REVIEW ARTICLE

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Testicular Cancer — Discoveries and Updates

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THERE HAVE BEEN SUBSTANTIAL ADVANCES IN THE TREATMENT OF TESTICULAR CANCER. Fifty years ago, a diagnosis of metastatic testicular cancer meant a 90% chance of death within 1 year. Today, a cure is expected in 95% of all patients who have received a diagnosis of testicular cancer and in 80% of patients with metastatic disease. This review highlights recent discoveries, updates in care, and existing controversies in the treatment of patients with testicular cancer.

In the United States, the incidence of testicular cancer, which is highest among whites and lowest among blacks, has increased steadily over the past 20 years.[1] In some parts of northern Europe, the incidence has doubled, and in Denmark and Norway, 1% of men will receive a diagnosis of testicular cancer during their lifetime.[2,3] Genetic and environmental factors appear to play a role in this increase in incidence. The risk of testicular cancer is 8 to 10 times as high in a brother of a person with testicular cancer and 4 to 6 times as high in a son of a person with testicular cancer as in a brother or son of an unaffected family member.[4] Genetic disorders, including Down's syndrome and the testicular dysgenesis syndrome, are also associated with increased risks of testicular cancer.[3]

Cryptorchidism, which occurs in 2 to 5% of boys born at term, is the most well-characterized risk factor for testicular cancer.[5,6] The timing of orchiopexy influences the future risk of testicular cancer. In a study involving 16,983 men with cryptorchidism, the relative risk of testicular cancer was 2.2 among those who underwent orchiopexy before 13 years of age, as compared with 5.4 among those who underwent orchiopexy at 13 years of age or older, suggesting that hormonal changes at puberty are a factor in the risk of testicular cancer among boys.[5] However, 90% of persons with testicular cancer do not have a history of cryptorchidism.

Recent investigations have shed light on the malignant transformation of normal gonocytes into germ-cell tumors (Fig. 1). Germ-cell tumors appear to develop as a result of a tumorigenic event in utero that leads to a precursor lesion classified as intratubular germ-cell neoplasia.[7,8] Approximately 90% of germ-cell tumors are associated with adjacent intratubular germ-cell neoplasia, which carries a 50% risk of testicular cancer within 5 years. Intratubular germ-cell neoplasia is derived from gonocytes that maintain their ability to develop into germinal and somatic tissues; although these gonocytes may be regarded as pluripotent, they have failed to differentiate into spermatogonia.[8] The invasive potential of intratubular germ-cell neoplasia is not attained until after hormonal changes occur during puberty. Seminomas consist of transformed germ cells that resemble the gonocyte but are blocked in their differentiation. Embryonal carcinoma cells resemble undifferentiated stem cells, and their patterns of gene expression are similar to those of stem cells and intratubular germ-cell neoplasms[9,10]; choriocarcinomas and yolk-sac tumors have extraembryonic differentiation, and teratomas have somatic differentiation.

Studies have identified several genetic loci that confer a predisposition to testicular cancer.[11-13] The variant with the highest effect size was detected at 12q21,

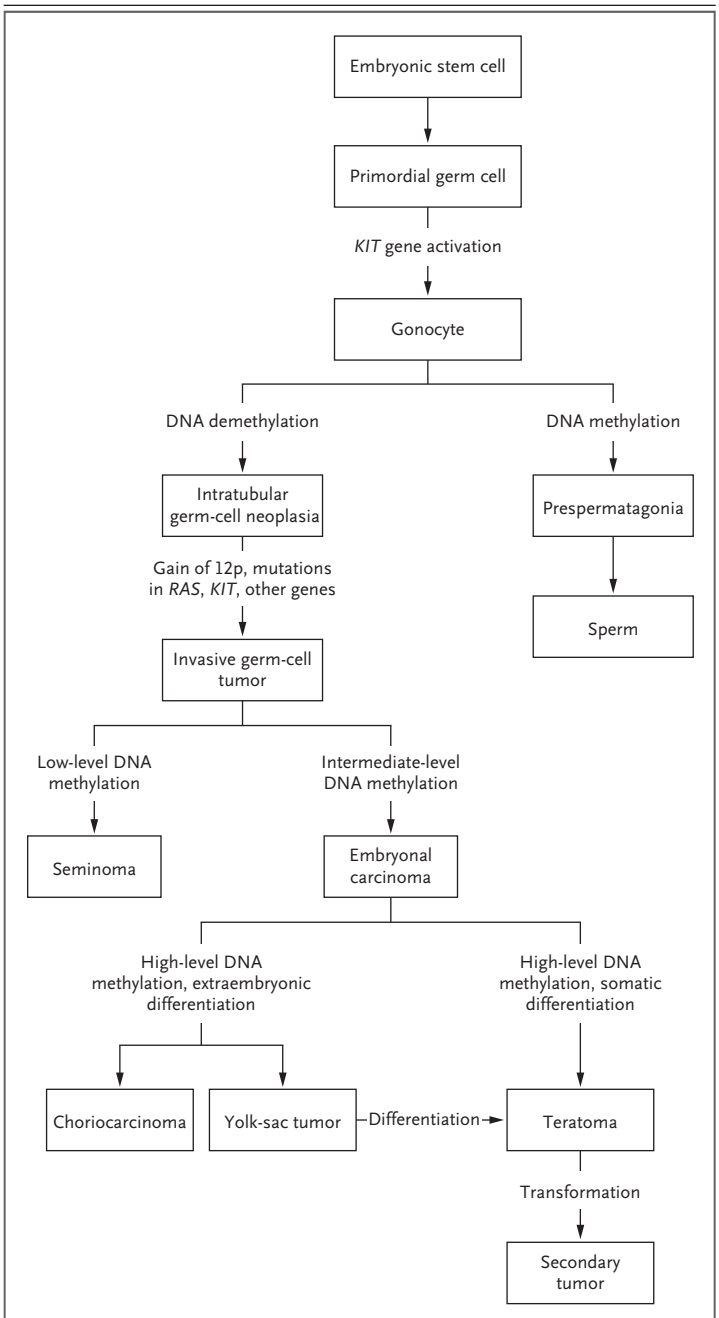

Figure 1. Potential Pathogenesis of Germ-Cell Tumors.

the location of the genes encoding the proteins involved in KITLG–KIT signaling.[14] The development of intratubular germ-cell neoplasia may involve aberrantly activated KITLG–KIT in utero, which induces arrest of embryonic germ cells at the gonocyte stage; subsequently, overexpression of embryonic transcription factors such as NANOG, sex-determining-region Y–box 17 (SOX17), and octamer-binding transcription factor 3–4 (OCT3/4, also known as POU domain, class 5, transcription factor 1 [POU5F1]) leads to suppression of apoptosis, increased proliferation, and accumulation of mutations in gonocytes.[15] Distinct gene expression through epigenetic regulation, including DNA methylation, may result in the formation of the different histologic subtypes.[16] Gonocytes have almost completely demethylated DNA, which facilitates the accumulation of mutations during cell replication and the development of intratubular germ-cell neoplasia. The patterns of hypomethylation seen in germ-cell tumors are consistent with the primordial germ-cell origin of seminomas and nonseminomatous germ-cell tumors in which genomic imprinting has been erased.[16]

Most patients with testicular cancer receive a diagnosis when the disease is in stage I and present with a testicular mass. Less frequently, patients report back pain (secondary to enlarged retroperitoneal lymph nodes) or symptoms of metastatic disease, including cough, hemoptysis, pain, and headaches. Scrotal ultrasonography revealing a hypoechoic mass is diagnostic of testicular cancer; in these patients, a testicular biopsy should never be performed, since it may contaminate the scrotum or alter the lymphatic drainage of the tumor. A radical inguinal orchiectomy is diagnostic and therapeutic. Using immunohistochemical analysis, expert pathologists should determine the histologic composition of the tumor (including the percentages of each histologic type in the tumor) and should provide key information, including the size of the tumor and the presence or absence of lymphovascular invasion. Accurate staging is critical; the stage should be determined with the use of computed tomography (CT) of the chest, abdomen, and pelvis and measurement of the levels of beta subunit of human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP), as well as of lactate dehydrogenase, which is not specific for testicular cancer but is rather an indicator of the bulk of disease (Table 1).

STAGE I SEMINOMA

Most patients with clinical stage I seminoma are cured with orchiectomy. Adjuvant radiotherapy was the standard treatment for many years and

was instrumental to the cure before the advent of effective chemotherapy (Table 2). Over the past 20 years, the dose and field of radiation have been considerably reduced, and in many instances radiotherapy has been eliminated altogether.

Most patients today are treated with active surveillance, although some still receive radiotherapy consisting of 20 Gy to the ipsilateral retroperitoneal lymph nodes (sometimes including the inguinal lymph nodes, depending on whether the patient had undergone prior surgery involving the inguinal, pelvic, or scrotal areas) or adjuvant carboplatin therapy. More relapses are associated with surveillance than with radiotherapy or chemotherapy (20% vs. 4%), but the long-term survival is nearly 100%, irrespective of the initial option chosen.[17,18,20] A recent study implicated involvement of the rete testis or a primary tumor larger than 4 cm in diameter as a risk factor for relapse.[21] In one study involving 1822 patients with stage I seminoma who were followed by active surveillance for a median of 15.4 years, the incidence of relapse was 19.5% at a median of 13.7 months. The 10-year cancer-specific survival rate was 99.6%.[17] According to guidelines of the National Comprehensive Cancer Network (NCCN), active surveillance consists of physical examination, measurement of levels of tumor markers (AFP and β-hCG), and abdominal and pelvic CT every 3 to 4 months for the first 2 years, every 6 to 12 months in years 3 and 4, and annually thereafter.

STAGE II SEMINOMA

For some patients with low-volume stage II seminoma (disease confined to the retroperitoneal lymph nodes, with the lymph nodes ≤3 cm in diameter), 30 to 36 Gy of radiation to the paraaortic and ipsilateral iliac lymph nodes remains a standard treatment.[19] In other patients, the preferred treatment is chemotherapy with bleomycin, etoposide, and cisplatin (also known as BEP) for three cycles or etoposide and cisplatin for four cycles. Chemotherapy is preferred for patients with bulkier disease, since the rate of relapse is higher with radiotherapy alone.[22] Cures are achieved in 98% of patients. Residual masses detected on radiographic assessment, which usually indicate desmoplasia, are commonly seen after chemotherapy. Surgical extirpation can be challenging, and the incidence of residual seminoma is low; therefore, residual masses smaller than 3 cm in diameter are usually not resected and are followed by observation. Masses larger than 3 cm carry a higher risk of containing seminoma, and positron-emission tomographic imaging is sometimes performed 6 weeks after completion of therapy to aid in the decision to resect or observe.[23]

STAGE I NONSEMINOMATOUS GERM-CELL TUMOR

Most patients with a nonseminomatous germ-cell tumor (every histologic type of germ cell except for a seminoma) present with clinical stage I disease (Table 3). Treatment options after orchiectomy include active surveillance, nerve-sparing retroperitoneal lymph-node dissection, and adjuvant BEP for one or two cycles; each of these options is associated with 99% long-term cure rates.[24,25,28,30] Patients are characterized as high-risk (relapse rates of 50% with surveillance) or low-risk (relapse rates of 15% with surveillance) according to the presence or absence of lymphovascular invasion.[24] Kollmannsberger et al. recently reported a long-term cure rate of 99%, irrespective of the initial risk category, among 1034 patients who had stage I nonseminomatous germ-cell tumor and were followed by active surveillance.[24] We prefer surveillance for nearly all patients who adhere to therapy. NCCN guidelines recommend visits every 1 to 2 months in year 1, every 2 months in year 2, every 3 months in year 3, every 4 months in year 4, every 6 months in year 5, and annually thereafter. Chest radiography, physical examinations, and measurement of levels of tumor markers are recommended at each visit. Abdominal CT is recommended every 3 to 4 months in year 1, every 4 to 6 months in year 2, every 6 to 12 months in years 3 and 4, once in year 5, and every 1 to 2 years thereafter.

Some centers prefer surveillance for low-risk patients and adjuvant therapy for high-risk patients. In one study involving 745 patients, adjuvant BEP was recommended, but not required, if lymphovascular invasion was present and adjuvant BEP or active surveillance was recommended, but not required, if lymphovascular invasion was absent.[26] Approximately 41% of patients who had lymphovascular invasion had a relapse of disease during active surveillance as compared with

Table 1. Staging and Risk Stratification of Germ-Cell Tumors.*

Stage and Risk Category	Primary Tumor	Lymph-Node Status	Metastasis Status	Serum Tumor-Marker Level
IA	Involvement of the testis with or without involvement of the tunica albuginea; no involvement of the tunica vaginalis	No lymph-node involvement or lymphovascular invasion	No evidence	Normal after orchiectomy
IB	Involvement of the testis and tunica vaginalis, spermatic cord, or scrotum	No lymph-node involvement; lymphovascular invasion	No evidence	Normal after orchiectomy
1S	Involvement of the testis with or without involvement of the tunica albuginea, tunica vaginalis, spermatic cord, or scrotum	No lymph-node involvement; with or without lymphovascular invasion	No evidence	Remains elevated and increases after orchiectomy
IIA	Same as 1S	<5 retroperitoneal lymph nodes, each ≤2 cm	No evidence	Normal or slightly high: LDH <1.5× ULN, β-hCG <5000 mIU/ml, and AFP <1000 ng/ml
IIB	Involvement of the testis with or without involvement of the tunica albuginea, tunica vaginalis, spermatic cord, or scrotum	>5 retroperitoneal lymph nodes or at least one lymph node >2 cm but ≤5 cm	No evidence	Same as IIA
IIC	Involvement of the testis with or without involvement of the tunica albuginea, tunica vaginalis, spermatic cord, or scrotum	Retroperitoneal lymph nodes >5 cm	No evidence	Same as IIA
IIIA	Involvement of the testis with or without involvement of the tunica albuginea, tunica vaginalis, spermatic cord, or scrotum	Positive or negative lymph nodes	Distant lymph nodes or lungs	Same as IIA
IIIB	Involvement of the testis with or without involvement of the tunica albuginea, tunica vaginalis, spermatic cord, or scrotum	Positive or negative lymph nodes	Distant lymph nodes or lungs	LDH 1.5–10× ULN, β-hCG 5000–50,000 mIU/ml, AFP 1000–10,000 ng/ml, or all of these values
IIIC	Involvement of the testis with or without involvement of the tunica albuginea, tunica vaginalis, spermatic cord, or scrotum	Positive or negative lymph nodes	Nonpulmonary visceral metastases	Normal or elevated : LDH >10× ULN, β-hCG >50,000 mIU/ml, or AFP >10,000 ng/ml, or all of these values
Seminoma				
Low-risk	Any primary site	Positive or negative lymph nodes	No nonpulmonary visceral metastases	Normal AFP, any β-hCG, any LDH
Intermediate- risk	Any primary site	Positive or negative lymph nodes	Nonpulmonary visceral metastases	Normal AFP, any β-hCG, any LDH

Nonseminomatous germ-cell tumor				
Low-risk	Testis or retroperitoneal lymph nodes	Positive or negative lymph nodes	No nonpulmonary visceral metastases	AFP <1000 ng/ml, β-hCG <5000 mIU/ml, and LDH <1.5× ULN
Intermediate-risk	Testis or retroperitoneal lymph nodes	Positive or negative lymph nodes	No nonpulmonary visceral metastases	AFP ≥1000 and ≤10,000 ng/ml or β-hCG ≥5000 and ≤50,000 mIU/ml or LDH ≥1.5× ULN and ≤10× ULN
High-risk	Testis or retroperitoneal or mediastinal lymph nodes	Positive or negative lymph nodes	Any site if primary site is anterior mediastinal lymph nodes; nonpulmonary visceral metastases if primary site is testis or retroperitoneal lymph nodes	Any of the following levels independently confers high risk: AFP >10,000 ng/ml, β-hCG >50,000 mIU/ml, or LDH >10× ULN

* AFP denotes alpha-fetoprotein, β-hCG beta human chorionic gonadotropin, LDH lactate dehydrogenase, and ULN upper limit of the normal range.

only 13.2% of patients who did not have lymphovascular invasion. After one cycle of BEP, only 3.2% of the patients who had lymphovascular invasion had a relapse, and only 1.3% of the patients who did not have lymphovascular invasion had a relapse.

We think that administering BEP for one cycle in patients with lymphovascular invasion can reduce the odds that these patients will require BEP for three cycles. Others have raised concerns over this strategy, arguing that pathological staging and interpretation of the results are not universally accurate, and the long-term risk of receiving BEP for one cycle is unknown.[27] Another option is retroperitoneal lymph-node dissection, which reduces the probability that chemotherapy will be required and eliminates the need for abdominal CT after dissection of these lymph nodes if no disease is detected.[29]

STAGE II NONSEMINOMATOUS GERM-CELL TUMOR

Patients with a low-volume stage II nonseminomatous germ-cell tumor (disease confined to the retroperitoneal lymph nodes, with the lymph nodes <3 cm in diameter) and normal β-hCG and AFP levels after orchiectomy are generally treated with retroperitoneal lymph-node dissection, although care must be individualized. Patients with higher-volume stage II disease or increasing levels of markers should receive chemotherapy (BEP for three cycles or etoposide and cisplatin for four cycles).[31] Cures are achieved in 95 to 99% of patients.

Retroperitoneal lymph-node dissection is the standard treatment after chemotherapy in patients with stage II or III disease who have had a serologic complete response but have persistently enlarged retroperitoneal lymph nodes. However, the role of retroperitoneal lymph-node dissection after chemotherapy in patients who have serologic and radiographic evidence of remission remains controversial. We do not advocate retroperitoneal lymph-node dissection if retroperitoneal lymph nodes have normalized on CT. A 15-year cancer-specific survival rate of 97% is reported with this approach.[32] Other researchers recommend retroperitoneal lymph-node dissection after chemotherapy in most patients because of the presence of viable germ-cell tumor and teratoma in some patients with normal-size retroperitoneal lymph

Table 2. Treatment Options for Stage I Seminoma.*

Option	Outcomes	Advantages	Disadvantages	Reference
Active surveillance	20% relapse rate; 99% long-term cancer-specific survival rate	Most patients require no treatment; long-term outcomes excellent	Adherence is essential; higher doses of radiotherapy or 9–12 wk of chemotherapy required if disease recurs	Mortensen et al.,[17] Soper et al.,[18] Oldenburg et al.[19]
Radiotherapy	4% relapse rate; 99% long-term cancer-specific survival rate	Reduces relapses; reduces odds of need for 9–12 wk of chemotherapy; reduces frequency of abdominal imaging	Short-term side effects, including fatigue, nausea, diarrhea; uncertainty in staging may lead to undertreatment of some patients; long-term risks of secondary cancer	Soper et al.,[18] Oldenburg et al.,[19] Oliver et al.[20]
Carboplatin (one or two cycles)	4% relapse rate; 99% long-term cancer-specific survival rate	Reduces relapses; reduces odds that patient will need 9–12 wk of chemotherapy or radiotherapy	Short-term side effects, including fatigue, nausea; risk of complications of neutropenia; uncertainty in staging may lead to undertreatment of some patients; long-term risks of carboplatin unknown	Oldenburg et al.,[19] Oliver et al.[20]

* Stage I seminoma is defined as disease that is confined to the testis with no evidence of spread to the chest, abdomen, or pelvis and normal levels of serum AFP and β-hCG after orchiectomy.

nodes on CT.[33] A meta-analysis of retroperitoneal lymph-node dissection after chemotherapy showed necrosis in 70% of patients, teratoma in 25%, and active cancer in 5%. However, among patients who underwent surveillance, the pooled estimate of relapse was only 5%, with 3% having a relapse in the retroperitoneal lymph nodes only. In this analysis, of the 15 men who had a relapse in the retroperitoneal lymph nodes only, 2 died of disease. Therefore, retroperitoneal lymph-node dissection after chemotherapy can be avoided in approximately 95% of men if patients with a complete response on serologic and radiographic testing are followed with active surveillance.[34]

STAGE III TESTICULAR CANCER

The discovery of *cis*-diamminedichloroplatinum (known as cisplatin) in 1965, a landmark event in the history of oncology, revolutionized the treatment of testicular cancer (Table 4).[51] The addition of cisplatin to the regimen of vinblastine plus bleomycin in 1974 resulted in a 5-year survival rate of 64%; this rate was unprecedented as compared with rates associated with contemporaneous chemotherapy.[52] Researchers from Memorial Sloan Kettering Cancer Center (MSKCC) established etoposide and cisplatin for four cycles as a standard option in low-risk patients,[35] and BEP supplanted the regimen of cisplatin, vinblastine, and bleomycin on the basis of superior outcomes in a phase 3 study.[36] In low-risk patients, the outcome after three cycles of BEP was found to be equivalent to the outcome after four cycles.[37,38] For patients with low-risk metastatic disease, standard therapy remains BEP for three cycles or etoposide and cisplatin for four cycles. A direct comparison of the efficacy of these two regimens in patients with low-risk disease favored BEP for three cycles (event-free survival rate of 91% with BEP for three cycles and 86% with etoposide and cisplatin for four cycles, at 4 years), although the difference was not significant ($P=0.14$).[39] The management of residual radiographic abnormalities after chemotherapy requires expertise in surgery, with individualized care involving urologists, thoracic surgeons, general surgeons, and otolaryngologists. Patients with such abnormalities should be referred to centers of excellence in the management of testicular cancer.

In 1997, the International Germ Cell Cancer Collaborative Group introduced a risk-stratification system (Table 1).[53] This system takes into account the primary tumor site (testis versus mediastinum), metastatic sites, and amplitude of serum tumor-marker levels to estimate risk categories. Three risk groups were defined: low-risk (>90% rate of cure), intermediate-risk (75% rate of cure), and high-risk (50% rate of cure). Patients with low-risk disease receive BEP for three cycles or etoposide and cisplatin for four cycles.

Table 3. Treatment Options after Orchiectomy for Stage I Nonseminomatous Germ-Cell Tumor.*

Option	Outcomes	Advantages	Disadvantages	Reference
Active surveillance	30% relapse rate overall; 15% relapse rate in low-risk group; 50% relapse rate in high-risk group; 99% long-term cancer-specific survival rate	Most patients require no treatment; long-term outcomes excellent even if patients require treatment for relapse	Adherence is essential; retroperitoneal lymph-node dissection or 9–12 wk of chemotherapy still required in 30% of patients	Kollmannsberger et al.,[24] Schmoll et al.,[25] Tandstad et al.,[26] Nichols et al.[27]
Retroperitoneal lymph-node dissection	20–30% relapse rate; 99% long-term cancer-specific survival rate	Cures some patients with pathological stage II disease; avoids the need for chemotherapy in some patients; retroperitoneal lymph node is not a site of recurrence	Surgical risk; normal histologic findings in most patients; chemotherapy sometimes required to manage relapsed disease	Schmoll et al.,[25] Albers et al.,[28] de Wit and Bosl[29]
Bleomycin, etoposide, and cisplatin (one or two cycles)	1–5% relapse rate; 99% long-term cancer-specific survival rate	Substantially reduces the likelihood that patient will require 9–12 wk of chemotherapy in the future	Overtreatment in at least 70% of patients; long-term risks of this regimen unknown; chemotherapy sometimes required to manage relapsed disease	Schmoll et al.,[25] Tandstad et al.,[26] Albers et al.,[28] Westermann and Studer[30]

* A stage I nonseminomatous germ-cell tumor is defined as disease that is confined to the testis with no evidence of spread to the chest, abdomen, or pelvis and normal levels of serum AFP and β-hCG after orchiectomy.

Patients with intermediate-risk or high-risk disease receive triple-drug therapy (usually BEP or etoposide plus ifosfamide plus cisplatin [VIP]) for four cycles.

Investigators have not been able to increase the cure rates among patients with intermediate-risk or high-risk disease beyond those achieved with four cycles of BEP or VIP[40-45] (Table 4). Some investigators have advocated intensification of therapy according to the rate of decrease in levels of tumor markers (an independent prognostic variable indicating chemoresistance in patients with high-risk disease) after the first or second cycle of BEP.[45] This strategy resulted in fewer relapses requiring salvage therapy and appeared to improve overall survival in a retrospective analysis[41] but not in a separate prospectively designed trial testing another regimen.[44] Recently, a regimen of paclitaxel plus ifosfamide plus cisplatin (TIP) has been studied in high-risk patients and has resulted in a complete response rate of 74% and a 3-year overall survival rate of 97%.[54] A randomized trial of BEP versus TIP is ongoing (ClinicalTrials.gov number, NCT01873326).

RELAPSED DISEASE

The most effective treatment of patients with relapsed germ-cell tumors remains controversial. Patients who have a relapse after initial chemotherapy can still be cured with second-line and even third-line regimens and should preferentially be referred to centers of excellence in testicular cancer. Commonly used regimens include VIP, vinblastine plus ifosfamide plus cisplatin, and TIP.[46-48]

In 1986, researchers at Indiana University investigated high-dose chemotherapy in patients with relapsed germ-cell tumors and observed cures, even as a third-line regimen.[55] In 1996, peripheral-blood stem-cell transplantation replaced bone marrow transplantation for the treatment of recurrent germ-cell tumors in patients at Indiana University.[49] Among the first 184 patients treated with high-dose chemotherapy and peripheral-blood stem-cell transplantation for germ-cell tumors that had progressed after first-line cisplatin-based chemotherapy, cures were achieved in 70% of the patients who received the second-line regimen and in 45% of the patients who received a third-line or subsequent regimen. Some patients had an increase in tumor-marker levels between the first and second cycle of high-dose chemotherapy. Nearly all these patients had a decrease in levels of tumor markers after their second course of high-dose chemotherapy, and 28% of this subgroup remained disease-free.[56] Cumulative doses of etoposide have been associ-

Table 4. Treatment Options for Stage III and Relapsed Testicular Cancer.

Treatment	Comments	Reference
Low-risk stage III		
Three cycles of bleomycin, etoposide, and cisplatin or four cycles of etoposide and cisplatin	>90% cure rate	Bosl et al.,[35] Williams et al.,[36] Einhorn et al.,[37] de Wit et al.,[38] Culine et al.[39]
Intermediate-risk stage III		
Four cycles of bleomycin, etoposide, and cisplatin or four cycles of etoposide, ifosfamide, and cisplatin	70–80% cure rate	de Wit et al.,[40] Nichols et al.[41]
Four cycles of paclitaxel, bleomycin, etoposide, and cisplatin	Improved progression-free survival, but not overall survival as compared with four cycles of bleomycin, etoposide, and cisplatin	de Wit et al.,[40] Nichols et al.[41]
High-risk stage III		
Four cycles of bleomycin, etoposide, and cisplatin or four cycles of etoposide, ifosfamide, and cisplatin	50–60% cure rate	Nichols et al.,[41] Motzer et al.,[42] Droz et al.,[43] Daugaard et al.,[44] Fizazi et al.[45]
Two cycles of bleomycin, etoposide, and cisplatin, followed by two cycles of high-dose chemotherapy	No better than four cycles of bleomycin, etoposide, and cisplatin, but more toxic	Nichols et al.,[41] Motzer et al.,[42] Droz et al.,[43] Daugaard et al.,[44] Fizazi et al.[45]
One cycle of etoposide, ifosfamide, and cisplatin, followed by three cycles of high-dose chemotherapy	No better than four cycles of bleomycin, etoposide, and cisplatin, but more toxic	Nichols et al.,[41] Motzer et al.,[42] Droz et al.,[43] Daugaard et al.,[44] Fizazi et al.[45]
One cycle of bleomycin, etoposide, and cisplatin, followed by two cycles of paclitaxel, bleomycin, etoposide, and cisplatin, followed by two cycles of bleomycin, ifosfamide, and cisplatin	Improved progression-free survival over four cycles of bleomycin, etoposide, and cisplatin in patients with inadequate decrease in levels of tumor markers	Nichols et al.,[41] Motzer et al.,[42] Droz et al.,[43] Daugaard et al.,[44] Fizazi et al.[45]
Relapsed disease		
Vinblastine, ifosfamide, and cisplatin; or etoposide, ifosfamide, and cisplatin; or four cycles of paclitaxel, ifosfamide, and cisplatin; high-dose chemotherapy, treatment determined in TIGER trial (when available)	For standard-dose therapy, cisplatin is frequently combined with two drugs that the patient did not receive in the first-line regimen (e.g., paclitaxel, ifosfamide, and cisplatin if the patient has already received bleomycin, etoposide, and cisplatin)	Loehrer et al.,[46] Loehrer et al.,[47] Kondagunta et al.,[48] Einhorn et al.,[49] Feldman et al.[50]

ated with an increased risk of leukemia, and acute leukemia developed in 3 of 184 patients in the Indiana University series.

Investigators from MSKCC have also evaluated high-dose chemotherapy, incorporating paclitaxel and ifosfamide as induction chemotherapy and stem-cell mobilization, followed by three cycles of high-dose carboplatin and etoposide and peripheral-blood stem-cell transplantation. They reported a 5-year survival rate of 52%.[50] Patients who had a satisfactory decrease in tumor-marker levels during high-dose chemotherapy had superior progression-free and overall survival; however, even patients with unsatisfactory decreases in tumor-marker levels could be cured.[57]

Two prospective phase 3 trials that have addressed the role of high-dose chemotherapy versus standard-dose salvage therapy have shown mixed results. No significant difference in survival was reported in a randomized trial of VIP for four cycles versus VIP for three cycles followed by high-dose chemotherapy with carboplatin and etoposide plus cyclophosphamide for one cycle, a regimen that is no longer used today.[58] A second study compared one cycle of VIP followed by high-dose chemotherapy with carboplatin and etoposide for three cycles (group A) with VIP for three cycles followed by one cycle of high-dose chemotherapy (group B).[59] This study was discontinued after 216 patients were enrolled because of excess deaths in group B. At 1 year, the rate of overall survival was 80% in group A and 61% in group B, and the rate of treatment-related death was 4% in group A and 16% in group B, favoring a longer course of high-dose chemotherapy. The updated 5-year overall survival rate was 49% in group A versus 39% in

Table 5. Key Remaining Challenges in Testicular Cancer.

Challenge	Research Goals
Intermediate and high-risk disease	To compare paclitaxel, ifosfamide, and cisplatin with bleomycin, etoposide, and cisplatin; intensification of therapy according to decrease in level of tumor markers; incorporation of new agents into existing regimens
Unresectable teratoma	To use new agents, including CD4/6 inhibitors
Late relapse of disease	To understand the biologic and molecular differences between early and late relapse in order to identify potential therapeutic targets
Malignant transformation of teratoma	To understand the biologic and molecular basis for malignant transformation of teratoma in order to identify potential therapeutic targets and make systemic therapy more effective
Management of brain metastases	To use an international database to characterize the role of surgical resection and radiotherapy in outcomes
Recurrent disease after high-dose chemotherapy	To explore the mechanisms underlying resistance to chemotherapy and study new agents; to compare standard-dose chemotherapy with high-dose chemotherapy
Survivorship	To understand the genetic basis of long-term risks of chemotherapy

group B, again favoring a longer course of high-dose chemotherapy.

The challenge today is to determine which patients should receive standard salvage chemotherapy and which patients should be considered for high-dose chemotherapy and peripheral-blood stem-cell transplantation. Patients with recurrent disease have been classified into risk categories.[60] In one study involving 1500 patients, high-dose chemotherapy appeared to be more effective in most risk groups, including the group with the poorest prognosis, in which 27% of the patients who received high-dose chemotherapy, as compared with only 3% of those who received standard-dose salvage therapy, were cured.[60] Other studies have shown that high-risk patients, including those with primary mediastinal nonseminomatous germ-cell tumors, can be cured with high-dose chemotherapy; this result is rarely seen with standard-dose therapy. Some clinicians advocate the use of high-dose chemotherapy in most patients as the second-line regimen, whereas others have proposed the use of high-dose chemotherapy only in high-risk patients, those who have had a relapse after receiving ifosfamide-based chemotherapy, or those who have had a relapse after two lines of standard salvage therapy.

A randomized trial (TIGER, or a Randomized Phase III Trial of Initial Salvage Chemotherapy for Patients with Germ-Cell Tumors) is under way to compare standard-dose chemotherapy with high-dose chemotherapy in patients with relapsed disease. This study randomly assigns patients to receive TIP for four cycles or ifosfamide plus paclitaxel for two cycles followed by high-dose carboplatin and etoposide for three cycles.

SURVIVORSHIP

Since most patients will survive after a diagnosis of testicular cancer, clinicians must be vigilant to reduce the long-term risks of therapy and limit unnecessary morbidity and early mortality. van Walraven et al.[61] explored the issue of second cancers related to diagnostic imaging in more than 2500 survivors of testicular cancer, and they reported no increased risk of secondary cancers. However, follow-up was only a median of 11 years and may not have been sufficient to observe late secondary cancers.

Therapeutic radiation has been recognized as a risk factor for secondary cancers. However, studies also implicate chemotherapy in the risk of cancers of the kidney, thyroid, soft tissue, bladder, stomach, and pancreas, as well as in the risk of lymphoma and leukemia.[62-65]

Survivors of testicular cancer are also at risk for late relapse of disease (defined as relapse >2 years after remission), as well as for the metabolic syndrome; cardiovascular disease; infertility; neurotoxic, nephrotoxic, and pulmonary toxic effects; Raynaud's phenomenon; psychosocial disorders;

and hypogonadism, which may confer a predisposition to sexual dysfunction, fatigue, depression, and osteoporosis.[66-69] Retrograde ejaculation may develop postoperatively in men who have undergone retroperitoneal lymph-node dissection. The most comprehensive study to date is under way to understand the genetic susceptibility to the long-term toxic effects of platinum-based chemotherapy in survivors of testicular cancer.

CONCLUSIONS

Although most patients with testicular cancer will be cured and can expect decades of additional life, thousands of men around the world will still die from testicular cancer every year, and many challenges remain (Table 5). Cytotoxic chemotherapy remains the mainstay of therapy for advanced disease. Early efforts with molecularly targeted therapies have been disappointing.[70-73] Meanwhile, researchers from across the globe continue to collaborate on clinical trials, share discoveries, and debate unsettled questions. It is because of this cooperative spirit that remarkable progress has been made to cure current and future generations of men with testicular cancer.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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