.—For stage I pediatric patients, the management includes orchiectomy followed by close observation.[114,115] Metastatic yolk sac tumor or recurrence should be treated with adjuvant chemotherapy. In children with yolk sac tumor, there is evidence of a predilection for hematogenous spread without lymph node involvement.[124] Because only a minority of metastatic prepubertal yolk sac tumors have metastases limited to the retroperitoneum,[115] retroperitoneal lymph node dissection is usually reserved for patients with recurrent retroperitoneal masses following chemotherapy.[124] Overall, the survival of children with yolk sac tumor is excellent.[115] Treatment in adult cases, which is similar to that of other nonseminomatous GCTs, is discussed in the management section.

Choriocarcinoma

Pure choriocarcinoma is extremely rare and accounts for less than 1% of testicular tumors.[55,56] However as a component, choriocarcinoma is seen in approximately 8% of mixed GCTs.[54]

Clinical Features.—Patients with choriocarcinoma are typically in the second or third decades of life. Most cases present with metastatic symptoms, including hemoptysis, gastrointestinal bleeding, or neurologic symptoms rather than a testicular mass. The testis itself usually appears normal or even small because of the regression of the primary site, although depending on the extent of hemorrhage, sometimes it may appear enlarged.[56]

Choriocarcinoma is associated with very high values of hCG (>100 000 mIU/mL). Because of cross reactivity of hCG with luteinizing and thyroid-stimulating hormones, some patients may present with symptoms related to endocrine abnormalities, including gynecomastia and hyperthyroidism, respectively.[56]

Pathologic Features.—On gross examination, choriocarcinoma appears as a hemorrhagic nodule, which is often surrounded by a rim of gray-white tissue at the periphery. Occasionally, the tumor is totally burnt out and only a fibrous scar is discernible.[125]

Microscopically, choriocarcinoma is composed of an admixture of 2 cell components, syncytiotrophoblasts and cytotrophoblasts. The individual syncytiotrophoblasts are multinucleated with dark eosinophilic cytoplasm and multiple irregular large hyperchromatic nuclei. The cytotrophoblasts are uniform, medium-sized polygonal cells with abundant cytoplasm, single nuclei, and distinct cytoplasmic border. These cells are usually randomly arranged in solid nests or sheets within a background of hemorrhagic necrosis. In more differentiated areas, syncytiotrophoblasts classically cap or wrap clusters of cytotrophoblasts in a villouslike arrangement (Figure 11).

Monophasic choriocarcinoma is a variant of choriocarcinoma with a monomorphic appearance mainly composed of cytotrophoblasts with inconspicuous syncytiotrophoblastic cells.[126] Because cytotrophoblasts without combination with syncytiotrophoblasts are histologically nondescript, a monophasic choriocarcinoma may resemble seminoma, embryonal carcinoma, or the solid variant of yolk sac tumor.

The testicular counterpart of placental site trophoblastic tumor has been described in only a few cases.[126,127] These tumors were predominantly composed of a proliferation of intermediate trophoblast. The neoplastic cells showed diffuse immunoreactivity for human placental lactogen and patchy staining for hCG.

Cystic trophoblastic tumors are uncommon lesions described in retroperitoneal resections after chemotherapy in patients with GCTs.[128] These lesions consist of circumscribed small cysts lined by a predominance of mononucleated trophoblastic cells with smudged nuclei and infrequent mitotic figures. These lesions appear to have little aggressive potential, and their presence in postchemotherapy resections does not warrant additional treatment.

Of note, scattered syncytiotrophoblasts, which may be seen in about 20% of pure seminomas, should not be misinterpreted as foci of choriocarcinoma. The combination of

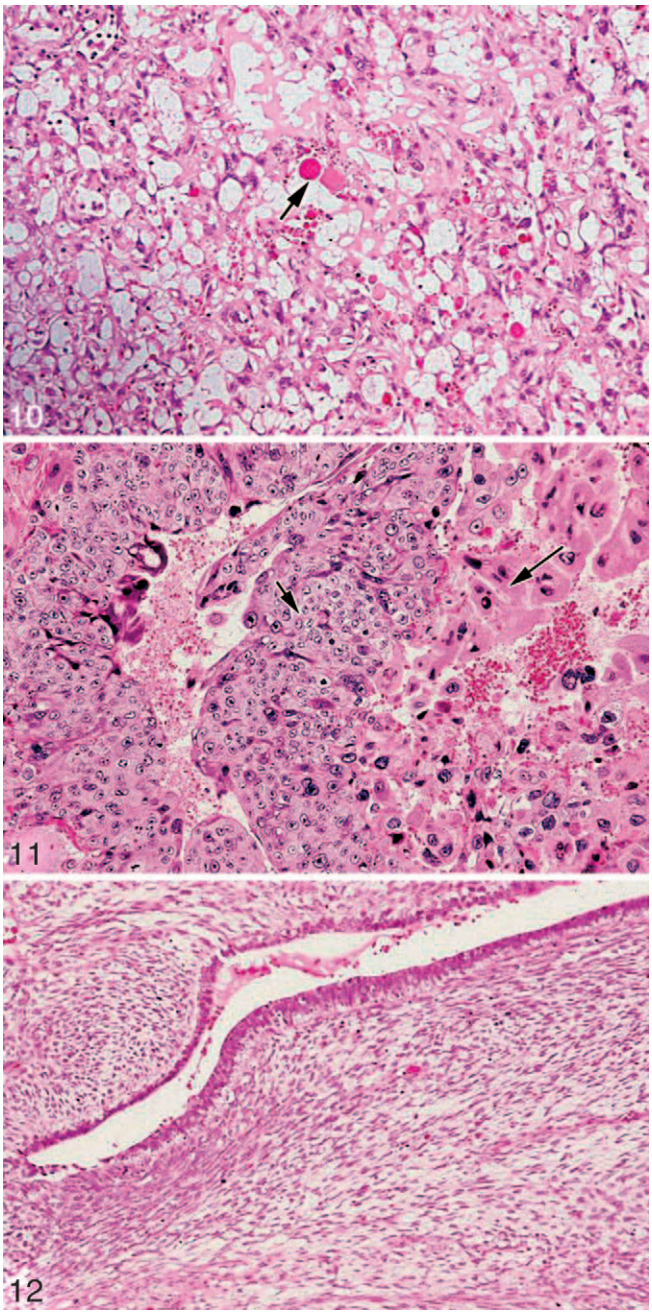

Figure 10. *Characteristic round, homogeneous eosinophilic hyaline globules (arrow) in a reticular background of yolk sac tumor (hematoxylin-eosin, original magnification ×200).*

Figure 11. *Choriocarcinoma showing an admixture of syncytiotrophoblasts with multiple nuclei and eosinophilic cytoplasm (long arrow) wrapping around a cluster of cytotrophoblasts (short arrow) (hematoxylin-eosin, original magnification ×200).*

Figure 12. *Immature teratoma composed of an epithelial component surrounded by immature cellular spindle cell stroma (hematoxylin-eosin, original magnification ×200).*

seminoma with choriocarcinoma is extremely rare in our experience. In addition, we have not seen cases of seminoma with choriocarcinoma without other GCT components.

Immunoprofile.—Immunostaining for hCG is constantly positive in syncytiotrophoblasts and also in transitional cells between syncytiotrophoblasts and cytotrophoblasts (intermediate trophoblasts), but it is usually negative in cytotrophoblasts.[79] Inhibin[129] stains cytotrophoblasts and intermediate trophoblasts. Intermediate trophoblasts, if present, may also stain for human placental lactogen and human leukocyte antigen G, a nonclassical MHC class I antigen.[130] Cytokeratin is positive in all of the cell types.[131] Vimentin is negative, but carcinoembryonic antigen may be positive in syncytiotrophoblasts.[132] The PLAP immunostain is positive in 50% of choriocarcinomas.[59] Glypican 3 has been recently demonstrated to be expressed in choriocarcinoma, with stronger immunoreactivity in syncytiotrophoblasts compared with cytotrophoblasts.[123]

Prognosis.—Because of its predilection for rapid hematogenous dissemination, choriocarcinoma has a worse prognosis than other types of GCT.[133] In fact, the prognosis of a pure choriocarcinoma is worse than a ''mixed GCT with choriocarcinomatous component.''[14] There is a high incidence of brain metastasis because of the propensity for angioinvasion.[134] Choriocarcinoma also commonly involves the retroperitoneal lymph nodes. Both higher values of hCG and greater proportion of choriocarcinoma elements in a GCT are indicative of a more adverse outcome. The management does not differ from the management of any other histologic types of nonseminomatous GCT.

Teratoma

Teratomas are tumors composed of variable types of tissue representing 1 or more of the germinal layers of endoderm, mesoderm, and ectoderm. A tumor composed of only 1 of the 3 germ layers is defined as monodermal teratoma. Mature teratomas are composed of entirely mature well-differentiated components. In contrast, immature teratomas contain embryonic or fetallike tissues, which are typically accompanied by mature elements.

Teratoma occurs in both children and adults, but the biologic behavior of the tumor is substantially different between the 2 groups. In adults, teratoma as a pure neoplasm is uncommon (only 2%–3% of all GCTs); however, as a component, it is present in almost 50% of mixed GCTs.[135] In contrast in children, almost all teratomas are pure neoplasms. Teratoma is the second most common prepubertal testicular neoplasm after yolk sac tumor, accounting for 14% of these tumors.[19] Most prepubertal teratomas are exclusively composed of mature tissues; nevertheless, all of them behave in a benign manner regardless of the mature or immature nature of their components.[19] On the other hand, most postpubertal teratomas are immature, although even purely mature teratomas in adults are at risk of metastases. In other words, the immaturity of teratomatous components is not an indicator of poor biologic behavior in the primary tumor; rather, the age of the patient is important. Most teratomas in children are diploid and lack amplification of short arm of chromosome 12; in contrast, teratomas in postpubertal patients are aneuploid and have isochromosome 12p.[136]

Clinical Features.—Most prepubertal teratomas are seen in children younger than 4 years with a mean age of 20 months.[137] Children typically present with a testicular mass detected by the parents. Most postpubertal cases are young adults presenting with testicular swelling or sometimes with symptoms associated with metastasis. In a series from Indiana, nearly 37% of adult patients with pure teratoma presented with advanced disease.[138]

Pathologic Features.—On gross examination, teratomas

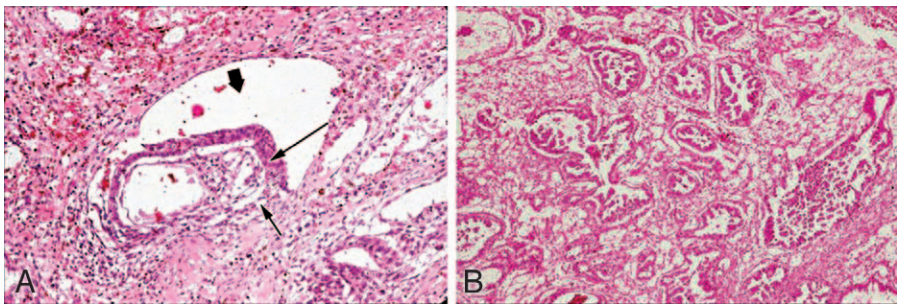

Figure 13. *A, Polyembryoma with an embryoid body composed of a mixture of embryonal carcinoma (long arrow) and yolk sac tumor (short arrow) with an associated amnion-like cavity (thick arrow) (hematoxylin-eosin, original magnification ×100). B, Diffuse embryoma characterized by a diffuse intermingling of embryonal carcinoma and yolk sac tumor of approximately equal amount (hematoxylin-eosin, original magnification ×100).*

are usually well-circumscribed, solid, firm, nodular or multicystic tumors. Their cut surface is heterogeneous as an expression of variable tissue types. Cysts may be filled with clear serous fluid, pearly gelatinous, or mucinous material.[56,102] Cartilage or bony spicules may be grossly discernible. Other grossly recognizable tissues including sebaceous material, hair, and teeth, unlike ovarian teratoma, are not common findings in a testicular teratoma.

In microscopic examination, variable ectodermal, endodermal, and mesodermal tissues admixed in either a disorganized or an organized arrangement are seen. Pure mature teratomas are composed of tissue components resembling adult somatic tissues. The most common components are different types of epithelium, neural tissue, glandular tissue, and cartilage, although virtually any other mature somatic components may be present. Significant cytologic atypia is frequently seen in mature elements of postpubertal teratomas, signifying the aneuploid nature of teratomas in adults.

Immaturity in a teratoma is defined as tissues that cannot be recognized as adult tissue elements (Figure 12) or those that resemble embryonic or fetal tissue. Most immature teratomatous elements of GCTs are cellular spindle mesenchymal components, but immature neural and epithelial elements are also seen. The spindle cells show frequent mitoses.

The vascular invasive component of postpubertal testicular teratoma may include either the teratomatous elements or the precursor cells that have the capacity to differentiate into various cell lines. Therefore, the cellular components of metastatic sites may differ from those of their primary tumor counterpart.

Orchiectomy is curative in pure teratomas in prepubertal patients. The treatment in adults is discussed later with other nonseminomatous GCTs.

Dermoid Cyst

It is controversial whether the rare dermoid cyst of the testis should be classified as a specialized form of mature teratoma or separately. Dermoid cysts characteristically contain cysts lined by keratinizing squamous epithelium associated with skin appendages; however, noncutaneous mature teratomatous elements may also exist in a dermoid cyst.[56] In contrast to postpubertal teratoma, dermoid cyst is not associated with IGCNU and also does not have any malignant potential.[139] Because teratomas in adults and dermoid cysts are prognostically different, it is important to extensively sample the lesion as well as the uninvolved testicular parenchyma to exclude any immature teratomatous components or IGCNU in the adjacent testis before rendering the diagnosis of dermoid cyst.

Mixed GCTs

Mixed GCTs of the testis are the second most common GCTs in adults (following seminoma), comprising 30% to 50% of the cases.[54,113] Tumors that contain seminoma occur at a later age than those without a seminomatous component. Mixed GCTs are rarely seen in prepubertal gonads. Serum elevation of AFP and hCG are common, correlating with the presence of yolk sac tumor elements and syncytiotrophoblastic cells (either singly or as part of choriocarcinoma), respectively.

Grossly, mixed GCTs have a variegated cut surface, reflecting their various tissue components. The most common histologic subtypes in a mixed GCT in order of frequency are embryonal carcinoma, teratoma, yolk sac tumor, seminoma, and choriocarcinoma.[140] The histologic appearance of various types of GCTs is identical to that of their pure form. These components are present in variable proportions and in most cases are distributed haphazardly throughout the tumor. Yolk sac tumor is the most frequently overlooked component in a mixed GCT.[113] Of all possible histologic combinations, some of the commonly observed forms include embryonal carcinoma/teratoma and embryonal carcinoma/seminoma, reflecting the high frequency of embryonal carcinoma in mixed GCTs.[56] In classifying more than 6000 testis tumors, Mostofi[141] found that in about 60% of cases, more than 1 histologic elements was present, and the most frequent combination was embryonal carcinoma, yolk sac tumor, teratoma, and syncytiotrophoblasts. Yet in another series, embryonal carcinoma/teratoma was the most commonly observed combination.[54]

For mixed GCTs, all components present in the tumor should be listed in the pathology report along with the approximate proportion of each component, in particular that of embryonal carcinoma. The significance of embryonal carcinoma proportion in a mixed GCT is discussed in the section on management of nonseminomatous GCTs.

Polyembryoma and Diffuse Embryoma

Polyembryoma and diffuse embryoma are 2 distinct forms of mixed GCTs. Polyembryoma consists of a mixture of embryonal carcinoma and yolk sac tumor with an associated amnion-like cavity, forming embryoid bodies (Figure 13, A) dispersed in a myxoid stoma. In diffuse embryoma, there is an intermingling of embryonal carcinoma and yolk sac tumor of approximately equal amount (Figure 13, B) arranged diffusely in a necklacelike pattern, in which a single layer of yolk sac tumor covers the embryonal carcinoma as a collaret.[56]

Treatment of Nonseminomatous Tumors

The treatment for nonseminomatous or mixed GCT largely depends on whether the tumor is localized to the testis or has already metastasized to the retroperitoneal lymph nodes or other sites. Most nonseminomatous GCTs including the pure variants initially metastasize to the retroperitoneum; however, embryonal carcinoma and choriocarcinoma may concomitantly metastasize via vascular invasion and go to distant sites early in the course of disease.[142] Initial clinical and radiographic examination (clinical staging) provides clues to the best management of patients with nonseminomatous GCTs.

Because of the high likelihood of retroperitoneal lymph node involvement in patients with nonseminomatous GCTs, the standard management for a localized disease (stage I) is nerve-sparing retroperitoneal lymph node dissection. One of the advantages of this management is to have a true staging procedure that provides a mean for discovery of microscopic retroperitoneal metastasis. Moreover, the procedure alone is curative in a high percentage of cases. Because in the past, retroperitoneal node dissections rendered a high percentage of patients sterile (dry ejaculation), current surgery attempts to preserve the sympathetic and parasympathetic ganglia.

Another management option for localized disease is surveillance. Because some patients may relapse even 1 year after orchiectomy, surveillance requires at least 2 years of follow-up; therefore, it is long and expensive, necessitating monthly chest x-rays, computed tomography/magnetic resonance imaging of the abdomen every 3 months, and monthly determination of serum markers. Thus, not all patients are good candidates for surveillance; for example, patients with psychiatric problems or drug addicts are not selected for this treatment approach. Many other patients by choice may not elect such prolonged monitoring either. In addition, patients with high risk of occult retroperitoneal metastasis should be excluded from surveillance management. For example, patients with pure embryonal carcinoma are not good candidates because a high percentage may have microscopic metastatic disease. Several studies have shown that the presence of embryonal carcinoma in excess of 80% in the primary tumor and vascular invasion are independent predictors for metastatic disease in patients with clinical stage I mixed GCTs.[143–146] The presence of these factors indicates a high-risk group that would be best to exclude from surveillance therapy. Overall, the cure rate for patients with nonseminomatous GCTs in clinical stage I exceeds 95%.[9]

The management for metastatic disease to the retroperitoneum (stage II disease) is either retroperitoneal lymph node dissection or chemotherapy. Persistent elevation of serum markers after orchiectomy is usually indicative of metastatic disease. With low-volume disease (nonbulky stage II), both treatments render similar results. As an exception, patients with a prominent teratoma component in the primary usually undergo retroperitoneal lymph node dissection instead of chemotherapy. If these patients are initially treated with chemotherapy, the teratoma component in the retroperitoneum may not respond and continues to grow (growing teratoma syndrome).

Initial chemotherapy is indicated for both bulky stage II and stage III disease, which may be followed by postchemotherapy surgery to eradicate any form of residual disease if present. One clinically important pathologic finding in the evaluation of postchemotherapy residual tissue is the presence of embryonal carcinoma component, which requires implementation of additional chemotherapy.[142] Existing teratoma, in contrast, does not impose additional therapy, although the presence of neuroectodermal components in a metastatic site imparts a poor prognosis. Combination chemotherapy has resulted in complete remission in 70% to 80% of patients with distant metastasis.[147]

SOMATIC MALIGNANCIES ARISING IN TESTICULAR GCT

Most somatic malignancies arising in testicular GCTs originate from teratomatous component of a mixed GCT, but occasionally they may derive from yolk sac tumor.[148,149] Some sarcomas, as described before, may also develop from dedifferentiation of spermatocytic seminoma.[98–101]

The somatic malignancies arising in GCTs include various types of sarcomas, including undifferentiated spindle cell tumors or differentiated forms (eg, rhabdomyosarcoma or leiomyosarcoma), primitive neuroectodermal tumor, and carcinomas.[148–151] Somatic malignancies can arise in the primary GCT or in the metastatic sites. Somatic tumors confined to the testis generally do not affect the prognosis of GCT; in contrast, those developing in the extratesticular sites, especially primitive neuroectodermal tumor and rhabdomyosarcoma, are likely associated with a poor prognosis.[150–152]

Recognition of somatic malignancy from primitive type tissues within teratomas at times can be difficult. Malignancy of mesenchymal elements is characterized by an expansile growth of a pure mesenchymal component (stromal overgrowth), that is, a microscopic field in excess of that viewed with a $\times 4$ objective.[153] This criterion is adapted from the definition of stromal overgrowth in malignant transformation of phyllodes tumor of the breast. The presence of stromal invasion, on the other hand, is a useful criterion for defining malignancy of epithelial elements.

Most somatic tumors arising in GCTs have manifested following chemotherapy. Approximately 3% to 6% of patients with metastatic GCTs treated with chemotherapy have shown malignant transformation.[148,151] It should be noted that chemotherapy by itself is not a prerequisite for the development of these tumors. Rather, it is the destruction of chemosensitive GCTs that allows the pre-existing somatic malignancies, which are nonresponsive to chemotherapy, to manifest after chemotherapy.[148] Surgical resection is the treatment of choice in these tumors.

CONCLUSION

Because decision on the mode of therapy largely relies on pathologic classification of GCTs, pathology reports should include factors that are prognostically significant or have implications for therapeutic decision. The increased interest in surveillance-only management of non–high-risk patients with stage I disease necessitates accurate identification of high-risk patients in whom surveillance is not recommended. Vascular invasion and the proportion of embryonal carcinoma component in a mixed GCT, which are both reliable prognosticators for identification of high-risk patients, can be best evaluated through careful examination of an appropriately sampled testicular neoplasm. The differences in management between seminoma and nonseminoma tumors as well as the potential for only focal existence of nonseminomatous components

necessitate adequate sampling of testis tumors for microscopic examination before a diagnosis of seminoma is made (in general, 1 section per 1-cm tumor diameter, including areas with differing appearances). An elevated serum AFP level virtually excludes a diagnosis of pure seminoma, even though microscopic evaluation does not appreciate the nonseminomatous germ cell elements. Although based on a small study, minor elevations of serum AFP (<16 ng/mL) may not be necessarily indicative of the presence of a yolk sac component.[154]

To help the clinician select the best treatment for individual patients, the following information should be provided in the pathology report of a testicular GCT: (1) gross features such as tumor size, tumor necrosis, or hemorrhage; (2) local extension, including invasion into the spermatic cord or scrotum, and the status of spermatic cord margin; (3) tumor classification group: seminoma versus nonseminoma (pure or mixed forms); (4) for mixed GCT, a list of various histologic components in the tumor with the approximate percentage of each component; (5) presence or absence of vascular or lymphatic invasion; and (6) presence of IGCNU in uninvolved testicular parenchyma.

Overall, the management of testicular GCTs results in a 90% to 95% cure rate.[5] The high success rate with therapy underlines the importance of accurate pathologic diagnosis of GCTs. Pathologists, therefore, should be fully aware of histologic variants of these diverse tumors.

References

1. Wu X, Groves FD, McLaughlin CC, Jemal A, Martin J, Chen VW. Cancer incidence patterns among adolescents and young adults in the United States. *Cancer Causes Control.* 2005;16:309–320.
2. Devesa SS, Blot WJ, Stone BJ, Miller BA, Tarone RE, Fraumeni JF Jr. Recent cancer trends in the United States. *J Natl Cancer Inst.* 1995;87:175–182.
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin.* 2006;56:106–130.
4. Krain LS. Testicular cancer in California from 1942 to 1969: the California Tumor Registry experience. *Oncology.* 1973;27:45–51.
5. Raghavan D. Testicular cancer: maintaining the high cure rate. *Oncology (Williston Park).* 2003;17:218–228.
6. Talerman A. Germ cell tumours. *Ann Pathol.* 1985;5:145–157.
7. Surveillance, Epidemiology, and End Results (SEER) Program. Available at: www.seer.cancer.gov. SEER*Stat Database: Mortality—All COD, with State, Total U.S. (1969–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005. Underlying mortality data provided by NCHS (www.cdc.gov/nchs). Accessed April 2005.
8. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer.* 2003;97:63–70.
9. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. *N Engl J Med.* 1997;337:242–253.
10. Zheng T, Holford TR, Ma Z, Ward BA, Flannery J, Boyle P. Continuing increase in incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, 1935–1992. *Int J Cancer.* 1996;65:723–729.
11. Bergstrom R, Adami HO, Mohner M, et al. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. *J Natl Cancer Inst.* 1996;88:727–733.
12. Collins DH, Pugh RC. Classification and frequency of testicular tumours. *Br J Urol.* 1964;36:1–11.
13. Mostofi F, Price E. *Tumors of the Male Genital System.* Washington, DC: Armed Forces Institute of Pathology; 1973:16. *Atlas of Tumor Pathology*; 2nd series, fascicle 8.
14. Mostofi FK, Spaander P, Grigor K, Parkinson CM, Shakkebaek NE, Oliver RT. Consensus on pathological classifications of testicular tumours. *Prog Clin Biol Res.* 1990;357:267–276.
15. Dixon F, Moore R. *Tumors of the Male Sex Organs.* Washington, DC: Armed Forces Institute of Pathology; 1952:50–52. *Atlas of Tumor Pathology*; 1st series, fascicle 32.
16. Grigor KM. A new classification of germ cell tumours of the testis. *Eur Urol.* 1993;23:93–100.
17. Motlik K, Stejskalova A, Abrahamova J. [Classification of germinal tumors of the testis]. *Cesk Patol.* 1986;22:198–209.
18. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.* Lyon, France: IARC Press; 2004:218–249. *World Health Organization Classification of Tumours.*
19. Weissbach L, Altwein JE, Stiens R. Germinal testicular tumors in childhood: report of observations and literature review. *Eur Urol.* 1984;10:73–85.
20. Reuter VE. Origins and molecular biology of testicular germ cell tumors. *Mod Pathol.* 2005;18(suppl 2):S51–S60.
21. Soosay GN, Bobrow L, Happerfield L, Parkinson MC. Morphology and immunohistochemistry of carcinoma in situ adjacent to testicular germ cell tumours in adults and children: implications for histogenesis. *Histopathology.* 1991;19:537–544.
22. Guinand S, Hedinger C. [Atypical intratubular germ cells and testicular germ cell tumors in children]. *Ann Pathol.* 1981;1:251–257.
23. Jacobsen GK, Henriksen OB, von der Maase H. Carcinoma in situ of testicular tissue adjacent to malignant germ-cell tumors: a study of 105 cases. *Cancer.* 1981;47:2660–2662.
24. Dieckmann KP, Skakkebaek NE. Carcinoma in situ of the testis: review of biological and clinical features. *Int J Cancer.* 1999;83:815–822.
25. Giwercman A, Bruun E, Frimodt-Moller C, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. *J Urol.* 1989;142:998–1001.
26. Rogers E, Teahan S, Gallagher H, et al. The role of orchiectomy in the management of postpubertal cryptorchidism. *J Urol.* 1998;159:851–854.
27. Bettocchi C, Coker CB, Deacon J, Parkinson C, Pryor JP. A review of testicular intratubular germ cell neoplasia in infertile men. *J Androl.* 1994;15(suppl):14S–16S.
28. Giwercman A, Thomsen JK, Hertz J, et al. Prevalence of carcinoma in situ of the testis in 207 oligozoospermic men from infertile couples: prospective study of testicular biopsies. *BMJ.* 1997;315:989–991.
29. Hoei-Hansen CE, Rajpert-De Meyts E, Daugaard G, Skakkebaek NE. Carcinoma in situ testis, the progenitor of testicular germ cell tumours: a clinical review. *Ann Oncol.* 2005;16:863–868.
30. Dieckmann KP, Loy V. Prevalence of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasms. *J Clin Oncol.* 1996;14:3126–3132.
31. von der Maase H, Rorth M, Walbom-Jorgensen S, et al. Carcinoma in situ of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients. *Br Med J (Clin Res Ed).* 1986;293:1398–1401.
32. Linke J, Loy V, Dieckmann KP. Prevalence of testicular intraepithelial neoplasia in healthy males. *J Urol.* 2005;173:1577–1579.
33. el Naggar AK, Ro JY, McLemore D, Ayala AG, Batsakis JG. DNA ploidy in testicular germ cell neoplasms: histogenetic and clinical implications. *Am J Surg Pathol.* 1992;16:611–618.
34. Summersgill B, Osin P, Lu YJ, Huddart R, Shipley J. Chromosomal imbalances associated with carcinoma in situ and associated testicular germ cell tumours of adolescents and adults. *Br J Cancer.* 2001;85:213–220.
35. Rodriguez E, Houldsworth J, Reuter VE, et al. Molecular cytogenetic analysis of i(12p)-negative human male germ cell tumors. *Genes Chromosomes Cancer.* 1993;8:230–236.
36. Rosenberg C, van Gurp RJ, Geelen E, Oosterhuis JW, Looijenga LH. Overrepresentation of the short arm of chromosome 12 is related to invasive growth of human testicular seminomas and nonseminomas. *Oncogene.* 2000;19:5858–5862.
37. Loftus BM, Gilmartin LG, O'Brien MJ, Carney DN, Dervan PA. Intratubular germ cell neoplasia of the testis: identification by placental alkaline phosphatase immunostaining and argyrophilic nucleolar organizer region quantification. *Hum Pathol.* 1990;21:941–948.
38. Jacobsen GK, Norgaard-Pedersen B. Placental alkaline phosphatase in testicular germ cell tumours and in carcinoma-in-situ of the testis: an immunohistochemical study. *Acta Pathol Microbiol Immunol Scand A.* 1984;92:323–329.
39. Koide O, Iwai S, Baba K, Iri H. Identification of testicular atypical germ cells by an immunohistochemical technique for placental alkaline phosphatase. *Cancer.* 1987;60:1325–1330.
40. Burke AP, Mostofi FK. Placental alkaline phosphatase immunohistochemistry of intratubular malignant germ cells and associated testicular germ cell tumors. *Hum Pathol.* 1988;19:663–670.
41. Izquierdo MA, Van d V, Ark-Otte J, et al. Differential expression of the c-kit proto-oncogene in germ cell tumours. *J Pathol.* 1995;177:253–258.
42. Rajpert-De Meyts E, Skakkebaek NE. Expression of the c-kit protein product in carcinoma-in-situ and invasive testicular germ cell tumours. *Int J Androl.* 1994;17:85–92.
43. Looijenga LH, Stoop H, de Leeuw HP, et al. POU5F1 (OCT3/4) identifies cells with pluripotent potential in human germ cell tumors. *Cancer Res.* 2003;63:2244–2250.
44. de Jong J, Stoop H, Dohle GR, et al. Diagnostic value of OCT3/4 for preinvasive and invasive testicular germ cell tumours. *J Pathol.* 2005;206:242–249.
45. Jones TD, Ulbright TM, Eble JN, Cheng L. OCT4: a sensitive and specific biomarker for intratubular germ cell neoplasia of the testis. *Clin Cancer Res.* 2004;10:8544–8547.
46. Marks A, Sutherland DR, Bailey D, et al. Characterization and distribution of an oncofetal antigen (M2A antigen) expressed on testicular germ cell tumours. *Br J Cancer.* 1999;80:569–578.
47. Sesterhenn IA, Davis CJ, Furusato B. M2A antigen (Podoplanin) distribution in prepubertal and adult testes and testicular tumors. *Mod Pathol.* 2006;19:159A. Abstract 737.
48. Badve S, Morimiya A, Agarwal B, Cheng L, Ulbright TM, Saxena R. Podoplanin: a histological marker for seminoma. *Mod Pathol.* 2006;19:129A. Abstract 589.
49. Giwercman A, von der Maase H, Skakkebaek NE. Epidemiological and clinical aspects of carcinoma in situ of the testis. *Eur Urol.* 1993;23:104–110.

50. Montironi R. Intratubular germ cell neoplasia of the testis: testicular intraepithelial neoplasia. *Eur Urol.* 2002;41:651–654.
51. Giwercman A, von der Maase H, Berthelsen JG, Rorth M, Bertelsen A, Skakkebaek NE. Localized irradiation of testes with carcinoma in situ: effects on Leydig cell function and eradication of malignant germ cells in 20 patients. *J Clin Endocrinol Metab.* 1991;73:596–603.
52. Dieckmann KP, Besserer A, Loy V. Low-dose radiation therapy for testicular intraepithelial neoplasia. *J Cancer Res Clin Oncol.* 1993;119:355–359.
53. Fischer CG, Waechter W, Kraus S, Fuentecilla PE, Weidner W, Dudeck J. Urologic tumors in the Federal Republic of Germany: data on 56,013 cases from hospital cancer registries. *Cancer.* 1998;82:775–783.
54. Krag Jacobsen G, Barlebo H, Olsen J, et al. Testicular germ cell tumours in Denmark 1976–1980: pathology of 1058 consecutive cases. *Acta Radiol Oncol.* 1984;23:239–247.
55. Ulbright TM. Testicular and paratesticular tumors. In: Mills SE, ed. *Sternberg's Diagnostic Surgical Pathology.* 14th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2004:2173–2176.
56. Ro JY, Amin MB, Sahin AA, Ayala AG. Tumors and tumorous conditions of the male genital tract. In: Fletcher CDM, ed. *Diagnostic Histopathology of Tumors.* 2nd ed. London, England: Churchill Livingstone; 2000:733–838.
57. Jacobsen GK, von der Maase H, Specht L. Histopathological features of stage I seminoma treated with orchidectomy only. *J Urol Pathol.* 1995;3:85–94.
58. Hedinger C, von Hochstetter AR, Egloff B. Seminoma with syncytiotrophoblastic giant cells: a special form of seminoma. *Virchows Arch A Pathol Anat Histol.* 1979;383:59–67.
59. Niehans GA, Manivel JC, Copland GT, Scheithauer BW, Wick MR. Immunohistochemistry of germ cell and trophoblastic neoplasms. *Cancer.* 1988;62:1113–1123.
60. Weissbach L, Bussar-Maatz R, Lohrs U, et al. Prognostic factors in seminomas with special respect to HCG: results of a prospective multicenter study: Seminoma Study Group. *Eur Urol.* 1999;36:601–608.
61. Damjanov I, Niejadlik DC, Rabuffo JV, Donadio JA. Cribriform and sclerosing seminoma devoid of lymphoid infiltrates. *Arch Pathol Lab Med.* 1980;104:527–530.
62. Young RH, Finlayson N, Scully RE. Tubular seminoma: report of a case. *Arch Pathol Lab Med.* 1989;113:414–416.
63. Zavala-Pompa A, Ro JY, el Naggar AK, et al. Tubular seminoma: an immunohistochemical and DNA flow-cytometric study of four cases. *Am J Clin Pathol.* 1994;102:397–401.
64. Talerman A. Tubular seminoma. *Arch Pathol Lab Med.* 1989;113:1204.
65. Takeshima Y, Sanda N, Yoneda K, Inai K. Tubular seminoma of the testis. *Pathol Int.* 1999;49:676–679.
66. Henley JD, Young RH, Wade CL, Ulbright TM. Seminomas with exclusive intertubular growth: a report of 12 clinically and grossly inconspicuous tumors. *Am J Surg Pathol.* 2004;28:1163–1168.
67. Ulbright TM, Young RH. Seminoma with tubular, microcystic, and related patterns: a study of 28 cases of unusual morphologic variants that often cause confusion with yolk sac tumor. *Am J Surg Pathol.* 2005;29:500–505.
68. Florentine BD, Roscher AA, Garrett J, Warner NE. Necrotic seminoma of the testis: establishing the diagnosis with Masson trichrome stain and immunostains. *Arch Pathol Lab Med.* 2002;126:205–206.
69. Kademian M, Bosch A, Caldwell WL, Jaeschke W. Anaplastic seminoma. *Cancer.* 1977;40:3082–3086.
70. Cockburn AG, Vugrin D, Batata M, Hajdu S, Whitmore WF. Poorly differentiated (anaplastic) seminoma of the testis. *Cancer.* 1984;53:1991–1994.
71. Bobba VS, Mittal BB, Hoover SV, Kepka A. Classical and anaplastic seminoma: difference in survival. *Radiology.* 1988;167:849–852.
72. Johnson DE, Gomez JJ, Ayala AG. Anaplastic seminoma. *J Urol.* 1975;114:80–82.
73. Zuckman MH, Williams G, Levin HS. Mitosis counting in seminoma: an exercise of questionable significance. *Hum Pathol.* 1988;19:329–335.
74. Hori K, Uematsu K, Yasoshima H, Sakurai K, Yamada A. Contribution of cell proliferative activity to malignancy potential in testicular seminoma. *Pathol Int.* 1997;47:282–287.
75. Bailey D, Marks A, Stratis M, Baumal R. Immunohistochemical staining of germ cell tumors and intratubular malignant germ cells of the testis using antibody to placental alkaline phosphatase and a monoclonal anti-seminoma antibody. *Mod Pathol.* 1991;4:167–171.
76. Leroy X, Augusto D, Leteurtre E, Gosselin B. CD30 and CD117 (c-kit) used in combination are useful for distinguishing embryonal carcinoma from seminoma. *J Histochem Cytochem.* 2002;50:283–285.
77. Tickoo SK, Hutchinson B, Bacik J, et al. Testicular seminoma: a clinicopathologic and immunohistochemical study of 105 cases with special reference to seminomas with atypical features. *Int J Surg Pathol.* 2002;10:23–32.
78. Ferreiro JA. Ber-H2 expression in testicular germ cell tumors. *Hum Pathol.* 1994;25:522–524.
79. Jacobsen GK, Jacobsen M. Alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) in testicular germ cell tumours: a prospective immunohistochemical study. *Acta Pathol Microbiol Immunol Scand A.* 1983;91:165–176.
80. Jones TD, Ulbright TM, Eble JN, Baldridge LA, Cheng L. OCT4 staining in testicular tumors: a sensitive and specific marker for seminoma and embryonal carcinoma. *Am J Surg Pathol.* 2004;28:935–940.
81. Cheng L. Establishing a germ cell origin for metastatic tumors using OCT4 immunohistochemistry. *Cancer.* 2004;101:2006–2010.
82. Cheville JC, Rao S, Iczkowski KA, Lohse CM, Pankratz VS. Cytokeratin expression in seminoma of the human testis. *Am J Clin Pathol.* 2000;113:583–588.
83. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers: International Germ Cell Cancer Collaborative Group. *J Clin Oncol.* 1997;15:594–603.
84. Testis (ICD-0 C62). In: Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumours.* 5th ed. New York, NY: Wiley-Liss; 1997:174–179.
85. Chung P, Parker C, Panzarella T, et al. Surveillance in stage I testicular seminoma. *Can J Urol.* 2002;9:1637–1640.
86. Warde P, Specht L, Horwich A, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *J Clin Oncol.* 2002;20:4448–4452.
87. von der Maase H, Specht L, Jacobsen GK, et al. Surveillance following orchidectomy for stage I seminoma of the testis. *Eur J Cancer.* 1993;29A:1931–1934.
88. Thomas GM. Over 20 years of progress in radiation oncology: seminoma. *Semin Radiat Oncol.* 1997;7:135–145.
89. Porcaro AB, Antoniolli SZ, Maffei N, Beltrami P, Bassetto MA, Curti P. Management of testicular seminoma advanced disease: report on 14 cases and review of the literature. *Arch Ital Urol Androl.* 2002;74:81–85.
90. Talerman A. Spermatocytic seminoma: clinicopathological study of 22 cases. *Cancer.* 1980;45:2169–2176.
91. Stoop H, van Gurp R, de Krijger R, et al. Reactivity of germ cell maturation stage-specific markers in spermatocytic seminoma: diagnostic and etiological implications. *Lab Invest.* 2001;81:919–928.
92. Verdorfer I, Rogatsch H, Tzankov A, Steiner H, Mikuz G. Molecular cytogenetic analysis of human spermatocytic seminomas. *J Pathol.* 2004;204:277–281.
93. Chung PW, Bayley AJ, Sweet J, et al. Spermatocytic seminoma: a review. *Eur Urol.* 2004;45:495–498.
94. Aristizabal S, Davis JR, Miller RC, Moore MJ, Boone MLM. Bilateral primary germ cell testicular tumors: report of four cases and review of the literature. *Cancer.* 1978;42:591–597.
95. Gilbert JB, Hamilton JB. Studies in malignant tumor of the testis, IV: bilateral testicular cancer. Incidence, nature, and bearing upon management of the patient with a single testicular cancer. *Cancer Res.* 1942;21:125–129.
96. Steiner H, Gozzi C, Verdorfer I, Mikuz G, Bartsch G, Hobisch A. Metastatic spermatocytic seminoma—an extremely rare disease. *Eur Urol.* 2006;49:183–186.
97. Matoska J, Ondrus D, Hornak M. Metastatic spermatocytic seminoma. A case report with light microscopic, ultrastructural, and immunohistochemical findings. *Cancer.* 1988;62:1197–1201.
98. True LD, Otis CN, Delprado W, Scully RE, Rosai J. Spermatocytic seminoma of testis with sarcomatous transformation: a report of five cases. *Am J Surg Pathol.* 1988;12:75–82.
99. Matoska J, Talerman A. Spermatocytic seminoma associated with rhabdomyosarcoma. *Am J Clin Pathol.* 1990;94:89–95.
100. Floyd C, Ayala AG, Logothetis CJ, Silva EG. Spermatocytic seminoma with associated sarcoma of the testis. *Cancer.* 1988;61:409–414.
101. Burke AP, Mostofi FK. Spermatocytic seminoma: a clinicopathologic study of 79 cases. *J Urol Pathol.* 1993;1:21–32.
102. Ro JY, Grignon DJ, Amin MB, Ayala AG. *Atlas of Surgical Pathology of the Male Reproductive Tract.* 1st ed. Philadelphia, Pa: WB Saunders; 1997:115–146.
103. Albores-Saavedra J, Huffman H, Alvarado-Cabrero I, Ayala AG. Anaplastic variant of spermatocytic seminoma. *Hum Pathol.* 1996;27:650–655.
104. Dekker I, Rozeboom T, Delemarre J, Dam A, Oosterhuis JW. Placental-like alkaline phosphatase and DNA flow cytometry in spermatocytic seminoma. *Cancer.* 1992;69:993–996.
105. Cummings OW, Ulbright TM, Eble JN, Roth LM. Spermatocytic seminoma: an immunohistochemical study. *Hum Pathol.* 1994;25:54–59.
106. Decaussin M, Borda A, Bouvier R, et al. [Spermatocytic seminoma: a clinicopathological and immunohistochemical study of 7 cases]. *Ann Pathol.* 2004;24:161–166.
107. Zeeman AM, Stoop H, Boter M, et al. VASA is a specific marker for both normal and malignant human germ cells. *Lab Invest.* 2002;82:159–166.
108. Pendlebury S, Horwich A, Dearnaley DP, Nicholls J, Fisher C. Spermatocytic seminoma: a clinicopathological review of ten patients. *Clin Oncol (R Coll Radiol).* 1996;8:316–318.
109. Mostofi FK, Sesterhenn IA, Davis CJ Jr. Developments in histopathology of testicular germ cell tumors. *Semin Urol.* 1988;6:171–188.
110. Rodriguez PN, Hafez GR, Messing EM. Nonseminomatous germ cell tumor of the testicle: does extensive staging of the primary tumor predict the likelihood of metastatic disease? *J Urol.* 1986;136:604–608.
111. Berney DM, Lee A, Randle SJ, Jordan S, Shamash J, Oliver RT. The frequency of intratubular embryonal carcinoma: implications for the pathogenesis of germ cell tumours. *Histopathology.* 2004;45:155–161.
112. Battifora H, Sheibani K, Tubbs RR, Kopinski MI, Sun TT. Antikeratin antibodies in tumor diagnosis: distinction between seminoma and embryonal carcinoma. *Cancer.* 1984;54:843–848.
113. Mostofi FK, Sesterhenn IA, Davis CJ Jr. Immunopathology of germ cell tumors of the testis. *Semin Diagn Pathol.* 1987;4:320–341.
114. Kaplan GW, Cromie WC, Kelalis PP, Silber I, Tank ES Jr. Prepubertal yolk sac testicular tumors—report of the testicular tumor registry. *J Urol.* 1988;140:1109–1112.

115. Ross JH, Rybicki L, Kay R. Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. *J Urol.* 2002;168:1675–1678.
116. Talerman A. The incidence of yolk sac tumor (endodermal sinus tumor) elements in germ cell tumors of the testis in adults. *Cancer.* 1975;36:211–215.
117. Talerman A, Haije WG, Baggerman L. Serum alphafetoprotein (AFP) in patients with germ cell tumors of the gonads and extragonadal sites: correlation between endodermal sinus (yolk sac) tumor and raised serum AFP. *Cancer.* 1980; 46:380–385.
118. Wu JT, Book L, Sudar K. Serum alpha fetoprotein (AFP) levels in normal infants. *Pediatr Res.* 1981;15:50–52.
119. Ulbright TM, Amin MB, Young RH. *Tumors of the Testis, Adnexa, Spermatic Cord, and Scrotum.* Washington, DC: Armed Forces Institute of Pathology; 1999. *Atlas of Tumor Pathology*; 3rd series, fascicle 25.
120. Ulbright TM, Roth LM, Brodhecker CA. Yolk sac differentiation in germ cell tumors: a morphologic study of 50 cases with emphasis on hepatic, enteric, and parietal yolk sac features. *Am J Surg Pathol.* 1986;10:151–164.
121. Eglen DE, Ulbright TM. The differential diagnosis of yolk sac tumor and seminoma: usefulness of cytokeratin, alpha-fetoprotein, and alpha-1-antitrypsin immunoperoxidase reactions. *Am J Clin Pathol.* 1987;88:328–332.
122. Mostofi FK. Histological change ostensibly induced by therapy in the metastasis of germ cell tumors of testis. *Prog Clin Biol Res.* 1985;203:47–60.
123. Zynger DL, Dimov ND, Luan C, Teh BT, Yang XJ. Glypican 3: a novel marker in testicular germ cell tumors. *Am J Surg Pathol.* 2006;30:1570–1575.
124. Grady RW, Ross JH, Kay R. Patterns of metastatic spread in prepubertal yolk sac tumor of the testis. *J Urol.* 1995;153:1259–1261.
125. Lopez JI, Angulo JC. Burned-out tumour of the testis presenting as retroperitoneal choriocarcinoma. *Int Urol Nephrol.* 1994;26:549–553.
126. Ulbright TM, Young RH, Scully RE. Trophoblastic tumors of the testis other than classic choriocarcinoma: ''monophasic'' choriocarcinoma and placental site trophoblastic tumor: a report of two cases. *Am J Surg Pathol.* 1997;21:282–288.
127. Suurmeijer AJ, Gietema JA, Hoekstra HJ. Placental site trophoblastic tumor in a late recurrence of a nonseminomatous germ cell tumor of the testis. *Am J Surg Pathol.* 2004;28:–830833.
128. Ulbright TM, Henley JD, Cummings OW, Foster RS, Cheng L. Cystic trophoblastic tumor: a nonaggressive lesion in postchemotherapy resections of patients with testicular germ cell tumors. *Am J Surg Pathol.* 2004;28:1212–1216.
129. Pelkey TJ, Frierson HF Jr, Mills SE, Stoler MH. Detection of the alpha-subunit of inhibin in trophoblastic neoplasia. *Hum Pathol.* 1999;30:26–31.
130. Singer G, Kurman RJ, McMaster MT, Shih I. HLA-G immunoreactivity is specific for intermediate trophoblast in gestational trophoblastic disease and can serve as a useful marker in differential diagnosis. *Am J Surg Pathol.* 2002;26:914–920.
131. Clark RK, Damjanov I. Intermediate filaments of human trophoblast and choriocarcinoma cell lines. *Virchows Arch A Pathol Anat Histopathol.* 1985;407: 203–208.
132. Lind HM, Haghighi P. Carcinoembryonic antigen staining in choriocarcinoma. *Am J Clin Pathol.* 1986;86:538–540.
133. McKendrick JJ, Theaker J, Mead GM. Nonseminomatous germ cell tumor with very high serum human chorionic gonadotropin. *Cancer.* 1991;67:684–689.
134. Bredael JJ, Vugrin D, Whitmore WF Jr. Autopsy findings in 154 patients with germ cell tumors of the testis. *Cancer.* 1982;50:548–551.
135. von Hochstetter AR, Hedinger CE. The differential diagnosis of testicular germ cell tumors in theory and practice: a critical analysis of two major systems of classification and review of 389 cases. *Virchows Arch A Pathol Anat Histol.* 1982;396:247–277.
136. Schneider DT, Schuster AE, Fritsch MK, et al. Genetic analysis of childhood germ cell tumors with comparative genomic hybridization. *Klin Padiatr.* 2001;213:204–211.
137. Brosman SA. Testicular tumors in prepubertal children. *Urology.* 1979; 13:581–588.
138. Leibovitch I, Foster RS, Ulbright TM, Donohue JP. Adult primary pure teratoma of the testis: the Indiana experience. *Cancer.* 1995;75:2244–2250.
139. Ulbright TM, Srigley JR. Dermoid cyst of the testis: a study of five postpubertal cases, including a pilomatrixoma-like variant, with evidence supporting its separate classification from mature testicular teratoma. *Am J Surg Pathol.* 2001; 25:788–793.
140. Mosharafa AA, Foster RS, Leibovich BC, et al. Histology in mixed germ cell tumors: is there a favorite pairing? *J Urol.* 2004;171:1471–1473.
141. Mostofi FK. Proceedings: testicular tumors: epidemiologic, etiologic, and pathologic features. *Cancer.* 1973;32:1186–1201.
142. Ro JY, Dexeus FH, el Naggar A, Ayala AG. Testicular germ cell tumors: clinically relevant pathologic findings. *Pathol Annu.* 1991;26(pt 2):59–87.
143. Moul JW, Heidenreich A. Prognostic factors in low-stage nonseminomatous testicular cancer. *Oncology (Williston Park).* 1996;10:1359–1368, 1374.
144. Heidenreich A, Sesterhenn IA, Mostofi FK, Moul JW. Prognostic risk factors that identify patients with clinical stage I nonseminomatous germ cell tumors at low risk and high risk for metastasis. *Cancer.* 1998;83:1002–1011.
145. Amato RJ, Ro JY, Ayala AG, Swanson DA. Risk-adapted treatment for patients with clinical stage I nonseminomatous germ cell tumor of the testis. *Urology.* 2004;63:144–148.
146. Heidenreich A, Sesterhenn IA, Mostofi FK, Moul JW, Engelmann UH. [Histopathologic and biological prognostic factors of clinical stage I non-seminomatous germ cell tumors: implications for risk-adjusted therapy]. *Urologe. A* 1999;38:168–178.
147. Bosl GJ, Gluckman R, Geller NL, et al. VAB-6: an effective chemotherapy regimen for patients with germ-cell tumors. *J Clin Oncol.* 1986;4:1493–1499.
148. Ulbright TM, Loehrer PJ, Roth LM, Einhorn LH, Williams SD, Clark SA. The development of non-germ cell malignancies within germ cell tumors: a clinicopathologic study of 11 cases. *Cancer.* 1984;54:1824–1833.
149. Michael H. Nongerm cell tumors arising in patients with testicular germ cell tumors. *J Urol Pathol.* 1998;9:39–60.
150. Comiter CV, Kibel AS, Richie JP, Nucci MR, Renshaw AA. Prognostic features of teratomas with malignant transformation: a clinicopathological study of 21 cases. *J Urol.* 1998;159:859–863.
151. Ahmed T, Bosl GJ, Hajdu SI. Teratoma with malignant transformation in germ cell tumors in men. *Cancer.* 1985;56:860–863.
152. Michael H, Hull MT, Ulbright TM, Foster RS, Miller KD. Primitive neuroectodermal tumors arising in testicular germ cell neoplasms. *Am J Surg Pathol.* 1997;21:896–904.
153. Ro JY, Amato RJ, Ayala AG. What does the pathology report really mean? *Semin Urol Oncol.* 1996;14:2–7.
154. Nazeer T, Ro JY, Amato RJ, Park YW, Ordonez NG, Ayala AG. Histologically pure seminoma with elevated alpha-fetoprotein: a clinicopathologic study of ten cases. *Oncol Rep.* 1998;5:1425–1429.