

*Medical Progress***TESTICULAR GERM-CELL CANCER**

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**A**PPROXIMATELY 95 percent of malignant tumors arising in the testis are germ-cell tumors, a term that indicates their origin in primordial germ cells. Germ-cell tumors also occasionally arise in extragonadal primary sites, and their management follows that of testicular germ-cell tumors. More than 90 percent of patients with newly diagnosed germ-cell tumors are cured, and delay in diagnosis correlates with a higher stage at presentation for treatment.<sup>1,2</sup> Management has changed substantially in the past 20 years, largely because of the ability of cisplatin-containing combination chemotherapy to cure advanced disease.<sup>3</sup> In this review, we discuss recent developments in our understanding of germ-cell-tumor biology, in the classification of disease stages, and in treatment.

**EPIDEMIOLOGY**

Approximately 7200 new cases of germ-cell tumor, the commonest solid tumor in men between the ages of 15 and 34,<sup>4</sup> will be diagnosed in the United States in 1997. The worldwide incidence has more than doubled over the past 40 years.<sup>5</sup> The incidence varies according to geographic area; it is highest in Scandinavia, Germany, and New Zealand, intermediate in the United States, and lowest in Asia and Africa.

Germ-cell tumors are seen principally in whites. Recent data show a white-to-black incidence ratio of approximately 5 to 1, and a report from the U.S. military showed a relative incidence of 40 to 1.<sup>6</sup> The cause of germ-cell tumors is unknown. Familial clustering has been observed, particularly among siblings.<sup>7</sup> Cryptorchidism and Klinefelter's syndrome are predisposing factors in the development of germ-cell

tumors arising from the testis and mediastinum, respectively.<sup>8</sup> Orchiopexy performed before puberty reduces the risk of germ-cell tumors and improves the ability to observe the testis. Human immunodeficiency virus infection may result in a higher incidence of germ-cell tumors, but this association requires further study.<sup>9,10</sup> Despite anecdotal evidence associating exposure to diethylstilbestrol with the development of this tumor,<sup>11,12</sup> epidemiologic studies have failed to identify an association.<sup>13</sup>

**HISTOLOGY AND TUMOR BIOLOGY****Histology**

Carcinoma in situ (intratubular germ-cell neoplasia) is the precursor of invasive germ-cell tumors and is found in essentially every case of testicular germ-cell tumor.<sup>14-16</sup> Carcinoma in situ usually becomes an invasive germ-cell tumor in a median period of approximately five years.<sup>17</sup>

Germ-cell tumors are classified as seminomatous or nonseminomatous, reflecting their origin in primordial germ cells and their remarkable ability to differentiate in vivo (Table 1).<sup>18</sup> Most nonseminomatous germ-cell tumors include multiple cell types, and seminoma may be a component. When seminomatous and nonseminomatous areas are both present in a tumor, management should follow that for nonseminomatous tumors, since these tumors are more clinically aggressive. Therefore, a tumor is diagnosed as a seminoma only if the histologic results show pure seminoma and if the serum concentration of alpha-fetoprotein, a marker of nonseminomatous tumors, is normal.

Seminomas account for approximately one half of all testicular germ-cell tumors and are most frequent in the fourth decade of life. There may be a high mitotic rate (anaplastic), syncytiotrophoblastic giant cells, and an increased serum concentration of human chorionic gonadotropin (hCG), but these do not influence management.<sup>19</sup> Spermatocytic seminoma is a rare histologic variant that is not associated with carcinoma in situ; thus, its relation to other germ-cell tumors is uncertain.<sup>20</sup> Spermatocytic seminomas rarely metastasize, and they present almost exclusively in elderly men. The only recommended treatment is radical orchiectomy.

The incidence of nonseminomatous germ-cell tumors peaks in the third decade of life. These tumors are composed of embryonal carcinoma, teratoma, choriocarcinoma, and yolk-sac carcinoma (endodermal-sinus tumor) cell types. Embryonal carcinoma is the most undifferentiated cell type, with totipoten-

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tial capacity to differentiate to the other nonseminomatous cell types. Embryonal carcinoma may produce elevated serum concentrations of hCG, alpha-fetoprotein, or both.

Choriocarcinoma consists of cytotrophoblasts and syncytiotrophoblasts. Pure choriocarcinoma is rare and is usually associated with widely metastatic disease and high serum concentrations of hCG. Yolk-sac tumors mimic the embryonic yolk sac histologically and nearly always produce alpha-fetoprotein. Pure yolk-sac histologic findings are frequently present in germ-cell tumors arising in the mediastinum.

Teratoma is composed of somatic cell types from two or more germ-cell layers (ectoderm, mesoderm, or endoderm). Mature teratomas consist of adult-type differential cell types, such as cartilage or mucin-producing glandular epithelium. Immature teratomas are tumors with partial somatic differentiation, similar to that seen in a fetus. On rare occasions, a teratoma develops aggressive growth and histologically resembles a somatic cancer such as rhabdomyosarcoma, adenocarcinoma, or primitive neuroectodermal tumor.<sup>21</sup> This is called a teratoma with malignant transformation, and it may occur in the setting of a germ-cell tumor arising from any primary site.<sup>21</sup> Acute leukemia has been associated with germ-cell tumors arising from the mediastinum.<sup>22</sup>

**Genetics**

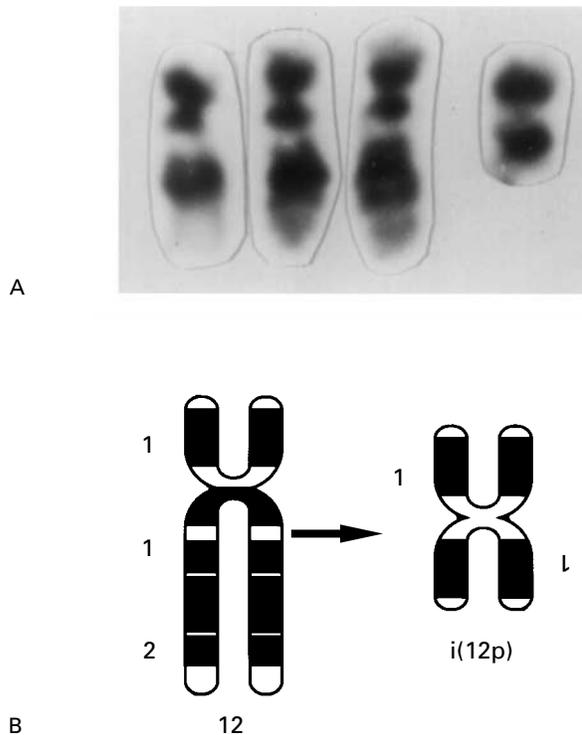
Germ-cell tumors are nearly always hyperdiploid and are frequently triploid or tetraploid.<sup>23</sup> Hyperdiploidy implies that chromosomal endoreduplication is one early event in germ-cell transformation.<sup>24</sup> Germ-cell tumors have at least one X and one Y chromosome, implying that transformation occurs in a germ cell before meiotic anaphase.

An isochromosome of the short arm of chromosome 12, i(12p), is a specific genetic marker of germ-cell tumors and has been identified in all histologic subtypes and in carcinoma in situ (Fig. 1).<sup>25,26</sup> In germ-cell tumors not displaying i(12p), excess 12p genetic material has been found on marker chromosomes with aberrant banding consisting of repetitive 12p segments.<sup>27</sup> Therefore, excess 12p genetic material is present in all germ-cell tumors and represents one of the earliest genetic events in malignant transformation. The i(12p) chromosomal marker has been identified in the acute leukemia associated with mediastinal germ-cell tumors and in teratomas with malignant transformation, establishing the clonal germ-cell-tumor origin of these cell types.<sup>28,29</sup>

In addition to genomic gain (hyperdiploidy and excess 12p copy number), widespread genetic loss is also frequent.<sup>25,30</sup> Chromosome 12q displays two common sites of nonrandom loss. At band 12q22.2, a homozygous deletion has been observed, suggesting that a tumor-suppressor gene exists that may be

**TABLE 1. HISTOLOGIC CLASSIFICATION OF TESTICULAR NEOPLASMS.**

Germ-cell tumors
Seminoma
Classic (typical)
Anaplastic
Spermatocytic
Embryonal carcinoma
Teratoma
Mature
Immature
Mature or immature, with malignant transformation
Choriocarcinoma
Yolk-sac tumor (endodermal-sinus tumor)
Mixed germ-cell tumor (specify all individual cell types)
Sex-cord-stromal tumors
Sertoli-cell tumor
Leydig-cell tumor
Granulosa-cell tumor
Both germ-cell and gonadal stromal elements
Gonadoblastoma
Adnexal and paratesticular tumors
Adenocarcinoma of rete testis
Mesothelioma
Miscellaneous neoplasms
Carcinoid
Lymphoma
Cysts



**Figure 1. A Genetic Marker of Germ-Cell Tumors.**

Panel A shows abnormalities of 12p in a male with three normal chromosomes 12 and an isochromosome of the short arm of the chromosome, i(12p) (modified from Bosl et al.,<sup>5</sup> with the permission of the publisher). Panel B shows a normal chromosome 12 and the i(12p) chromosomal marker.

specific to germ-cell tumors.<sup>31</sup> Therefore, genetic loss must also be an early transformational event.

#### Immunohistochemical Markers

Seminomas do not express markers of somatic differentiation such as keratins. Embryonal carcinoma, choriocarcinoma, and yolk-sac carcinoma express low-molecular-weight keratins.<sup>32</sup> Both seminomatous and nonseminomatous germ-cell tumors express placental alkaline phosphatase.<sup>33</sup> These immunohistochemical markers are sometimes useful for evaluating malignant tumors of uncertain origin.

### DIAGNOSIS

#### Clinical Presentation

A painless testicular mass is pathognomonic of a primary testicular tumor, occurring in a minority of patients. The majority present with diffuse testicular pain, swelling, hardness, or some combination of these findings. Since infectious epididymitis or orchitis is more common than tumor, a trial of antibiotic therapy is often undertaken. If testicular discomfort does not abate or findings do not revert to normal within two to four weeks, a testicular ultrasound examination is indicated. On ultrasonography, the typical germ-cell tumor is intratesticular and may produce one or more discrete hypoechoic masses or diffuse abnormalities with microcalcifications. Bilateral tumors are rare at diagnosis, but in 2 percent of patients with one testicular germ-cell tumor, a metachronous new primary tumor will develop in the remaining testis. Hence, all patients are taught self-examination.

A radical inguinal orchiectomy with ligation of the spermatic cord at the internal ring is required for all patients with suspected testicular tumors. Since the testis embryologically originates in the genital ridge and descends during fetal life through the abdomen and inguinal canal into the scrotum, the primary lymphatic and vascular drainage of the testis is to the retroperitoneal lymph nodes (the primary landing zones) and the renal or great vessels, respectively. Transscrotal orchiectomy is contraindicated, because it leaves the inguinal portion of the spermatic cord intact and predisposes the patient to scrotal skin and inguinal and pelvic nodal metastases.

Ninety-five percent of tumors originating in the testis are germ-cell tumors (Table 1). Fewer than 10 percent of all germ-cell tumors arise from extragonadal primary sites, with the mediastinum and retroperitoneum the most common. Retroperitoneal primary tumors may present with back pain (psoas-muscle invasion) or an abdominal mass. Patients with mediastinal primary tumors usually present with shortness of breath, chest pain, or superior vena cava syndrome. An adequate biopsy is required to identify the tumor type and to perform immunohistochemical and genetic studies. In all extragonadal

presentations, testicular ultrasound examination is necessary to rule out the testis as the primary site.

#### Pattern of Metastases

Regional metastases first appear in retroperitoneal lymph nodes below the renal vessels. Right testicular tumors usually metastasize to nodes between the aorta and the inferior vena cava (interaortocaval nodes), and left testicular tumors to nodes lateral to the aorta (para-aortic).<sup>34,35</sup> Superiorly, the lymphatics empty into the cisterna chyli, sometimes leading to retrocaval and posterior mediastinal adenopathy. Left supraclavicular adenopathy and pulmonary nodules may occur with or without retroperitoneal disease. Liver, bone, or brain is rarely seen as the sole site of metastasis.

#### Radiographic Evaluation

Computed tomographic (CT) imaging of the abdomen and pelvis and chest radiography are required. Lymph nodes in the retroperitoneal landing zones that measure between 10 and 20 mm are involved by germ-cell tumors in about 70 percent of cases.<sup>36</sup> CT imaging of the chest is required if mediastinal, hilar, or lung parenchymal disease is suspected. CT or magnetic resonance imaging of the brain is performed in patients with neurologic signs or symptoms.

#### Serum Tumor Markers

Alpha-fetoprotein production is restricted to nonseminomatous germ-cell tumors, specifically embryonal carcinoma and yolk-sac tumor. Increased alpha-fetoprotein concentrations may be seen at any stage; between 40 and 60 percent of patients with metastases have increased serum concentrations. Conditions other than germ-cell tumors in which elevated alpha-fetoprotein concentrations may be detected in serum include liver damage (infectious or drug- or alcohol-induced), hepatocellular carcinoma, and other cancers arising from the gastrointestinal tract.

Increased serum concentrations of hCG may be observed in both seminomas and nonseminomatous tumors. Since the  $\alpha$  subunit is common to several pituitary hormones, radioimmunoassays for hCG are directed at the  $\beta$  subunit. Increased hCG concentrations are seen in 40 to 60 percent of patients with metastatic nonseminomatous germ-cell tumors, and 15 to 20 percent of patients with metastatic seminomas. Causes of false positive hCG results include cross-reactivity of the antibody with luteinizing hormone and treatment-induced hypogonadism.

A third serum marker, lactate dehydrogenase, is less specific but has independent prognostic value in patients with advanced germ-cell tumors. Serum lactate dehydrogenase concentrations are also increased in approximately 60 percent of patients with nonseminomatous germ-cell tumors and 80 percent of those with seminomatous germ-cell tumors.<sup>37,38</sup>

Serum tumor-marker concentrations are determined before, during, and after treatment and throughout long-term follow-up. Increased or rising concentrations of alpha-fetoprotein, hCG, or both, without radiographic or clinical findings, imply active disease and are sufficient reason to initiate treatment if likely causes of false positive results have been ruled out. After surgery and chemotherapy, the concentrations of tumor markers should decrease according to their known half-lives. The serum half-lives of alpha-fetoprotein and hCG are 5 to 7 days and 30 hours, respectively. A plateau or slow clearance suggests residual active disease.<sup>39</sup>

#### Classification of Disease Stages

In North America, the extent of a germ-cell tumor is classified as follows: stage I disease is limited to the testis, epididymis, or spermatic cord; stage II disease is limited to the retroperitoneal lymph nodes and divided into stages IIA (nodes less than 2 cm in maximal diameter), IIB (nodes between 2 and 5 cm in diameter), and IIC (nodes greater than 5 cm in diameter); stage III disease is metastatic to supradiaphragmatic nodal or visceral sites.

Recently, the American Joint Committee on Cancer and the Union Internationale contre le Cancer revised the tumor–node–metastasis system of classification.<sup>5</sup> Stage I is subdivided into tumors with or without lymphatic or vascular invasion and those patients with persistently elevated alpha-fetoprotein or hCG concentrations in the absence of clinical or radiographic evidence of metastatic disease. Stage II includes retroperitoneal nodal disease without distant metastases, with or without increased marker levels. Stage III includes presentations with only distant metastases or high serum tumor-marker values. This is the first time the tumor–node–metastasis system of classification has been expanded to include a prognostically important tumor-specific marker.

### THERAPY FOR LOW-STAGE GERM-CELL TUMORS

#### Seminoma

After radical inguinal orchiectomy, patients with stage I, IIA, or IIB disease are treated with radiation to the retroperitoneal and ipsilateral pelvic lymph nodes. Prophylactic mediastinal radiation therapy is not given, since relapse in the mediastinum occurs in few patients.<sup>40</sup> Relapse occurs in approximately 4 percent of patients with stage I seminomas and 10 percent of patients with stage IIA or IIB seminomas.<sup>40-45</sup> Chemotherapy cures more than 90 percent of patients who have a relapse after radiation therapy.<sup>37</sup> Thus, approximately 99 percent of patients with low-stage seminomas are ultimately cured.

Surveillance has been suggested as an alternative to radiation therapy for stage I seminoma.<sup>46,47</sup> With-

out radiation therapy, between 15 and 20 percent of patients have a relapse. The median time to relapse is 12 months, and relapse may occur more than 5 years after presentation.<sup>47</sup> Since the morbidity associated with radiation therapy is low, surveillance for stage I seminoma is generally not recommended in the United States.

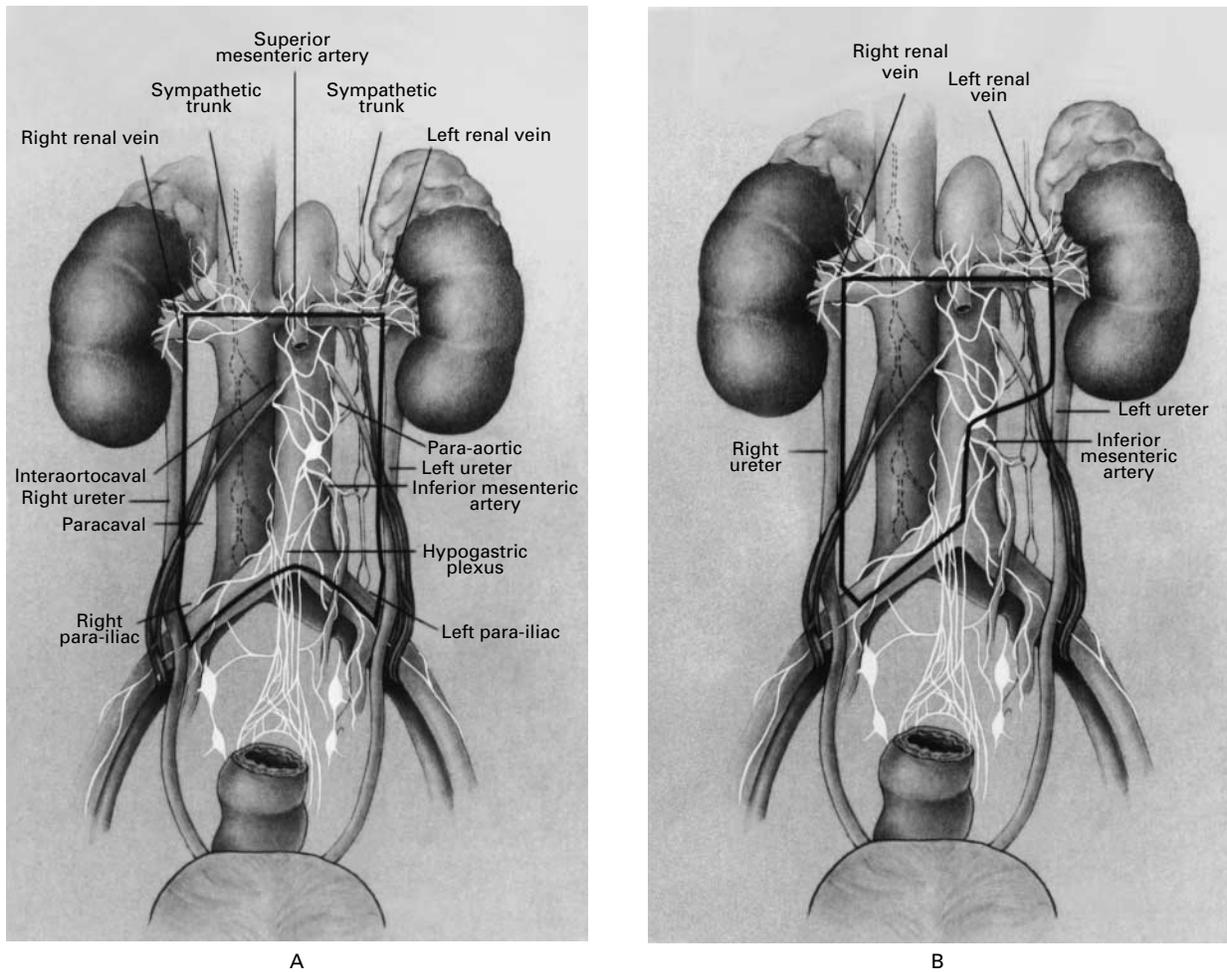
#### Stage I Nonseminomatous Tumor

The rate of cure for patients with nonseminomatous tumors in clinical stage I exceeds 95 percent. Twenty percent of patients with stage I tumors with no lymphatic or vascular invasion or invasion into the tunica albuginea, spermatic cord, or scrotum are discovered to have regional lymph-node or distant metastases at operation. Surveillance and nerve-sparing retroperitoneal lymph-node dissection are both standard treatment options.<sup>48,49</sup>

The strategy of surveillance is predicated on a high cure rate with chemotherapy in patients who have a relapse and rigorous adherence to standardized, periodic follow-up evaluations. Approximately 20 percent of patients will have a relapse (usually in the retroperitoneum) and require chemotherapy.<sup>48,50-54</sup>

The alternative approach is a nerve-sparing retroperitoneal lymph-node dissection. About 20 percent of patients will have involved lymph nodes.<sup>49,55</sup> The principal complication of bilateral dissection (Fig. 2A) is retrograde ejaculation and infertility. The sympathetic nerves can be spared by dissecting the nerves or avoiding the nerve-containing anatomical region. Recent nerve-dissection techniques preserve antegrade ejaculation in about 90 percent of cases. Template dissections avoiding the contralateral sympathetic chain, postganglionic sympathetic fibers, and hypogastric plexus (Fig. 2B) preserve ejaculation in about 80 percent of patients.<sup>56,57</sup> If the lymph nodes are not involved with tumor, the disease is managed with periodic follow-up alone. If the resected lymph nodes are involved with tumor, management follows the principles for stage II disease.

The presence of lymphatic, vascular, scrotal, or spermatic-cord invasion by the primary testicular tumor increases the likelihood of retroperitoneal nodal involvement to 50 percent or greater. In this setting, nerve-sparing retroperitoneal lymph-node dissection is preferable to surveillance because of the high likelihood of relapse with the latter.<sup>55</sup> A few reports recommend two cycles of chemotherapy rather than retroperitoneal lymph-node dissection for these high-risk patients with stage I disease.<sup>58-60</sup> Relapses are rare, but the length of follow-up is variable, and the long-term risks have not been determined. Since most patients would never need chemotherapy if nerve-sparing retroperitoneal lymph-node dissection had been performed, chemotherapy in this situation is generally not recommended in the United States.



**Figure 2.** Modified Bilateral Retroperitoneal Lymph-Node Dissection. Panel A shows a standard dissection (dark outline). The anatomical locations of the lymph nodes are shown. Panel B shows a modified nerve-avoiding template for a right testicular tumor. (Courtesy of Memorial Sloan-Kettering Cancer Center.)

Patients with persistently increased concentrations of alpha-fetoprotein, hCG, or both, but without other clinical evidence of disease after orchiectomy, usually have disease outside the retroperitoneum.<sup>61,62</sup> These patients should undergo three or four cycles of standard chemotherapy rather than surgery.

**Stage II Nonseminomatous Tumor**

Patients with stage II nonseminomatous tumors are treated initially with either retroperitoneal lymph-node dissection or chemotherapy, depending on the extent of disease, serum tumor-marker concentrations, and the presence or absence of tumor-related symptoms. Asymptomatic patients with solitary retroperitoneal lymph nodes less than 3 cm in diameter as assessed by CT imaging generally undergo retroperitoneal lymph-node dissection. After a properly

performed operation, recurrences within the retroperitoneum are rare.

Retroperitoneal lymph-node dissection is often curative. Relapse rates average less than 35 percent when the pathological examination shows that any lymph node involved with tumor is 2 cm or less in diameter and five or fewer nodes are involved.<sup>63-66</sup> Adjuvant chemotherapy is not generally indicated in this setting, because most patients would be treated unnecessarily, and the cure rate is the same with chemotherapy at relapse as long as the patient reports for follow-up examinations.

Adjuvant chemotherapy is an important consideration when any involved node is more than 2 cm in diameter, at least six nodes are involved, or there is extranodal invasion. A majority of patients in this group have a relapse if adjuvant chemotherapy is not

given. Two cycles of adjuvant cisplatin-based chemotherapy will cure approximately 99 percent of patients.<sup>64,65,67-70</sup> Although the rate of cure is the same when chemotherapy is withheld until relapse, patients who receive adjuvant therapy require fewer cycles of chemotherapy and avoid additional surgery. Two cycles of etoposide plus cisplatin with or without bleomycin are administered at three-week intervals (Table 2).

**CHEMOTHERAPY FOR ADVANCED DISEASE**

Initial chemotherapy is required in approximately one third of patients with germ-cell tumors. Patients with clinical stage IIC disease and primary retroperitoneal and mediastinal seminomas receive initial chemotherapy, since relapse is frequent when these patients are treated with radiation therapy only.<sup>40,42,44,71,72</sup> Patients also receive initial chemotherapy if they have nonseminomatous stage III germ-cell tumors or stage II disease with multifocal retroperitoneal lymph-node involvement, lymph nodes more than 3 cm in diameter, or tumor-related back pain.

The first combination chemotherapy regimens containing cisplatin, vinblastine, and bleomycin (with or without other drugs) resulted in complete remission in 70 to 80 percent of patients with metastatic germ-cell tumors.<sup>38,73</sup> Subsequent studies showed that prolonged maintenance chemotherapy was unnecessary,<sup>74</sup> and vinblastine was replaced by etoposide, which is less toxic and probably more efficacious.<sup>75</sup> Serious adverse effects of combination chemotherapy include neuromuscular toxic effects,<sup>75</sup> death from myelosuppression or bleomycin-induced pulmonary fibrosis,<sup>75</sup> and Raynaud's phenomenon.<sup>76</sup>

The high cure rate and substantial toxicity of combination chemotherapy resulted in an effort to identify patients more likely ("good-risk") and less likely ("poor-risk") to be cured with standard chemotherapy. Extent of disease and serum tumor-marker concentrations were identified as independent predictors of prognosis,<sup>77-79</sup> and previously untreated patients with metastatic disease were subdivided into good-risk and poor-risk groups (Table 3).

**Good-Risk Patients**

Treatment programs for patients with good-risk germ-cell tumors were designed to maximize the efficacy and minimize the toxicity of the treatment. Since bleomycin has pulmonary toxicity, contributes to myelosuppression,<sup>80</sup> and is associated with Raynaud's phenomenon, reduction of exposure to bleomycin was the focus of most trials in good-risk patients (Table 4).

Elimination of bleomycin was evaluated in three randomized trials. Four cycles of etoposide (500 mg per square meter of body-surface area per cycle) and cisplatin were found to be therapeutically equivalent

**TABLE 2. COMMONLY USED CHEMOTHERAPY REGIMENS FOR METASTATIC GERM-CELL TUMORS.\***

TUMOR STATUS	REGIMEN
Previously untreated — good risk	Four cycles of etoposide (100 mg/m <sup>2</sup> IV daily for 5 days) and cisplatin (20 mg/m <sup>2</sup> IV daily for 5 days) administered at 21-day intervals or Three cycles of etoposide (100 mg/m <sup>2</sup> IV daily for 5 days), cisplatin (20 mg/m <sup>2</sup> IV daily for 5 days), and bleomycin (30 units IV weekly on days 2, 9, and 16) administered at 21-day intervals
Previously untreated — poor risk	Four cycles of etoposide (100 mg/m <sup>2</sup> IV daily for 5 days), cisplatin (20 mg/m <sup>2</sup> IV daily for 5 days), and bleomycin (30 units IV weekly on days 2, 9, and 16) administered at 21-day intervals
Previously treated — first-line salvage therapy	Ifosfamide (1.2 g/m <sup>2</sup> IV daily for 5 days), mesna (400 mg/m <sup>2</sup> IV every 8 hr for 5 days), and cisplatin (20 mg/m <sup>2</sup> IV daily for 5 days) plus either vinblastine (0.11 mg/kg of body weight IV on days 1 and 2) or etoposide (75 mg/m <sup>2</sup> IV daily for 5 days)

\*IV denotes intravenous.

to a five-drug treatment program that contained cisplatin, vinblastine, bleomycin, dactinomycin, and cyclophosphamide.<sup>81</sup> In the study conducted by the European Organization for the Research and Treatment of Cancer, four cycles of bleomycin, etoposide, and cisplatin were compared with four cycles of etoposide and cisplatin, and the proportion of patients who had a complete response was higher in the three-drug arm.<sup>88</sup> However, the etoposide dose in this European study was 360 mg per square meter per cycle; the results cannot be compared with those of the American trials, which used a two-drug regimen with an etoposide dose of 500 mg per square meter per cycle. The Eastern Cooperative Oncology Group compared three cycles of bleomycin, etoposide, and cisplatin with three cycles of etoposide and cisplatin. This study was terminated early because of an increased number of adverse events (relapse or failure to achieve complete remission) in the two-drug group.<sup>83</sup>

A study by the Eastern Cooperative Oncology Group evaluated the effect of reducing the number of bleomycin cycles.<sup>82</sup> The study compared the efficacy of three and four cycles of bleomycin, etoposide, and cisplatin. Disease-free survival and overall survival were equal in both groups of patients. Two randomized trials compared the efficacy of cisplatin and carboplatin. These studies were undertaken because carboplatin has less neurologic and gastrointestinal toxicity than cisplatin. Both trials showed that chemotherapy programs that substituted carboplatin for cisplatin had inferior efficacy.<sup>84,85</sup> Therefore, these carboplatin-containing programs have no

**TABLE 3. RISK CLASSIFICATIONS USED TO ASSIGN PATIENTS IN CLINICAL TRIALS.\***

Risk Group	SLOAN-KETTERING	INDIANA	INTERNATIONAL	
			SEMINOMA	NONSEMINOMA
Good risk	Any seminoma	Elevated hCG, AFP, or both	Any hCG elevation	AFP, <1000 ng/ml
	Nonseminoma with probability of complete response $\geq 0.5$ on the basis of a mathematical model that incorporates the number of sites of metastasis and the serum LDH and hCG concentrations	Cervical nodes (with or without nonpalpable retroperitoneal nodes) Unresectable but nonpalpable retroperitoneal disease Minimal pulmonary metastases (<5 per lung field, largest <2 cm), with or without nonpalpable abdominal disease Palpable ( $\geq 10$ cm) abdominal mass as only disease Moderate pulmonary metastases (5–10 per lung field, largest <3 cm) or a mediastinal mass <50% of intrathoracic diameter or a solitary pulmonary metastasis >2 cm (with or without nonpalpable abdominal disease)	Any LDH elevation Nonpulmonary visceral metastases absent Any primary site	hCG, <5000 mIU/ml LDH, <1.5 $\times$ upper limit of normal Nonpulmonary visceral metastases absent Gonadal or retroperitoneal primary tumor
Intermediate risk	—	—	Nonpulmonary visceral metastases present Any hCG elevation Any LDH elevation Any primary site	AFP, <1000 ng/ml hCG, <5000 mIU/ml LDH, <1.5 $\times$ upper limit of normal Nonpulmonary visceral metastases absent Gonadal or retroperitoneal primary site
Poor risk	A nonseminomatous extragonadal primary tumor Nonseminoma with probability of complete response <0.5	Advanced pulmonary metastases (mediastinal mass >50% of intrathoracic diameter or >10 pulmonary metastases per lung field or multiple pulmonary metastases, largest >3 cm), with or without nonpalpable abdominal disease Palpable abdominal mass and pulmonary metastases Hepatic, osseous, or CNS metastases	—	Mediastinal primary site Nonpulmonary visceral metastases present (e.g., bone, liver, brain) AFP, >10,000 ng/ml hCG, >50,000 mIU/ml LDH, >10 $\times$ upper limit of normal

\*The classifications are those of the Memorial Sloan-Kettering Cancer Center,<sup>77</sup> Indiana University,<sup>78</sup> and the International Germ Cell Cancer Collaboration Group.<sup>79</sup> LDH denotes lactate dehydrogenase, hCG human chorionic gonadotropin, AFP alpha-fetoprotein, and CNS central nervous system.

role in the initial treatment of any patient with a germ-cell tumor.

In aggregate, these trials establish that four cycles of standard etoposide (500 mg per square meter per cycle) and cisplatin or three cycles of bleomycin, standard etoposide, and cisplatin were effective and well tolerated and, in conjunction with adjunctive surgery, cured approximately 90 percent of good-risk patients. Four cycles of etoposide and cisplatin have not been compared in a randomized trial with three cycles of cisplatin, etoposide, and bleomycin. An additional cycle of treatment is required with the etoposide-plus-cisplatin regimen, but the nine treatments with bleomycin are avoided.

**Poor-Risk Patients**

Between 20 and 25 percent of patients with advanced germ-cell tumors present with hepatic, osseous, or brain metastases, high serum concentrations of tumor markers, or mediastinal nonseminomatous primary tumors. These features are associated with a low likelihood of cure,<sup>77-79</sup> and clinical trials are directed at improving treatment efficacy.

Standard therapy is four cycles of conventional-dose bleomycin, etoposide, and cisplatin (Table 2). New agents and dose-intensive therapy have been evaluated. A randomized trial compared bleomycin, etoposide, and 100 mg of cisplatin per square meter per cycle with bleomycin, etoposide, and 200 mg of cisplatin per square meter per cycle.<sup>86</sup> The higher dose of cisplatin was associated with more neurotoxicity and myelosuppression but not with greater efficacy (Table 4). In another randomized trial, ifosfamide replaced bleomycin, but no therapeutic benefit was observed and toxicity was greater.<sup>87</sup>

Reports that high-dose therapy with stem-cell rescue cured a minority of patients with refractory disease as third-line therapy<sup>89,90</sup> led to the study of dose-intensive regimens as a part of early therapy. One study incorporated high-dose carboplatin plus etoposide into first-line therapy for poor-risk patients. High-dose therapy was associated with less treatment-related toxicity in these patients than in heavily pretreated patients.<sup>91</sup> Moreover, there was a suggestion that survival was better in these patients than in those receiving combination therapy with conven-

**TABLE 4.** RANDOMIZED TRIALS OF CHEMOTHERAPY IN GOOD-RISK AND POOR-RISK PATIENTS.\*

STUDY	RISK STATUS OF PATIENTS	CLASSIFICATION SYSTEM	REGIMEN	DRUG STUDIED	CYCLES	PERCENT WITH COMPLETE REMISSION	RESULT
Bosl et al. <sup>81</sup>	Good	Sloan-Kettering	VAB-6	Bleomycin	3	85	Regimens same
			EP		4	82	
Einhorn et al. <sup>82</sup>	Good	Indiana	BEP	Bleomycin	4	92	Regimens same
			BEP		3	92	
Loehrer et al. <sup>83</sup>	Good	Indiana	BEP	Bleomycin	3	86	3 cycles EP inferior
			EP		3	69	
Bajorin et al. <sup>84</sup>	Good	Sloan-Kettering	EP	Carboplatin	4	87	4 cycles EC inferior
			EC		4	76	
Horwich et al. <sup>85</sup>	Good	EORTC MRC	BEP	Carboplatin	4	90	4 cycles BEC inferior
			BEC		4	80	
Nichols et al. <sup>86</sup>	Poor	Indiana	BEP	Cisplatin	4	61	Double-dose cisplatin not superior
			BEP(200)		4	63	
Nichols et al. <sup>87</sup>	Poor	Indiana	BEP	Ifosfamide	4	57	Ifosfamide not superior
			VIP		4	56	

\*EORTC denotes European Organization for the Research and Treatment of Cancer; MRC Medical Research Council; VAB-6 vinblastine, bleomycin, cisplatin, dactinomycin, and cyclophosphamide; E etoposide; P 100 mg of cisplatin per square meter per cycle; P(200) 200 mg of cisplatin per square meter per cycle; B bleomycin; C carboplatin; V etoposide (VP-16); and I ifosfamide.

tional doses of cisplatin.<sup>91</sup> As a result, a national intergroup trial is comparing standard therapy with two cycles of combination therapy using high doses of carboplatin and stem-cell rescue in poor-risk patients.

**SURGERY AFTER CHEMOTHERAPY**

Surgical resection of residual disease is necessary in patients with nonseminomatous germ-cell tumors who have normal serum tumor-marker status after cisplatin-containing chemotherapy. The presence of necrotic debris or mature teratoma in pathological specimens requires no further therapy; between 5 and 10 percent of patients with such findings will relapse. If viable residual germ-cell tumor is completely resected, two additional cycles of chemotherapy will maximize the rate of cure.<sup>92,93</sup> Enlargement of tumor masses in the context of declining or normal tumor-marker values generally represents growing teratoma and requires surgical resection.<sup>94,95</sup> In contrast, persistently elevated serum concentrations of either alpha-fetoprotein or hCG after initial chemotherapy are associated with viable, often unresectable, residual germ-cell tumors; additional chemotherapy is recommended, rather than surgical resection. Patients with residual retroperitoneal masses undergo bilateral retroperitoneal lymph-node dissection. About 45 percent of residual retroperitoneal masses display necrotic debris or fibrosis on pathological examination, and 40 percent have evidence of teratoma. The degree of tumor shrinkage has been reported to be a predictive factor. Among 15 patients with no teratoma in the primary tumor and more than 90 percent shrinkage in tumor volume,

no resected tumor specimen was found to have either teratoma or viable cancer.<sup>96</sup> In other studies, between 10 and 20 percent of such patients had viable residual disease or mature teratoma in the resected specimen.<sup>92,97,98</sup>

The biologic features of teratoma and the likelihood of cure with salvage chemotherapy are considerations. Mature and immature teratomas appear histologically to be benign but arise from malignant germ-cell tumors. A minority of resected teratoma specimens involve teratoma with malignant transformation.<sup>99</sup> These malignant transformed cell types (for example, rhabdomyosarcoma) are no longer sensitive to cisplatin-based chemotherapy. Patients relapsing after complete remission who are treated with salvage chemotherapy have a cure rate of only 25 percent.<sup>100,101</sup> This contrasts with the 50 to 70 percent cure rate in patients with completely resected viable disease who undergo two cycles of postoperative chemotherapy.<sup>92,93</sup> Positron-emission tomography may identify residual disease but does not distinguish teratoma from necrosis.<sup>102</sup> These data suggest that retroperitoneal lymph-node dissection should be performed whenever there is radiographic evidence of residual disease. Whether patients with bulky retroperitoneal disease and normal results on abdominal CT after chemotherapy should undergo retroperitoneal lymph-node dissection remains controversial. The frequency of teratoma and viable residual disease in resected pulmonary nodules and mediastinal lymph nodes is similar to that in the abdomen.<sup>92</sup> Therefore, residual disease at these sites is also resected.

## SECOND- AND THIRD-LINE CHEMOTHERAPY

Patients who do not have a complete remission with first-line chemotherapy or who have a relapse after complete remission have been treated with ifosfamide plus cisplatin-containing salvage chemotherapy (Table 2). Approximately 25 percent are cured when ifosfamide plus cisplatin-containing chemotherapy is given as second-line therapy.<sup>100</sup>

High-dose chemotherapy with stem-cell rescue is the treatment of choice for patients who are not cured by less intensive therapy. Third-line therapy with two cycles of high-dose carboplatin plus etoposide, with or without cyclophosphamide (or ifosfamide), and with stem-cell rescue cures approximately 20 percent of patients in whom previous therapy with cisplatin and ifosfamide failed.<sup>90,103,104</sup>

Prognostic factors determine which patients should receive high-dose chemotherapy with stem-cell rescue as second-line therapy. Patients with testicular germ-cell tumors who do not have a complete initial remission have a cure rate of less than 10 percent with conventional-dose ifosfamide-based therapy.<sup>105</sup> They should be treated with high-dose etoposide plus carboplatin. In contrast, high-dose chemotherapy generally has no long-term benefits in patients who have germ-cell tumors that progress within one month of cisplatin treatment, who have very high hCG concentrations, or who have tumors with non-seminomatous histologic characteristics that arise from a mediastinal primary site.<sup>104,106</sup>

Complete and partial responses to paclitaxel have been reported in approximately 25 percent of patients in whom prior therapy was unsuccessful.<sup>107,108</sup> Paclitaxel as part of combination chemotherapy is under study in high-dose and conventional-dose second- and third-line chemotherapy programs.

## TREATMENT SEQUELAE

Nausea, vomiting, and nephrotoxicity associated with cisplatin-containing chemotherapy are well controlled by 5-hydroxytryptamine antagonists and adequate hydration.<sup>109</sup> Hypomagnesemia is frequent after cisplatin-based chemotherapy and is associated with Raynaud's phenomenon.<sup>110</sup> Neuromuscular toxic effects were ameliorated by the substitution of etoposide for vinblastine.<sup>75</sup> Pulmonary toxic effects from bleomycin occur rarely but must be considered before undertaking surgical procedures. Severe neutropenia and thrombocytopenia are uncommon with initial cisplatin-based chemotherapy, but they are frequent and potentially life-threatening during ifosfamide-containing second-line chemotherapy<sup>111</sup> and high-dose chemotherapy programs. Therefore, hematopoietic growth factors are used prophylactically with these regimens.

Infertility may result from retrograde ejaculation

after retroperitoneal lymph-node dissection or as a result of toxic effects of chemotherapy or radiotherapy on the germ cells of the remaining testis. A minority of patients with germ-cell tumors are infertile at diagnosis; the majority are either subfertile (having decreased sperm count or motility) or normally fertile.<sup>112</sup> Although fertility may be maintained,<sup>113</sup> sperm banking should be considered for patients undergoing surgery, chemotherapy, or radiation therapy.

Second cancers are rare. A second testicular primary germ-cell tumor occurs in approximately 2 percent of patients. The risk of gastrointestinal cancer, particularly gastric cancer, is increased in patients who receive radiation therapy for seminoma.<sup>114</sup> Also, a higher frequency of sarcomas was reported in patients followed for more than 10 years after treatment of germ-cell tumors.<sup>115</sup> Acute nonlymphocytic leukemia characterized by 11q translocation occurs in 0.1 to 0.5 percent of patients receiving a cumulative total of 2000 mg of etoposide per square meter (i.e., three or four cycles of standard chemotherapy).<sup>116,117</sup> A higher likelihood of acute leukemia has been associated with higher cumulative doses of etoposide.<sup>118</sup>

Sarcoidosis before or after the diagnosis of germ-cell tumors appears to be more frequent in patients with germ-cell tumors.<sup>119</sup> It must be considered when pulmonary nodules, pulmonary infiltrates, or paratracheal adenopathy occurs in the absence of elevated concentrations of tumor markers after long disease-free intervals, or in cases of seminoma without retroperitoneal disease.

## MIDLINE TUMORS OF UNCERTAIN HISTOGENESIS

Midline tumors of uncertain histogenesis occur mostly in young men, have a midline location or pulmonary nodules, and have histologically unclassifiable features. Cisplatin-containing chemotherapy cures 10 to 15 percent of such patients, suggesting that a minority have unrecognized germ-cell tumors.<sup>120,121</sup> Approximately 25 percent of these tumors have the i(12p) chromosomal marker, documenting germ-cell origin.<sup>122</sup> The presence of i(12p) identifies the tumor subgroup most sensitive to chemotherapy. The absence of i(12p) is associated with a low likelihood of response to cisplatin-based chemotherapy.<sup>29,122</sup> Other histogenetic origins have also been identified when these tumors are subjected to genetic analysis.<sup>122</sup> Molecular or cytogenetic studies should be performed, when possible, to establish a specific diagnosis in patients with midline tumors of uncertain histogenesis.

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