Testicular Cancer: I

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I. INTRODUCTION

This is the first of a 2-part manual on testicular cancer. The first part discusses epidemiology, biology, diagnosis, and staging of germ cell tumors (GCTs) as well as treatment of early stage seminomatous and nonseminomatous GCTs. The second part discusses treatment of good-prognosis advanced stage disease and of poor-prognosis GCTs, management of residual masses, salvage chemotherapy, toxicities of treatment, and mediastinal GCTs. Both parts contain sample board review questions and answers for self-assessment. The second part will be published as “Testicular Cancer: II” in the Hospital Physician Oncology Board Review Manual, Volume 6, Part 4.

II. EPIDEMIOLOGY

A. Incidence and mortality

1. Testicular cancer is relatively rare, with roughly 7000 new cases reported annually in the United States.\(^1\)

a. The incidence of testicular cancer is highest between the ages of 20 and 44 years. It is the most common malignancy in Caucasian men between the ages of 20 and 34 years. The median age at diagnosis is 33 years; occurrence is rare in individuals younger than 15 years or older than 54 years.\(^1\)

b. The incidence of testicular cancer is highest among Caucasian men (5.3/100,000) and lowest among African American men (1.0/100,000); the number of Latino and Asian American men affected is between these values.\(^1\)

2. Almost all patients with testicular cancer are cured; the 5-year survival rate is approximately 95%.\(^1\) The incidence of testicular cancer increased by about 50% between the early 1970s and the late 1990s, although mortality fell by 70% during the same period.\(^1\)

B. Risk factors

1. Cryptorchidism (undescended testicle) is the most clearly established risk factor for testicular GCTs, although the increased risk is largely eliminated by early surgical correction. In men with cryptorchidism, both the undescended and the contralateral testicles are at increased for developing cancer.

2 Hospital Physician Board Review Manual
2. Men with a brother or father who has had a GCT are at increased risk.2
3. Patients with testicular feminization syndrome (androgen resistance syndrome) have an increased incidence of GCTs.4
4. Mumps orchitis, testicular trauma, inguinal hernias, early puberty, and sedentary lifestyle have also been implicated as risk factors for GCTs. Increased serum levels of gonadotropins (which can result from conditions that cause testicular atrophy) may increase the risk for developing GCTs.2,3

C. Genetic events
1. Nearly all men with GCTs have an increased number of copies of the short-arm of chromosome 12, which are most often present as isochromosomes i(12p). The presence of i(12p) is almost pathognomonic for GCTs.4
2. The specific genes involved have not been identified.5,6

III. BIOLOGY OF TESTICULAR CANCER

A. Histology
1. Almost all testicular cancers are GCTs, which are divided into 2 major categories: seminomas and nonseminomas. Most GCTs contain more than one cell type and these are referred to as mixed GCTs.
   a. Pure seminomas (40% of all GCTs) occur most frequently in patients who are 30 to 40 years old. Of all GCTs, they are the most sensitive to both radiation and chemotherapy. Rare variants of seminomas include spermatocytic seminoma (which is most common in men older than 40 years and is associated with a good prognosis) and anaplastic seminoma (which tends to present at a more advanced stage).
   b. Nonseminomatous GCTs (NSGCTs) account for 60% of all GCTs; they occur most commonly in men who are approximately 17 to 32 years of age. Although highly sensitive to chemotherapy, NSGCTs are not sensitive to radiation and they carry a slightly less favorable prognosis than pure seminomas. Mixed GCTs containing seminomatous elements are considered nonseminomatous GCTs for prognostic and treatment purposes. The histologic categories of nonseminomatous GCTs include embryonal carcinoma, teratoma, choriocarcinoma, and endodermal sinus tumor (yolk-sac tumor).
2. Other testicular tumors
   a. Sex cord/gonadal stromal tumors include Leydig cell tumors, Sertoli cell tumors, and granulosa cell tumors. These are rare tumors and are usually benign.
   b. Carcinoid tumor
   c. Lymphoma or plasmacytoma
   d. Carcinoma of the rete testes
   e. Sarcomas

B. Serum tumor markers. Three serum tumor markers play important roles in the management of GCTs: α-fetoprotein (AFP), the β-subunit of human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH). They are used to assess prognosis, aid in treatment decisions, and monitor for relapse. These markers should be measured in all candidates for orchiectomy before surgery. Seminomas do not make AFP; therefore, an elevation of this marker excludes the diagnosis of pure seminoma regardless of the findings on histological evaluation, unless some other condition associated with increased AFP levels (such as hepatitis or liver metastases) is present. More than 80% of metastatic nonseminomatous GCTs are associated with an increased AFP and/or β-hCG, whereas fewer than 20% of seminomas have increased β-hCG. Note that normal values for AFP, β-hCG, and LDH vary from laboratory to laboratory.
1. AFP is associated with embryonal carcinoma and yolk-sac tumors. It is also associated with hepatocellular carcinoma, hepatitis, and ataxia telangiectasia. The serum half-life is 4 to 7 days. Levels above 1000 and 10,000 ng/mL are associated with intermediate and poor prognosis, respectively (normal AFP < 15 ng/mL).7
2. β-hCG is increased in almost all cases of choriocarcinoma but can be moderately increased in pure seminomas. This marker, which is uniformly increased during pregnancy, can also be increased in other genitourinary cancers and in various other malignancies. The serum half-life of hCG is roughly 24 hours. Levels of hCG more than 5000 and 50,000 IU/L are associated with intermediate and poor prognosis, respectively.7
3. LDH levels increase in many different diseases, and this marker has no diagnostic utility in GCTs. This marker does play a role in...
assessing prognosis, monitoring response to treatment, and post-treatment surveillance in GCTs, most typically in seminomas. The serum half-life of LDH is roughly 24 hours. Levels more than 1.5 and 10 times the upper limit of normal are associated with intermediate and poor prognosis, respectively.7

C. Natural history
1. Lymphatic drainage and metastatic spread
   a. Management of testicular GCTs is based on the observation that these cancers tend to spread first to the retroperitoneal lymph nodes before metastasizing to more distant sites. One exception to this finding is choriocarcinoma, which tends to spread hematogenously and often presents with visceral metastases.
   b. Lymphatic drainage of the testicles proceeds superiorly adjacent to the spermatic cord before progressing to the retroperitoneum, where it follows the great vessels. Cancers of the left testicle tend to metastasize first to the para-aortic, preaortic and, less often, interaortocaval zones. Tumors of the right testicle typically spread first to the interaortocaval, precaval and, less often, preaortic zones.
   c. In the absence of retroperitoneal metastases, pelvic lymph nodes are rarely involved unless the scrotum has been violated by a surgical procedure (eg, biopsy) or by tumor invasion.
   d. In more advanced disease, lymphatic involvement may include mediastinal and supraclavicular lymph nodes.
   e. Visceral metastases most often involve the lungs followed by liver. In patients with disseminated choriocarcinoma, metastases are commonly to the brain.
2. Significance of GCT histology
   a. Pure seminomas have the best prognosis among GCTs because patients tend to present at an earlier stage and tend to be more responsive to treatment. Pure seminomas are limited to the testis approximately 66% of the time, and fewer than 10% have visceral metastases.
   b. Embryonal carcinoma is the most common cell type found in NSGCTs, and it has a tendency to metastasize early. Most patients with this tumor present with metastatic disease. In mixed GCTs, the percentage of the tumor that is composed of embryonal carcinoma correlates with the likelihood of metastatic disease. Embryonal carcinomas often result in increased AFP levels.
   c. Teratomas contain elements of at least 1 of the 3 germinal layers. Benign in children, these tumors have metastatic potential in teenagers and adults. They are rare in their pure form but are present in most mixed GCTs. Teratomas are less aggressive than other NSGCTs, but they tend to be less sensitive to chemotherapy. Surgical excision of residual masses after chemotherapy plays an important role in the management of these tumors. Patients with residual teratoma after chemotherapy have a much better prognosis than patients with residual elements of other tumor types. One of the major concerns about teratomas is their capacity to undergo malignant degeneration into sarcomas, carcinomas, and other malignancies. Primarily for this reason, residual teratomas must be resected if present after chemotherapy.
   d. Choriocarcinomas in their pure form are very rare (< 0.5% of GCTs) and have the worst prognosis of any type of GCT. They metastasize early, most commonly to lung, liver, and brain. Choriocarcinomas almost always result in increased serum β-hCG.
   e. Yolk-sac tumors (or endodermal sinus tumors) are also rare in their pure form but are often present in mixed GCTs. Of all GCTs, they are most strongly associated with AFP production. Patients with clinical stage I NSGCTs containing yolk-sac tumor elements appear to have a lower risk of relapse than those in whom this cell type is absent.

IV. DIAGNOSIS

A. Clinical presentation. Testicular cancer is typically characterized by a testicular mass or testicular enlargement; pain may or may not be present. The mass may be mistaken for epididymitis if an ultrasound is not performed. Other symptoms result from metastatic disease. Bulky retroperitoneal lymphadenopathy can result in back or
flank pain, a palpable abdominal mass, or ureteral obstruction and renal failure. Pulmonary metastases can result in chest pain, shortness of breath, and hemoptysis. Mediastinal GCTs often cause dyspnea, chest pain, cough, and/or fever.

B. Evaluating testicular masses. Testicular GCTs are generally rapidly growing cancers; therefore, early evaluation of testicular pain or enlargement is important. The work-up of testicular masses includes bilateral manual exam of the testicles along with complete physical exam with an attentive search for lymphadenopathy, abdominal masses, gynecomastia or breast tenderness, and focal neurologic deficits. Testicular enlargement generally warrants an ultrasound, which can accurately distinguish cancer from epididymitis, testicular torsion, hydrocele, varicocele, or spermatocele. Physical exam and ultrasound must include both testicles because testicular cancer is associated with a 2% to 4% incidence of cancer in the contralateral testicle.

C. Radical (inguinal) orchiectomy. If a testicular mass suspicious for malignancy is seen on ultrasound, then serum levels of tumor markers (β-hCG, AFP, and LDH) should be evaluated. The patient should have an urgent radical orchiectomy that should not be delayed for longer than a few days. Orchiectomy is performed based on the results of the physical exam and ultrasound. Malignancy is only confirmed by pathological evaluation of the orchiectomy specimen. Trans-scrotal testicular biopsy, orchiectomy, or fine needle aspiration should never be performed to evaluate testicular abnormalities because violation of the scrotum can disrupt lymphatic drainage and complicate the management. Radical orchiectomy consists of an inguinal incision between the internal and external rings. The ipsilateral testis and spermatic cord are withdrawn from scrotum through the external ring into the operative field. Although testicular biopsy or exploration is rarely done, this is the point at which it would occur. If a radical orchiectomy is being performed, the spermatic cord is cut at the level of the internal ring, then the testis and distal spermatic cord, accompanied by the testicular vessels and associated lymph tissue, are sent for pathologic evaluation.

markers are essential for staging testicular cancers. If pathology shows a testicular GCT, an abdominal and pelvic computed tomography (CT) scan should be performed unless scanning was done preoperatively. If the abdominal and pelvic CT scans show no evidence of malignancy, a plain chest radiograph or a chest CT scan should be performed. Pulmonary metastases are rarely seen in the absence of retroperitoneal disease. However, if the patient has evidence of retroperitoneal lymphadenopathy or other metastatic disease in the abdomen, a chest CT should be obtained. In patients with choriocarcinoma who have visceral metastases and a high level of β-hCG, a head CT should be considered, although there is no consensus on the β-hCG threshold for this study. Other sites should be imaged as indicated by abnormal findings on history or physical examination. Positron emission tomography has no role in the evaluation of GCTs at this time, and magnetic resonance imaging is rarely indicated.

B. Pathologic staging of the primary tumor. Staging includes determining which of the various histologic types of GCT are present and noting various features with prognostic importance. Seminomas are distinguished from nonseminomatous GCTs, and, in mixed GCTs, the proportion of each cell type within the tumor is noted. The presence of lymphovascular invasion (tumor stage T2), a high percentage of embryonal cell carcinoma, or pure choriocarcinoma are associated with higher likelihood of metastatic disease. Invasion of the scrotum (tumor stage T4), the spermatic cord (stage T3), or the tunica vaginalis (stage T2) is also associated with a higher likelihood of metastatic disease (Table 1). The size of the primary tumor is no longer considered in staging testicular cancers.

C. Staging systems. Several different staging systems exist for testicular cancer. One of the most commonly accepted systems is from the American Joint Committee on Cancer (Tables 1 and 2). In addition, an international consensus classification system divides advanced GCTs into good-, intermediate-, and poor-risk groups (Table 3). A unique aspect of staging testicular cancer is that serum tumor markers contribute substantially to staging and thus to treatment decisions (Table 2).

1. Stage I indicates tumors that have no detectable lymph node or visceral metastases anywhere. Clinical stage I tumors reflect staging by CT scan, whereas pathologic stage can only be determined by performing a retroperitoneal
lymph node dissection (RPLND) to rule out microscopic metastases.

2. Stage II includes tumors with regional lymph node metastases, β-hCG levels less than 5000 IU/L, AFP levels less than 1000 ng/mL, and LDH levels less than 1.5 times the upper limit of normal. Regional lymph nodes are the retroperitoneal and testicular vein lymph nodes. If the scrotum has been violated by surgery or by cancer, inguinal and pelvic lymph nodes may also be considered regional lymph nodes.

3. Stage III represents tumors that (1) have either spread to lymph nodes beyond the retroperitoneum or to any organ, or (2) that involve regional lymph nodes only but are associated with a β-hCG level of 5000 IU/L or more, an AFP level of 1000 ng/mL or more, or an LDH level of 1.5 or more times the upper limit of normal. Patients with visceral metastases limited to the lungs have a better prognosis than those with metastases to other organs.

D. Classification of metastatic GCTs. The International Germ Cell Consensus Classification of metastatic GCTs (Table 3) divides stage II and III testicular GCTs into good-, intermediate-, and poor-prognosis groups. Seminomas are associated with either good or intermediate prognosis based solely on the presence or absence of nonpulmonary visceral metastases. No seminomas are included in the poor-prognosis group.

1. Seminomas with good and intermediate prognosis have metastases limited to lymph nodes and/or lungs. Whether the prognosis is good or intermediate is determined by levels of β-hCG, AFP, and LDH. Poor-risk NSGCTs include tumors with nonpulmonary visceral metastases, tumors with very high serum tumor markers, and all NSGCTs with the primary tumor in the mediastinum (this last group is not classified as testicular cancer).

VI. TREATMENT OF EARLY STAGE PURE SEMINOMAS

A. Stage I pure seminomas

1. Overview. Stage I seminomas carry a particularly excellent prognosis with a long-term survival from 97% to more than 99%.

The main
challenge in treating stage I seminoma is minimizing treatment-related toxicity and avoiding mistakes in management that could result in a missed opportunity to cure the disease.

2. **Radiation therapy.** Surveillance studies indicate that roughly 85% of clinical stage I patients are cured by orchiectomy alone, although the remaining 15% will relapse. Therefore, standard postorchiectomy management involves radiation therapy to the retroperitoneal, common-iliac, and external-iliac lymph nodes at a relatively low total dose of 25 to 30 Gy. Radiation therapy lowers the relapse rate to about 3%. Acute toxicity includes dyspepsia, nausea, diarrhea, peptic ulcer disease, and possibly impaired fertility.

Historically, late toxicity included an increased incidence of gastrointestinal and genitourinary malignancies as well as melanoma and leukemia. Whether the incidence of secondary malignancies is increased after contemporary radiation therapy (ie, regimens that are currently being used) is not known. Contraindications to retroperitoneal radiation include a horseshoe kidney, a history of RPLND for previous testicular cancer, and, in some instances, inflammatory bowel disease. After radiation therapy, patients need regular follow-up evaluation for a minimum of 5 years to monitor for recurrence.

3. **Surveillance.** With only 15% of stage I seminoma patients relapsing and with the extremely high long-term survival after radiation therapy or chemotherapy for relapse, surveillance remains an option for seminoma. However, postorchiectomy radiation therapy remains the current standard of care. Studies of surveillance of stage I seminoma report an aggregate cause-specific survival rate of more than 99%. Median time to relapse is 12 to 16 months, with some relapses occurring more than 5 years after orchiectomy. Surveillance involves frequent physical examinations and chest radiographs as well as periodic CT scans of the abdomen and pelvis. Older age at diagnosis (older than 34 years), tumor size less than 3 cm in diameter, and the absence of lymphovascular invasion are associated with a lower risk of relapse for patients undergoing surveillance. Arguments against surveillance emphasize the following points:

a. The total radiation dose used to treat relapsed disease is higher than the dose given in the postorchiectomy setting; thus, the risk of radiation toxicity may be greater in patients who relapse.

b. Salvage chemotherapy—which typically involves 3 cycles of bleomycin, etoposide, and cisplatin (BEP)—is associated with various early and late toxicities, including potentially fatal bleomycin pulmonary toxicity, neutropenic sepsis, and secondary leukemia.

c. Surveillance requires an extremely high level of compliance and reliability from the patient and must be continued for more than 5 years because of the risk of late relapses.

4. **Adjunctive chemotherapy.** This approach remains experimental. Several small studies have evaluated postorchiectomy single-agent

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<th>Table 2. Testicular Cancer Stages*</th>
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TNM = tumor, necrosis, metastasis.

*See Table 1 for definitions of TNM and serum tumor markers.

chemotherapy using carboplatin with a goal of avoiding the toxicities of radiation therapy and salvage chemotherapy as well as the compliance challenges of surveillance. Unlike the BEP regimen, carboplatin is not associated with pulmonary or vascular toxicity or with an increased risk for secondary leukemia. Carboplatin is much less likely than cisplatin to result in substantial renal or neurologic toxicity. A single cycle of carboplatin is not adequate; however, 2 cycles appear to be appropriate. The largest reported series using 2 cycles of carboplatin included 107 patients, 80% of whom had T1 tumors. With a median follow-up of more than 6 years, no relapses have occurred. A phase III trial comparing this approach to radiation therapy is currently accruing patients; however, until that trial is reported, adjuvant chemotherapy remains experimental.

5. **Salvage chemotherapy for relapsed seminoma.** Patients who relapse after adjuvant radiation therapy most often have recurrence in mediastinal, supraclavicular, cervical, or pelvic lymph nodes or in the lungs. Recurrence within the irradiated field is highly unusual. Salvage chemotherapy in this setting typically consists of 3 cycles of BEP, but a fourth cycle should be given if the patient has nonpulmonary visceral metastases. Patients who have elected surveillance rather than radiation therapy and who relapse in the retroperitoneum only are treated like other seminoma patients with stage II disease. Recurrences outside the retroperitoneum are treated with chemotherapy as previously described.

B. **Stage II pure seminomas**

1. **Overview.** Stage II seminomas are classified as either bulky or nonbulky disease. Bulky stage II seminomas (lymph node mass > 5 cm) carry a worse prognosis with a disease-free survival rate of 85% to 95%, and nonbulky stage II seminomas have a cure rate between 95% and 100%, including those who

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Table 3. Prognostic Categories for Disseminated Germ Cell Tumors

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<th>Risk</th>
<th>Seminoma</th>
<th>Nonseminomatous Germ Cell Tumors</th>
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| **Good risk** | Any primary tumor, any LDH, 
β-hCG, any nodal and pulmonary metastases, and 
AFP within normal limits | Testicular primary tumor, and LDH < 1.5 × normal, and 
AFP < 1000 ng/mL, and 
β-hCG < 5000 IU/L                                                                 |
| **Intermediate risk** | Nonpulmonary visceral metastases, and 
AFP within normal limits | Retroperitoneal primary and/or intermediate tumor markers 
(LDH = 1.5–0 × normal 
AFP = 1000–10,000 ng/mL 
β-hCG = 5000–50,000 IU/L)                                                        |
| **Poor risk** | Mediastinal primary tumor, and/or highly increased markers 
(LDH > 10 × normal 
AFP > 10,000 ng/mL 
β-hCG > 50,000 IU/L) | Testicular primary tumor, and LDH < 1.5 × normal, and 
AFP < 1000 ng/mL, and 
β-hCG < 5000 IU/L                                                                 |

**Note:**
- AFP = α-fetoprotein; β-hCG = β–human chorionic gonadotropin; LDH = lactate dehydrogenase.
- Stage II and III testicular germ cell tumors.

relapse and receive salvage therapy. The total radiation dose is typically 30 to 35 Gy.17

3. Bulky stage II seminomas are treated like good-prognosis advanced stage seminomas using 3 cycles of BEP chemotherapy. Decisions regarding whether to use radiation or chemotherapy are based on tumor size; the cut-off value varies between 5 and 10 cm at different cancer centers; however, we recommend a cut-off of 5 cm. Thus, seminomas less than 5 cm are usually treated with radiation, whereas seminomas more than 5 cm are treated with chemotherapy at our center. Patients with bulky stage II seminomas may present with hydronephrosis, a palpable abdominal mass, and/or renal failure.

VII. TREATMENT OF EARLY STAGE NONSEMINOMATOUS GERM CELL TUMORS

A. Stage I nonseminomatous GCTs

1. Overview. Clinical stage I testicular NSGCTs carry an excellent prognosis with a long-term disease-free survival of about 98%. To be considered stage I, patients with increased levels of tumor markers (ie, AFP, LDH, β-hCG) must have normal levels after orchiectomy. Patients whose markers remain increased are presumed to have metastatic disease and are treated with chemotherapy. Management strategies include surveillance, RPLND, and adjuvant chemotherapy. NSGCTs are substantially less radiosensitive than seminomas, and radiation therapy has no role in managing early-stage disease.

2. Prognostic indicators. Treatment decisions about stage I NSGCTs are based largely on estimates of the individual patient’s likelihood of relapsing without additional treatment. Overall, roughly 25% to 30% of clinical stage I patients have occult metastatic disease, which in most cases is limited to retroperitoneal lymph nodes. Several pathologic features of the primary tumor help identify which patients are at a high risk for recurrence. The presence of lymphovascular invasion or a high proportion of embryonal carcinoma (30% is often cited as the cut-off value) are each associated with a higher risk for relapse. When both features are present, patients have a greater than 50% probability of micrometastatic disease. If neither is present and the patient has no other poor-risk features, the risk of recurrence is about 10%. Locally advanced clinical stage I tumors (T2 to T4) have also been associated with a higher relapse rate.

3. Surveillance

a. Highly reliable patients with a low likelihood of micrometastatic disease are good candidates for surveillance. Patients with T3 or T4 disease are generally discouraged from surveillance because of their high risk of relapse and their potential for unusual patterns of lymphatic spread. Surveillance is justified by the complications and toxicities associated with RPLND and chemotherapy as well as by the ability to successfully salvage almost all patients who relapse. Five-year survival in low-risk patients undergoing surveillance has been reported at 98% by the British Medical Research Council.18

b. Different centers use different surveillance protocols. At the author’s center, the following protocol is used. During surveillance, serum tumor markers, chest radiographs, and physical examination are repeated at every scheduled visit. During the first year, patients are seen every month. Abdominal and pelvic CTs are performed every 2 months for the first 6 months and every 3 months during months 7 to 12. During the second year, patients are seen every 2 months; abdominal and pelvic CTs are performed every 3 months. During the third year, patients are evaluated and CT scans are performed every 3 months. During the fourth year, patients are evaluated and CT scans are performed every 6 months. After the fifth year, patients are evaluated and CT scans are performed once a year; this surveillance is continued indefinitely.

Most relapses occur in the first 1 to 2 years, but late relapses are observed. Relapses beyond year 5 are rare. Rigorous adherence to the surveillance schedule is imperative, and patients who miss or postpone their appointments should be advised to consider abandoning surveillance and undergoing treatment. Patients should only be considered for surveillance
if they are likely to show up for the numerous office visits and tests.

4. Staging RPLND offers 2 major potential benefits to clinical stage I patients. It can cure a substantial number of patients who are discovered to have small volume retroperitoneal lymph node metastases (ie, pathologic stage IIA or IIB), and it provides peace of mind and a less rigorous surveillance schedule for those whose lymph nodes show no cancer (pathologic stage I). Roughly 10% of patients found to be pathological stage I will relapse, and most of these relapses occur early and in the thorax. Relapses more than 2 years after RPLND are very rare. If the RPLND reveals lymph node metastases, then patients are deemed pathologic stage II and must undergo adjuvant chemotherapy or surveillance (see Section VII. A. 5.). Interestingly, patients found to only have microscopic stage II disease with fewer than 6 nodes involved have about the same risk for relapse as pathologic stage I patients, which is approximately 10%.19

5. Adjuvant chemotherapy after orchiectomy for clinical stage I patients with high risk for relapse has produced favorable results in the few studies that have been published, but none of these studies was randomized. The role of chemotherapy in this population remains controversial because of the potential for long-term toxicity and even death from chemotherapy. Nonetheless, 2 cycles of chemotherapy (most typically BEP is used) appear to reduce the risk for relapse from approximately 50% to less than 5%, and survival is on the order of 99%.20–22 Adjuvant chemotherapy appears to produce results that are comparable to RPLND, although RPLND has a much longer track record. Patients who are at low risk for relapse are generally not considered to be candidates for adjuvant chemotherapy.

B. Stage II nonseminomatous GCTs

1. Overview. Clinical stage II patients with testicular NSGCTs have a long-term disease-free survival of about 97% to 98%. Management consists of RPLND, chemotherapy, or both. Treatment strategy is guided by the goal of minimizing toxicity and avoiding the use of combined modality therapy where possible. Choice of therapy is guided by histologic factors, tumor bulk, and serum tumor markers. Patients whose postorchietomy serum tumor markers fail to normalize in the time frame predicted (by the biological half-lives of the markers) are presumed to have stage III disease and are treated with chemotherapy (see “Testicular Cancer: II” in Hospital Physician Oncology Board Review Manual, Volume 6, Part 4).

2. RPLND can cure about 85% to 90% of patients with stage IIA NSGCTs without using adjuvant chemotherapy. For pathologic stage IIB and IIC disease, most patients will relapse unless adjuvant chemotherapy is given. Moreover, RPLND becomes more morbid in patients with IIC or bulkier IIB disease. Risk of post-RPLND relapse is higher in patients who have predominantly embryonal carcinoma. The ideal candidate for RPLND is thus the patient with clinical stage IIA or IIB disease who has a substantial amount of teratoma in the primary tumor and, at most, a small proportion of embryonal carcinoma.

3. Primary chemotherapy. Chemotherapy for clinical stage II NSGCTs is given either as primary therapy or as post-RPLND adjuvant therapy. Patients with clinical stage IIC disease are considered to have advanced stage disease and are treated accordingly (see “Testicular Cancer: II” in Hospital Physician Oncology Board Review Manual, Volume 6, Part 4). Primary chemotherapy for patients with clinical stage IIA and IIB NSGCTs has consisted of at least 3 cycles of cisplatin-based chemotherapy; patients having less than a complete response to chemotherapy are considered for subsequent RPLND. The rationale for primary chemotherapy for these patients lies in the goal of not subjecting patients to both chemotherapy and surgery. Only a few published trials have evaluated primary chemotherapy for these patients; however, 66% to 75% of the patients were able to avoid RPLND.23,24 Factors associated with the need for post-chemotherapy RPLND include the presence of teratoma in the primary tumor (teratomas are not very sensitive to chemotherapy) and bulky retroperitoneal metastases. Good candidates for primary chemotherapy include patients with predominantly embryonal cell carcinoma in their primary tumor, patients with bulky or bilateral IIB disease, patients who are highly adverse to surgery, and patients who are likely
to have trouble cooperating with post-RPLND surveillance.

4. **Adjuvant chemotherapy** after RPLND consists of 2 cycles of either BEP or, less often, etoposide and cisplatin (EP). Decisions about whether to give adjuvant chemotherapy or to perform surveillance depend on tumor bulk as well as patient preference and reliability. Only 10% to 15% of patients with IIA disease relapse after RPLND; however, 50% of IIB patients and most of IIC patients undergoing this treatment relapse. Although patients with microscopic disease involving fewer than 6 lymph nodes may be excellent candidates for surveillance, management decisions for patients with larger tumor volume are more difficult.

A randomized controlled trial assigned pathologic stage II patients either (1) to surveillance or (2) to adjuvant chemotherapy after RPLND using either 2 cycles of BEP or cisplatin, vinblastine, and bleomycin (PVB). This study found that although approximately 50% of those undergoing surveillance relapsed, survival (97% overall) was equivalent in the 2 arms because those who relapsed were successfully salvaged. Relapse is rare after adjuvant chemotherapy. Patients who relapse while on surveillance receive a minimum of 3 cycles of cisplatin-based chemotherapy. Although adjuvant chemotherapy exposes patients who would not relapse to unnecessary toxicity, it also lessens the number of cycles of chemotherapy for those who would relapse if surveillance were used to manage them.

Surveillance requires that both the physician and the patient adhere strictly to the schedule of office visits and tests. Surveillance schedules vary from center to center but in the first 2 years include frequent physical examinations, serum tumor marker measurement, and chest radiographs as well as regular chest CT scans. Relapses more than 2 years after RPLND are rare, but surveillance at progressively longer intervals should be continued for at least 5 years.

**BOARD REVIEW QUESTIONS**

Choose the single best answer for each question.

1. A patient has recent development of pain and enlargement of the left testicle. Ultrasound reveals hypoechoic testicular masses. Serum tumor markers are measured, and the patient is referred for a radical orchiectomy. Laboratory tests show normal serum levels of \( \beta \)-hCG and LDH, but the serum AFP level is 100 ng/mL. Pathologic examination shows that the testicle contains a tumor consisting of pure seminoma with lymphovascular invasion. CT scans of the chest, abdomen, and pelvis reveal no evidence of lymphatic or visceral metastases. Postorchiectomy serum tumor markers are normal. Each of the following management schemes is appropriate for this patient EXCEPT:

   A) Close surveillance with frequent physical examinations, tumor marker measurements, and periodic CT scans
   B) RPLND
   C) Two cycles of cisplatin-based chemotherapy
   D) Retroperitoneal radiation therapy

2. In a patient with stage I testicular germ cell tumor (GCT), which of the following pathologic findings would NOT be associated with a higher risk for micrometastatic disease?

   A) Presence of yolk-sac tumor
   B) Tumor contains more than 50% embryonal carcinoma
   C) Tunica vaginalis invasion
   D) Lymphovascular invasion
   E) Scrotal invasion

**DETAILED ANSWERS**

1. (D) Retroperitoneal radiation therapy. This patient has a clinical stage I mixed GCT. Although pure seminomas can cause elevations in serum \( \beta \)-hCG or LDH levels, they are not associated with elevations in the AFP level. AFP is produced by embryonal carcinoma and yolk-sac tumors. Elevations in AFP thus exclude the diagnosis of pure seminoma. Mixed GCTs are not very radiosensitive, and radiation plays no major role in their management except when it is used to treat brain metastases. In the United States, stage I mixed GCTs are typically managed with either surveillance or RPLND. Two cycles of BEP is an option; this approach is common in Europe.

2. (A) Presence of yolk-sac tumor. Many studies of clinical stage I patients who are managed with surveillance have attempted to identify factors for predicting the risk for recurrence. The pathology findings that have the strongest association with distant recurrence are lymphovascular invasion and locally advanced tumors.
(T2 to T4). Many studies have also found that tumors with a high proportion of embryonal carcinoma are more likely to recur. However, embryonal carcinomas tend to display lymphovascular invasion, so it has been difficult to confirm that the presence of embryonal carcinoma increases the risk of recurrence in the absence of lymphovascular invasion. On the other hand, some evidence indicates that the presence of yolk-sac tumor in the testicle is associated with a lower risk of recurrence.

REFERENCES