Review of Late Complications of Treatment and Late Relapse in Testicular Cancer

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Key Words
Testicular cancer, late complications, late relapse, cardiovascular toxicity, fertility, second primary neoplasms.

Abstract
With testicular cancer, a disease with a cure rate of 95%, the challenge is to restore quality of life to pretreatment levels and sustain it long-term. Although the implementation of guidelines and optimization of treatment modalities over the past years have served this purpose, some complications remain inevitable and experts are still challenged with late complications of outdated treatment standards. This article focuses on the late complications of cisplatin-based chemotherapy without disregarding those of currently applied intradiaphragmatic radiation. The most serious long-term complications of chemotherapy or radiotherapy are cardiovascular toxicity and second malignancies, as each has a 25-year risk of approximately 16%. Compared with the general population, risk for second malignancies remains significantly increased for at least 35 years after treatment. Chemotherapy-related cardiovascular toxicity is probably a result of both direct endothelial damage induced by cisplatin and indirect hormonal and metabolic changes. The increased incidence of the metabolic syndrome identified in long-term survivors is most likely associated with the lower testosterone levels reported. Cisplatin-based chemotherapy affects not only Leydig cells but also Sertoli and germ cells, resulting in infertility in 30% to 50% of testicular cancer patients treated with chemotherapy. Chronic neurotoxicity occurs in half of men, whereas permanent ototoxicity and some degree of renal function impairment occur in up to 30%. Pulmonary fibrosis, occurring in 5% to 10% of patients treated with bleomycin, is fatal in 1%. Although current treatment of advanced disease has changed its natural course, we are challenged by an increasing incidence of late relapse, an entity with a distinct tumor biology characterized by latency and chemoresistance.

The management of germ cell tumors is a paradigm of success among solid tumors. Metastatic testicular cancer (TC) has been transformed from a rapidly lethal illness to one routinely cured by chemotherapy.

For a malignant disease with a cure rate of 95%, the challenge is to restore quality of life to pretreatment levels and sustain it long-term. Although germ cell tumors constitute only 2% of all human malignancies, this need is underscored by the age group affected and the increasing incidence. A recent effort has been made to optimize treatment strategies (i.e., retain efficacy and minimize toxicity). The implementation of treatment guidelines, use of less toxic and more effective chemotherapeutic agents, reduction of radiotherapy dose and field delivery, and increasing preference for surveillance in low-stage disease are already serving this purpose. However, some complications remain inevitable, and late complications of outdated treatment standards are still a concern. Notwithstanding the success in the treatment of advanced disease, a different challenge presented is an increased incidence in late relapse, that is now estimated to be 2% to 6%.

Late Complications of Treatment

Vascular Toxicity

Cardiovascular Toxicity: Since 1979, when damage to the coronary arteries was first reported, increasing evidence has suggested that cardiovascular complications are among the gravest of TC treatment.
According to reports on the largest patient cohorts studied, men who undergo cisplatin-based chemotherapy and radiotherapy, mainly mediastinal, have an increased risk for cardiovascular disease compared with the general male population and men who only undergo orchiectomy.\(^5\)\(^\text{-}^\text{11}\)

Van den Belt-Dusebout et al.\(^4\) recently reported on cardiovascular disease incidence after a median follow-up of 18.2 years in 2512 patients who were 5-year survivors of TC treated between 1965 and 1995. The estimated 25-year actuarial risk for a cardiovascular disease–related event was 16.5%, which was similar to that for developing second malignancies (15.7%).\(^14\)

The combination of chemotherapy and radiotherapy doubled the risk for myocardial infarction (MI) (standardized incidence ratio [SIR] = 2.06), whereas chemotherapy alone conferred a moderate risk increase of 1.46 compared with the general population. Neither surgery nor infradiaphragmatic radiation affected MI risk. Interestingly, patients with nonseminomatous germ cell tumors experienced a twofold MI risk at younger ages (< 45 years), which significantly decreased for survivors aged 55 years or older. Analyses of smaller cohorts of TC survivors also suggest that patients experience cardiovascular events at an earlier age after undergoing cisplatin-based chemotherapy.\(^\text{10}\)

This is probably caused by chemotherapy or radiation accelerating endothelial damage in patients already predisposed. In the multivariate analysis, recent smoking, mediastinal radiotherapy, and cisplatin, vinblastine, and bleomycin (PVB) contributed to cardiovascular disease risk. Chemotherapy slightly increased MI risk (SIR = 1.46). In fact, PVB was associated with a 1.9-fold increased risk for MI, whereas bleomycin, etoposide, and cisplatin (BEP) was associated with only a 1.5-fold increased risk for cardiovascular disease. Shorter follow-up times or improved prevention and treatment of cardiac ischemia may account for this finding.

At a follow-up of 10.2 years, Huddart et al.\(^9\) analyzed 992 patients registered in the United Kingdom between 1982 and 1992. They reported a twofold or greater risk for myocardial ischemia seen after chemotherapy alone (relative risk [RR], 2.59; 95% confidence interval [CI], 1.15–5.84), radiation therapy (RR, 2.40; 95% CI, 1.04–5.45), and combined therapy (RR, 2.78; 95% CI, 1.09–7.07) compared with the surveillance group. The investigators identified a 2.4-fold increased risk after infradiaphragmatic irradiation not confirmed by Van den Belt-Dusebout.\(^8\)

Zagars et al.\(^1\) also identified an excessive cardiovascular mortality among seminoma survivors not undergoing mediastinal irradiation when followed up beyond 15 years, although this finding has no satisfactory explanation.

Fossa et al.,\(^12\) Zagars et al.,\(^1\) and Hanks et al.\(^1\) reported on cardiovascular mortality. After analyzing 3378 patients treated between 1962 and 1997, Fossa et al. confirmed a slight but significantly increased mortality ratio from diseases of the circulatory system (standard mortality rate 1.2; 95% CI, 1.0–1.5). A comparison of mortality among patients according to period of treatment indicated no increase with the introduction of cisplatin. This treatment period also coincides with the discontinuation of mediastinal radiotherapy, confinement of infradiaphragmatic fields, and introduction of better treatment modalities for cardiovascular disease. Finally, follow-up with cisplatin-based therapy is not enough to exclude the possibility of a delayed effect.

Zagars et al.\(^1\) focused on mortality in 453 long-term survivors of stage I and II seminoma treated with orchiectomy and radiation therapy between 1951 and 1999. The risk for cardiac-related death compared with the general population was statistically significant beyond 15 years, when it almost doubled. In the multivariate analysis, prophylactic mediastinal irradiation was the only factor significant for mortality. The older study by Hanks et al.\(^1\) also identified a more than twofold increase in cardiac mortality.

Myocardial damage induced by chest irradiation is well described and characterized by the experience in Hodgkin disease and breast cancer. This article focuses on the mechanisms belying cardiovascular damage after cisplatin-based chemotherapy.

Chronic endothelial damage plays an important role in the development of cardiovascular toxicity. Microalbuminuria, decreased fibrinolysis, and inflammation, which are considered to reflect widespread endothelial dysfunction and early atherosclerosis, have been reported in up to 22% of long-term TC survivors after a median follow-up of 7 years after chemotherapy.\(^1\)\(^\text{16}\) Whether cisplatin-based chemotherapy induces cardiovascular toxicity directly or indirectly is still debated.

Direct Cisplatin Effects: Nuver et al.\(^17\) investigated the acute vasculature-related effect of cisplatin-based chemotherapy in TC patients. The principal findings included significant increases in von Willebrand factor
levels and a small but statistically significant increase in carotid intima media thickness acutely following chemotherapy. Increased intima media thickness has been associated with MI and stroke.\textsuperscript{30} Although these findings are not sufficient to generally account for permanent endothelial damage caused acutely by chemotherapy, they allow experts to speculate that cisplatin, detected in the plasma even 20 years after treatment,\textsuperscript{31} may stimulate the endothelium chronically. Furthermore, higher levels of fibrinogen, C-reactive protein, plasminogen activator inhibitor (PAI-1), and tissue-type plasminogen activator have been reported in long-term TC survivors treated with chemotherapy. This evidence should be considered along with reports of hyperreninemia, hypomagnesemia, and hyperaldosteronemia in normotensive men after cisplatin-based chemotherapy for TC.\textsuperscript{32,33} Clustering of cardiovascular risk factors resembling the metabolic syndrome was seen in TC patients who had undergone chemotherapy and had an increased PAI-1,\textsuperscript{34} raising the question of the indirect effect of chemotherapy-induced metabolic and hormonal changes on the development of premature atherosclerosis.

**Indirect Cisplatin Effects:** Gietema et al.\textsuperscript{35} first reported on the association between the metabolic syndrome and low testosterone levels in TC survivors who underwent chemotherapy. Nuver et al.\textsuperscript{23} confirm this finding and conclude that low testosterone may play a role in the development of the metabolic syndrome in long-term TC survivors, probably through its association with increased body mass index (BMI). The increased incidence of metabolic syndrome components, such as hypertension, increased BMI, dyslipidemia, and insulin resistance, has been well established in long-term TC survivors.\textsuperscript{24-29} Low testosterone, occurring in 10% to 30% of TC survivors, has been associated with the metabolic syndrome irrespective of TC and its treatment.\textsuperscript{23,25,30,31} In fact, a study by Laaksonen et al.\textsuperscript{32} suggests that nondiabetic middle-aged men with low testosterone are more likely to have the metabolic syndrome independent of BMI. An inverse association between intima media thickness and testosterone levels, although not independent of BMI, has also been reported.\textsuperscript{33}

Finally, although hypercholesterolemia is common in TC survivors, it cannot be directly associated with treatment. Reports from relatively small cohorts have conflicted depending on the control used, and a recent epidemiology report on the positive correlation between serum cholesterol level and TC incidence should be considered when evaluating analyses that used healthy men as controls.\textsuperscript{30,34,35}

**Raynaud’s Phenomenon:** Raynaud’s phenomenon is the most common vascular toxicity associated with currently used chemotherapeutic regimens and is observed in up to 37% of TC survivors.\textsuperscript{36,37} It is characterized by diffuse vascular narrowing in the hands of these patients, documented by arteriograms.\textsuperscript{36} Although Raynaud’s phenomenon is believed to be a vascular toxic effect of bleomycin, possible synergistic effects of cisplatin and vinblastine in the pathogenesis of the phenomenon have also been suggested. Symptoms may not appear for many months after chemotherapy and may persist for at least half of affected men. Smoking has been associated, although not conclusively, with an increased risk of this complication after chemotherapy.

**Recommendations:** Intervention for modifiable cardiovascular risk factors is especially important in TC survivors. Although no standard guidelines are available, physicians should be aware of the possible increased risk of cardiovascular disease at a younger-than-expected age and should consider appropriate risk-reducing strategies, such as treating hypertension and hypercholesterolemia, and advising patients to refrain from smoking, maintain a healthy body weight, and exercise regularly. New potential targets for treatment of Raynaud’s phenomenon are currently derived from experimental observations that may, if found effective, help relieve TC survivors of this complication.\textsuperscript{38}

**Second Cancer**

The increased incidence of second malignancies observed in patients with a history of TC is mainly attributed to treatment, with the exception of contralateral TC. Several registry-based reviews have identified an RR of 1.4 to 2.9 after treatment independent of TC histology. Travis et al.\textsuperscript{39} recently reported the largest meta-analysis on second solid cancers in 40,576 TC survivors from 14 European and North American registries followed up for a median of 11.3 years. This cohort includes a subset of patients who were followed up for a longer period in previous reports.\textsuperscript{40-42} Risk was found to increase with intensified therapy, younger age at diagnosis, and time of follow-up. In fact, this risk remains significantly increased for at least 35 years after treatment compared with that for the general population. Risks for a second solid tumor doubled among TC survivors treated with radiotherapy alone (RR,
The 15-year cumulative risk was reported to be 73% of cases with antisperm antibodies. Although no consensus exists, there is probably consistent with the change in therapeutic modalities.

Travis et al. included hematologic malignancies in their older meta-analysis of 28,843 patients surviving at least 1 year after being diagnosed with TC and treated between 1935 and 1993. Secondary leukemia was associated with radiotherapy and chemotherapy. Acute lymphoblastic leukemia and acute nonlymphocytic leukemia were 3 to 5 times more frequent than expected. Fossa et al., in their analysis of 876 patients treated for TC between 1956 and 1977, reported a significantly increased risk for second cancer (RR, 1.58; 95% CI, 1.2–2.0; P < .01), especially if radiotherapy was given (RR, 4.13; P < .01), although infradiaphragmatic radiotherapy alone did not increase this risk significantly. The most common malignancy was lung cancer. In an analysis of a subset of 1909 patients included in the Travis meta-analysis, van Leeuwen et al. suggested a protective effect of chemotherapy against contralateral TC, which is supported by other investigators.

The report from Zagars et al. based on a cohort of 453 seminoma patients treated with radiotherapy between 1951 and 1999, estimated an almost doubled cancer-related mortality. The most common malignancy was lung cancer. The British report by Horwich et al. on 859 seminoma patients treated with radiotherapy between 1961 and 1980, with a mean follow-up of 10 years, did not identify an excess risk for second malignancies, except for those with leukemia (RR, 6.2; 95% CI, 2.7–14.8).

In a large, population-based series of nearly 30,000 patients in the United States with unilateral TC, a 12.4-fold increased risk of developing a metachronous contralateral TC compared with the general population was reported. The 15-year cumulative risk was estimated to be 1.9% (95% CI, 1.7%–2.1%). Increased risk was highest during the first 5 years after orchiectomy and decreased thereafter. Metachronous contralateral TC diagnosis did not affect 10-year overall survival which was estimated at 93% (95% CI, 88%–96%). Survival after synchronous contralateral TC was 85% (95% CI, 78%–90%). Patients with seminomatous unilateral TC had a higher risk for metachronous contralateral TC than patients with a nonseminomatous unilateral TC.

Recommendations: Although no consensus exists, the authors would recommend that TC survivors be encouraged to adopt practices that are consistent with a healthy lifestyle. Screening guidelines for the general population should be followed. Compared with the general population, TC survivors have an increased risk for metachronous TC, yet low cumulative risk and favorable overall survival are in accordance with the current U.S. approach of not performing a biopsy on the contralateral testis.

Parenthood

Fertility: Subfertility is associated with TC and its treatment. Approximately half of all patients have defective spermatogenesis at diagnosis, whereas men with abnormal semen analyses have up to 20-fold greater incidence of TC compared with the general population. It may be speculated that a preexisting defect in germ cells leads to both cancer and defective spermatogenesis. Local effects of the tumor itself, including the paracrine action of the secretory substances of the tumor (hormones, cytokines) and a disruption of the blood–testis barrier, allowing autoantibody formation against sperm, can cause impaired spermatogenesis. Guazzieri et al. reported antisperm antibodies in 73% of patients with TC compared with 8% of healthy control subjects.

Most men experience temporary azoospermia after cisplatin-based chemotherapy for TC, with recovery of some spermatogenesis in approximately 50% of patients after 2 years and 80% after 5 years. Lampe et al. studied spermatogenesis recovery in a cohort of 178 TC patients treated with cisplatin-based chemotherapy. Almost half of the patients were azoospermic (24%) or oligospermic (23.5%) at diagnosis. Normospermic patients had a much
higher chance of recovering spermatogenesis after chemotherapy. Intensified chemotherapy and increasing age have a negative impact on spermatogenesis recovery. Interestingly, 20% of pretreatment oligospermic and azoospermic patients were eventually normospermic.

Animal studies have provided evidence that testicular injury caused by cisplatin exposure is a result of Leydig, Sertoli, and germ cell dysfunction. A reduction in leutinizing hormone (LH) receptors on Leydig cells is probably responsible for the decreased serum and intratesticular testosterone. The inter-Sertoli cell junctions making up the blood–testis barrier become leaky and a decrease in serum and epididymal androgen-binding protein levels occurs. This may occur even at low cisplatin doses. Finally, cisplatin induces apoptosis to germ cells.

Surgical injury to sympathetic nerves and ganglia during retroperitoneal lymph node dissection may cause dry ejaculation, resulting in either true retrograde ejaculation or loss of seminal emission into the posterior urethra. Radiation therapy, especially as applied in the past, could also confer risk for infertility.

Infertility is not the only barrier to parenthood after cancer. Some survivors are burdened by medical bills, are denied affordable medical or life insurance, or have difficulty attracting a partner because of their medical liabilities. Cancer treatment may delay or interrupt career development, further decreasing financial resources.

Approximately 1 of 3 men will pursue parenthood after treatment, and 1 of 3 of these will be unable to conceive (Table 1). The impact on fertility is greater with intensified treatment, increased dose of cisplatin, or combined chemotherapy with radiation, reaching a maximum failure risk of approximately 50%.

Brydoy et al. reported on the largest cohort of patients undergoing treatment between 1980 and 1994. Of 1433 patients, 918 attempted conception after diagnosis and 90% were successful. After treatment, 554 (39%) attempted conception, with a 65% overall success. Orchiectomy had almost no impact on parenthood (85%). The effect of cisplatin-based chemotherapy on fertility depended on cumulative cisplatin. Doses greater than or equal to 850 mg reduced success in parenthood to only 38% compared with 62% for lower doses. In the multivariate analysis, other factors that predicted posttreatment parenthood were having children before treatment, ejaculatory function, and marital status.

The report by Huddart et al. on 680 patients treated between 1982 and 1992 confirms a trend toward lower success rates for conception in groups undergoing chemotherapy, irrespective of cisplatin dose and including patients treated with carboplatin (overall success rates of 85% with surveillance and 71% with any chemotherapy; \( P = .028 \)). In this report, 30% of patients attempted conception, with a 77% overall success rate. However, this cohort included many patients who underwent surveillance. Of couples who attempted conception after treatment for TC, Huyghe et al. reported that only two thirds were successful.

Brydoy et al. identified that the modified treatment modalities introduced in the late 1980s favored the chance of fathering a child. This improvement was not just caused by the introduction of surveillance, because it did not change when orchiectomy patients were omitted from analysis. Other smaller reports also suggest a reduced risk for treatment-induced infecundity with the introduction of modified treatment modalities.

Gonadal Function: Gonadal dysfunction is common in patients with a history of TC even when treated with orchiectomy alone. Almost all studies addressing gonadal function in TC survivors have reported an increase in both LH and follicle-stimulating hormone (FSH) and a decrease in testosterone levels after chemotherapy. Longer follow-up shows that this effect seems to be partially recovering. Increased FSH levels occurred in 41% to 71% of cases, most frequently among patients who underwent combination therapy. Men with higher FSH levels were more likely to be unable to conceive.

Testosterone was reduced in approximately 10% to 34% of TC survivors, depending on treatment intensity (Table 2). Lower testosterone significantly reduces sexual interest and enjoyment and impairs the quality of life that is related to hormonal function. In addition, lower testosterone is associated with increased BMI and incidence of the metabolic syndrome.

Mutagenic Potential of Semen: The rate of congenital anomalies before or after treatment doesn’t differ from that of the general population. Spermon et al. recorded congenital malformations in approximately 4% of children born before or after treatment.
Table 1: Latest Reports on Fertility After Treatment for Testicular Cancer

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Median Period of Follow-Up (y)</th>
<th>Median Seminoma/Nonseminoma (%)</th>
<th>Overall Success in Conception (%)</th>
<th>Attempt to Conceive (%)</th>
<th>Seminoma/Nonseminoma Treatment (%)</th>
<th>Cohort Parenthood After Chemo/ Radio therapy</th>
<th>Parenthood After Chemo/ Radio therapy</th>
<th>Parenthood After Surveillance</th>
<th>Parenthood After RPLND</th>
<th>Parenthood After RPLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brydoy et al., 2005</td>
<td>13.3</td>
<td>131/143 (90%)</td>
<td>90%</td>
<td>35%</td>
<td>65%</td>
<td>65%</td>
<td>7%</td>
<td>81%</td>
<td>NA</td>
<td>82%</td>
</tr>
<tr>
<td>Huddart et al., 2005</td>
<td>10.2</td>
<td>169/207 (82%)</td>
<td>43/57 (71%)</td>
<td>32</td>
<td>90%</td>
<td>39%</td>
<td>65%</td>
<td>Cisplatin &gt; 850 mg/m²</td>
<td>62%</td>
<td>113/183 (62%)</td>
</tr>
<tr>
<td>Huyghe et al., 2004</td>
<td>8.4</td>
<td>168/228 (74%)</td>
<td>48/52 (82%)</td>
<td>34</td>
<td>77%</td>
<td>71%</td>
<td>71%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Herr et al., 1998</td>
<td>11.1</td>
<td>169/183 (91%)</td>
<td>48/52 (82%)</td>
<td>34</td>
<td>77%</td>
<td>71%</td>
<td>71%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Recommendations: More recent treatment standards preserve fertility, including introducing surveillance as a primary therapy option after orchietomy, using modified unilateral or nerve-sparing RPLND, administering less chemotherapy, and limiting radiation dose and extent of fields.

Cryopreservation is the recommended modality to preserve fertility. The effect of cryopreservation on sperm is similar in patients with TC and donors.68,69 Men who desire future children and who will receive treatment that may impair their fertility should be fully informed about this option. Even though cryopreservation is not covered by most insurance companies in the United States, and probably less than 10% of patients will eventually use it, available evidence suggests that infertility resulting from cancer treatment may be associated with psychosocial distress.70,71 Although other options exist, most survivors prefer to have biological offspring, and having banked sperm was found to be a positive factor in coping emotionally with cancer, even if samples were never used.72 Most reports confirm that lack of information is the predominant reason for not pursuing sperm banking. Hormone supplementation is necessary for symptomatic men with obvious potency problems.

Neurotoxicity–Ototoxicity

Cisplatin is well documented to confer considerable risk for acute and chronic peripheral and central neurotoxicity and ototoxicity. Paclitaxel, ifosfamide, and vinblastine are also associated with neurotoxicity. The dorsal root ganglion is the primary target of cisplatin-induced damage characterized by high levels of platinum–DNA binding and apoptosis of dorsal root ganglion neurons.73 The neuropathy is characterized by selective sensory loss in the extremities with relative sparing of motor units. The main clinical manifestations are paresthesias, dysesthesias, disturbances of position, and vibratory sensations. Ototoxicity is probably caused by cisplatin damage to the secretory mechanism of the organ of Corti and manifests as high-frequency hearing loss and tinnitus.

Symptomatic and asymptomatic abnormalities (detected with neurophysiologic testing or vibration threshold) have been reported...
in up to 76% of patients after chemotherapy for TC, depending on the diagnostic methods. Patients who already have neuropathic symptoms due to diabetes mellitus or those with hereditary neuropathies might be more vulnerable. Although acute neurotoxicity usually disappears after chemotherapy, 20% to 60% of patients experience persistent symptoms beyond 6 years. The incidence of ototoxicity, similar to that of neurotoxicity, varies considerably according to the diagnostic methods used. The estimated frequency of chronic ototoxicity is 10% to 40%. Development of neurotoxicity starts at cumulative doses of cisplatin of 300 mg/m². Almost all patients experience neurotoxicity at a dose of 500 to 600 mg/m², and high-frequency hearing loss and persistent tinnitus at doses greater than 650 mg/m². Repeated daily low doses seem to be less toxic than higher single doses. Vinca alkaloids, preexisting hearing impairment, and an increased cisplatin infusional rate may increase the risk for ototoxicity.

Recommendations: No effective treatment for neurotoxicity may be recommended for standard use in daily practice. Further studies are warranted to confirm beneficial effects attributed to neuroprotective agents, such as gabapentin, or behavioral changes. Many patients experience improvement over time. Fractionating chemotherapy over 5 days rather than 3 might reduce the risk for neurologic toxicity.

Pulmonary Toxicity
Pulmonary toxicity is the most feared and dose-limiting toxicity of bleomycin. Several distinct pulmonary syndromes have been associated with the use of bleomycin, such as bronchiolitis obliterans with organizing pneumonia (BOOP), eosinophilic hypersensitivity, and, most commonly, interstitial pneumonitis, which may ultimately progress into fibrosis. The latter, bleomycin-induced pneumonitis (BIP), occurs in 0% to 46% of the patients treated with bleomycin-containing chemotherapy, depending on the criteria used for the diagnosis since it may range from subclinical to fatal. Prospective studies have delineated the rate of clinical pulmonary toxicity occurring with 270 IU of bleomycin. Pulmonary fibrosis will eventually occur in approximately 5% to 10% of patients and is fatal in 1% to 2%. Steroids, although used widely, in the acute phase may not be effective in preventing fibrosis. The central event in the development of BIP is endothelial damage of the lung vasculature due to bleomycin-induced cytokines and free radicals. Risk factors include age older than 70 years, prior chest radiotherapy, impaired renal function especially in men older than 40 years, high inspired oxygen concentration, doses older than 360 IU, history of cigarette smoking, supplemental oxygen exposure, the presence of visceral metastases, and combination chemotherapy with cisplatin at lower-than-expected doses. Toxicity may also be potentially increased with the use of granulocyte colony-stimulating factor.

O’Sullivan et al. reported on the largest cohort of patients (N = 835) treated with bleomycin-containing regimens for germ-cell tumors between 1982 and 1999. They reported that 6.8% of patients experienced pulmonary toxicity, ranging from radiograph/computed tomography changes to dyspnea,

### Table 2 Reports on Gonadal Dysfunction Following TC Treatment

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N Patients</th>
<th>Median Follow-Up (y)</th>
<th>Treatment</th>
<th>High FSH (%)</th>
<th>High LH (%)</th>
<th>Low Testosterone (%)</th>
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<tbody>
<tr>
<td>Huddart et al., 57</td>
<td>680</td>
<td>10.2</td>
<td>Surveillance</td>
<td>41</td>
<td>6</td>
<td>11</td>
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<td></td>
<td></td>
<td></td>
<td>Chemotherapy</td>
<td>49</td>
<td>10</td>
<td>13</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Radiotherapy</td>
<td>45</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemotherapy/ Radiotherapy</td>
<td>71</td>
<td>22</td>
<td>34</td>
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<tr>
<td>Strumberg et al., 65</td>
<td>32</td>
<td>&gt; 13</td>
<td>Chemotherapy</td>
<td>75</td>
<td>47</td>
<td>12</td>
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<tr>
<td>Bokemeyer et al., 29</td>
<td>63</td>
<td>4.8</td>
<td>Chemotherapy</td>
<td>63</td>
<td>33</td>
<td>10</td>
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<td>Brenemmann et al., 57</td>
<td>73</td>
<td>1</td>
<td>Chemotherapy</td>
<td>89</td>
<td>7</td>
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<tr>
<td></td>
<td>28</td>
<td>&gt; 8</td>
<td>Chemotherapy</td>
<td>64</td>
<td>33</td>
<td>3.5</td>
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</tbody>
</table>

Abbreviations: FSH, follicle-stimulating hormone; LH, leuteinizing hormone.
Table 3 Reports on Late Relapse of Testicular Cancer

<table>
<thead>
<tr>
<th>Markers Positive (%)</th>
<th>Site of Relapse</th>
<th>Presence of Cancer (%)</th>
<th>Median Time to Relapse (%)</th>
<th>N Patients</th>
<th>N Patients Late Relapse (%)</th>
<th>Symptoms Present (%)</th>
<th>&gt;5 y (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retroperitoneum: 37</td>
<td>Mediastinum: 87</td>
<td>1997–1999</td>
<td>21</td>
<td>5</td>
<td>5.4</td>
<td>5</td>
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<tr>
<td></td>
<td>Retroperitoneum: 32</td>
<td>Mediastinum: 81</td>
<td>1979–1994</td>
<td>21</td>
<td>81</td>
<td>58</td>
<td>52</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NA, not available.

with 1% of patients dying from this toxicity. The median time from the start of bleomycin administration to documented lung toxicity was 4.2 months (range, 1.2–8.2). On multivariate analysis, the factors independently predicting increased risk for bleomycin pulmonary toxicity were glomerular filtration rate less than 80 mL/min (hazard ratio [HR], 3.3), age older than 40 years (HR, 2.3), stage IV disease at presentation (HR, 2.6), and cumulative dose of bleomycin greater than 300 IU (HR, 3.5). Major surgery after bleomycin administration did not predict bleomycin toxicity, even though several studies have associated bleomycin toxicity with oxygen therapy.

Initial symptoms include an inspiratory lag (decreased chest excursion on one side compared with the other) or inspiratory crepitations, bibasilar crepitations, a nonproductive cough, and altered pattern of dyspnea on exertion. Pulmonary functions may show a decrease in carbon monoxide diffusing capacity.

**Recommendations:** The lack of a predictive test for clinically significant lung toxicity and the uncertainty of treatments for the condition are important considerations in bleomycin pulmonary toxicity. Withholding therapy is paramount at the first sign of toxicity. There are no data on what time interval is safe between the last dose of bleomycin and oxygen therapy. TC survivors should be advised that theoretically there is a risk of developing pulmonary damage due to exposure to a higher partial pressure of inspired oxygen, as would be the case in scuba diving. In the case of a pending operation, baseline pre-operative studies, such as pulmonary function tests, carbon dioxide diffusion capacity, room air blood gases, and chest radiography, may help
Late Complications and Relapse in Testicular Cancer

predict patients with compromised pulmonary functions as a result of bleomycin treatment at risk for complications.

Renal Toxicity
Long-term renal toxicity, induced by either cisplatin-based chemotherapy or radiotherapy is estimated to occur in 20% to 30% of TC survivors.86-92

Effects of cisplatin may range from mild biochemical changes to acute renal failure and chronic renal insufficiency. A persistent reduction in glomerular filtration rate of 20% to 30% has been found in 20% to 30% of TC survivors after cisplatin-based treatment.87,89 Persistent hypomagnesemia and hyperuricemia have been found in 30% to 35% of patients.91,92 The pathogenesis of cisplatin nephrotoxicity remains unclear. The cumulative dose of cisplatin administered and high peak plasma concentrations, especially after cisplatin doses greater than or equal to 500 mg/m², have been associated with nephrotoxicity.93,94 Co-administration of nephrotoxins can exacerbate glomerular dysfunction.95,96 Considerable conflict exists as to the long-term outcome of glomerular defects, with some reports of improvement, others of persistence, and even some of progression of renal dysfunction.

Because most para-aortic radiotherapy fields include a portion of the kidney, and the radiation tolerance dose of the kidney is approximately 20 Gy, the recent dose reduction potentially limits renal toxicity significantly.

Recommendations: Hyperhydration and forced diuresis used routinely during cisplatin administration reduce the probability of renal complications. Furthermore, maintaining relatively low peak plasma concentrations of free platinum by administering it at a daily dose of 20 mg/m² over 5 consecutive days further reduces this risk.

Late Relapse
The incidence of late relapse (LR) of TC, originally reported in case series format, has recently increased to 1.5% to 6.0% (Table 3).88-90 The introduction of cisplatin-containing regimens dramatically changed the natural history of advanced disease and may be the reason for this increase. Time to LR ranges from 2 to 32 years with a median of 6 years.99 Sixty to 70% of patients with LR experience recurrence more than 5 years from initial diagnosis.

LR has been associated with increased tumor burden at initial diagnosis, absence of primary RPLND, and presence of teratoma after primary therapy.95-97 Shahidi et al. found LR to be more frequent in metastatic nonseminoma, with a 1% annual risk for recurrence between 5 and 10 years.

Most reports associate symptomatic relapse with a poorer outcome.3,94-96 Alpha-fetoprotein, the dominant marker of LR, suggests a poor prognosis at a value greater than 100 IU.97

In the differential diagnosis, metastasis must be excluded from a second primary or primary extragonadal germ cell tumor. The most common site of relapse is the retroperitoneum, accounting for 47% to 80% of cases regardless of stage, clinical presentation, or prior treatment, followed by the lung and mediastinum (Table 3). This therefore suggests that an inadequately controlled retroperitoneum is a major predisposing factor.

The biology of LR tumors is apparently different from primary tumors because they exhibit a long latency period and chemoresistance, with a cure rate of 26% to 69%.95-101 Surgery, referred to as surgical salvage, is the preferred treatment in patients with a solitary metastasis, and is combined with chemotherapy in select cases.

Recommendations for Follow-Up: The increasing incidence of LR and the poor prognosis of symptomatic relapse highlight the necessity for lifelong follow-up in at least select TC survivors. Surgical resection of teratoma, malignant transformation, and chemotherapy-resistant viable germ cell tumor, and adequately controlling disease in the retroperitoneum may also minimize the probability of LR.

Conclusions
Although cancer therapy represents a double-edged sword, the remarkable gains in survival provided by treatments for TC far outweigh the risks for late complications. The reported analyses must be reviewed critically and generalized to modern practice cautiously. The modifications in TC treatment over the past 2 decades probably will have considerably less impact on the quality of lives of survivors, although careful follow-up is necessary to reliably quantify long-term risk.

References


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