Long-term and late effects of germ-cell testicular cancer treatment and implications for follow-up

Chapter 2


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Abstract

Germ-cell testicular cancer (TC) represents a malignancy with very high cure rates. After the introduction of cisplatin-based chemotherapy in the late 1970s, the 5-year survival rate has increased considerably, and is currently above 95%. Since TC usually is diagnosed before the age of 40, these men can expect to live for another 40-50 years after being successfully treated. This success, however, is hampered by an increased risk of long-term and late effects of treatment. Secondary malignant neoplasms and cardiovascular disease represent the most common potentially life-threatening late effects typically occurring more than 10 years after treatment. Other long-term effects include pulmonary toxicity, nephrotoxicity, neurotoxicity, decreased fertility, hypogonadism and psycho-social problems. The incidence and time to onset of these various side-effects vary according to treatment type and intensity. There is still little knowledge about underlying mechanisms and genetic susceptibility of the various adverse effects. Apart from treatment burden, it is not yet possible to identify patients who are at high risk for certain late effects after TC treatment.

In this clinical review, we present the current status regarding different somatic and psychosocial long-term late effects after treatment for TC, based on Medline searches and our own research. Moreover, we postulate recommendations for general medical evaluations that should begin after treatment is completed and continue during follow-up.
Introduction

The treatment of germ-cell (GC) testicular cancer (TC) represents a medical success story with today’s 5-year survival rates exceeding 95%.1 The improved prognosis is primarily due to the effectiveness of cisplatin-based chemotherapy in the treatment of advanced disease, timing of surgery to remove residual disease, and the establishment of effective salvage regimens.2

TC affects mostly young men at their peak of family life, reproduction, education and career, with a life expectancy of 40-50 years after successful cancer treatment. Consequently, there has been an increased attention towards long-term effects of cancer treatment during the last decade, which has resulted in attempts to decrease treatment-related toxicity while maintaining the high cure rates.3 Despite these attempts, treatment-related toxicity has emerged as an important issue for this young patient population. But since studies of late effects of cancer treatment are retrospective in nature, it should be pointed out that the current knowledge represents complications of treatment administered several years to decades ago.4

Long-term survivors are defined as individuals who are disease-free 5 years or more after primary treatment.4 Some side-effects of cancer treatment develop during treatment and may persist during follow-up, e.g. peripheral neuropathy. These side-effects are referred to as long-term effects, while late effects become manifest months to years after completion of treatment.4 Secondary non-GC cancers and cardiovascular disease are examples of late effects. These represent the most serious and potentially life-threatening effects of cancer treatment.

Apart from treatment burden, it is presently not possible to identify patients at high risk for certain somatic long-term and late effects of TC treatment. A recent review paper on TC survivorship has recommended specific future research directions to elucidate the underlying mechanisms of the long-term and late effects.5

Based on Medline searches and our own research, we herein summarize the current knowledge regarding the different somatic and psychosocial long-term and late effects after TC treatment. We postulate recommendations for maintaining health and general medical evaluations that should begin after treatment and continue beyond the 10-year follow-up.

Methods

Medline databases were used to identify original articles and reviews on long-term and late effects of TC treatment. The phrases used during the search process included “testicular cancer” or “germ cell cancer” combined with “survivors”, “late effects”, “morbidity”, or “long-term effects” and phrases reflecting the different toxicities (e.g. “myocardial infarction”; “cardiovascular disease”, “hypertension”). Articles published during the past two decades were preferentially included. Only articles published in English until 31st of December 2011 were reviewed. The majority of included publications were based on participants who were in a durable complete remission, preferably long-term survivors as previously defined. The list of references was reviewed by all authors of this review.
Most studies on late effects of cancer treatment have been retrospective in nature. Thus, no prospective randomized trials on late effects from testicular cancer treatment have been published.

**Secondary malignant neoplasms**

The development of a non-GC second malignancy represents one of the most severe late effects following treatment for TC. In addition, 1-5% of TC survivors (TCSs) develop a contralateral TC which probably reflects common etiologic factors. A contralateral TC is not regarded a late effect of treatment and we make no further comment on its origin or management.

In a series of 40,576 TCSs, the overall post-TC observed/expected (O/E) ratio for developing a solid second cancer was 1.55 (95% confidence interval [CI] 1.48-1.62) in 10-year survivors, which is in agreement with other large population-based studies (Table 1). The O/E ratio was 2.6 (95% CI 2.1-3.2) for leukemia, mostly acute myeloid leukemias (AML) and lymphoblastic leukemias. Concern has been raised regarding the association between etoposide and AML. However, the absolute risk of etoposide-induced AML after four cycles or less of standard chemotherapy is very low, and was reported to be less than 0.2% in chemotherapy-treated patients. The risk of etoposide-induced AML is probably dose-dependent, and after high-dose etoposide the risk of AML has been ranging from 0.5% to 2.6% in several studies. Therapy-related leukemia is usually diagnosed within the first 10 years after treatment for TC. Solid second malignancies are generally diagnosed after a latency of at least 10 years and may be induced by both radiotherapy and chemotherapy (Table 1).

Most radiation-induced malignancies are located within or close to initial abdominal radiation fields (bladder, stomach, pancreas and colon cancer). The statistically increased relative risks for solid cancers after cytotoxic treatment (Table 1) are to a great extent based on “old fashioned” cytotoxic treatment with larger radiotherapy fields and higher radiation and chemotherapy doses than used today. The role of modern risk-adapted treatment on the late development of a solid second cancer is less clear.

The radiation exposure from repeated CT scans during follow-up could theoretically contribute to an increased risk for solid cancers. Theoretical estimates of lifetime cancer risk range from 1.9% for an 18-year old to 1.2% for a 40-year old patient during surveillance for stage I TC, but these are estimated phantom data, not patient data, and should be interpreted with caution. These hypotheses, based on extrapolations from Hiroshima and other data, are not supported at this time by clinical studies that demonstrate that such risk exists. A recent publication by van Walraven et al did not find any association between radiation exposure and risk of second cancers in 2569 men after treatment for low-grade TC, but the follow-up time was only median 11.2 years. Hence, given the very low risk, the relative risk/benefit should be considered when making decisions about the use of CT in patient care. Some guidelines recommend MRI instead of CT during follow-up to reduce the risk of radiation-induced cancer, but there is no definitive study at this time.
Table 1. Second cancers (solid tumors and leukemias) in long-term testicular cancer survivors (TCSs).

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of diagnosis</th>
<th>No. of patients</th>
<th>Patient characteristics</th>
<th>Risk of second cancer compared with gen pop</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travis (2005) (7)</td>
<td>1943-2001</td>
<td>40,576 (20,984 10-y survivors)</td>
<td>Chemotherapy Radiotherapy CT and RT Data from population-based cancer registries.</td>
<td>1.8 (1.3-2.5) (RR) 2.0 (1.9-2.2) 2.9 (1.9-4.2)</td>
<td>TCSs are at significantly increased risk of solid cancers for at least 35 years after treatment. The risk for second cancer decreased with increasing age at testicular cancer diagnosis. Cancers of the lung (RR 1.5), colon (RR 2), bladder (RR 2.7) pancreas (RR 3.6) and stomach (RR 4.0) accounted for 60% of the total excess.</td>
</tr>
<tr>
<td>Richiardi (2006) (8)</td>
<td>1943-2000</td>
<td>29,511</td>
<td>Data from population-based cancer registries. No treatment details were included.</td>
<td>Overall SIR was 1.65 (1.57-1.73) for solid tumors after median 8.3 years follow-up. SIRs for most solid cancers ranged between 1 and 2, and increased with increasing follow-up.</td>
<td></td>
</tr>
<tr>
<td>Van den Belt-Dusebout (2007) (9)</td>
<td>1965-1995</td>
<td>2707 (5-y survivors)</td>
<td>Surgery only Radiotherapy Chemotherapy RT and CT Data from population-based cancer registries.</td>
<td>Overall SIR was 1.7 (1.5-1.9) after median 17.6 years follow-up. The risk of second cancer was 2.6 (1.7-4.0) after infradiaphragmatic RT and 2.1 (1.4-3.1) after chemotherapy in comparison to surgery only. Secondary leukemia developed in 89 patients, with an EAR at 108. per 100,000 person years. Statistically significantly elevated risks were observed for acute myeloid leukemia and acute lymphoblastic leukemia. Excess cumulative leukemia risk was 0.23% by 30 years after TC diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Howard (2008) (10)</td>
<td>1943-2001</td>
<td>42,722 (1-y survivors)</td>
<td>Surgery only Radiotherapy Chemotherapy RT and CT Data from population-based cancer registries.</td>
<td>Overall SIR was 1.6 (0.8-2.9) (O/E) 2.7 (1.9-3.6) 3.9 (1.8-7.3) 4.5 (0.7-13.8)</td>
<td>Secondary leukemia developed in 89 patients, with an EAR at 108. per 100,000 person years. Statistically significantly elevated risks were observed for acute myeloid leukemia and acute lymphoblastic leukemia. Excess cumulative leukemia risk was 0.23% by 30 years after TC diagnosis.</td>
</tr>
</tbody>
</table>

Abbreviations: No, numbers; gen pop, general population; y, years; RT, radiotherapy; CT, chemotherapy; RR, relative risk SIR, standardized incidence ratio; EAR, excess absolute risk.
Cardiovascular disease and Raynaud’s phenomenon

Cardiovascular disease
Case reports on potentially life-threatening cardiovascular disease (CVD) during or shortly after treatment date back to the 1980s. The frequency of late cardiac morbidity among TCSs was reported for the first time in 2000 by Meinardi et al., among 87 patients aged ≤50 years at the time of analysis. Subsequent reports on CVD in TCSs estimated the magnitude of the problem. Zagars et al. reported on cardiac mortality in survivors of testicular seminoma treated with radiotherapy only. Of note, the cardiac-specific standardized mortality ratio (SMR) was first after 15 years of follow-up significantly elevated at 2.02 (99% CI 1.22-3.16). A large international study by Fosså et al. in 38,907 at least one-year TCSs reported a SMR for all circulatory diseases of 1.58 (95% CI 1.25-2.01) in men who received chemotherapy after 1975.

Table 2 summarizes the prevalence of coronary artery disease (CAD) found in recent studies, subdivided in different treatment groups. In a large nationwide cohort study performed by Van den Belt-Dusebout et al., non-seminoma survivors younger than 45 years had a significantly increased standardized incidence ratio for myocardial infarction (MI) at 2.06 (95% CI 1.15-3.41). A substantial part of the analysis was based on patients treated with regimens no longer used, thus supplementary studies are needed to ascertain the burden of the current standard regimens. A recent Norwegian study reported a significantly increased risk of CAD after bleomycin, etoposide and cisplatin (BEP) in comparison to age-matched controls, but this publication did not include mortality.

Mechanisms behind treatment-induced CVD are not yet accurately elucidated. Both direct vascular damage and indirect effects through gradual development of CVD risk factors may contribute to the eventual cardiovascular damage. A significantly higher prevalence of hypertension was found in chemotherapy-treated TCSs, while diabetes was more prevalent after radiotherapy alone or in combination with chemotherapy, as compared with patients treated with other modalities and healthy controls. In particular, the clustering of CVD risk factors into the metabolic syndrome might be the mediating link between cytotoxic treatment and CVD. Patients treated with cisplatin-based chemotherapy more often develop the metabolic syndrome in comparison to controls or other treatment groups.

Inflammation and endothelial dysfunction play an important role in the pathogenesis of atherosclerosis. Microalbuminuria, and circulating levels of von Willebrand factor and plasminogen activating inhibitor 1 (PAI-1), markers representing endothelial dysfunction, are all significantly more prevalent in chemotherapy-treated TCSs. Cisplatin is detectable in serum several years after administration, and it is hypothesized that small amounts of cisplatin may continuously stimulate the endothelium. However, there are no data to support that hypothesis. C-reactive protein was recently proposed as a potential marker for cardiovascular disease in TCSs, suggesting chronic endothelial activation.
Raynaud’s phenomenon
Many patients experience Raynaud’s phenomenon (RP) both during and after treatment. This typical white discoloration of the digits and subsequent pain and redness is prevalent in 15-45% in chemotherapy-treated TCSSs several years after treatment. The phenomenon is thought to be a consequence of direct vascular damage in the digital arteries, but neurologic effects may also be involved in the abnormal vasoregulation causing vasospasms. Bleomycin is considered as the key predictor of RP. However, the cumulative cisplatin dose may also contribute.
**Table 2. Risk of coronary artery disease (CAD) in long-term testicular cancer survivors (TCSs).**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of diagnosis</th>
<th>No. of patients</th>
<th>Median fu (range), y</th>
<th>Treatment characteristics</th>
<th>Statistical method</th>
<th>Risk of CAD (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huddart (2003) (19)</td>
<td>1982-1992</td>
<td>992</td>
<td>10 (0-20)</td>
<td>Surgery only Radiotherapy Chemotherapy CT and RT</td>
<td>RR</td>
<td>1.0 (reference)†</td>
<td>No restrictions regarding follow-up duration. RR adjusted for age. “Cardiac event” as measured endpoint, see definition below.</td>
</tr>
<tr>
<td>Van den Belt-Dusebout</td>
<td>1965-1995</td>
<td>2339 (5-y survivors)</td>
<td>18 (5-38)</td>
<td>Surgery only RT infradiaphragmatic (inf) RT mediastinum (med) Chemotherapy CT and RT inf CT and RT med &lt;45 years 45-54 years ≥54 years</td>
<td>SIR Treatment groups</td>
<td>0.8 (0.5-1.2)</td>
<td>MI events &gt;5 years after diagnosis. Cardiovacular data were obtained from medical records and through questionnaires sent to patients’ general practitioners. Compared with age-matched controls.</td>
</tr>
</tbody>
</table>

Abbreviations: No, numbers; fu, follow-up; y, years; SIR, standardized incidence ratio; MI, myocardial infarction; AP, angina pectoris; CT, chemotherapy; RT, radiotherapy; RR, relative risk; CVB, cisplatin, vinblastine and bleomycin; BEP, bleomycin, etoposide and cisplatin; HR, hazard ratio; ns, not significant; CVD, cardiovascular disease.

*Inclusion criterion: age ≤50 at time of analysis.
†The endpoint was “cardiac event” defined as (1) patient died from a MI or similar cardiac related episode; (2) angina or MI reported on GP forms; (3) cardiac abnormality on the assessment form at the long-term follow-up clinic visit; (4) angina or chest pain reported on clinic visit; (5) cardiac surgery for coronary artery disease.
Pulmonary toxicity

Pulmonary toxicity was identified as the major dose-limiting side-effect of bleomycin treatment already in the 1970s. Bleomycin may cause pneumonitis, occasionally progressing to pulmonary fibrosis during or shortly after administration of bleomycin. As there are no agreed criteria to define bleomycin pulmonary toxicity (BPT), the long-term prevalence of patients with non-fatal BPT varies between 7% and 21%. Fatal BPT has been reported to occur in 1-3% of patients treated with bleomycin. In a British study where 835 patients were evaluated median 7.4 years following treatment, multivariate analyses showed that decreased renal function (hazard ratio [HR] 3.3), age above 40 years (HR 2.3), initial stage IV disease (HR 2.6) and cumulative bleomycin dose >300,000 IU (300 units) were associated with increased risks of BPT. Interestingly, the bleomycin hydrolase genotype was not found to be associated with the development of BPT or with changes in pulmonary function tests.

Prior studies evaluating pulmonary function after treatment for TC concluded that possible reductions in the pulmonary function during or shortly after treatment were normalized during follow-up. In a Norwegian study reporting long-term spirometry data from 1,049 TC survivors after median 11 years follow-up, men treated with large cumulative cisplatin doses and/or pulmonary surgery had significantly decreased spirometry variables compared with men treated with surgery only. Only cisplatin dose (p=0.007) and age (p=0.008) were significantly associated with restrictive lung disease in multivariate analyses that included cumulative bleomycin (maximum: 360,000 IU/360 units), etoposide and vinblastin doses. The reduced pulmonary function was subclinical in the majority of these patients.

Population-based epidemiological studies have shown an association between pulmonary function and all-cause mortality. Furthermore, TCSs cured by chemotherapy after 1975 are at a 2.5-fold increased risk to die of respiratory disease compared with the normal population. The lungs are highly vascularized organs, and chemotherapy-induced endothelial dysfunction is a possible mechanism that is involved in the reduced pulmonary function.

Nephrotoxicity

Nephrotoxicity is a well-recognized acute and long-term effect of both radio- and chemotherapy for TC. Studies in animals and humans have shown that cisplatin damages the proximal and distal tubular epithelium and collecting ducts, and in the rat it also produces glomerular damage at the highest doses. A statistically significant increase in serum creatinine and a decrease in serum magnesium (Mg) from baseline measurements are often detectable after 4 cycles of standard cisplatin-based therapy. Mg loss may lead to hypomagnesemia, hypokalemia, and hypocalcemia. Less commonly, cisplatin may also induce sodium wasting and proteinuria, particularly after high cumulative cisplatin doses. Studies also show that neither serum creatinine nor calculated creatinine clearance based on 24h urine collections is a sensitive measure of renal damage. The severity of renal damage during cisplatin treatment can be limited by vigorous hydration during treatment, but it cannot be completely avoided.
existing intrinsic renal disease augments cisplatin nephrotoxicity, as does the co-administration of other nephrotoxic drugs. The acute nephrotoxic effects of cisplatin may be partly, but not completely, reversible. Long-term studies of renal function show persistent changes from baseline values years after completion of treatment, with little evidence of improvement over time.\textsuperscript{57, 58, 71, 72} The increased prevalence of loss of albumin in the urine (microalbuminuria) with increasing follow-up duration may be considered a sign of vascular damage within the kidney.\textsuperscript{73} The clinical implications of these changes are unclear, but they may possibly contribute to a reported increase in cardiovascular toxicity, including hypertension and myocardial infarction observed in patients a decade or more after cisplatin-based treatment.\textsuperscript{29-25} Renal artery stenosis several years after para-aortic irradiation, resulting in severe hypertension, has been reported in some case reports.\textsuperscript{75, 74} Thus, men who develop severe hypertension after abdominal irradiation should be investigated for renal artery stenosis.

In one report, significant increases in serum renin and aldosterone levels were reported in a majority of normotensive patients at a median of 26 months (range 9-54 months) after treatment.\textsuperscript{71} More recent data have shown a relationship between reduced glomerular filtration rate and the presence of microalbuminuria, with an increased risk of cardiovascular and all-cause mortality in a general population, and support an association between decreased renal function and risk of sudden cardiac death.\textsuperscript{75-77}

**Neuro- and ototoxicity**

**Peripheral neuropathy**

Cisplatin-induced neuropathy is typically sensory neuropathy of the distal limbs, with paresthesias being the core symptom. Cisplatin causes degeneration of large dorsal root ganglia neurons with loss of myelinated fibres, both distally in the limbs and proximally in the spinal cord, although other mechanisms may be involved as well.\textsuperscript{78, 79} The reported incidence of persistent peripheral neuropathy varies according to applied treatment and dose as well as method of assessment. A frequency of 20-40\% has typically been stated.\textsuperscript{80} Three large studies with long follow-up have been published during recent years.\textsuperscript{37-39} In the Norwegian cohort, 28\% of TCSSs who received \( \leq \) 4 cycles of cisplatin-based chemotherapy reported paresthesias, as opposed to 46\% following \( \geq 5 \) cycles and 10\% after orchiectomy alone.\textsuperscript{37} Rossen et al. reported similar findings (chemotherapy: 31\%; surveillance: 9\%),\textsuperscript{38} while peripheral neuropathy was somewhat less frequent in the study by Glendenning et al. where 1/3 had received carboplatin-based chemotherapy.\textsuperscript{39} Paresthesias of the lower limbs may also be associated with abdominal radiation.\textsuperscript{77} In severe cases, symptomatic treatment might be tried, but an effective treatment has not been documented.\textsuperscript{81}

**Otitotoxicity**

Cisplatin-induced ototoxicity represents a distinct feature of cisplatin’s side effects and is presumably caused by selective damage to the outer hair cells of the cochlea,\textsuperscript{82} leading to tinnitus
and hearing impairment, typically affecting the high frequencies. Reported persistent ototoxicity varies widely with method of investigation, and applied treatment. Bokemeyer et al. reported persistent ototoxic symptoms in 5 to 65%, depending on cisplatin dose.\textsuperscript{83, 84} Ototoxic symptoms beyond 5 years following cisplatin-based treatment have been reported in 21-24\% of TCSs.\textsuperscript{37, 38} The five-day BEP regimen seems preferable to the three-day regimen in regard of minimizing ototoxicity, particularly if 4 cycles are administered.\textsuperscript{37, 85}

The considerable inter-individual variations observed may be due to polymorphisms in glutathione S-transferases,\textsuperscript{86, 87} or other candidate genes associated with cisplatin-induced neuro- and ototoxicity.\textsuperscript{88, 89}

**Cognitive function**

Cognitive function in TCSs has been addressed in a few studies 1-11 years following TC treatment.\textsuperscript{85, 90-93} Although some report cognitive complaints (self-reported) to be rather common irrespective of cancer treatment or to increase following chemotherapy (≤4 cycles),\textsuperscript{92, 93} a permanent decline in neuropsychological performance has not been documented in any study. Cognitive complaints have rather been related to emotional distress and fatigue.

**Avascular necrosis**

Testicular cancer survivors treated with chemotherapy seem to have an increased risk of developing avascular necrosis (osteonecrosis) compared to patients treated for other solid tumors (REF Shim Drug Safety 2008).\textsuperscript{94} The exact reason for this vulnerability is not known, but is probably multifactorial. Most reported cases have also received corticosteroids. The femoral head is most commonly affected, often bilaterally.\textsuperscript{94, 95} Based on three reports, Winquist et al estimated an overall crude incidence of 1.5\% following chemotherapy for testicular cancer. Cook et al reported an overall prevalence of 3.8\% in 103 consecutive patients invited to attend an MRI scan of the hips.\textsuperscript{96} Avascular necrosis should be suspected in patients presenting with pain in the inguinal region (or upper thigh/buttocks). A limp and decreased hip motion may also be present. If suspected, an MRI should be performed in case of normal plain x-ray, and the involvement of an orthopedic surgeon in the management of these patients is imperative.\textsuperscript{94}

**Hypogonadism**

Subnormal testosterone values have been reported in TCSs treated with chemotherapy compared to healthy controls,\textsuperscript{30} and following more than four chemotherapy cycles,\textsuperscript{97, 98} or combination of chemotherapy and RT when compared to men treated with surgery only.\textsuperscript{99} Subclinical Leydig cell dysfunction with increased LH has been found in several studies.\textsuperscript{84, 97, 98, 100-102} In long-term follow-up studies where similar reference levels for testosterone were applied (<10nmol/l or <2.6ng/ml), overall 12\%-16\% had subnormal testosterone values or used androgen replacement therapy (ART).\textsuperscript{97-99} Similar estimates were found in the Norwegian cohort,
where overall 15%, ranging from 8% to 18% depending on treatment, of men younger than 65 years had hypogonadism by this definition (testosterone $<10$ nmol/l or used ART) (Fig 1, $p=.014$) (personal communication, M Brydøy).

**Figure 1.** Fraction of men with “manifest or subclinical” hypogonadism according to treatment in the Norwegian cohort. Dark blue (lower): Used androgen replacement therapy (ART) at follow-up (manifest hypogonadism); Medium blue (middle): low s-testosterone ($<10$ nmol/l) at follow-up (manifest hypogonadism); Light blue (upper): Elevated s-LH ($\geq 12$ IU/l) and normal s-testosterone at follow-up (subclinical hypogonadism). $P=.014$ for manifest hypogonadism (ART or low testosterone) versus normal testosterone, $P<.001$ for any hypogonadism (ART, low testosterone and/or elevated LH) versus no hypogonadism. RT, radiotherapy; $\leq 850$ mg, cumulative cisplatin dose $\leq 850$ mg; $>850$ mg, cumulative cisplatin dose $>850$ mg.
Low testosterone levels are significantly associated with increased prevalence of the metabolic syndrome(103) and an increased risk for CVD mortality as well as respiratory disease mortality in epidemiological studies.\textsuperscript{104, 105} Subclinical hypogonadism might also enhance the risk of osteoporosis, although data on this subject are inconclusive.\textsuperscript{106, 107} The relatively high frequency of Leydig cell dysfunction implies that the hormonal status of TC survivors should be regularly assessed. However, there is currently no evidence supporting testosterone replacement therapy to prevent late effects such as CVD, and treatment decisions should be guided by clinical symptoms.(108)

**Fertility and sexuality**

**Fertility**
At long-term follow-up of cohorts of TC survivors with known intentions to conceive a child, overall post-treatment conception and paternity rates vary from 49% to 82% (Table 3).\textsuperscript{99, 109-112} Some investigators report an association between the likelihood of paternity with cumulative chemotherapy dose,\textsuperscript{110, 113} but preservation of antegrade ejaculation following RPLND is the most critical factor for conception without use of cryopreserved sperm.\textsuperscript{110, 111} After primary RPLND, Beck et al. recently reported that 99% preserved antegrade ejaculation after nerve-sparing surgery,\textsuperscript{114} higher than 91-93% previously reported.\textsuperscript{115, 116} After nerve-sparing post-chemotherapy RPLND, 71-89% retain antegrade ejaculation,\textsuperscript{116-119} compared to 25% following full bilateral post-chemotherapy RPLND.\textsuperscript{120}
### Table 3. Post treatment conception and paternity rates among testicular cancer (TC) survivors with known intentions to conceive a child following TC treatment (donor insemination excluded)*

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>No. of TC survivors included</th>
<th>Median fu (range), y</th>
<th>Treatment characteristics</th>
<th>Conception/paternity according to treatment</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spermon (2003)</td>
<td>88 (120 pre)</td>
<td>7 (2-19)</td>
<td>Surveillance RPLND RT ≤4 CT cycles ≤4 CT cycles + RPLND (primary or secondary)</td>
<td>No significant differences between treatment groups.</td>
<td>59% (52/88) fathered following TC treatment, including cryopreserved semen in 74% (38/88) conceived within one year of attempts. Prior to TC treatment, 78% (93/120) fathered, 66% (79/120) conceived within one year of attempts.</td>
</tr>
<tr>
<td>Huyghe (2004)</td>
<td>164 (228 pre)</td>
<td>8 (3-27)</td>
<td>RT 2-4 chemotherapy cycles</td>
<td></td>
<td>67% (110/164) conceived following TC treatment compared to 91% (208/228) prior to TC. Cumulative conception rates lower following RT than chemotherapy. (P&lt;0.01)</td>
</tr>
<tr>
<td>Huddart (2005)</td>
<td>207</td>
<td>At least 5 y</td>
<td>Surveillance Chemotherapy RT Chemotherapy/RT</td>
<td>88% (85%)† conceived 75% (71%)† conceived 85% (82%)† conceived 83% (67%)† conceived</td>
<td>82% (169/207) conceived following TC treatment (including infertility treatment in 10), 77% (159/207) conceived without infertility treatment (p&lt;.03 for chemotherapy vs surveillance) Men with elevated FSH less likely to have conceived (68%) than men with normal FSH levels (91%). (P&lt;.001)</td>
</tr>
<tr>
<td>Brydøy (2005)</td>
<td>552</td>
<td>11 (4-21)</td>
<td>Surveillance RPLND RT Cisplatin ≤ 850 mg‡ Cisplatin &gt;850 mg‡</td>
<td>81% fathered (92% 15-yr) 77% fathered (78% 15-yr) 65% fathered (72% 15-yr) 62% fathered (64% 15-yr) 38% fathered (48% 15-yr)</td>
<td>65% (361/552) had fathered by follow-up (without cryopreserved sperm, but including other infertility treatments in 36), 71% overall 15-yr actuarial post-treatment paternity rates (p&lt;.001 according to treatment group) Dry ejaculation was the most negative predictor. Men diagnosed 1989-1994 were more likely to have fathered than men diagnosed 1980-1988. (P&lt;.001)</td>
</tr>
</tbody>
</table>

*Numbers are post-treatment when not specified as pre-treatment (pre). Abbreviations: No, numbers; fu, follow-up; y, years; RPLND, retroperitoneal lymph node dissection; CT, chemotherapy; RT, radiotherapy; FSH, follicle stimulating hormone.
†Without infertility treatment. The use of cryopreserved semen was not specified.
‡Both chemotherapy groups included patients additionally treated with RT or RPLND.
§Rates refer to 15-yr actuarial rates.
Lampe et al. defined prognostic groups for spermatogenic recovery based on repeated sperm analyses pre- and post-chemotherapy in 178 men. Overall, 80% recovered some spermatogenesis by 4 years after chemotherapy, if not azoospermic (<1 mill/ml) prior to treatment. Carboplatin-based regimens and ≤4 cycles were positively related to recovery. Petersen et al. found that 19% were azoospermic 5 years after 4 BEP cycles, and 47% after ≥3 cycles of a more dose intensive regimen. Gandini et al. reported that 94% and 97% had recovered some spermatogenesis two years after RT and 2 to 4 cycles of chemotherapy, respectively.

Information regarding fertility following more recently introduced chemotherapy regimens is sparse. Recovery of spermatogenesis following high-dose chemotherapy with stem cell support has also been reported (5/10 patients). Patients should be informed that the recovery from chemotherapy-induced azoospermia may take several years. Furthermore, offering cryopreservation is obligatory prior to chemotherapy.

**Sexuality**

Besides impaired ejaculatory function, groups of TCSs are reported to experience decreased drive and increased erectile dysfunction when compared to controls. Some also report decreased sexual satisfaction. Dahl et al. found that overall sexual problems were expressed by 39% of TCSs versus 36% in controls. Interestingly, among men aged 20-39 years, sexual satisfaction was significantly better compared to controls. Tuinman et al. showed that couples established after a TC diagnosis were less sexually satisfied than couples founded pre-diagnosis. However, data within this field are conflicting.

**Psychosocial health**

**Fatigue**

A significantly higher frequency of chronic (> 6 months' duration) cancer-related fatigue (CRF) was reported among long-term TCSs in Norway compared with the normative male population (17% and 10%, respectively). Significantly higher levels of interleukin-1 receptor antagonist and C-reactive protein were observed in TCSs with CRF compared to TCSs without CRF, indicating an association between fatigue and inflammation.

**Mental health**

Compared to samples of men from the general population, significantly increased levels of anxiety among Norwegian TCSs were associated with peripheral neuropathy, fear of recurrence, economic concerns, alcohol abuse, sexual difficulties, younger age, and a history of treatment for mental problems. It is not clear whether TCSs experience more depressive disorders than the general population, since a significantly increased prevalence has been reported in some studies, but not others.
Lifestyle
A recent American study confirmed a previous Norwegian finding of high prevalence of current smoking and problem drinking among TCSs. Their intake of fruit and vegetables was low. However, TCSs were more likely to engage in regular exercise that cancer-free controls.134

Employment
In the U.S., levels of unemployment among TCSs are similar to men in the general population.135 Similarly, Norwegian TCSs reported comparable levels of work engagement as age-matched men in the general population.136 Fleer et al. highlighted the importance of employment on health-related quality of life in TCSs.137 No data are available with regard to work ability 10 or more years after diagnosis of TC.

Health-related quality of life (HRQoL)
In most studies, overall HRQoL of TCSs, as assessed by validated questionnaires, has been similar to that of normative samples of age-matched men.138, 139 Although findings may accurately reflect HRQoL status, these results may also be due to either "response shift"140 or the use of instruments that are not targeted to the concerns of TCSs. In one investigation, a subgroup of approximately 15% TCSs reported decreased HRQoL.138

Impact of lifestyle factors
Cancer survivors, in general, are high health care utilizers with several distinct health care issues.4, 141, 142 For TCSs, in particular, the young age at diagnosis and high cure rate, lead to long-term consequences of therapy which have a greater impact on their lives, families, and society at large than the acute complications from the cytotoxic therapies.22, 25, 143, 144 While treatment-associated long-term risks and complications are brought on by cytotoxic treatment, genetic predisposition and/or common lifestyle factors,145-148 lifestyle is the only variable subjected to change. In line with this, Aziz argue that the follow-up care of cancer patients should provide the opportunity for maintaining health by lifestyle interventions.4 Prevention such as promoting smoking cessation, better nutrition, and promoting a non-sedetary lifestyle may play key roles in reducing the impact of potential adverse effects of previous cancer therapy.149-151 In a large Dutch population of TCSs, the relative risk of CVD attributed to recent smoking was 2.6, while the corresponding factor for cisplatin-based chemotherapy was 1.9.24 In a Norwegian population of long-term TCSs, smoking was associated with decreasing pulmonary function as well as increasing neurological side-effects.37, 53 Additionally, smoking increases the overall risk of a second malignancy.9 Thus, lifestyle interventions may be particularly important for TCSs due to the long life expectancy and their increased vulnerability. These interventions may start early in the follow-up period. Demark-Wahnefried and coworkers focus on the “teachable moment” which the cancer diagnosis provides and argue that oncology care providers should not only lead their patients away from disease, but also promote lifestyle changes that may improve the length and quality of life of their patients.142 However, of 160 German TC patients who did smoke at the time of diagnosis, most changed their tobacco habit, but only 29% managed to quit smoking within 10 years post diagnosis.152 In a randomized physical training intervention in
a Norwegian population of long-term TCSs, training had significant effect on cardiorespiratory fitness among the young and middle-aged, but had no favorable effect on patients’ experience of fatigue, mental distress, or health-related quality of life. Hence, substantial intervention efforts may be required for limited effects, but the potential for improved health and reduced morbidity in long-term TCSs is definitely present.

Conclusions and recommendations for follow-up

In this review we have presented the current status regarding different somatic and psychosocial effects after TC treatment. Current knowledge about adverse effects is based on therapy administered years to decades ago. Although cisplatin-based chemotherapy still is the cornerstone in the treatment of TC, we do not have long-term data regarding the consequences from receiving one or two cycles of BEP or carboplatin in the adjuvant setting, or from receiving other chemotherapy agents such as paclitaxel. Thus, there is clearly a need for ongoing research to elucidate long-term and late effects from current treatment strategies and to minimize the long-term morbidity after TC treatment. To achieve this goal, better knowledge about the pathophysiology behind the long-term complications, defining risk factors for developing long-term morbidity and identification of predictive factors for adverse effects is required.

During follow-up of TC patients, there is a gradual shift of focus from detection of tumor recurrence to identification of late effects of treatment and promotion of general health in TCSs. We should recommend our patients to maintain a healthy life-style to reduce the risk of serious late effects as second cancers and CVD. Every cancer patient should have an informative end-of-treatment summary at completion of the treatment together with a survivorship care plan. The focus of the survivorship care plan will change with increasing follow-up duration from early detection of a relapse to measures to maintain health. This survivorship care plan includes tools for acquiring and maintaining a healthy life style and a formal regular check on cardiovascular risk factors and gonadal status. A survivorship care plan can be implemented in addition to the routine oncological follow-up or when the routine follow-up with the oncologist is terminated and taken over by another healthcare giver. If so, there has to be a proper transition of further follow-up with a solid and clear survivorship plan (Fig 2). Currently, the distribution of survivorship plans is recommended in Norway, Sweden and the Netherlands. There are so far no data evaluating the use of a survivorship plan.

In conclusion, the treatment success of men with TC is hampered by the emergence of long-term and late effects of treatment. Knowledge about adverse effects is crucial for all physicians involved in treatment and follow-up of TC patients, and attention towards prevention and identification of adverse effects is essential for these young men.
Survivorship care plan to be discussed with and delivered to the patient (and other health care providers) during uro-oncological follow-up

You were operated year ______ for testicular cancer, subtype:
☐ Seminoma     ☐ Non-seminoma

☐ No dissemination of disease was confirmed
☐ Dissemination of disease was confirmed to________________________

Treatment
☐ No additional treatment
☐ Chemotherapy (year:____, regimen:____, number of cycles:____)
☐ Radiotherapy (year:____, field:____, total dose:____)
☐ Additional surgery (year:____, type of surgery:____)

Hospital:________________________
Responsible doctor:________________
Telephone:_______________________

You have completed the treatment for testicular cancer. This survivorship care plan should be shown in case of future contacts with the health services.

Some side-effects from testicular cancer treatment may emerge during the years after treatment, for example sub-normal values of male hormone testosterone. In addition, men previously treated with chemotherapy and/or radiotherapy have an increased risk for hypertension, overweight, elevated cholesterol levels and cardiovascular disease. Thus, it is advisable to keep away from smoking, avoid overweight and exercise regularly.

Although the risk of a new tumor in the remaining testicle is low, regular self-exams are important. Furthermore, another cancer type may develop after treatment with chemotherapy and/or radiotherapy.

Apart from routine regular visits for potential disease recurrence we recommend assessments every 2-3 year to check for long-term and late effects of the cancer treatment. The purpose of these controls is to identify and possibly treat risk factors for the development of cardiovascular disease. In case of identified modifiable cardiovascular risk factors, patients can be referred for appropriate cardiovascular risk management.

We recommend that the following are controlled by the general practitioner:

1) Blood pressure, height, weight, waist and hip circumference

2) Blood samples including fasting lipids (total cholesterol, HDL and LDL cholesterol, triglycerides), fasting glucose and hormones (testosterone, FSH and LH)

3) Clinical examination in case of any symptoms

Figure 2. Survivorship care plan to be delivered to the patient at completion of treatment. The plan includes a treatment summary and short information about side-effects from testicular cancer treatment, focusing on modifiable cardiovascular risk factors.
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Chapter 2
