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Cancer Management Chapter 15: Testicular cancer

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Testicular cancer, although an uncommon malignancy, is the most frequently occurring cancer in young men. In the year 2009, an estimated 8,400 cases of testicular cancer will be diagnosed in the United States, and approximately 380 men will succumb to the disease. For unknown reasons, the incidence of this cancer has increased since the turn of the century, from 2 cases per 100,000 population in the 1930s, to 3.7 cases per 100,000 population from 1969 to 1971, to 5.4 cases per 100,000 population from 1995 to 1999. The greatest rise has been observed in Puerto Rico (1973 to 1997: 220%). This trend seems greatest for the development of seminoma.

Most testicular tumors are of germ-cell origin. These cancers are uniquely sensitive to chemotherapy and are considered the model for the treatment of solid tumors. Perhaps the most controversial area in the management of germ-cell tumors is the proper approach to early-stage disease (ie, surveillance vs primary retroperitoneal lymphadenectomy for nonseminomatous germ-cell tumors [NSGCTs] or radiation therapy for seminomas). In advanced disease, chemotherapy plays an essential role, but novel treatment regimens are currently being evaluated through multi-institution clinical trials.

Epidemiology

Age

Testicular cancer can occur at any age, but it is most common between the ages of 15 and 35 years. There is a secondary peak in incidence after age 60. Seminoma is the most common histology in the older population, but it is rare in those younger than age 10. There is a slightly increased prevalence of testicular cancer among fathers and brothers of testicular cancer patients.

SEER data show the incidence of testicular cancer in the United States continues to increase, albeit at an overall slower rate. Over the past 3 decades, the ratio of seminoma to NSGCT increased from 50/50 to 60/40 in whites and from 60/40 to 70/30 in blacks. National estimates of annual medical expenditures placed the total cost of treatment at $21.8 million in 2000, representing an increase of 10% over the total in 1994 (*Sokoloff MH, et al: J Urol 177:2030-2041, 2007*).

Race

Testicular cancer is rare among blacks (1.6/100,000 population), yet black men present with higher grade disease and have significantly worse survival at 5 and 10 years. The incidence of this cancer has

increased in whites during the 20th century but has remained flat in blacks. Non-Hispanic white patients typically present with disease at early stages when compared with black, Native-American, Hawaiian, and Hispanic patients.

Geography
Denmark has the highest incidence of testicular cancer; the Far East has the lowest incidence of this disease.

Primary site
Germ-cell tumors present most commonly in the testes (90%) and only infrequently in extragonadal sites (10%). The most common extragonadal sites (in decreasing order of frequency) are the retroperitoneum, mediastinum, and pineal gland. Many patients presumed to have a primary retroperitoneal germ-cell tumor may have an occult germ-cell tumor of the testicle. This possibility should be evaluated with testicular ultrasonography, especially when the retroperitoneal tumor is predominantly one-sided.

Survival
The 5-year survival rate for all patients with testicular cancer is ~95%. Cure rates are highest for early-stage disease, which is treated primarily with surgery or radiation therapy (early seminoma), and lower for advanced disease, for which chemotherapy is the primary therapy (Table 1).

Table 1: Anticipated cure rates in patients with germ-cell tumors, according to disease stage

Stage	Incidence at presentation (%)	Cure rate (%)
I (testis alone)	40	100
II (extension to retroperitoneal lymph nodes)	40	98
III (disseminated disease)	20	80

Etiology and risk factors

The specific cause of germ-cell tumors is unknown, but various factors have been associated with an increased risk of this malignancy.

Prior testicular cancer
Perhaps the strongest risk factor for germ-cell tumors is a history of testicular cancer. Approximately 1% to 2% of patients with testicular cancer will develop a second primary in the contralateral testis over time. This represents a 500-fold increase in incidence over that noted among the normal male population.

The risk of contralateral testicular cancer was studied in a large population-based cohort of men diagnosed with testicular cancer before the age of 55. For 29,515 cases reported from 1973 through 2001 to the NCI's SEER Program, the 15-year cumulative risk of developing metachronous contralateral testicular cancer was 1.9%, reaffirming the practice of not performing a biopsy on the contralateral testis at initial presentation.

Wood and Elder conducted an extensive review of the data about cryptorchidism as it related to testicular cancer. The relative risk of testicular cancer in cryptorchidism is 2.75 to 8. A relative risk of 2 to 3 has been noted in patients who undergo orchiopexy by ages 10 to 12 years. Patients who undergo orchiopexy after age 12 or no orchiopexy are 2 to 6 times as likely to have testicular cancer (*Wood HM et al: J Urol 181:452-461, 2009*).

Cryptorchidism
Patients with cryptorchidism have a four- to eight-fold increased risk of developing germ-cell tumors when compared with their normal counterparts. Orchiopexy, even at an early age, appears to reduce the incidence of germ-cell tumor only slightly (if at all). For an undescended testis, the most common malignant histology is seminoma. For those undergoing early orchiopexy, the most common malignancy

is non-seminoma. Of note, in ~10% of patients with cryptorchidism who develop germ-cell tumors, the cancer is found in the normally descended testis. Biopsies of nonenlarged cryptorchid testes demonstrate an increased incidence of intratubal germ-cell neoplasm, a presumed precursor lesion.

Genetics
Klinefelter's syndrome (47XXY) is associated with a higher incidence of germ-cell tumors, particularly primary mediastinal germ-cell tumors. For first-degree relatives of individuals affected with 47XXY, approximately a 6- to 10-fold increased risk of germ-cell tumors has been observed. In addition, patients with Down's syndrome have been reported to be at increased risk for germ-cell tumors. Also thought to be at greater risk are patients with testicular feminization, true hermaphrodism, persistent Müllerian syndrome, and cutaneous ichthyosis. In a genome-wide analysis of gene expression, PEPP-2 (x-linked homeobox gene), otoancorin (OTOA), and a kinase anchor protein (AKAP4) represent 3 candidate genes for diagnostic and therapeutic targets in testicular cancer.

Family history
Although familial testicular cancer has been observed, its incidence among first-degree relatives remains low. One investigator, however, reported a sixfold increased risk among male offspring of a patient with testicular cancer.

Environment
Numerous industrial occupations and drug exposures have been implicated in the development of testicular cancer. Although exposure to diethylstilbestrol (DES) in utero is associated with cryptorchidism, a direct association between DES and germ-cell neoplasm is weak at best.

Virtually all adult patients with germ-cell tumors have increased copies of isochromosome 12p, usually as i(12p). This is a useful marker in patients with undifferentiated tumors who fit the clinical profile of patients with germ-cell malignancy. In addition, mutations in v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KITi) have also been observed in seminoma, especially in tumors of primary mediastinal origin. The clinical significance of this observation is unknown at present).

Reports have suggested an increased risk of testicular cancer among individuals exposed to exogenous toxins, such as Agent Orange and solvents used to clean jets. One author has suggested that, based on epidemiologic evidence, exposure to ochratoxin A correlated with incidence data for testicular cancer.

Prior trauma, elevated scrotal temperature (secondary to the use of thermal underwear, jockey shorts, and electric blankets), and recurrent activities such as horseback riding and motorcycle riding do not appear to be related to the development of testicular cancer.

No supporting findings substantiate a viral etiology.

Fertility
An increased risk of infertility exists for men with unilateral testicular cancer successfully treated with orchiectomy. For example, 40% of patients have subnormal sperm counts, and, by 1 year, 25% continue to have subnormal sperm counts.

Signs and symptoms

Local disease

Scrotal mass
The most common complaint of patients on presentation is a painless scrotal mass that, on physical

examination, cannot be separated from the testis. This finding distinguishes the mass from epididymitis. Not infrequently, the mass may be painful and, thus, may mimic epididymitis or testicular torsion.

Hydrocele
Approximately 20% of patients with germ-cell tumors have an associated hydrocele.

Inguinal adenopathy
Patients generally do not have inguinal adenopathy in the absence of prior scrotal violation.

Other symptoms
These include low back pain (from retroperitoneal adenopathy) and gynecomastia (usually bilateral). In cases of massive retroperitoneal lymphadenopathy, abdominal pain, nausea, vomiting, and constipation may be reported.

Disseminated disease
Patients with disseminated germ-cell tumors usually present with symptoms from lymphatic or hematogenous dissemination. Mediastinal adenopathy may be associated with chest pain or cough. Supraclavicular lymphadenopathy may also be present.

The cumulative 10-year risk of developing metachronous testicular cancer for patients with extragonadal germ-cell tumors is 10.3%. Patients with extragonadal tumors of the retroperitoneum and NSGCTs have a 14.3% 10-year risk for the development of metachronous testicular cancer. Some, however, may have previously undiagnosed occult testicular primary tumors.

Levels of actin-ß-106/193/384 fragments in cell-free DNA levels were increased in patients with testicular cancer when compared with controls, with up to 87% sensitivity and 95% specificity. This analysis was predictive of stage III disease in 7 patients. The high sensitivity of cell-free DNA could assist in the management of testicular cancer, especially when traditional serum markers are not elevated (*Ellinger J et al: J Urol 181:363-371, 2008*)

Hematogenous spread to the lungs may be associated with dyspnea, cough, or hemoptysis. Infrequently, patients with extensive disease may present with signs and symptoms of CNS metastases or bone pain from osseous metastases (most common in patients with seminoma).

Metastases to the liver are not uncommon and may manifest as fullness in the upper abdomen or vague abdominal discomfort. More likely, they will be identified on CT scan in an otherwise asymptomatic patient.

Primary mediastinal germ-cell tumors
Primary mediastinal germ-cell tumors are associated with several unique syndromes, including Klinefelter's syndrome and acute megakaryocytic leukemia. In addition, mediastinal tumors have a great propensity for the development of non–germ-cell malignant histology as a major component of the tumor (eg, embryonal rhabdomyosarcoma, adenocarcinoma, and peripheral neuroectodermal tumor).

Screening and diagnosis

Screening

Self-examination
Testicular self-examination is both simple to learn and safe to perform. The rarity of testicular cancer however, calls into question the value of routine aggressive screening procedures.

Testicular biopsy
Testicular biopsy of a suspicious lesion is not recommended. Approximately 95% of patients with a mass within the testicle have a malignancy. Orchiectomy is the preferred treatment for patients with a testicular mass.

Carcinoma in situ (CIS) appears to be the precursor lesion for most testicular germ-cell tumors, except spermatocytic seminoma. Most patients harboring CIS can be expected to develop testicular cancer, but with a latency period of a decade or more. The incidence of CIS in infertile men is about 0.6%. In patients with prior testicular cancer, biopsy will reveal CIS in the contralateral testis at a rate of approximately 5% to 6%. Men with a history of cryptorchidism and presumed extragonadal germ-cell tumor are at greater risk for CIS. Some investigators suggest routine biopsy of the contralateral testis in men with CIS.

Diagnosis

Ultrasonography
Ultrasound can reliably identify masses within the testis. In virtually all patients, ultrasonography can distinguish a testicular lesion from an extratesticular mass and may detect lesions that are not palpable on physical examination. Ultrasonographic findings cannot consistently differentiate benign lesions from malignant tumors of the testis (95% of such masses are malignant). Most patients with testicular cancer, and especially those with seminoma, have lesions that are hypoechoic when compared with adjacent tissue. NSGCT however, may cause mixed signals, including hyperechoic masses, which are commonly seen with teratoma.

Serum markers
Serum levels of -subunit human chorionic gonadotropin (-hCG) and -fetoprotein (AFP) are elevated in approximately 80% to 85% of patients with extensive germ-cell tumors. Patients with pure seminoma may have elevated levels of -hCG but not of AFP (a significantly elevated AFP level usually indicates the presence of NSGCT elements). False-positive -hCG levels can be seen in patients who have hypogonadism (cross-reactivity with luteinizing hormone) or who use marijuana; AFP levels may be elevated in patients with liver dysfunction or hepatitis.

Inguinal orchiectomy
When a testicular mass is discovered, the patient should undergo an orchiectomy through an inguinal incision.

Trans-scrotal incisions or biopsies
These procedures should not be performed, as they ultimately lead to aberrant lymphatic drainage from the tumor.

Staging evaluation

The principal objective of the staging evaluation is to ascertain whether the patient has early-stage disease (which is amenable to local therapy), or disseminated disease (which requires chemotherapy).

Chest x-ray
A chest x-ray can determine whether or not a patient has gross supradiaphragmatic metastases, which would mandate initial chemotherapy.

Chest CT
In patients with a normal chest x-ray, chest CT is recommended in both patients with seminoma and

those with NSGCT when abdominal adenopathy is found to rule out occult metastases within the lungs or mediastinum. If such metastases are present, the patient should be treated with primary chemotherapy.

Abdominopelvic CT
This test provides important information about the retroperitoneal lymph nodes. Usually, periaortic adenopathy is noted on the ipsilateral side of the primary tumor. Patients with primary retroperitoneal germ-cell tumors often show an enlarged retroperitoneal mass in the midline. Although hepatic metastases are infrequent, CT presently is the most viable method of determining these metastatic lesions.

Positron emission tomography (PET)
18Fluorodeoxyglucose is emerging as a significant adjunct in staging and follow-up. Seminomas are FDG-avid. In some cases, nodal and extranodal metastases not appreciated on CT scans may be noted with FDG-PET. The optimal use of FDG-PET is in patients with residual masses following systemic therapy for pure seminoma. In such cases, the scans should be performed at least 3 to 4 weeks beyond the last course of chemotherapy. As teratoma is not PET-avid, its usefulness in NSGCTs is limited.

Other scans
In the absence of symptoms or signs, a CT scan (or MRI) of the head and radionuclide bone scan are unnecessary. A lymphangiogram is rarely used today to identify microscopic nodal involvement in patients with stage I disease who choose to undergo surveillance. PET scans may be useful in patients with residual disease following chemotherapy for seminoma. If a PET scan is positive in such patients, surgical resection of the residual mass is indicated. Otherwise, the residual mass can be simply followed with periodic radiographic evaluation.

Pathology

Germ-cell tumors are classified into two broad histologic categories: seminoma and NSGCT. Patients with seminoma who have increased AFP levels or any focus of NSGCT components (including teratoma) are considered to have an NSGCT.

Seminoma
Seminoma is the most common single histology, accounting for approximately 30% of all germ-cell tumors. Up to 10% of seminomas have focal syncytiotrophoblastic cells, which are believed to be the source of -hCG in some cases. Elevated AFP levels connote NSGCT.

Spermatocytic seminoma
This is a rare subset of germ-cell tumors, often grows to a large size, occurs almost exclusively in men older than age 50, and rarely, if ever, metastasizes.

Nonseminomatous germ cell tumors

Embryonal carcinoma
This lesion is composed of large pleomorphic cells with different architectural patterns. This tumor may be associated with an elevation in the serum levels of -hCG and/or AFP.

Endodermal sinus tumor (yolk sac carcinoma)
This is the most common testicular tumor seen in infants and young children. Like embryonal carcinoma, the yolk sac tumor

Table 2: Staging systems for testicular cancer

Royal Marsden system	TNM system	Description
I	Tx, N0, M0	Disease confined to the testis and peritesticular tissue
II	Tx, N1 or N2a, M0	< 6 positive lymph nodes without extension into retroperitoneal fat; no node > 2 cm (infradiaphragmatic)
A < 2 cm B 2–5 cm C > 5–10 cm D > 10 cm		
	Tx, N2b, M0	≥ 6 positive lymph nodes, well encapsulated and/or retroperitoneal fat extension; any node > 2 cm
	Tx, N3, M0	Any node > 5 cm
III	Tx, Nx, M1	Supradiaphragmatic and infradiaphragmatic adenopathy (no extralymphatic metastasis)

has a variety of architectural patterns. This tumor is associated with an elevated serum level of AFP.

IV Disseminated disease (lungs, liver, bone)

Choriocarcinoma
As a pure entity, choriocarcinoma is one of the least common germ-cell tumors. These tumors have a great propensity for hematogenous spread, often skipping the retroperitoneum. Choriocarcinoma is associated with an increased serum level of -hCG.

Teratoma
The teratoma is a generally benign tumor with elements from each of the germ layers (ectoderm, mesoderm, and endoderm). Teratoma is uncommonly seen as the sole histology in primary tumors, but it is frequently associated with other histologic elements, including those previously mentioned. Of patients with residual disease following chemotherapy for NSGCT, about 45% have evidence of teratoma in resected specimens.

A subset of patients with immature teratoma that contains non–germ-cell histologies (eg, sarcoma, adenocarcinoma) has been reported. In contrast to most teratomas, these tumors may grow locally and can be lethal. In addition, late recurrences of both teratoma and carcinoma have been reported in patients with teratoma. Serum markers are normal in patients with pure teratoma.

Pattern of spread

Testicular cancer spreads in a fairly predictable fashion: from the testicle to the retroperitoneal lymph nodes and, later, hematogenously to the lungs or other visceral sites. Only 10% of patients present with hematogenous metastases (usually in the lungs) in the absence of discernible retroperitoneal adenopathy.

Staging systems
Clinical staging systems (Royal Marsden and TNM systems) for testicular cancer are outlined in Table 2 . These staging systems help define the population for appropriate primary therapy.

Table 3: IGCCCG criteria for good- and poor-risk testicular cancer patients treated with chemotherapy

NONSEMINOMA
Good prognosis
All of the following:
• AFP < 1,000 ng/mL, β-hCG < 5,000 IU/L, and LDH < 1.5 × upper limit of normal
• Nonmediastinal primary
• No nonpulmonary visceral metastasis
Intermediate prognosis
All of the following:
• AFP = 1,000–10,000 ng/mL, β-hCG = 5,000–50,000 IU/L, or LDH = 1.5–10 × normal
• Nonmediastinal primary site
• No nonpulmonary visceral metastasis
Poor prognosis
Any of the following:
• AFP > 10,000 ng/mL, β-hCG > 50,000 IU/L, or LDH > 10 × normal
• Mediastinal primary site
• Nonpulmonary visceral metastasis
SEMINOMA
Good prognosis
• No nonpulmonary visceral metastasis
Intermediate prognosis
• Nonpulmonary visceral metastasis

IGCCCG = International Germ-Cell Cancer Collaborative Group; AFP = α-fetoprotein; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase

Good- and poor-risk subgroups
For patients with NSGCTs who are candidates for chemotherapy, other staging systems (such as those by Indiana University and MSKCC) were developed to segregate patients into good- and poor-risk categories. More recently, the IGCCCG formulated a classification that more clearly defines good- and poor-risk disease (Table 3), that is currently being used to stratify patients in ongoing trials.

Treatment

Stage I or II disease

Surgery
Initial intervention for testicular cancer is radical inguinal orchiectomy. Orchiectomy may be deferred temporarily in patients with advanced-stage disease in whom the diagnosis of NSGCT can be made on clinical grounds (elevated markers). In such patients, an orchiectomy must be performed sooner or later, as there is incomplete penetration of chemotherapy into the testes.

Further therapy hinges on the pathologic diagnosis. In general, most clinical stage I tumors are typically followed with surveillance. Patients with pure seminomas (normal AFP level with or without an elevated -hCG level) are treated with radiotherapy or chemotherapy, whereas most NSGCTs are treated with surgery and/or chemotherapy.

Inguinal orchiectomy In addition to removal of the testis, the spermatic cord is dissected high into the retroperitoneum. The vas deferens is isolated from the testicular vessels and ligated separately with a permanent suture. Also, the testicular vessels are freed from the peritoneum and carefully ligated with a permanent suture.

Retroperitoneal lymph node dissection (RLND) for NSGCTs For patients with NSGCTs and either no evidence or a small volume of disease on CT (stage I [N0] or stage II [N1, N2a, N2b] disease), RLND is generally indicated because it (1) accurately and definitively defines the presence or absence of retroperitoneal metastases and (2) removes the retroperitoneum as a site of recurrence, thus obviating the need for surveillance with CT.

RLND can be accomplished transperitoneally or retroperitoneally through a thoracoabdominal approach. The thoracoabdominal approach is more technically difficult but eliminates the risk of postoperative small bowel obstruction and usually requires a shorter hospital stay.

Nerve-sparing surgery Regardless of the approach, urologic oncologists recommend a unilateral, nerve-sparing procedure. For right-sided tumors, the medial border of the template is the midpoint of the aorta, and, for left-sided tumors, the medial border is the midpoint of the inferior vena cava (IVC). The sympathetic trunks responsible for normal bladder neck closure during ejaculation course lateral to the aorta on the left side and behind the IVC on the right side. Below the inferior mesenteric artery, both sympathetic trunks send branches to the region anterior to the aorta. The branches coalesce and then pass to the bladder neck.

Critical aspects of nerve-sparing surgery include preservation of the ipsilateral sympathetic nerve trunk and bilateral preservation of branches below the level of the inferior mesenteric artery. In our experience and that of other authors, it is possible to maintain normal ejaculatory function in virtually all patients using this technique.

TABLE 4: Chemotherapy regimens for testicular cancer

Drug/combination	Dose and schedule
BEP	
Bleomycin	30 IU IV bolus on days 2, 9, and 16
Etoposide	100 mg/m² IV infused over 30 minutes on days 1–5
Platinol (cisplatin)	20 mg/m² IV infused over 15–30 minutes on days 1–5
Repeat cycle every 21 days for 3 or 4 cycles.	
NOTE: Treat patients every 21 days on schedule, regardless of the granulocyte count. Reduce etoposide dose by 20% in patients who previously received radiotherapy or had granulocytopenia with fever/sepsis during the previous cycle. Patients receiving 4 cycles of BEP should undergo pulmonary function tests at baseline and at 9 weeks.	
Williams SD, Birch R, Einhorn LH, et al: N Engl J Med 316:1435–1440, 1987	
EP	
Etoposide	100 mg/m² IV infused over 30 minutes on days 1–5
Platinol (cisplatin)	20 mg/m² IV infused over 15–30 minutes on days 1–5
Repeat cycle every 21 days for 4 cycles.	
NOTE: Treat patients every 21 days on schedule, regardless of the granulocyte count. Reduce etoposide dose by 20% in patients who previously received radiotherapy or had granulocytopenia with fever/sepsis during the previous cycle.	
de Wit R, Roberts JT, Wilkinson PM, et al: J Clin Oncol 19:1629–1640, 2001	
VIP	
VePesid (etoposide)	75 mg/m²/d IV on days 1–5
Ifosfamide	1.2 g/m²/d IV on days 1–5
Platinol (cisplatin)	20 mg/m²/d IV on days 1–5
Mesna	400 mg IV bolus prior to the first ifosfamide dose, then 1.2 g/m²/d IV infused continuously on days 1–5
Repeat cycle every 21 days for 4 cycles.	
Loehrer PJ, Lauer R, Roth BJ, et al: Ann Intern Med 109:540–546, 1988	
TIP (salvage therapy)	
Taxol (paclitaxel)	175 mg/m² on day 1
Ifosfamide	1 g/m² on days 1–5
Platinol (cisplatin)	20 mg/m² on days 1–5
Mesna	400 mg IV bolus prior to the first ifosfamide dose, then 1.2 g/m²/d IV infused continuously on days 1–5
Repeat cycle every 21 days for 4 cycles.	
Kondagunta GV, Bacik J, Donadio A, et al: J Clin Oncol 23:6549–6555, 2005; Mead GM, Cullen MH, Huddart R, et al: Br J Cancer 93:178–184, 2005	
VeIP (salvage therapy)	
Vinblastine	0.11 mg/kg/d on days 1 and 2
Ifosfamide	1.2 g/m²/d IV on days 1–5
Platinol (cisplatin)	20 mg/m²/d IV on days 1-5
Mesna	400 mg/m² IV bolus prior to first ifosfamide dose, then 1.2 g/m²/d IV infused continuously for 5 days
Repeat cycle every 21 days for 4 cycles.	
Loehrer PJ, Lauer R, Roth BJ, et al: Ann Intern Med 109:540–546, 1988; Miller KD, Loehrer PJ, Gonin R, et al: J Clin Oncol 15:1427–1431, 1997	

Table prepared by Ishmael Jaiyesimi, DO

Surveillance (NSGCTs)

In patients with clinical stage I disease (normal serum markers and normal CT scans of the chest and abdomen), surveillance is a reasonable option. In unselected patients with clinical stage I NSGCTs, the risk of recurrence is approximately 25%. Thus, close follow-up with chest x-ray, analysis of serum markers (-hCG and AFP), and physical exam should be performed (Table 5).

When followed up in this way, most patients will be detected with low-volume disease. If recurrence occurs, such cases should be curable with 3 cycles of BEP (bleomycin, 30 IU/wk × 9/wk; etoposide, 100

mg/m2/d; and Platinol [cisplatin], 20 mg/m2/d) or 4 cycles of EP (etoposide plus cisplatin at the same doses; see Table 4). If patients recur with higher volume disease (ie, intermediate or poor prognosis), up to 50% may not be cured. Thus, diligent follow-up is crucial.

TABLE 5: Follow-up schedule for germ-cell tumor

Surveillance	Chest X-ray	βhCG/AFP	Chest CT	ABD/ Pelvic CT
Clinical stage I seminoma	q4mo, years 1–2	q4mo, years 1–2	—	q4mo, years 1–2
	q6mo, years 3–5	q6mo, years 3–5	—	q6mo, years 3–5
	After 5 years, annually	After 5 years, annually	—	As indicated
Clinical stage I NSGCT	q2mo, year 1	q2mo, year 1	—	q4mo, years 1–2
	q4mo, year 2	q4mo, year 2	—	q6mo, years 3–5
	q6mo, years 3–5	q6mo, years 3–5	—	As indicated
	After 5 years, annually	After 5 years, annually	—	As indicated
Following chemotherapy complete remission ± surgical RLND	q2mo, year 1 q4mo, year 2 q6mo, years 3–5 After year 5, annually	q2mo, year 1 q4mo, year 2 q6mo, years 3–5 After year 5, annually	— — — —	q4mo, years 1 & 2* — q6mo, years 3–5* As indicated
Following treatment for mediastinal or other GCT salvage	q2mo, year 1 q4mo, year 2 q6mo, years 3–5 After year 5, annually	q2mo, year 1 q4mo, year 22 q6mo, years 3–5 After year 5, annually	q4mo, years 1–2* q6mo, years 3–5* — —	As indicated As indicated — As indicated

*For patients with resected teratoma only.

Radiation therapy

Seminomas of the testes are exquisitely sensitive to irradiation. This characteristic, combined with their predictable lymphatic spread, makes these cancers amenable to radiotherapy. Since low radiation doses are used, acute and late side effects are few.

Stage I disease

Fields and doses The radiotherapy portals have traditionally included the retroperitoneal lymph nodes from T10 to L5 and the ipsilateral hemipelvis, including the inguinal scar. However, studies that reduced the size of the retroperitoneal field and omitted hemipelvis irradiation in selected patients (eg, those who have not undergone prior orchiopexy or other pelvic, inguinal, or scrotal surgery) favor smaller treatment volumes. A study by Fossa and colleagues randomized 478 men with stage I seminomas to receive irradiation of the para-aortics (T11 to L5) and ipsilateral hemipelvis versus irradiation of the para-aortics only. The actuarial rate of 3-year freedom from relapse was about 96% for both groups, although there were more pelvic relapses in patients given retroperitoneal radiation therapy only. Pelvic and/or inguinal failures occurred in < 5% of these patients. The few failures observed following radiotherapy most often occurred in the next echelon of lymph node drainage sites, such as the mediastinum or left supraclavicular fossa.

The smaller treatment volume reduces the dose to the remaining testicle and probably the risk of secondary malignancy. The ipsilateral hemipelvis is treated only when there is a history of ipsilateral inguinal surgery. Violation of the inguinal region can alter the testicular lymphatic drainage pathway to the para-aortic region. The hemiscrotum is often treated if the tumor penetrated the tunica albuginea, a trans-scrotal incision was performed, or orchiopexy was performed for cryptorchidism. However, this practice has been questioned, since the incidence of scrotal failure is low, even in the presence of these risk factors. In fact, some surgeons advocate the use of trans-scrotal exploration in order to rule out benign lesions.

Side effects The acute side effects of radiotherapy are limited to nausea, vomiting, and, infrequently, diarrhea, all of which usually can be readily controlled with medication. Long-term complications recently reported at the MDACC demonstrated increased mortality ratios for overall, cardiac-specific, and secondary cancer deaths for men treated with radiation therapy for seminoma between 1951 and 1999. No difference in mortality risk was noted in the first 15 years following treatment; however, over the entire period, the all-cause mortality risk was 1.59. The cardiac-specific mortality rate after 15 years was 1.61, and the secondary cancer mortality rate was 1.91.

Permanent infertility from scattered irradiation to the contralateral testis is uncommon, whereas prolonged aspermia for more than 1 year may occur, especially with irradiation of the hemiscrotum. Nevertheless, sperm banking is recommended for patients concerned about childbearing.

Prophylactic radiotherapy vs surveillance vs chemotherapy Primary lymphatic drainage of the testes is to the para-aortic lymph nodes from the level of the renal vessels to the bifurcation of the aorta. Although ipsilateral pelvic nodal failures and, to a much lesser extent, inguinal failures occur following

tumor resection by inguinal orchiectomy in patients with stage I disease, these sites are at a much lower risk of failure than the para-aortic region. Based on surveillance data, the overall incidence of disease failure without radiotherapy is 15% to 27% (median, 20%), whereas only 2% to 5% (median, 3%) of patients who are treated with radiotherapy relapse. Relapse rates with surveillance appear to be lower in patients with primary tumors smaller than 4 cm and no evidence of rete testis involvement.

The identification of prognostic factors makes surveillance an attractive alternative to the more conventional approach of radiotherapy in selected patients. Follow-up in patients undergoing surveillance is rigorous, because disease progression usually is not associated with symptoms until the tumor burden is large. Surveillance requires abdominopelvic CT scans and chest x-rays at 3- to 4-month intervals for about 3 years and then at 6-month intervals for at least an additional 2 years. Late failures beyond 5 years have been observed. Salvage rates reported in patients who relapse while undergoing surveillance are approximately 90% initially, with ultimate salvage rates after relapse of approximately 95%. Those patients who do develop recurrence usually receive 4 cycles of EP.

Surveillance guidelines for stage I seminoma were reported by investigators from Princess Margaret Hospital based on a systematic review of 17 prospective studies with a total of 5,561 patients. Follow-up with abdominopelvic CT scan and chest x-ray was recommended three times a year for years 1 and 2, twice a year for years 3 and 4, and then annually until year 10 (*Martin JM, et al: Cancer 109:2248-2256, 2007*).

Thus, in summary, various options exist for the primary treatment of clinical stage I seminoma, including radiation therapy and observation with monitoring of serum markers, CT, and chest x-ray. Primary chemotherapy has decreased risk of recurrence comparable to radiation therapy, but it still requires abdominal CT imaging for follow-up. Risk-adapted therapy has not yet defined the optimal population for primary chemotherapy.

Stage II disease

Fields and doses The radiotherapy fields are similar to those used for stage I disease, except that they are widened to include any retroperitoneal or pelvic adenopathy with a 2- to 3-cm margin. In the past, mediastinal and supraclavicular treatment was standard in patients with stage II disease. However, data from several series revealed only a 3% rate of mediastinal/supraclavicular relapse. In addition, late cardiac toxicity has been reported. Although treatment to supradiaphragmatic sites has largely been abandoned in these cases, one report indicates that the rate of failure in the left supraclavicular fossa is higher than was previously believed. An analysis from another group indicates the opposite, however, that supradiaphragmatic radiotherapy for stage IIA-B seminoma is unnecessary. The overall actuarial rate of freedom from disease at 5 years for patients with retroperitoneal adenopathy < 2 cm (IIA) is 95%, 2 to 5 cm (IIB) is 90%, and > 5 and < 10 cm (IIC) is 85%.

Follow-up guidelines after radiotherapy for stage I seminoma based on the frequency and patterns of recurrence were reported from the group at Princess Margaret Hospital. Biannual visits were recommended in the first 3 years following treatment and annually during years 4 through 6. Chest x-ray should be performed with each visit as well as pelvic CT for men treated with para-aortic RT alone (*Martin JM, et al: Cancer 109:2248-2256, 2007*).

Involved areas are usually treated with 30 to 36 Gy, and uninvolved areas are treated with 20 to 25 Gy. There is no evidence of a dose-response effect above 25 Gy for uninvolved areas and above 35 Gy for involved areas. Failures within the irradiated volume are anecdotal.

Chemotherapy

Stage I seminomas Several studies have evaluated the role of primary chemotherapy, typically carboplatin as adjuvant therapy, for clinical stage I seminoma. Single-cycle carboplatin has been studied as an alternative to adjuvant radiotherapy in a randomized trial conducted by the UKMRC/EORTC. At a median follow-up of 4 years, 3-year relapse-free survival rates were similar among the 1,477 randomized patients. However, first-echelon retroperitoneal nodal recurrences were more common in the chemotherapy group (74% vs 9%), raising concern regarding the efficacy of single-cycle carboplatin. Retroperitoneal nodal recurrences following radiotherapy are typically marginal misses at the edge of the treatment field.

Further questioning the role of single-cycle carboplatin in stage I disease, a pooled analysis of two randomized trials in advanced-stage disease demonstrated that single-agent carboplatin is inferior to cisplatin-based combination therapy. Phase II results evaluating two cycles of carboplatin (400 mg/m2) for prophylactic treatment of stage I seminomas were more promising. However, acute toxicity (ie, the degree of lethargy and time missed from work) is unlikely to be less than that of a 2-week course of radiotherapy. A risk-adjusted method has also been evaluated, but, thus far, these chemotherapy options do not preclude the necessity for continued surveillance with computerized tomography. In summary, observation, radiation therapy, and chemotherapy can be considered options after careful, informed decision-making.

A randomized comparison of adjuvant radiotherapy in 625 patients showed that 20 Gy in 10 treatments was as effective as 30 Gy in 15. With a median follow-up of 61 months, the absolute difference in 2-year relapse rates was 0.7%, with an estimated increase in the 2-year relapse rate associated with the lower dose of no more than 3%. When combining an additional 469 patients randomized between 20 Gy and 30 Gy as part of a subsequent trial, the estimated increase in relapse rates associated with the lower dose was further reduced, to less than 0.5% (*Jones WG, et al: J Clin Oncol 23:1200-1208, 2005*).

Stage II seminomas Those with larger lymph node metastases are typically treated with platinum-based chemotherapy. Among patients who are candidates for radiotherapy, it is essential that renal function be preserved in case chemotherapy is necessary for salvage treatment. Recent preliminary evidence indicates that the 5-year freedom-from-failure rates may be improved to 97% by administration of neoadjuvant carboplatin combined with reduced-field radiotherapy. Alternatively, systemic therapy alone (BEP × 3 vs EP × 4) may be used in lieu of radiation therapy.

Stage II NSGCTs Over the past several years, the threshold for primary surgery in patients with stage II disease on CT scans has changed. At present, masses > 3 cm in greatest cross-sectional diameter or those with more extensive longitudinal lymphatic spread are generally handled primarily with chemotherapy. For patients with tumor sizes 3 cm, primary RLND is considered the standard approach. Up to 25% of patients with enlarged lymph nodes on CT scans will have pathologic stage I (false-positive) disease by RLND.

Adjuvant chemotherapyThe risk of systemic recurrence is 5% to 10% in patients with pathologic stage I nonseminomas, 15% to 30% in those with completely resected stage IIA (N2a) disease, and 30% to 50% in those with stage IIB (N2b) disease. Recurrence usually occurs in the lungs within the first 24 months after surgery. The risk of retroperitoneal recurrence in patients with stage I, IIA, or IIB disease is < 1% after a properly performed RLND. Following RLND, patients with complete resection of stage II disease can be considered candidates for adjuvant chemotherapy.

The decision of whether or not to prescribe adjuvant therapy following lymph node dissection is somewhat arbitrary and often depends on the patient's social circumstances and likelihood of adhering to close follow-up. A patient with completely resected carcinoma who undergoes RLND has a 70% chance of cure; thus, the majority of patients will never need chemotherapy. However, these patients

must be monitored carefully with chest x-rays and serum marker determinations every month for 1 year, every 2 months for an additional year, and then every 6 months for the next 3 years. (CT scanning is not performed routinely unless clinically indicated.) The 30% of patients followed in such a manner who do develop recurrence will present with a tumor of low volume (eg, small pulmonary metastases or elevated serum markers); nearly 100% of these patients should be cured with appropriate systemic therapy.

However, some patients with resected stage II disease elect to receive adjuvant chemotherapy to minimize the risk of cancer recurrence. For such therapy, two cycles of BEP (bleomycin, 30 IU/wk × 8; etoposide, 100 mg/m2 on days 1 to 5 and 29 to 34; and cisplatin, 20 mg/m2 on days 1 to 5 and 29 to 34) are recommended (Table 4). In a patient who agrees to close follow-up, the chance of dying of cancer should be negligible in either scenario. For patients who have persistently elevated or increasing serum markers following RLND or who have undergone incomplete lymph node dissection, 3 cycles of BEP are indicated.

In a study of 75 patients with stage I NSGCTs, compliance with clinical examinations was 61.5% in year 1 and 35.5% in year 2, whereas compliance with abdominal/pelvic CT was only 25.0% and 11.8% in years 1 and 2, respectively. Careful selection of highly motivated patients for surveillance is indicated.

Stage III disease

Seminomas

Chemotherapy is the treatment of choice for patients with stage III seminomas (see Table 4). The management of patients with bulky disease after chemotherapy (residual mass: > 3 cm) is somewhat controversial. Investigators at MSKCC suggested that such patients require consolidation with radiotherapy or surgical removal of radiographically evident disease. Data from the Royal Marsden Hospital and the Centre Léon Bérard reported a relapse rate of 10% to 15% in patients with residual masses with or without postchemotherapy surgery or radiotherapy, supporting the practice of observation in patients with residual masses following chemotherapy. FDG-PET may be helpful in the decision to treat residual masses > 3 cm but should be performed 4 to 6 weeks after the last course of chemotherapy.

SEER data showed that the use of adjuvant radiation therapy for stage I seminoma is declining. In 3,125 men diagnosed with stage I seminoma from 1990 through 2004, there was a significant association between later year of diagnosis and a decrease in adjuvant radiotherapy recommendation. Compared with men diagnosed from 1990 to 1994, men diagnosed between 2000 and 2004 were less likely to have adjuvant radiotherapy (odds ratio = .49, 95% CI = .37-.63, P < .001). From 1990 to 1994, 85.3% were recommended to receive radiotherapy compared with 78.7% from 2000 to 2004. An overwhelming majority of patients are still recommended to receive radiotherapy in the United States (*Hoffman KE et al: J Clin Oncol 26:3937-3942, 2008*).

NSGCTs

As mentioned previously, patients with NSGCTs being treated with chemotherapy can be classified as having good- or poor-risk disease (see Table 3).

Good-risk disease Three cycles of BEP given every 3 weeks or, alternatively, 4 cycles of EP at the same dosages appear to yield equivalent results. More than 90% of good-risk patients should be cured with these therapies.

Two prospective randomized trials comparing cisplatin with carboplatin in good-risk patients with disseminated germ-cell tumors have demonstrated inferior results for carboplatin-containing regimens.

The quality of surveillance for stage I testis cancer in the community was reported from private insurance claims between 2002 and 2007. Seven hundred men underwent radical orchicotomy and 279 were managed with surveillance. Compliance with surveillance follow-up protocols developed at referral centers was poor. Nearly 30% of all surveillance patients received no abdominal imaging, chest imaging, or tumor marker tests within the first year of diagnosis (*Yu HY et al: J Clin Oncol 27:4327-4332, 2009*).

Postchemotherapy resection Patients having persistent radiographic disease with normal serum markers 4 to 6 weeks following chemotherapy for an NSGCT, should undergo surgical resection when possible. In patients with a seminoma, a residual mass > 3 cm, and an abnormal PET scan, resection is also recommended.

Postresection chemotherapy Histologic examination of residual disease will reveal necrotic fibrous tissue in approximately 45% of such cases, benign teratoma in about 45%, and persistent carcinoma in about 10% to 15%. If persistent carcinoma is detected in the resected specimen, 2 additional cycles of EP should be administered. For patients with complete resection of mature and immature teratoma or necrosis, no additional therapy is needed.

Poor-risk disease A cohort of patients with disseminated germ-cell tumors presents with advanced or poor-risk disease. “Poor risk” has been variously defined (see Table 3) but represents a patient population with a cure rate of 50% with standard cisplatin-based combination chemotherapy. Irradiation is useful in the treatment of metastatic NSGCTs to the brain.

Chemotherapy During the past few years, several trials have evaluated a variety of combination regimens in patients with poor-risk disease (Table 4). They include the use of high-dose therapy, sequential therapy, and VIP (VePesid [etoposide], ifosfamide, and Platinol [cisplatin]). VIP appears to be therapeutically equivalent to BEP; however, for most patients with advanced disease, BEP is the preferred regimen, because it produces less myelosuppression. In patients with underlying pulmonary dysfunction, VIP is preferred.

In a study by Bhatia et al, 65 patients with recurrent testicular cancer were treated with tandem cycles of high-dose etoposide plus carboplatin followed by peripheral stem-cell transplantation (SCT) as initial salvage therapy. With a median follow-up of 39 months, 37 patients (57%) remain continuously disease-free, with 3 additional patients (5%) disease-free with subsequent surgery. There was no treatment-related mortality.

A prospective intergroup trial evaluating high-dose chemotherapy and SCT was recently published. This trial comparing 4 cycles of BEP with 2 cycles of BEP followed by 2 tandem courses of high-dose chemotherapy plus SCT in previously untreated patients with poor-risk disease was recently completed.

Postchemotherapy resection The ultimate goal of combination chemotherapy in these patients is the resolution of all radiographically visible disease and the normalization of tumor markers. If residual radiographic abnormalities persist in the lungs and/or abdomen, surgical resection of residual disease is indicated.

Postchemotherapy RLND must clear the region of residual disease. In general, postchemotherapy resections are extremely difficult, and incomplete resections are unacceptable. After the retroperitoneum is cleared of persistent radiographic disease, persistent pulmonary lesions are resected. In cases with

residual disease in the retroperitoneum and thorax, RLND should be performed first. If necrosis is found, the disease within the chest can be observed. If teratoma or cancer is noted, the supradiaphragmatic disease should be resected.

A recent update to an Australian trial compared 3 vs 4 cycles of BEP given to patients with good-prognosis germ-cell tumors. At an 8-year follow-up, the survival benefit was maintained with the 3-cycle regimen (*Grimison PS et al: J Clin Oncol [15S]: abstract 6016, 2009*).

Complicating factors associated with postchemotherapy resection include the risk of oxygen toxicity secondary to bleomycin as well as intense fibrosis and adherence of residual disease to the aorta and other vital retroperitoneal organs. Inspired oxygen levels must remain below 35% to prevent bleomycin-related acute respiratory distress syndrome, which has a fatality rate 50%.

After successful resection, the only visible structures remaining should include the back muscles, nerves, anterior spinous ligament, aorta, IVC, renal vessels, kidneys, and ureters. Up to 20% of patients with advanced abdominal disease may require resection of a kidney or even the IVC. Operative mortality in centers with experience performing resection of these advanced-stage tumors should be < 2%. Although intra-, postoperative, and late complication rates were higher between groups receiving open primary or postchemotherapeutic RLND, they were not significantly different when the procedure was performed by fellowship-trained urologists.

Postresection chemotherapy As mentioned, 2 additional cycles of chemotherapy are indicated for patients with persistent viable carcinoma in the resected specimen. For patients with resected teratoma of nonviable necrotic tissue, no additional chemotherapy is warranted.

Refractory or recurrent disease

Surgery

Some patients with recurrent disease appear to have localized or minimally metastatic disease. In such cases, “desperation” surgery may achieve a durable complete remission. A 25% cure rate was seen in a select group of patients with elevated serum markers who underwent such surgery at Indiana University. These patients had completely resected viable carcinoma without chemotherapy following surgery.

Salvage chemotherapy

Approximately 20% to 30% of patients with disseminated germ-cell tumors do not attain complete remission with induction chemotherapy or relapse after such therapy. These patients may be candidates for salvage chemotherapy. Occasional patients may be erroneously classified as having recurrent disease based on false-positive markers or abnormal radiographic findings. Some of these false-positive results may be due to a growing teratoma; pseudonodules from bleomycin-induced pulmonary disease; or elevated markers from other causes, such as an elevated -hCG level from marijuana usage, cross-reactivity with luteinizing hormone, or an elevated AFP level associated with hepatitis or liver dysfunction. Another cause of persistently elevated markers is a tumor sanctuary site (eg, in the testes or brain). Assuming that false disease progression has been ruled out, several approaches to salvage therapy can be used. When possible, autologous bone marrow transplant is preferred. It can achieve slightly more durable response rates than other options.

Ifosfamide is one of a few drugs (including etoposide, gemcitabine [Gemzar], and paclitaxel) that has clinical activity in patients with cisplatinrefractory disease. As second-line therapy, VeIP (vinblastine, 0.11 mg/kg on days 1 and 2 [total dose = .22 mg/kg]; plus ifosfamide, 1.2 g/m^2 [plus mesna (Mesnex)];

plus Platinol, 20 mg/m^2, both on days 1 to 5) produces durable complete remissions in ~30% of NSGCT patients and 50% of seminoma patients previously treated with BEP chemotherapy (Table 4). Toxicity, which is primarily hematologic, can be minimized with the use of a colony-stimulating growth factor.

A recent retrospective review by Einhorn et al evaluated 184 patients who had progressed on initial platinum-based therapy. They were treated with two consecutive courses of high-dose chemotherapy with carboplatin and etoposide followed by infusion of autologous peripheral-blood hematopoietic stem-cells. Of the 135 patients who received this treatment as second-line therapy, 94 were disease-free; 22 of 49 patients who received this treatment as third-line therapy or later were disease-free, and 18 of 40 platinum-refractory patients were disease-free (*Einhorn LH et al: N Engl J Med 357:340-348, 2007*).

Seminoma Patients with recurrent seminoma appear to be more sensitive to salvage therapy. In a study by Miller et al, 24 patients with seminoma were treated with VeIP as second-line therapy (following relapse after cisplatin-etoposide combination therapy). Of the 24 patients, 20 patients (83%) achieved a complete response, and 13 patients (54%) are long-term survivors, including 4 of 6 with extragonadal primary sites. Thus, initial salvage therapy in these patients should be VeIP (Table 4) rather than high-dose chemotherapy with bone marrow rescue.

High-dose chemotherapy with stem-cell rescue High-dose chemotherapy with tandem courses of carboplatin and etoposide plus autologous stem-cell rescue produces durable complete remission in 5% to 10% of patients whose disease is overtly refractory to cisplatin. When this approach is used in patients with recurrent, but not cisplatin-refractory, disease, improved response rates are observed; over 60% of all patients with recurrence of testicular cancer (excluding extragonadal recurrence) will be cured. Approximately 70% of patients treated with second-line therapy are curable with this approach.

Other agents Few drugs besides etoposide and ifosfamide have activity in patients with cisplatin-refractory disease. Oral etoposide given according to a chronic schedule (50 mg/m^2/d for 21 days) has produced objective responses in ~20% of patients who were previously treated with IV etoposide. Paclitaxel has a similar response rate in minimally pretreated patients (< 6 cycles). Gemcitabine produces a response rate of approximately 15% in patients with cisplatin-refractory disease.

The ECOG conducted a phase II trial of gemcitabine (1,000 mg/m2) plus paclitaxel (110 mg/m^2) given on days 1, 8, and 15 of a 4-week cycle for a maximum of 6 cycles in patients with recurrent germ-cell tumor not thought to be curable with standard chemotherapy or surgery. Of 28 evaluable patients, 6 responded, including 3 who had complete responses (2 of whom were free of disease at 15+ and 25+ months).

In a group of patients not considered to be curable with standard salvage chemotherapy, cisplatin plus epirubicin produced durable complete remissions in 7 of 30 patients.

A recent phase II clinical trial from Indiana University looked at patients who received paclitaxel plus gemcitabine following high-dose chemotherapy and tandem transplant. In all, 32 patients with progressive disease were treated with paclitaxel plus gemcitabine for maximum of 6 courses. A retrospective review indicated that 10 of 32 patients (31%) achieved an objective response, with 4 patients having partial remissions of 2-6 months and 6 patients having a complete response. Four of these 6 patients with compete responses were continuously disease-free at more than 20, 40, 44, and 57 months. Thus, long-term, disease-free survival is possible with paclitaxel plus gemcitabine in patients who have progressed after tranplant (*Einhorn LH et al: J Clin Oncol 25:513-516, 2007*).

Survivorship issues

Delayed toxicity from systemic therapy
Delayed toxicity from systemic therapy for germ-cell tumors has been well characterized. In the absence of signs and symptoms, specific monitoring for these late effects is not generally warranted. A number of late effects have been observed.

Fertility problems and fetal malformation
Fertility problems, manifested by azoospermia or oligospermia at or beyond 2 years, occur in 45% to 55% of treated patients. No increased risk of fetal malformation has been observed in the offspring of men previously treated with chemotherapy for testicular cancer.

Cardiovascular disease
The risk of hypertension or other cardiovascular disease may be increased in patients with testicular cancer who received chemotherapy, but this theory is controversial. The only exception is Raynaud's phenomenon, which occurs at a rate directly proportional to the number of cycles of cisplatin-based chemotherapy.

Renal and pulmonary toxicities
Although renal and pulmonary dysfunction can occur acutely during therapy, long-term consequences from therapy are uncommon.

Secondary malignancies
Perhaps of greatest concern is the development of secondary malignancies.

Late recurrence
The incidence of late recurrence is estimated at 3.2% in NSGCT and 1.4% in seminoma. These late recurrences typically occur beyond 5 years (longest: 32+ years) from primary therapy, frequently present with an elevated serum level of AFP, and are particularly resistant to salvage chemotherapy. Thus, surgical resection of disease is the primary treatment strategy.

Testicular cancer
Approximately 1% to 2% of patients may develop a second primary testicular cancer.

Other cancers
In a large series of 40,000 men by Travis et al, the relative risk for developing secondary tumors was 1.9 for 10-year survivors of testicular cancer and remained 1.7 for 35-year survivors. The greatest elevated risk was for cancers of the pleura, pancreas, bladder, and stomach. In another large retrospective analysis of 635 patients with extragonadal germ-cell tumors treated from 1975 to 1996, only an increased number of hematologic and skin malignancies were observed.

In a study of 75 patients with late recurrence, the 5-year cancer-specific survival (CSS) was 79% vs 36% for men undergoing complete or incomplete surgical resection respectively. The 5-year CSS for chemotherapy-naïve patients was 93% compared with 49% for men having a prior history of chemotherapy in their initial management (*Sharp DS et al: J Clin Onc 26:5624-5629, 2008*).

The contribution of chemotherapy and/or radiation therapy to the development of these other malignancies, as opposed to a natural propensity toward their development, is unknown. However, in several series, etoposide has been shown to pose an increased risk for the development of secondary leukemia (dose-related). At higher dosages (> 2 g/m^2 cumulative), etoposide has been associated with a greater incidence of acute leukemia. Very high dosages of etoposide with stem-cell rescue do not appear to be linked to a higher risk than standard-dose chemotherapy. In one paper by Travis and colleagues,

both increased dosages of radiation therapy and cisplatin were associated with an increased risk for acute leukemia. Although these risks are real, they still are low compared with the risk of death caused by testicular cancer. Nonetheless, indiscriminate use of chemotherapy for early-stage (stage I) disease should be tempered by the recognition of the long-term hazards of therapy.

Follow-up for relapse

Because the relapse rate for testicular cancer is low, patients with pathologically confirmed stage I NSGCTs require no further therapy, and follow-up can be accomplished easily with chest x-ray, tumor markers, and physical examination. Similarly, for patients who have stage II disease and receive adjuvant chemotherapy, the risk of relapse is low. For patients with either of these two clinical scenarios, follow-up tests (chest x-ray, serum markers) should be performed every 2 months for 1 year, every 4 months for the second year, every 6 months for years 3 through 5, and annually thereafter.

In patients with resected stage II NSGCTs who do not receive adjuvant chemotherapy, the follow-up tests are the same as those listed above. However, in these patients, follow-up tests are performed every month for 1 year, every 2 months for 2 years, every 6 months for years 3 through 5, and then annually.

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Abbreviations in this chapter

ECOG = Eastern Cooperative Oncology Group; IGCCCG = International Germ-Cell Cancer Collaborative Group; MDACC = The University of Texas M. D. Anderson Cancer Center; MSKCC = Memorial Sloan-Kettering Cancer Center; NCI = National Cancer Institute; SEER = Surveillance, Epidemiology and End Results; UKMRC/EORTC = United Kingdom Medical Research Council/European Organisation for Research and Treatment of Cancer