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Medical and Psychosocial Issues in Testicular Cancer Survivors

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Testicular cancer (TC) is the most frequent malignancy in men between 20 and 40 years of age, and the annual incidence rates are continuously increasing in the Western world.[1] Since the introduction of cisplatin-based chemotherapy, at least 90% of the patients are cured,[2] and testicular cancer survivors (TCSs) currently have a life expectancy similar to that of age-matched normal men, with posttreatment life spans of 30 to 50 years. Thus, an increasing number of TCSs experience survivorship problems related to the malignancy, its treatment, or both.

Treatment

Unilateral orchiectomy is the primary treatment of TC and yields the histologic diagnosis of seminoma and nonseminoma with equal frequency. Modern post-orchiectomy therapy of TC is based on the histologic type and the extent of disease. Risk-adapted treatment is based on a balance between malignancy-related risk factors, expected side effects, the likelihood of regular follow-up, and, not least, the patient's preference. As effective chemotherapy is available to salvage most of the patients who relapse, today's clinicians tend to administer the least toxic treatment schedule to both low-risk patients without metastases and to the good prognosis metastatic group.[3]

In patients with nonmetastatic seminoma, the standard adjuvant radiotherapy field currently comprises the intradiaphragmatic paraaortic lymph nodes,[4] which are irradiated to 20 Gy.[5] Surveillance[6] is a valid alternative, or the use of one cycle of chemotherapy.[7] *Surveillance* is also the standard policy in patients with nonmetastatic, nonseminomatous germ cell tumors,[8] with nerve-sparing retroperitoneal lymph node dissection (RPLND), or two cycles of chemotherapy as alternatives in selected patients.[9,10] In patients with metastatic disease, the standard *chemotherapy* regimen is cisplatin based, most often containing etoposide and bleomycin,[11,12] eventually modified by ifosfamide[13] or taxol in high-risk patients or used as salvage chemotherapy.[14] In patients with metastatic disease, induction chemotherapy is frequently followed by surgical resection of residual masses.[15]

Each of the foregoing principal therapeutic modalities (surgery, radiotherapy, chemotherapy) leads to transient short-term (less than 1 year) and long-term (1 year or more) side effects, and their severity often increases with combined treatment. Previous cross-sectional studies on long-term side effects in TCSs have predominantly examined the side effects within the first 5 years posttreatment. Relatively few studies have follow-up times beyond 5 years.

Not all long-term sequelae in TCSs are caused by treatment. Impaired posttreatment endocrine and exocrine gonadal function, for example, is related both to the germ cell malignancy itself and to its treatment. The development of a contralateral testicular tumor is treatment independent and represents primary germ cell carcinogenesis at another site. The diagnosis of a second, possibly treatment-related, malignancy must be clearly separated from a late relapse with non-germ cell differentiation. Leukemia in patients with mediastinal germ cell tumor may thus be treatment related or may arise on the background of the extragonadal germ cell malignancy,[16] recognizable by modern molecular biologic techniques.[17]

Second Malignancies

Solid Tumors

The most serious late toxicity of therapy for TC is the development of a non-germ cell malignancy, for simplicity referred to as second cancer. Although several investigations[18,19] have evaluated the risk of second cancers among patients with TC, few studies have estimated long-term risks among large numbers of TCSs, taking into consideration both histology and initial treatment. The largest study to date comprised more than 28,000 1-year TCSs (1935–1993) reported to population-based cancer registries in North America and Europe.[18] Second cancers were diagnosed in 1,406 patients [observed to expected ratio (O/E), 1.43; 95% confidence interval (CI), 1.36–1.51; absolute excess risk, 16 excess cancers per 10,000 men per year]. Second cancer risk was similar following seminomas (O/E, 1.4) and nonseminomatous tumors (O/E, 1.5).

TABLE 9.1. Relative risk of second malignancies following treatment of testicular cancer.

	Number of second cancers	*Relative risk*		
		All	*Seminoma*	*Nonseminoma*
All second cancers	1,406	1.43	1.42	1.50
All solid tumours	1,251	1.35	1.35	1.36
Stomach	93	1.95	1.73	2.95
Small intestine	12	3.18	4.35	—
Colon	105	1.27	1.30	1.32*
Rectum	77	1.41	1.58	0.92*
Pancreas	66	2.21	2.35	1.85*
Kidney	55	1.50	1.50	1.41*
Bladder	154	2.02	2.12	1.85
Melanoma	58	1.69	1.57	1.74
Thyroid	19	2.92	2.61	3.82
Connective tissue	22	3.16	3.46	2.40*
Non-Hodgkin's lymphoma	68	1.88	1.83	2.09
All leukemias**	64	2.13	1.92	2.78

*Nonsignificant.

**Statistical significance restricted to acute leukemia.

Source: Modified from Travis et al,[18] by permission of *Journal of the Naional Cancer Institute*, with emphasis on statistically significant ($P < 0.05$) observations.

Among all TCSs, significantly increased risks were observed for all malignancies taken together: malignant melanoma, acute lymphoblastic leukemia, acute nonlymphocytic leukemia, non-Hodgkin's lymphoma, and cancers of the stomach, colon, rectum, pancreas, kidney, bladder, thyroid, and connective tissue (Table 9.1). The risk of solid tumors increased with follow-up time since the diagnosis of TC and reached 1.5 after two decades (P trend, 0.00002). Twenty-year survivors of TC remained at significantly increased risk for cancers of stomach (O/E, 2.3), colon (O/E, 1.7), pancreas (O/E, 3.2), kidney (O/E, 2.3), bladder (O/E, 2.8), and connective tissue (O/E, 4.7). The cumulative risk of any second cancer 25 years after TC diagnosis was 15.7% (Figure 9.1, Table 9.2). The larger risk for seminoma patients (18.2%; 95% CI, 16.8–19.6) than for those with nonseminomatous tumors (11.1%; 95% CI, 9.3–12.9) most likely reflects the older mean age of the former group (39.2 years versus 29.8 years), given the similarity in the excess cumulative risks. The temporal distribution of increased risks and apportionment between treatment groups were consistent with the late sequelae of radiation for cancers of stomach, bladder, and possibly pancreas. These findings were thus consistent with the location of these organs in the infradiaphragmatic radiotherapy fields administered for TC. Although information on radiotherapy fields and dose are not registered in cancer registry records, Travis et al.[18] provided estimates of the average radiation doses received by stomach (mean, 13–26 Gy), bladder (mean, 22.4–45 Gy), and pancreas (mean, 16.7–33.8 Gy) at treatment doses of 25 and 50 Gy for seminomas and nonseminomatous germ cell cancer, respectively, using standard anteroposterior (AP)/posteroanterior paraaortic or inguinal iliac fields.[4]

Previous clinical series have found significantly eightfold-increased risks of stomach cancer ($n = 2$) following infra- and supradiaphragmatic irradiation for testicular tumors[20] and a four- to fivefold risk with abdominal radiotherapy ($n = 10$).[21] There are few data, however, that quantify the relationship between radiation dose and the risk of gastric cancer.[22] In particular, the precise impact of radiation field size and/or dose is not clearly defined for current infradiaphragmatic adjuvant

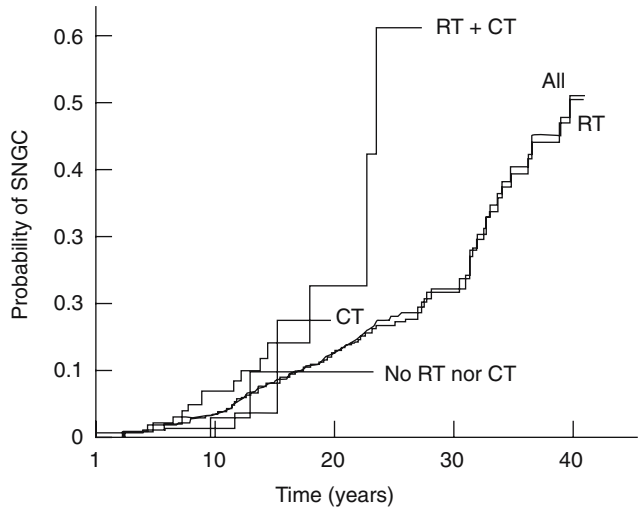

FIGURE 9.1. Cumulative risk of any second non-germ cell cancer by time from primary diagnosis for different treatment groups. (See Table 9.2.) *RT*, radiotherapy; *CT*, chemotherapy. (From Hoff Wanderas et al,[23] by permission of *European Journal of Cancer.*)

TABLE 9.2. Patients at risk at start of interval.[a]

Time from diagnosis (years)	*Treatment category (n)* *RT*	*CT*	*RT + CT*	*No RT or CT*	*All*
1–9	1,194	346	277	189	2,006
10–19	827	112	83	59	1,081
20–29	365	2	7	5	379
30–39	92	—	—	—	92

[a] See Figure 9.1 for further information and definitions.

radiotherapy. Therefore, the NCRI (National Cancer Research Institute, UK) Testis Cancer Clinical Studies Group has initiated a long-term follow-up study of 2,500 patients with stage I TC treated between 1962 and 1994 with infradiaphragmatic radiotherapy, recording the individual target fields and doses, and any salvage treatment as predictors of development of second cancer.

Before the use of cisplatin in TC therapy, few patients treated with chemotherapy only lived long enough to develop a secondary malignancy. To date, modern chemotherapy alone (e.g., bleomycin, etoposide, and cisplatin, or BEP) has not, to our knowledge, been associated with an increased risk of secondary solid tumors. The number of patients observed for more than 10 years after cisplatin-based chemotherapy is limited, however, and further follow-up will be required.

There is also little information on whether TC patients treated with both radiotherapy and chemotherapy are at greater risk of solid tumors than those who received radiation alone. Van Leeuwen et al.[21] found that the risk of all gastrointestinal cancers following radiotherapy alone (O/E, 2.9; 95% CI, 1.8–4.4; observed, 22) did not differ significantly from the risk (O/E, 5.5; 95% CI 1.1–15.9; observed, 3) in patients given both radiotherapy and chemotherapy, but low numbers in the latter group limit the statistical power to detect any difference.

Hoff Wanderas et al.[23] showed that the risk of all second non-germ cell cancers following radiotherapy alone (O/E, 1.58; 95% CI, 1.3–1.9; observed, 130) was significantly larger than the risk (O/E, 3.54; 95% CI, 2.0–5.8; observed, 15) after radiotherapy plus chemotherapy, but also pointed out that patients in the latter group frequently received multiple irradiation fields and larger doses. Further, many patients who received combined-modality therapy also received chemotherapy regimens that included doxorubicin.[23] Breslow and colleagues[24] reported that children (n = 234) given doxorubicin and more than 35 Gy of abdominal radiation for Wilm's tumor were at 36-fold risk (95% CI, 16–72; observed, 8) of second solid tumors, compared with no second tumors observed among children (n = 291) given doxorubicin alone.[24] These investigators[24] hypothesized that doxorubicin might inhibit the repair of radiation-induced damage, perhaps through its effects on topo-isomerase II. Evidence with regard to the human carcinogenicity of doxorubicin itself remains conflicting.[20]

Leukemias

TCS patients are at increased risk of leukemia[18,21,25–29]; however, there are few analytical studies that characterize in detail the contribution of both radiotherapy and chemotherapy to these cancers (see also Chapter 17). Travis and colleagues[16] conducted an international case-control investigation of secondary myelodysplastic syndrome or leukemia within a cohort of 18,567 1-year TCSs survivors of TC diagnosed between 1970 and 1993 and reported to eight population-based cancer registries in North America and Europe. For all patients (36 cases, 106 controls), detailed information on all treatment was gathered for chemotherapy drugs including cumulative dose and duration of chemotherapy. External-beam radiotherapy, usually to paraaortic and pelvic regions, was administered to 101 patients. Radiotherapy for 17 patients (restricted to 1970–1980) included mediastinal irradiation (mean dose, 35.0 Gy), in addition to abdominal and pelvic fields; 3 additional patients were given extended-field (abdomen/pelvis/chest) radiotherapy and alkylating agent chemotherapy. For patients who received radiation limited to abdomen and pelvis without alkylating agents, larger mean treatment doses were used for nonseminomatous tumors (35.4 Gy) than for seminomas (30.7 Gy). Daily radiotherapy logs for each patient were used to calculate an average dose to the active bone marrow.

For all TC patients, leukemia risk increased with increasing radiation dose to active bone marrow (P = 0.02), with patients given chest radiotherapy in addition to abdominal/pelvic fields accounting for much of the risk at higher doses.[16] A nonsignificant 3-fold-increased relative risk of leukemia was demonstrated after pelvic-abdominal radiotherapy (mean dose to bone marrow, 10.9 Gy) without alkylating agent chemotherapy; for patients who received additional supradiaphragmatic irradiation (mean dose to bone marrow 19.5 Gy), a significantly increased 11-fold risk was apparent. For patients given radiotherapy limited to abdomen and pelvis, the estimated relative risk (RR) of leukemia associated with a treatment dose of 25, 30, and 35 Gy was 2.2, 2.5, and 2.9, respectively; none of these estimates was statistically significant.

Radiation dose to active bone marrow and cumulative dose of cisplatin to treat TC were both predictive of elevated risks of leukemia (P = 0.001) in a statistical model that took into account all treatment parameters.[16] The highly significant dose–response relationship observed for total amount of cisplatin and leukemia risk was in accord with results in a study of women treated with platinum-based chemotherapy for ovarian cancer.[30]

Although the cumulative dose of etoposide used to treat TC did not contribute to leukemia risk when doses of cisplatin and radiation were taken into account, patients given etoposide also received larger amounts of cisplatin, making it difficult to tease apart any individual contributions to leukemia risk.[16] The predicted risk of leukemia associated with a cumulative cisplatin dose of 650 mg was 3.2 (95% CI, 1.5–8.4); larger cumulative doses (1,000 mg cisplatin) were associated with significantly increased sixfold risks. In terms of absolute risk, Travis et al.[16] estimated that of 10,000 testicular cancer patients treated with cisplatin-based chemotherapy with a cumulative cisplatin dose of about 650 mg and followed for 15 years, 16 excess leukemias might result.

Based on small numbers, prior studies have linked etoposide and cisplatin for TC with excess leukemias,[26–29] usually at high cumulative doses of etoposide (3,000 mg/m^2)[26] in contrast to the lower total doses administered in the study by Travis et al.,[30] which are similar to the dose of less than 2,000 mg/m^2 (33) used today. Smith et al.[31] reported that the 6-year cumulative risk of secondary leukemia among patients who received 1,500 to 2,999 mg/m^2 etoposide was small (0.7%), based on a survey of clinical trials. In a recent review of the literature, Kollmannsberger et al.[32] concluded that the cumulative incidence of leukemia for TC patients given etoposide at cumulative doses of less than 2,000 mg/m^2 and more than 2,000 mg/m^2 was 0.5% and 2% at a median of 5 years follow-up.

Whether combined radiochemotherapy for TC results in a larger risk of leukemia than chemotherapy alone has not

been well-studied. Van Leeuwen et al.[21] found no significant difference between the risk of leukemia following chemotherapy alone (one case) and combined modality therapy (two cases), but the small numbers precluded any opportunity to detect a difference. Similarly, in the case-control study by Travis et al.,[16] only a small number of patients were given combined-modality therapy (two cases and four controls), and the risk of leukemia (fivefold) was nearly identical for all investigated patients.

Contralateral TC

Three percent to 5% of the patients with unilateral TC develop a germ cell malignancy of the contralateral testicle.[33] The increased risk of contralateral TC in men with TC has generally been thought to reflect shared etiologic influences.[34] Few large studies,[33,35] however, have provided estimates of the risk for contralateral TC. The largest investigation[35] to date, based on 60 cases occurring in 2,201 men diagnosed with a first primary germ cell cancer (1953–1990), reported that the cumulative risk of a contralateral testicular cancer at 15 years of follow-up was 3.9% (95% CI, 2.8%–5.0%). The investigators also concluded that the risk was not significantly altered by treatment of the first cancer. Patients with a contralateral testicular cancer usually undergo a second orchiectomy with the subsequent need of lifelong androgen substitution.

Patients with extragonadal germ cell tumors (EGCT) are at a significantly elevated risk for subsequently developing TC, most probably based on the existence of carcinoma in situ in one or both testicles.[36,37] In a large, international study of 635 patients with EGCT conducted by Hartmann and colleagues,[36] the cumulative risk of developing a metachronous TC was 10.3% at 10 years. The treatment follows the risk-adapted strategies as for TC with principally the same long-term sequelae.

Based on the increased risk of developing a new gonadal germ cell tumor, TCSs and patients with a cured extragonadal tumor are recommended to perform regular testicular self-examination.

Gonadal Toxicity

Spermatogenesis and Leydig Cell Function

According to today's most relevant hypothesis, germ cell carcinogenesis starts in the primordial cells during the 8th week of embryonic life.[38] Deleterious environmental influences may result in aberrant gonadal development that subsequently manifests as testicular maldescent, testicular atrophy, reduced Lydig cell function, impaired spermatogenesis, or even germ cell malignancy. These etiologic factors together with tumor-related influences are the reasons why about 60% of unilaterally orchiectomized patients with newly diagnosed TC have impaired spermatogenesis before any additional treatment.[39–43] Impaired Leydig cell function and reduced sperm cell production may be found even in patients with TC before orchiectomy of the affected testicle.[41–43] Further, this etiologic hypothesis also explains why 10% to 15% of TCSs have permanently reduced exocrine and endocrine gonadal function even without having received chemotherapy or radiotherapy.[44,45]

The exocrine long-term gonadal function in TCSs has been extensively studied, although the available investigations do not clearly differentiate between cisplatin-based chemotherapy containing vinblastine from those containing etoposide or ifosfamide. Carboplatin seems to be less gonadotoxic than cisplatin.[46] Standard cisplatin-based chemotherapy (four cycles) and infradiaphragmatic radiotherapy (36 Gy or less) transiently reduces or abolishes spermatogenesis (low sperm counts; high serum follicle-stimulating hormone, FSH) with recovery starting 6 to 8 months after treatment discontinuation. These effects are dependent on the type of the radiation target field as well as types of cytotoxic drugs, number of cycles, and cumulative doses[4,39,40,42,47–59] (Figure 9.2, Table 9.3). Age above 35 years and reduced pretreatment gonadal function reduce the ability for such recovery.[52]

The Leydig cell function is affected by radiotherapy or chemotherapy at a lesser degree than spermatogenesis, but Nord et al.[45] demonstrated an increasing number of hypogonadal long-term TCSs in relation to treatment type and treatment intensity. According to this study 16% of the long-term TCSs are hypogonadal, most often subclinically, but 25% of these TCSs need androgen substitution.

There is no effective treatment available for TCSs who have become oligo- or azospermic as a result of cytotoxic treatment. Moreover, treatment with luteinizing hormone-releasing hormone (LH-RH) analogues together with chemotherapy has not shown sufficient gonadal protection either.[60] Pretreatment cryopreservation of sperm cells[61] and exogenous androgen substitution[62] thus remain the only means to ameliorate gonadotoxic long-term sequelae.

Somatic Aspects of Fertility

Posttreatment fertility is threatened by ejaculatory dysfunction, permanent azospermia, or high-grade oligospermia, and psychosocial distress.

After bilateral radical template RPLND[63,64] almost all TCSs have to face infertility problems as a result of postoperative "dry ejaculation." The introduction of unilateral and/or nerve-sparing procedures[10] has reduced this proportion to 10% to 15% even when the operation is performed following chemotherapy.[65] However, even though statistical analyses have proven that fertility-saving strategies have been successful in groups of patients prediction of posttreatment fertility is difficult in the *individual patient*. It is, therefore,

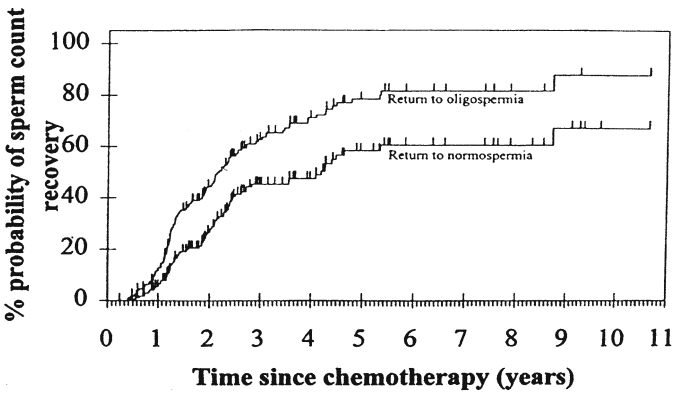

FIGURE 9.2. Recovery to oligospermia and normospermia in 178 patients after chemotherapy for testicular cancer. (From Lampe et al,[47] by permission of *Journal of Clinical Oncology.*)

TABLE 9.3. Long-term gonadal function in testicular cancer survivors.[a]

Author		*Number of patients*	*Observation time (months)*	*Sperm count (10^6/mL)*	*Azospermia*	*Elevated*		*Sub-normal testosterone*
						LH	*FSH*	
Surgery only								
Aass (1991)		33	24–48b	20[c]	11/24	1	8	5
Jacobsen (2000)		60	63	(0–222)[b]			10	
				37				
				(0–243)				
Radiotherapy								
Aass (1991)		36	24–48	11 (0–76)	9/22	2	13	4
Jacobsen (1997)								
Dog-leg		44	12	20 ± 14, 0[d]				
Paraaortic		24	12	49 ± 35, 6[d]				
Fosså (1999)								
Dog-leg		48	18		17/48			
Paraaortic		54	18		6/54			
Chemotherapy								
Cisplatin-based								
Standard								
Aass (1991)		42	24–48	65	5/17	5	17	6
Petersen (1994)		33	79	(0–166)	5/27	8	8	1
Stephenson (1995)		30	>24	6 (0–83)	6/30			
Palmieri (1996)		28	37		6/28	4	11	3
				35 (0–90)				
High dose or combined with radiotherapy	Aass (1991)	19	24–48			3	12	4
	Peterson (1994)	21	58	0 (0–70)	8/17	8	22	2
	Palmieri (1996)	10	36	8 (0–18)	3/10	6	8	2
Carboplatin	Reiter (1998)	22	48	(35–128)				
	Lampe (1999)	59	30		12/59			
Not specified	Bokemeyer (1996)	63	58			21	40	6
	Lampe (1999)	119	30		50/119			
	Strumberg (2002)	30	15			13	22	2

Blank spaces indicate that information is not provided.

[a] Limited to reports published after 1990.

[b] Range.

[c] Median.

[d] Mean ± standard deviation (only patients with pretreatment sperm count ≥10).

recommended that sperm banking[61] with the possibility of assisted fertilization[66] is offered to all patients with newly diagnosed TC who do not explicitly exclude future fatherhood (see also Chapter 19).

Gonadal Long-Term Effects of Treatment for Bilateral TC

Testicular radiotherapy (18–20 Gy) usually prevents the development of an invasive cancer in TCSs with cancer in situ in the contralateral testicle,[67] although with an increased risk of hypogonadism. Surgical testicle-saving strategies are recommended in case of small tumors.[68]

Neurologic Morbidity

Peripheral Neurotoxicity

Cisplatin-based chemotherapy leads to dose-dependent peripheral sensory neuropathy (paraesthesiae, pain) with a peak occurrence about 6 months after treatment initiation and a slight decrease thereafter.[53,69–73] Vinblastine displays an at least additive effect, whereas VP-16 is less neurotoxic.[11] About 20% of TCSs report peripheral sensory neuropathy ("quite a bit," "very much") 2 years after three or four cycles of BEP chemotherapy,[73] although objective measurements reveal persistent peripheral neuropathy in 70% to 80% of the patients.[74] The long-term peripheral sensory neuropathy is, however, only rarely handicapping, and most TCSs have "become used" to this problem at long-term follow-up.

Ototoxicity

Ototoxicity represents a specific long-term sequela in TCSs after cisplatin-containing chemotherapy,[53,57,69,73,75,76] with tinnitus and hearing loss in about 25% and 20% of the patients, respectively.[53,69,73] Audiograms indicate that cisplatin mostly decreases the auditory acuity above 4,000 Hz.[57] To decrease long-term ototoxicity, each cycle of standard chemotherapy (BEP) should be given during 5 days, in particular if more than three cycles are planned.[73]

Autonomic Neuropathy

The resection of sympathetic nerve fibers may lead to considerable persistent disturbance of blood flow and temperature sense in the legs.[77] The possibility exists that chemotherapy-induced long-term autonomic neurotoxicity contributes to vascular dysfunction.[78,79]

Because no effective treatment exists for cisplatin-induced peripheral neuropathy or ototoxicity, prevention of these late effects is essential by adequate hydration during drug administration and possibly by the supportive use of amifosfine.[80]

Nephrotoxicity

Cisplatin is highly nephrotoxic if sufficient hydration and diuresis are not provided during the drug's administration. Even then, four cycles of standard BEP may lead to chronic dose-dependent, though often subclinical, decrease of the glomerular function.[81]

Several authors have described persistent low serum magnesium and/or low phosphate levels after standard chemotherapy,[53,69] although not all investigators have been able to confirm these findings.[81,82] Carboplatin is less nephrotoxic than cisplatin, but doses of 1,500 mg/m^2 or more given over 3 days have a comparable effect as cisplatin 50 mg/m^2 applied on 1 day.[83]

Radiation target fields always include parts of the renal arteries, with the risk of postradiation subintimal fibrosis and reduction of the arterial flow. Fosså et al.[81] showed that infradiaphragmatic radiotherapy (30–40 Gy) leads to subclinical nephrotoxicity after a mean observation time of 11 years, in particular if combined with chemotherapy.

Cardiovascular Toxicity

Raynaud's Phenomenon

About 20% to 30% of TCSs report the development of Raynaud-like phenomenon after standard BEP chemotherapy that peak at 6 months after chemotherapy and subsequently slightly decrease to a persistent pathologic level.[53,56,73,76,84] These side effects are related to disturbance of autonomic innervation as well as thickening of the intima in small arteries with reduction of the blood vessel volume. Most studies point to bleomycin as an important etiological agent.[69] Interestingly, TCSs complaining of postchemotherapy Raynaud's phenomenon display an increased risk for erectile dysfunction.[78]

Cardiovascular Risk Factors and Major Events

Increased risk of postchemotherapy cardiovascular morbidity in TCSs as compared with TCSs on surveillance or men from the general population is evidenced in several studies[53,85–87] (Tables 9.4, 9.5). Today's chemotherapy for TC may even represent a high-risk factor for the development of a "metabolic syndrome" (diabetes mellitus, hypertension, hypercholesterolemia, obesity) and myocardial infarction.[86,88]

Huddart et al.[82] point out the possibility that partial heart irradiation during adjuvant radiotherapy may increase the risk of life-threatening cardiac events, as portions of the heart receive radiation doses of 30 to 90 cGy during current routine radiotherapy. TCSs having received former times mediastinal radiotherapy (30–40 Gy) for stage II or III TC represent a high-risk group for cardiac events and should be monitored accordingly.[89] These observations are in line with the findings of Fosså et al.[90] of an increased relative risk of cardiovascular mortality in TCSs treated from 1962 to 1993, most of them having received radiotherapy.

TABLE 9.4. Cardiovascular risk factors in TCSs.

Author	*Number of patients*	*Observation time (years)*[a]	*High cholesterol*[b]	*Reduced renal function*[c]	*Low Mg*[c]	*Hypertension*[b]	*Abnormal body mass index (BMI) increase*
Surgery only							
Meinardi (2002)	40	8	58%			8%	28%
Fosså (2003)	14	11		14%	7%		
Huddart (2003)	24	10	1%	8%	0%	9%	
Radiotherapy							
Fosså (2003)	18	11		28%	0%		
Huddard (2003)	230	10	3%	13%	0%	12%	
Chemotherapy							
Boyer (1992)	497			8–43%			
Osanto (1992)	43	4		15%			
Bokemeyer (2000)	63	5	32%	19%	18%	15%	32%
Meinardi (2000)	62	8	79%	31%	8%	39%	21%
Strumberg (2002)	32	15	81%			25%	48%
Fosså (2003)	44	11		30%	5%		
Huddard (2003)	390	10	2%	14%	0%	21%	
Chemotherapy + Radiotherapy							
Fosså (2003)	9	11		56%	0%		
Huddard (2003)	130	10	0%	27%	2%	13%	

[a] Median.

[b] Above.

[c] Below the institution's normal range.

TABLE 9.5. Cardiovascular events in TCSs: angina pectoris, myocardial infarction, cerebrovascular hemorrhage, cardiovascular death.

Author	*Number of patients*	*Median observation time (years)*	*Number of events*	*Age-adjusted RR*
Chemotherapy				
Boyer (1992)[a]	480	≥1	23	
Bokemeyer (1996)	63	5	2	
Meinardi (2000)[b86]	62	8	5	7.1 (1.9–18.3)[c]
Strumberg (2002)	32	15	1	
Cardiovascular mortality				
Huddart (2003)[b82]	992	10	68	
All treatment	242		9	Reference
Surgery only	230		22	2.40 (1.04–5.49)
Radiotherapy	390		26	2.59 (1.15–5.84)
Chemotherapy	130		11	2.78 (1.09–7.07)
Chemotherapy + radiotherapy				
Lagars (2004)	211	>15	23	1.95 (1.24–2.94)
Fosså (2004)[d90]				
Not specified	3,378	1962–1997	107	1.2 (1.0–1.5)

[a] Review.

[b] Mono-institutional.

[c] Numbers in parentheses, 95% confidence interval.

[d] Cancer Registry based.

Gastrointestinal Toxicity

With the target doses and target fields administered today,[4,91] the prevalence of slight gastrointestinal (GI) symptoms among TCSs[70,91,92] is only marginally above the proportion reported by the general population.[93] Major long-term GI problems such as peptic ulcer are observed in only 3% to 5% of the TCSs.[94,95] Target doses of 36 Gy or more or the combination of radiotherapy with radiosensitizing cytostatic drugs (adriamycin, cisplatin) increase the risk of persistent diarrhea and malabsorption.[70,96] Increased retroperitoneal fibrosis has occasionally been observed causing ureteric or biliary stenosis[97] or mimicking pancreatic cancer.[98]

Other Long-Term Toxicities

The typical acute toxicities of bleomycin of the skin and the lungs do not, in general, remain as long-term morbidities, whereas corticosteroid-related aseptic osteonecrosis represents a rare long-term complication in TCSs.[99]

Psychosocial and Quality-of-Life Issues

Introduction

Psychologic distress, health-related quality of life, as well as sexual dysfunction and paternity distress, have all been the focus for several quantitative and a few qualitative investigations in TCSs. Hardly any of these studies have randomized controlled designs.

TC involves an organ intrinsically associated with reproduction, sexuality, and masculine self-image, issues of importance to ill and healthy men alike. Global health-related quality of life (HRQoL) as assessed by available instruments does not cover these functions. The only available TC module[100] has not been completely validated. Paternity issues are regularly rated with unvalidated questions, whereas mental health and issues of sexuality have been studied by psychometrically validated and nonvalidated forms.

TCSs, similar to men in the general population, may have significant pretreatment problems such as unemployment, economical worries, mental disorders, relational problems, and other physical illnesses. The influence of such pretreatment issues on posttreatment adaptation is not well known because of the lack of prospective studies with sufficient sample sizes. Sociocultural differences in relationship to masculinity, sexuality, fertility, and employment should also be kept in mind when findings are compared across studies. Long-term TCSs also have problems in common with cancer patients in general, such as fear of recurrence and death. Coping ability has not been studied in either short- or long-term TCSs.

The overall conclusion so far is that long-term TCSs in general show good psychosocial adaptation; the mean HRQoL is at the level of the general male population. However, TCSs show a higher prevalence of anxiety disorders and some sexual dysfunctions.

Partnered Relationship in TCSs

In most studies, the majority of TCSs (70% to 90%) were in partnered relationships when TC was diagnosed. The rate of divorce and broken relationships for TCSs is 5% to 10% in most follow-up studies. Those couples that did separate saw the cancer as a significant factor in their breakup.[101,102]

Few wives found their husbands less attractive or masculine as TCSs, and in the few studies of wives, the majority found their sexual satisfaction unchanged.[103] The main concern of the wives was to have children, particularly if the couple had not achieved parenthood before the TC was diagnosed. Moynihan[104] found that 22% of partners had psychiatric morbidity, mainly anxiety and fertility worries.

Changes in Body Image

The studies published so far do not confirm any devastating effects on body image or feelings of masculinity as suggested by van Basten et al.[105] However, Gritz et al.[103] reported that 23% of patients perceived a permanent decrease in overall attractiveness. Rudberg et al.[84] reported that 15% of Swedish TCSs felt less attractive, whereas 33% was found in a sample from Japan.[106] No negative impact of orchidectomy was reported in a Scottish[107] and in an Italian sample.[108] These differences could reflect different cultural attitudes toward orchiectomy.

Health-Related Quality of Life

Posttreatment HRQoL is not identical to therapy-related psychologic or somatic morbidity, but relates to the patient's overall perception of physical and psychosocial well-being, including family life, leisure activity, and occupational situation. Older studies found that TCSs generally were strong, fit, and satisfied compared with controls.[103,109–111] Newer studies with validated instruments have confirmed that HRQoL generally is as good in TCSs as in the general male population.[112,113] Data from Norwegian TCSs (n = 1,409) with a mean follow-up age of 11 years show minimal differences on the eight dimensions of Short Form 36 (SF-36) compared with the general male population (n = 2673)[114] (Figure 9.3).

The influence of treatment modalities on HRQoL is still unsettled, mostly due to small samples with lack of statistical power. Joly et al.[113] found no differences (n = 71), while Rudberg et al.[112] (n = 277) found that those treated with intensive chemotherapy scored less favorably concerning HRQoL. In initially metastatic patients postchemotherapy RPLND did not worsen HRQoL as compared with chemotherapy alone.[115] Recently, Fosså et al.[73] reported that 2 years after chemotherapy, 36% of TCSs displayed improved and 13% deteriorated HRQoL, compared with baseline.

Mental Health

Most studies report a higher level of anxiety symptoms and higher prevalence of anxiety disorders among TCSs (20%) compared with controls and in the general population.[104,116,117] There is indication that a considerable proportion of TCSs live with a low feeling of safety.[117] It is unclear if there is more mental morbidity associated with the more-intensive treatment regimens. If the prevalence of depression is increased, it is also unsettled due to considerable overlap between depression and fatigue. The level of fatigue, but not of depression, was reported to be higher than in the general population, but lower than among male patients with Hodgkin's disease.[117] Fatigue was considered a major problem by many TCSs.[118]

During recent years, increasing attention has been paid to postchemotherapy cognitive mental disturbances in cancer patients.[119,120] In the European experience about 20% of the TCSs report decreased cognitive functions 2 years after four cycles of BEP.[73] In the future, prospective studies are highly needed to assess changes of cognitive functions in TCSs.

Social Functioning

The continuation of planned education and professional life after treatment obviously is of great importance for TCSs, but only few reports have dealt with this issue. Studies indicate that most TCSs continue in work.[105,108] Kaasa et al.[116] reported even greater work satisfaction in TCSs in general than in an age-matched population sample. There appears to be little change in relation to friends and social contacts.[112]

Obtaining bank loans and life insurance is a common problem for TCSs,[113] although national policies vary considerably.

Sexual Dysfunctions

Two systematic reviews of sexual functioning in TCSs[121,122] emphasize the considerable methodologic problems in the field. TC treatment can result in both physiologic changes in sexual functioning and trigger emotional reactions (e.g., sexual performance anxiety, fear of loss of control, uncertainty about the future). Fatigue and general malaise can have profound effect on libido, as can hair loss and weight loss. Emotional factors such as uncertainty about the future, anxiety, and loss of control may also inhibit libido. Generally,

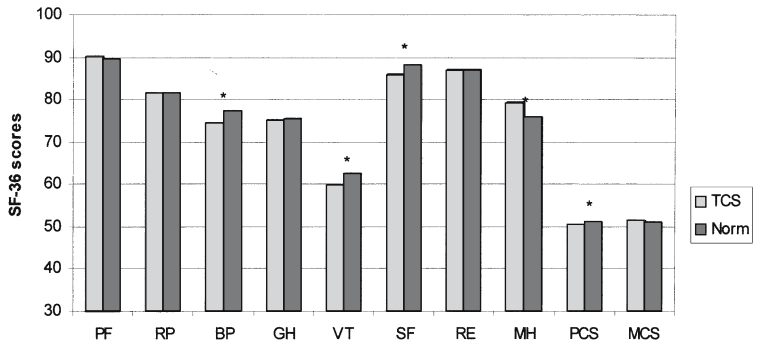

FIGURE 9.3. Health-related quality of life (SF-36) in testicular cancer survivors (TCSs) versus age-matched men from the general population. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical composite score; MCS, mental composite score. Norm data are age adjusted to mach the TCS. *P less than 0.05. (From A MyKletun et al,[114] by permission of *Journal of Clinical Oncology*.)

TABLE 9.6. Future directions.

Healthcare professionals	*Patients*
Clinical routine	
1. Thorough pretreatment counseling and information on expected unavoidable side effects	1. Psychologic acceptance of being a TCS, sometimes with unavoidable side effects
2. Use of risk-adapted therapy	2. Adoption of a healthy lifestyle (nonsmoking, weight control, physical activity)
3. Organization of long-term follow-up	3. Testicular self-examination
4. Evidence-based treatment of side effects, including psychosocial support, and structured intervention trials	
Research	
1. Prospective studies	
2. Biochemical pharmacokinetic and pharmacogenetic analyses	
3. Epidemiologic investigations comparing TCSs with other cancer survivors and the general population	

there seems to be a high correlation between sexual functioning before and after treatment for TC, whereas the relation to treatment modality is less clear.[123–125] Findings must be considered in relation to age[123] and to the prevalence in the general population.[126] Erectile dysfunction is, for example, reported at the same level as in the general population (approximately 10%).[127]

Thirty per cent to 50% of TCSs report a decrease in sexual functioning compared with before treatment for TC.[112,123–125,127] Two-thirds reported decreased sexual activity, and one-third was dissatisfied with their sexual functioning.[127]

Psychologic and behavioral features such as desire, orgasmic pleasure, sexual activity, and satisfaction are affected by all treatment modalities, even surveillance. Reduction or loss of orgasm, loss of desire, and sexual dissatisfaction all show a prevalence of approximately 20%, which is significantly higher than in the general population.[127] Even in the surveillance group, 25% of TCSs report negative changes, which is the same proportion as in the radiation group, whereas those with chemotherapy reported more dysfunctions.[122] Psychologic functioning plays a strong role for these sexual dysfunctions.[128,129]

Fertility Issues

Biologic inability to father a child presents a serious challenge to a man's perception of his masculinity, to his self-esteem, and to his intimate relations, although the inability to achieve paternity evokes different responses at various points in a man's life.

Rieker et al.[130] found that fertility distress was common, but was a major problem only among those childless and those with ejaculatory dysfunction. No significant relationship was, however, found between TC-related infertility and marital separation.[101,104]

Psychologic Interventions

A randomized controlled trial of psychologic support in relation to primary treatment of TC showed an effectiveness that hardly differed from that of nonintervention.[131] Treatment for sexual dysfunctions in TCSs has been scarcely described, but seems to follow general principles for such dysfunctions.

Summary and Future Directions

The introduction of cisplatin-based chemotherapy into the treatment of testicular cancer has been one of the largest successes during the past three decades in oncology. Both oncologists and TCSs, however, must accept that long-term toxicity cannot completely be avoided: 10% to 20% of TCSs develop long-term health problems, most of them only slightly interfering with the patients' quality of life.

To minimize treatment-induced side effects, oncologists should follow evidence-based risk-adapted therapeutic guidelines, thus avoiding over- and undertreatment (Table 9.6). Furthermore, TCSs must be educated about the importance of adopting a healthy lifestyle (smoking cessation, weight control, physical activity) to minimize life-threatening side effects such as cardiovascular toxicity. They should be offered long-term follow-up in specialized multidisciplinary cancer survivor clinics that follow structured clinical and research programs with the aim at an early phase to recognize side effects and, if possible, to intervene (for example, testosterone substitution in hypogonal TCSs). Such long-term follow-up of TCSs and other cancer survivors will enable large-scale comparative epidemiologic investigations. Avoiding unnecessary anxiety, a former TC patient should also be made aware of his increased risk of tumor development in the contralateral testicle, warranting regular self-examination. Only rarely the oncologist will have to discuss the excess risk of subsequent non-germ cell cancer, although this risk should always be considered by healthcare professionals seeing TCSs with "unusual" symptoms.

Many of the reports on TCSs' long-term toxicity rely on the patients' responses to questionnaires. However, during recent years clinical investigators increasingly have validated these responses by objective measures, such as clinical examinations and organ-specific functional tests.[45,79,82,86] Interestingly, such studies have demonstrated that, for example, cisplatin or cisplatin adducts are retained in the human body (plasma, liver, muscle) for at least 20 years.[132,133] Whether an association exists between such cisplatin retention and long-term toxicity should be studied in future analyses, which should also take into account pharmacogenetic and molecular biologic parameters. The results of such investigations will increase our understanding of the considerable variability of physical and psychosocial long-term toxicity and will assist the identification of risk groups.

So far, the medical literature on long-term survivorship in TC patients almost exclusively contains cross-sectional studies. Prospective investigations are needed to identify premorbid risk factors of physical and psychosocial long-term toxicity.

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