STAGE I NONSEMINOMA

Patients with radiographs and physical examination showing no evidence of disease and serum AFP and hCG concentrations that are either normal or declining to normal according to the known half-life have clinical stage I disease. Approximately 20–50% of such patients will have retroperitoneal lymph node metastases (pathologic stage II) but will still be cured in over 95% of cases. Depending on risk of relapse, which is determined by the pathology (see below), surveillance, a nerve-sparing retroperitoneal lymph node dissection (RPLND), or adjuvant chemotherapy (one to two cycles of bleomycin, etoposide, and cisplatin [BEP]) may be appropriate choices depending on *the availability of surgical expertise and patient and physician preference*. If the primary tumor shows no evidence for lymphatic or vascular invasion and is limited to the testis (T1, clinical stage IA), then the risk of relapse is only 10–20%. Because over 80% of patients with clinical stage IA nonseminoma are cured with orchiectomy alone and there is no survival advantage to RPLND (or adjuvant chemotherapy), surveillance is the preferred treatment option. This avoids overtreatment with the potential for both acute and long-term toxicities (see below). Surveillance requires patients to be carefully followed with periodic chest radiography, physical examination, CT scan of the abdomen, and serum tumor marker determinations. The median time to relapse is approximately 7 months, and late relapses (>2 years) are rare. Noncompliant patients can be considered for RPLND or adjuvant BEP.

If lymphatic or vascular invasion is present or the tumor extends *through* the tunica, spermatic cord, or scrotum (T2 through T4, clinical stage IB), then the risk of relapse is approximately 50%, and RPLND and adjuvant chemotherapy can be considered. Relapse rates are reduced to 3–5% after one to two cycles of adjuvant BEP. All three approaches (surveillance, RPLND, and adjuvant BEP) should cure >95% of patients with clinical stage IB disease.

RPLND is the standard operation for removal of the regional lymph nodes of the testis (retroperitoneal nodes). The operation removes the lymph nodes draining the primary site and the nodal groups adjacent to the primary landing zone. The standard (modified bilateral) RPLND removes all node-bearing tissue down to the bifurcation of the great vessels, including the ipsilateral iliac nodes. The major long-term effect of this operation is retrograde ejaculation with resultant infertility. Nerve-sparing RPLND can preserve anterograde ejaculation in ~90% of patients. Patients with pathologic stage I disease are observed, and only the <10% who relapse require additional therapy. If nodes are found to be involved at RPLND, then a decision regarding adjuvant chemotherapy is made on the basis of the extent of retroperitoneal disease (see "Stage II Nonseminoma" below). Hence, because less than 20% of patients require chemotherapy, of the three approaches, RPLND results in the lowest number of patients at risk for the late toxicities of chemotherapy.

STAGE II NONSEMINOMA

Patients with limited, ipsilateral retroperitoneal adenopathy ≤2 cm in largest diameter and normal levels of AFP and hCG can be treated with either a modified bilateral nerve-sparing RPLND or chemotherapy. The local recurrence rate after a properly performed RPLND is very low. Depending on the extent of disease, the postoperative management options include either surveillance or two cycles of adjuvant chemotherapy. Surveillance is the preferred approach for patients with resected "low-volume" metastases (tumor nodes ≤2 cm in diameter *and* <6 nodes involved) because the probability of relapse is one-third or less. For those who relapse, risk-directed chemotherapy is indicated (see section on advanced GCT below). Because relapse occurs in ≥50% of patients with "high-volume" metastases (>6 nodes involved, *or* any involved node >2 cm in largest diameter, *or* extranodal tumor extension), two cycles of adjuvant chemotherapy should be considered, as it results in a cure in ≥98% of patients. Regimens consisting of etoposide plus cisplatin (EP) with or without bleomycin every 3 weeks are effective and well tolerated.

Increased levels of either AFP or hCG imply metastatic disease outside the retroperitoneum; full-dose (not adjuvant) chemotherapy is used in this setting. Primary management with chemotherapy is also favored for patients with larger (>2 cm) or bilateral retroperitoneal nodes (see section on advanced GCT below).

STAGES I AND II SEMINOMA

Inguinal orchiectomy followed by immediate retroperitoneal radiation therapy or surveillance with treatment at relapse both result in cure in nearly 100% of patients with stage I seminoma. Historically, radiation was the mainstay of treatment, but the reported association between radiation and secondary malignancies and the absence of a survival advantage of radiation over surveillance has led many to favor surveillance for compliant patients. Approximately 15% of patients relapse, which is usually treated with chemotherapy. Long-term follow-up is essential, because approximately 30% of relapses occur after 2 years and 5% occur after 5 years. A single dose of carboplatin has also been investigated as an alternative to radiation therapy; the outcome was similar, but long-term safety data are lacking, and the retroperitoneum remained the most frequent site of relapse.

Generally, nonbulky retroperitoneal disease (stage IIA and small IIB) is treated with retroperitoneal radiation therapy. Approximately 90% of patients achieve relapse-free survival with retroperitoneal masses <3 cm in diameter. Due to higher relapse rates after radiation for bulkier disease, initial chemotherapy is preferred for all stage IIC and some stage IIB patients. Chemotherapy has been studied as an alternative to radiation for stage IIA and small stage IIB seminoma with lower recurrence rates compared with historical controls. These results, combined with studies demonstrating a threefold increase in the incidence of secondary malignancies and cardiovascular disease among patients who receive both radiation and chemotherapy (patients relapsing after radiation fall into this category), have led some experts to prefer chemotherapy for all stage II seminomas.

CHEMOTHERAPY FOR ADVANCED GCT

Regardless of histology, all patients with stage IIC and stage III and most with stage IIB GCT are treated with chemotherapy. Combination chemotherapy programs based on cisplatin at doses of 100 mg/m^2 plus etoposide at doses of 500 mg/m^2 per cycle cure 70–80% of such patients, with or without bleomycin, depending on risk stratification (see below). A complete response (the complete disappearance of all clinical evidence of tumor on physical examination and radiography plus normal serum levels of AFP and hCG for ≥1 month) occurs after chemotherapy alone in ~60% of patients, and another 10–20% become disease free with surgical resection of residual masses containing viable GCT. Lower doses of cisplatin result in inferior survival rates.

The toxicity of four cycles of the BEP is substantial. Nausea, vomiting, and hair loss occur in most patients, although nausea and vomiting have been markedly ameliorated by modern antiemetic regimens. Myelosuppression is frequent, and symptomatic bleomycin pulmonary toxicity occurs in ~5% of patients. Treatment-induced mortality due to neutropenia with septicemia or bleomycin-induced pulmonary failure occurs in 1–3% of patients. Dose reductions for myelosuppression are rarely indicated. Long-term permanent toxicities include nephrotoxicity (reduced glomerular filtration and persistent magnesium wasting), ototoxicity, peripheral neuropathy, and infertility. When bleomycin is administered by weekly bolus injection, Raynaud's phenomenon appears in 5–10% of patients. Other evidence of small blood vessel damage, such as transient ischemic attacks and myocardial infarction, is seen less often.

RISK-DIRECTED CHEMOTHERAPY

Because not all patients are cured and treatment may cause significant toxicities, patients are stratified into "good-risk," "intermediate-risk," and "poor-risk" groups according to pretreatment clinical features established by the International Germ Cell Cancer Consensus Group **(Table 116-1)**. For good-risk patients, the goal is to achieve