Longitudinal long-term outcomes after treatment for testicular cancer

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Abbreviations

AFP  Alpha-Fetoprotein (Tumor-marker)
BEP  Bleomycin, Etoposide and Cisplatin
BOP  Bleomycin, Vincristine and Cisplatin
BSFI  Brief Male Sexual Function Inventory
C  Controls
CF  Chronic Fatigue
CI  Confidence Interval
CS  Clinical Stage
CT  Chemotherapy
CVB  Cisplatin, Vinblastine and Bleomycin
CVD  Cardiovascular Disease
Dog-Leg  Radiotherapy: Para-Aortic and Ipsilateral Iliac Lymph Nodes
EACR  European Association of Cancer Research
EP  Etoposide and Cisplatin
FQ  Fatigue Questionnaire
FSH  Follicle Stimulating Hormone
GST  Glutathione S-Transferase
Gy  Radiotherapy: Gray (SI unit of absorbed radiation)
HADS  Hospital Anxiety and Depression Scale
HCG  Human Chorionic Gonadotropin (Tumor-marker)
HOP  Ifosfamide, vincristine and cisplatin
HRQoL  Health Related Quality of Life
IGCCCG  International Germ Cell Consensus Classification Group
IU  International Units
LDH  Lactate Dehydrogenase
LH  Luteinizing Hormone
NORIP  Nordic Reference Interval Project
NRH  Norwegian Radium Hospital
NTX  Neurotoxicity
<table>
<thead>
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<td>OR</td>
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<tr>
<td>OLR</td>
<td>Ordinal Logistic Regression Analysis</td>
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<tr>
<td>PVB</td>
<td>Cisplatin, Vinblastine, Bleomycin</td>
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<td>QoL</td>
<td>Quality of Life</td>
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<td>RMH</td>
<td>Royal Marsden Hospital</td>
</tr>
<tr>
<td>RP</td>
<td>Raynauds’ Phenomenon</td>
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<tr>
<td>RPLND</td>
<td>Retroperitoneal Lymph Node Dissection</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>S</td>
<td>Surgery</td>
</tr>
<tr>
<td>SCIN</td>
<td>Scale for Chemotherapy-Induced Neurotoxicity</td>
</tr>
<tr>
<td>SHBG</td>
<td>Sex Hormone Binding Globulin</td>
</tr>
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<td>SII</td>
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<tr>
<td>SWENOTECA</td>
<td>Swedish-Norwegian Testicular Cancer group</td>
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<tr>
<td>T</td>
<td>Testosterone</td>
</tr>
<tr>
<td>TC</td>
<td>Testicular Cancer</td>
</tr>
<tr>
<td>TCSs</td>
<td>Testicular Cancer Survivors</td>
</tr>
<tr>
<td>VIP</td>
<td>Etoposide, Ifosfamide and Cisplatin</td>
</tr>
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List of papers

I:  Impact of Long-Term Serum Platinum Concentrations on Neuro- and Ototoxicity in Cisplatin-Treated Survivors of Testicular Cancer.


II:  Longitudinal serum testosterone, LH and FSH levels in a population-based sample of long-term testicular cancer survivors.


III:  Increasing prevalence of chronic fatigue in 812 testicular cancer survivors: A longitudinal study

1. Introduction

1.1 Cancer, a general overview

For the last thirty years, the International Agency for Research on Cancer (IARC) has published regular estimates of the incidence of and mortality from cancer in broad areas of the world through its GLOBOCAN series. IARC recently warned there will be 22 million new cases of cancer each year within two decades. Comparatively, there were probably 14 million new cases of cancer worldwide in 2012.\textsuperscript{1}

In Norway, approximately 30000 new cases of cancer are reported annually.\textsuperscript{2} The trend of improved survival for almost all cancer types continues, and at the end of 2012, roughly 224000 Norwegians with at least one cancer diagnosis at some point in life were alive.\textsuperscript{2} The growing population of long-term cancer survivors (defined as diagnosed with cancer at least 5 years previously), has led to a greater focus on the long-term effects of cancer treatment.

Due to high survival rates in combination with increasing incidence, the prevalence of testicular cancer (TC) is rapidly increasing in Norway, from a prevalence of 4500 in the year 2002 to 6600 in 2012.\textsuperscript{2} As TC is the most curable solid cancer, and the disease typically presents in young individuals, Testicular Cancer Survivors (TCSs) provide an excellent group for survivorship research. Hopefully, a deeper insight into the mechanisms involved in the pathogenesis of long-term complications after cancer treatment will provide means to reduce these adverse events in future cancer patients. An increased awareness of the possible long-term effects may in time lead to prevention and/or early detection and treatment of adverse outcomes, possibly impacting positively on the quality of life (QoL) for long-term survivors.
1.2 Malignant Germ Cell Tumors

TC is the most common malignancy in adolescents and young males in Norway between the age of 15-49 years.2 Approximately 95% of all malignant testicular tumors are of germ cell origin, with seminomas and non-seminomas representing roughly 50% each.3 The remaining 5% that may affect the testes, like lymphomas, sarcomas and stromal tumors are not the subject of this thesis, and will therefore not be discussed.

Tumors arising from the midline with histopathologic characteristics of TC, but without concurrent tumors in the testicle, are called extragonadal germ cell tumors and account for about 2 to 5% of male malignant germ cell tumors. Carcinoma in situ (CIS), e.g. a progenitor of invasive TC, is demonstrated to be present in about one third of males with extragonadal germ cell tumors and the risk of invasive metachronous TC is considered substantial even after chemotherapy.4 For those with primary testicular cancer, CIS is present in about 2-5% of the males.5

1.3 Incidence, Etiology, and Pathogenesis

The incidence of malignant germ cell tumors has a distinct geographic distribution, with Norway and Denmark displaying the highest incidence rates globally (Figure 1). A recent decline in the incidence in Denmark leaves Norway with the highest incidence rate.6,7 Present incidence rates in Norway are approximately 12 cases per 100000 males a year, with a tripled incidence during the last 40 years. Interestingly, migration studies indicate that emigrating males maintain their original TC risk despite geographic relocation and also independently of age at migration, unlike other cancers like cancer of the breast, colon, stomach and ovaries, where the immigrants acquire the incidence of the host population.8
Although a number of studies have been performed to investigate possible risk factors for TC, its causes still remain largely unknown. However, genetic predisposition and gestational factors like estrogens are believed to play a major role. Brothers of TC patients have a 8-10 fold risk of TC, while sons of TC patients have a 4-6 fold risk when compared to the general population. The fact that siblings have a greater risk than sons of TC patients, underscores the possible effect of environmental disruptors in addition to genetic factors. Also, the rapid increase in the incidence of TC and the observation that sons of affected males tend to develop their TC at an earlier age than their fathers, underline the added impact from environmental effects, as the genetic composition in the population is not likely to change in the course of only one or two generations. The familial risk of TC has so far not been explained by any major single locus, but the combination of multiple susceptibility genes might contribute to the development of TC. Epidemiologic studies conclude that there is an increased risk of TC in first-borns and twins, especially dizygotic twins. The particularly high levels of estrogens of these pregnancies led to the hypothesis that high estrogen levels during pregnancy were connected to subsequent higher risk of TC. However, findings are conflicting, as mothers and sisters of TCSs have not been found to have higher rates of estrogen-related cancers like breast cancer. Nevertheless, the estrogen hypothesis also supports the hypothesis as to why the cohort of men born in Norway, Denmark and Sweden during World War II had a lower incidence of TC than cohorts born shortly before or after the war. It has been postulated that lower maternal body weight in this time period, led to lower insulin levels, thus reducing the suppression of SHBG and consequently giving higher levels of bio-available estrogens for trans-placental transfer to the fetus.

Skakkebæk et al introduced the hypothesis of Testicular Dysgenesis Syndrome (TDS) in 2001, stating that the four conditions cryptorchidism, hypospadias, low sperm count and TC are associated as part of a disturbed prenatal testicular development where hormonal
disruptors like estrogens, phthalates, Dichlorodiphenyltrichloroethane (DDT), and Polychlorinated biphenyls (PCBs), may play a role. The risk of TC in males with cryptorchidism is 7-8-fold higher than for healthy men.\textsuperscript{13}

Figure 1. Geographic distribution of testicular cancer in the Nordic countries.

1.4 Diagnosis

Clinically, TC typically presents as a large and “heavy” testicle or as a hard swelling in an otherwise normal testicle.\textsuperscript{14} For some, the first symptom of the disease might be lower back
pain, and this should raise suspicion of metastatic TC if the pain is persistent in young males. More rarely, examinations due to hemoptysis, deep vein thrombosis or seizures may lead to the diagnosis of TC. Tumor markers and ultrasound of the testicles are mandatory if TC is suspected, and the final histological diagnosis should be followed up by Computer Tomography (CT scan) of thorax, abdomen, and pelvis. Treatment is based on histopathological assessment of the testis, levels of Human Chorionic Gonadotropin (hCG), Alpha-fetoprotein (AFP), and Lactate Dehydrogenase (LD), and absence or the site of metastases.

The histopathological examination separates between seminoma and non-seminoma. Seminomas are tumors with quite homogenous cells and may express mildly elevated levels of hCG originating from syncytiotrophoblast cells present in about 10-20% of seminomas, while non-seminomatous tumors are usually more heterogeneous and may consist of teratoma, embryonal carcinoma, yolk-sac tumor, and chorio-carcinoma, either as a single- or mixed histology. In 10-20% of the patients with non-seminoma the primary tumor also contains seminomatous elements.

At diagnosis, hCG may be increased in 30-35% and 10-20% of patients with non-seminoma and seminomas respectively, while AFP is increased in 50-60% of non-seminoma patients, and is per definition never increased in seminomas. Although hCG can be mildly elevated in seminomas, levels above 200 IU/l is considered to indicate the presence of non-seminomatous elements and consequently leads to treatment as for non-seminomas. AFP is produced by yolk sac cells, and is only elevated in non-seminomas. If histopathological assessment concludes with seminoma, but AFP is rising, treatment should be as for non-seminomas. Together with LD, tumor markers provide valuable information with regards to possible micro metastases, prognosis, treatment effect and recurrences.
1.5 Staging

In Norway the Royal Marsden Hospital (RMH) Classification was used for staging of TCSs in the time period males in this study were treated (between 1980-1994), and is thus the classification referred to in this thesis.\textsuperscript{17} The clinical stages (CSs) are defined in table 1.

Table 1. Staging of TC according to the Royal Marsden Hospital Classification

<table>
<thead>
<tr>
<th>Staging</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Testicular tumor only</td>
</tr>
<tr>
<td>IM</td>
<td>Elevated levels of AFP and/or HCG without visible metastases</td>
</tr>
<tr>
<td>II</td>
<td>Infra-diaphragmatic lymphadenopathy</td>
</tr>
<tr>
<td>II A: &lt; 2cm</td>
<td>Infra-diaphragmatic lymphadenopathy</td>
</tr>
<tr>
<td>II B: 2-5cm</td>
<td></td>
</tr>
<tr>
<td>II C: &gt;5cm</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Supra-diaphragmatic lymphadenopathy</td>
</tr>
<tr>
<td>III A: &lt; 2cm</td>
<td>Supra-diaphragmatic lymphadenopathy</td>
</tr>
<tr>
<td>III B: 2-5cm</td>
<td></td>
</tr>
<tr>
<td>III C: &gt;5cm</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Extra-lymphatic metastases (lung, liver, bone, etc.)</td>
</tr>
</tbody>
</table>

In addition to the staging according to the RMH, the \textit{International Germ Cell Consensus Classification Group} (IGCCCG) established three prognostic groups as a basis for determining treatment for metastatic tumors in 1997.\textsuperscript{17,18}

1.6 Treatment principles for testicular cancer

The introduction of cisplatin in the late seventies rapidly turned TC treatment into a model for a curable cancer, and as many as 97% of affected males can now expect to be cured from their cancer.\textsuperscript{2} Numerous clinical trials have been performed in TC patients after the introduction of cisplatin, yielding knowledge regarding prognosis, adverse events and the number of cycles of chemotherapy (CT) necessary without compromising survival rates.\textsuperscript{19-25} The combination of bleomycin, etoposide and cisplatin (BEP) still remains the gold standard
in TC treatment as it was in the mid-eighties. Although cisplatin greatly improved survival rates, surgery (S) and radiotherapy (RT) were still considered important supplements in TC therapy during the study period, with S being the most important supplement for non-seminomas and RT considered the most important supplement for the seminomas. However, after the study period, some changes have been implemented.

1.6.1 Surgery during and after the study period 1980-1994

Retroperitoneal Lymph Node Dissection (RPLND) was in the early study period performed as a staging procedure after orchiectomy, and sometimes as adjuvant treatment for the early stages of non-seminoma. For those with metastatic non-seminoma, RPLND was performed more or less routinely after chemotherapy until the end of our study period. However, during the treatment period 1980-1994, the extent of RPLND was refined, and for the patients studied in this thesis, there was a gradual shift from bilateral templates to ipsilateral templates. Also, during the mid-1980s Donohue et al introduced nerve-sparing RPLND for TC patients, and this technique was more or less routinely performed after 1990.

As approximately 30% of residual lesions after chemotherapy for non-seminoma contain teratoma (26%) and for some other viable germ cell tumor components (7%), the post chemotherapy RPLND is still considered important. In the Swedish-Norwegian testicular cancer group (SWENOTECA), retroperitoneal lesions of 1 cm or more after chemotherapy for metastatic non-seminoma will be surgically removed, while those under 1 cm will be observed provided normalization of tumor markers. However, management of smaller residual lesions, possible predictors of the histology of residual lesions and the extent of RPLND after chemotherapy is still subject for discussion. RPLND is rarely performed in seminomas, except for some cases with persistent large retroperitoneal residual lesions.
1.6.2 Radiotherapy during and after the study period 1980-1994

As seminoma is a highly radiosensitive cancer, RT has traditionally played a more important role for this malignancy than in the less radiosensitive non-seminoma. However, before the cisplatin era, RT was also applied for non-seminomas in order to treat metastatic lymph nodes or as adjuvant mediastinal irradiation.

During the treatment period studied in this thesis, RT was applied only rarely in post-chemotherapy setting for non-seminomas, while it was routinely used as post-orchiectomy treatment for stage I seminomas and for early stage II seminomas. During the study period, target volumes and target doses were gradually reduced. After a study comparing relapse rates and toxicity associated with para aortic (PA) strip versus Dog Leg (DL) field (30Gy/15 fractions), the Norwegian Radium Hospital (NRH) in 1989 introduced PA strip (30Gy/15 fractions) as standard treatment for stage I seminomas with undisturbed lymphatic drainage. Lead shielding of the remaining testicle was routinely performed except for radiation volumes limited only to the PA strip.

At the end of the 90ies / early 2000, the results from two large trials were to be groundbreaking for the further management of stage I seminoma. Firstly, the results from a trial performed during 1995 to 1998 led to a further reduction of the radiation dose for the PA strip (20Gy/10 fractions). Secondly, another trial performed during 1996 to 2001, introduced the shift away from radiotherapy and towards adjuvant carboplatin or active surveillance as standard options for stage I seminomas in Europe. However, adjuvant radiotherapy (20Gy/10 fractions) against PA-field is still an option if carboplatin or active surveillance is not considered advisable. For stage IIA seminomas, radiotherapy towards DL-field (30Gy/15 fractions) represents an alternative to cisplatin-based chemotherapy.
Chemotherapy during and after the study period 1980-1994

Before the cisplatin era, 5-year survival rates for disseminated TC were below 25% (Table 1), and a broad range of various agents and combinations were investigated. Cisplatin was the first drug with a heavy metal combination to be tested for cancer therapy. Its discovery resulted from the unanticipated outcome when testing the effect of an electric field on bacteria. It was Barnett Rosenberg who found that mitoses of E. coli came to arrest when exposed to an electric field in the early sixties. Further investigations led to the conclusion that platinum ions from the electrodes induced this arrest. Rosenberg consequently suggested the same response from cancer cells, which eventually led to the first clinical trials with cisplatin starting in 1971. One of these early trials had remarkable results with complete remissions in three of the 11 TC patients who had not been cured with at that time available induction therapy. Importantly, this was the first time complete remissions were demonstrated in second line chemotherapy for solid cancer. In 1977 the Indiana University suggested the three-drug combination with cisplatin, vinblastine, bleomycin (PVB) to be a major advance in the treatment of metastatic TC due to the superiority of this regimen compared to other combination regimen when it came to complete remissions. Cisplatin was approved by the Food and Drug Administration (FDA) in 1978, and the same year the first patient received the drug in Norway.

From 1981 to 1984 a study comparing PVB and BEP concluded that survival after BEP was significantly higher for disseminated germ cell tumors, and with less toxic effects. Consequently, vinblastine was replaced by etoposide in the treatment of metastatic TC. After the introduction of BEP as standard treatment for metastatic TC, much effort has been put into identifying risk groups in order to adjust the intensity of treatment according to these groups, and dose-intensive regimens with cisplatin applied over 2 or 3 days instead of 5 days or regimen with particularly high doses of cisplatin were also explored. Nevertheless,
the BEP regimen still today represents the gold standard as the first-line regimen for treatment of metastatic TC.\textsuperscript{43}

After the risk-adapted report of SWENOTECA, stage I non-seminomas are now usually managed by either surveillance or one cycle of BEP.\textsuperscript{44} For those with metastatic disease, high-dose chemotherapy was eventually introduced for TC through randomized studies, and is now in Norway routinely applied in patients failing to respond satisfyingly to BEP and dose-intensification with ifosfamide- BEP or in those relapsing within two years after BEP.\textsuperscript{45,46} Hopefully, the exploration of molecular TC specific mechanisms might eventually lead to new therapeutic targets benefitting those with cisplatin resistant disease.

After Oliver et al in 2005 reported the non-inferiority of single dose carboplatin compared to RT for stage I seminomas with similar findings in their follow up data in 2011, carboplatin or active surveillance represent the standard options for stage I seminomas in Europe.\textsuperscript{32,47}

1.6.4 The commonly used cytotoxic agents during the study period

The cisplatin compound forms cross-links with DNA ultimately inducing apoptosis.\textsuperscript{48} Early studies found the major dose-limiting toxicity of cisplatin to be renal, with a relatively mild myelosuppressive effect.\textsuperscript{34} Supportive care with high fluid intake and forced diuresis during treatment reduced the incidence of acute renal toxicity. Severe nausea and vomiting, neurotoxicity, Raynaud’s phenomenon and ototoxicity are other acute side effects of cisplatin, although emesis has been less of an issue since the introduction of 3-hydroxytryptamine receptor inhibitors and substance P antagonists.\textsuperscript{34,49}

Etoposide belongs to the topoisomerase inhibitor drug class and acts through preventing re-ligation of DNA strands, thereby inducing apoptosis.\textsuperscript{48} The drug is primarily excreted renally with myelosuppression as the major dose-limiting toxicity.
Vinblastine is a vinca alkaloid acting as an antimicrotubule drug, leading to metaphase arrest.\textsuperscript{48} This drug is primarily excreted through the hepatobiliary system. Myelosuppression is the major dose-limiting toxicity and neurotoxicity is a common side-effect.

Bleomycin acts through the induction of free radicals, leading to DNA strand scission and tumor cell death.\textsuperscript{48} This drug is eliminated renally. The major dose limiting toxicity of bleomycin is pneumonitis, which may progress to pulmonary fibrosis during or shortly after treatment.\textsuperscript{50}

Table 2. The 5 year relative survival (%) for TCSs before and during the Cisplatin era.\textsuperscript{51}

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<td>All stages</td>
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<td>70.7</td>
<td>87.1</td>
<td>93.1</td>
<td>95.5</td>
<td>96.2</td>
<td>95.7</td>
<td>97.2</td>
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<td>Localized</td>
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<td>98.3</td>
<td>98.5</td>
<td>100.0</td>
<td>98.5</td>
<td>99.2</td>
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<td>86.3</td>
<td>97.0</td>
<td>98.1</td>
</tr>
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</table>
2. Survivorship

The acute side effects of treatment for TC may be severe, and although seldom life threatening, they comprise thromboembolic events, hematological and infectious complications, and severe lung-, cardiac- and nephrotoxicity.\textsuperscript{25,34,50,52-54} Well informed patients, carefully monitored hydration during therapy, a thorough medical history and examination with regards to possible risk factors of thromboembolic events and strict follow up of any symptoms of fever or infections during treatment, may ameliorate the risk of life threatening events.

Due to the remarkable improvement in the therapy of metastatic TC since the introduction of cisplatin, the vast majority of TCSs are now expected to live for 50 to 60 years after treatment. As a consequence, many clinical studies have focused on the long-term toxicity in TCSs. During the last two decades it has become evident that severe and even life threatening long-term adverse events may represent the prize for cure in some patients. As the goal of this thesis was to add knowledge with regards to the long-term effects after treatment for TC, any further mentioning of side effects will address the long-term sequelae persisting or presenting > 1 year after TC treatment.\textsuperscript{55}

2.1 Long-term retention of platinum

Platinum is one of the rarest elements in the Earth’s crust. It has many industrial uses like windings of high temperature furnaces, electrical contacts and electrodes, photography, biomedical devices, jewelry and dentistry. Also, in a move to reduce air pollution, catalytic converters using platinum group metals to oxidize exhaust emissions into less toxic substances are now fitted into new motor vehicles. Although this has reduced some of the toxic pollutants in exhaust gas, it also resulted in platinum group metals being deposited near
roadways, giving rise to concern considering the toxicity of these elements and their possible environmental impact.\textsuperscript{56}

Platinum is a heavy metal, and is also the most fundamental component of the chemotherapeutic agent cisplatin (\textit{cis-PtCl}_2 (\textit{NH}_3)_2). The seemingly selective destruction of tumor cells by cisplatin, and in particular germ cell tumors, has produced many hypotheses regarding possible mechanisms. Cisplatin is a neutral, square-planar coordination complex containing two relatively inert amine ligands and two relatively labile chloride groups in the cis-configuration. Three aspects are considered particularly important features of the reactivity of cisplatin; 1) the platinum position, 2) the complex being neutral, and 3) the dissociable groups. Within two hours after administration, approximately 90\% of cisplatin is tightly bound to plasma proteins, while the unbound 10\% is considered to be the biologically active fraction.\textsuperscript{57} Cisplatin undergoes hydration reactions where the chlorides are replaced by water, allowing platinum to coordinate with DNA within the cell, resulting in a bending of the double helix, and leading to ant proliferative effects including prevention of repair mechanisms, interruption of transcription and further leading to apoptosis of the cancer cells.\textsuperscript{57} Due to differences in pH in cancerous and healthy cells, platinum-based compounds target cancer cells due to their lower pH. Despite this targeting, it is a highly inefficient process where only about 1\% of the total dose of platinum actually binds to DNA as intended.\textsuperscript{58}

While many chemotherapeutic agents are completely eliminated from the body within hours or days after administration, cisplatin excretion proceeds slowly with an upper range of elimination of about 40\% in the first day, and with approximately 50\% elimination after 5 days of treatment. Further on, substantial elimination requires several half-lives increasing with follow up time.\textsuperscript{59,60} Several studies performed within 15 months after treatment with cisplatin show elevated concentrations of platinum in most organs, including brain, heart,
liver and kidney, and it is suggested that regeneration in storage tissues consequently releases platinum to the blood stream.\textsuperscript{61-65} The biokinetic behavior of platinum closely resembles that of other toxic metals, e.g. mercury and chromium, where serum and urine concentrations correlate with toxic outcomes.\textsuperscript{66}

Thompson et al performed a small electrophysiologic, morphologic, and toxicologic study as early as in 1984 on patients treated by cisplatin-based chemotherapy (autopsy in two patients).\textsuperscript{67} They found platinum concentrations to be similar in tumor tissue, sural nerves, and spinal ganglia, but lower in brain. The lower concentrations in brain tissue when compared to other neural tissues, were in concordance with previous animal studies, and further led to their hypothesis that this might explain the toxicity of peripheral nerves with a relative sparing of the central nervous system. A similar study concluded that platinum concentrations were localized to large cells of long fibers in the dorsal root ganglion rather than the peripheral nerves.\textsuperscript{61} Electrophysiological analyses of the neuronal involvement before, during and after cisplatin-based therapy, proposed that the primary site of involvement of cisplatin-based neuropathy is localized to the large cells of long fibers in the dorsal root ganglion, consistent with the above mentioned post-mortem study.\textsuperscript{61,68}

Importantly, Brouwers et al could demonstrate that approximately 10\% of platinum remains reactive long-term after platinum-based therapy.\textsuperscript{69} This long-term circulating Pt is believed to occur as a dissolved Pt salt in serum.\textsuperscript{69-71} Several studies of TCSs have demonstrated ongoing endothelial changes for more than 10 years after cisplatin administration, indicating a possible prolonged effect of residual platinum.\textsuperscript{72-74} Several reports indicate that vascular toxicity is one of the most important late effects of cisplatin-based chemotherapy in the treatment of men with advanced TC. Whether the ongoing exposure of residual circulating platinum is a contributing factor in the development of secondary cancers seen after treatment for TC remains unknown.
2.2 Peripheral neurotoxicity

Peripheral neurotoxicity is one of the most common long-term side effects after cisplatin-based therapy with a prevalence of approximately 20-30% in TCSs. The primary site of injury is the dorsal root ganglion, predominantly affecting large myelinated sensory fibers, with sparing of motor fibers. Clinically symptoms present in a symmetrical stocking-glove distribution, starting in the toes and fingers, spreading proximally. Patients typically complain of a “needle and pin” sensation that may be accompanied by numbness and disturbances in vibratory and position sense. Some may encounter reduced fine motor skills. During treatment with cisplatin-based chemotherapy, acute neuropathy is experienced to some extent by several patients, as demonstrated by the early clinical, electrophysiological, morphologic, and toxicological studies in 1984 by Thompson et al. Further studies have suggested that the peripheral neuropathy usually progresses for approximately 3-6 months after therapy, and then eventually improves in most patients, although recovery is often incomplete, depending on cumulative cisplatin dose and probably also dose intensity. The pathophysiologic mechanisms underlying the development of chemotherapy-related neuropathy are still not fully understood. Disruption of axoplasmic microtubule-mediated transport, distal axonal degeneration and in the dorsal ganglia by direct damage to the sensory nerve cell bodies have been suggested as possible etiological factors.

Currently, to our knowledge, there are no agents that prevent the clinical neurotoxicity of platinating agents. According to both a recent Cochrane Database review and Clinical Practice Guidelines from the American Society of Clinical Oncology based on systematic literature search, information on possible neuroprotective agents, such as acetylcysteine, amifostine, amitryptiline, calcium and magnesium, diethyldithiocarbamate, glutathione, nimodipine, Org 2766, all-trans-retinoic acid, rhuLIF, oxycarbazepine, or Vitamin E is
insufficient to conclude that they “prevented or limited neurotoxicity of platinum drugs among human patients”\textsuperscript{,80,81} With regard to existing chemotherapy-induced neuropathic pain conditions, available data support a moderate recommendation for the treatment with duloxetine.\textsuperscript{81} For other agents such as tricyclic antidepressants and gabapentine, trial results are inconclusive, however, as data support their benefit for other neuropathic pain conditions, they may also be offered to those suffering from chemotherapy-induced neuropathy due to their limited treatment options.

\subsection{2.3 Raynaud’s phenomenon}

Raynaud’s phenomenon (RP) is an abnormal vasospastic response to low temperatures or emotional stress causing reduced blood supply to the fingers and toes. As a result, hypoxia with a marked white or blue discoloration of fingers and toes appear with coldness, stiffness, and numbness during the attacks. The phenomenon is supposedly caused by a local defect in normal vascular responses in the cutaneous arterioles and digital arteries.\textsuperscript{78}

Teutsch et al were the first to describe RP after chemotherapy for TC in 1977 in males treated with a combination of vinblastine and bleomycin.\textsuperscript{82} Both bleomycin and cisplatin are believed to induce RP, and although reports are conflicting, a dose-dependent relationship is likely.\textsuperscript{25,49,83} Symptoms of RP may begin during or after chemotherapy, and will for most TCSs peak approximately 6 months after treatment.\textsuperscript{25} The prevalence of RP in TCSs after chemotherapy has been reported to be between 20 to 40 percent.\textsuperscript{49,75,83,84} Self-help measures such as wearing warm clothes and rechargeable thermo gloves when exposed to low temperatures and warming up vasospastic digits may ameliorate symptoms of RP. Vasodilators, primarily calcium channel blockers, maybe prescribed for secondary RP, although data on their effect on chemotherapy-induced RP are sparse.
2.4 Ototoxicity

During or after cisplatin-based therapy, many TCSs experience ototoxicity, typically manifested as tinnitus or a high-frequency hearing loss. Loss of outer hair cells in the organ of Corti and detachment of the myelin sheath of the spiral ganglion cells, are the pathogenic mechanisms for the ototoxicity experienced by many TCSs.\textsuperscript{85} Dependent on the number of chemotherapy cycles and the type of schedules applied, approximately 20-60\% of the TCSs report hearing loss and/or tinnitus to some extent.\textsuperscript{25,49,86} Development of ototoxicity is related to germ-line polymorphisms of the GST-P1 gene but is also correlated with pre-existing hearing loss or chronic noise exposure before therapy.\textsuperscript{87,88} A recent Cochrane review on “medical interventions for the prevention of platinum-induced hearing loss in children with cancer” found the available evidence insufficient to support the routinely use of any agent to prevent cisplatin-induced ototoxicity, however, methodological limitations of the reviewed studies were noted.\textsuperscript{89}

2.5 Hypogonadism and fertility

The testicles have two major functions: production of testosterone (endocrine) and generation of sperm cells (exocrine). Primary hypogonadism is due to testicular damage resulting in dysfunction of the Leydig cells or decreased sperm production. Biochemical hypogonadism with decreased testosterone levels, is frequently reported in cancer survivors, and in particular TCSs.\textsuperscript{90} When Leydig cell function is impaired, testosterone levels will be decreased, most often with a compensatory elevation of luteinizing hormone (LH) levels.\textsuperscript{90,91}

The especially high prevalence of hypogonadism in TCSs can mainly be explained by these four aspects: 1) orchiectomy, 2) TDS, 3) treatment after orchiectomy, and 4) ageing. As TCSs only have one testicle, the number of Leydig cells and spermatogonias is roughly
halved, consequently with a reduced testicular functional reserve for both sperm- and testosterone production. Of note, low spermatogenesis and a tendency towards lower testosterone levels are also part of the TDS, which is often present in these men already prior to their TC diagnosis.\textsuperscript{92}

Testosterone levels are usually within the normal range before chemotherapy in men with TC, and may remain within this range, although this depends on the intensity of the treatment and the length of the follow-up time.\textsuperscript{93-96} Changes in gonadotropin levels, however, occurs more frequently, especially for Follicle Stimulating Hormone (FSH), and can be seen during, shortly after, and also long-term after therapy.\textsuperscript{95,97-99} Of note, the “normal ranges” of these hormones should be adjusted for age as recommended by Bjerner et al, as males after the age of 30 experience a gradual decline in testosterone levels, accompanied by an increase in LH, FSH and Sex Hormone Binding Globuline (SHBG) levels.\textsuperscript{100} As a result of the physiological age-related decline in testosterone and the accompanying increase in SHBG, there is a relatively steep decline in the levels of free testosterone.

Fertility after therapy is an important aspect for most TCSs, and several studies report gonadal toxicity to be significantly correlated with cumulative cisplatin dose with long-term reduction in testosterone levels and higher rates of persistent azoospermia.\textsuperscript{101-105} Age of the TCSs at the time for treatment, pretreatment oligospermia, cumulative dose of chemotherapy and the number of cycles applied, are all factors impacting on recovery of spermatogenesis.\textsuperscript{101,103,106} No evidence of long-term fertility impairment after two courses of BEP chemotherapy for stage I disease was found by Cullen et al.\textsuperscript{107} However, most men develop a transient reduction in spermatogenesis after three to four cycles of chemotherapy.\textsuperscript{101,103,105,108} Approximately three years after CT, recovery of sperm production is found in approximately 70 percent of these males.\textsuperscript{101}
The introduction of nerve sparing techniques and the decrease in men undergoing RPLND have substantially reduced the frequency of retrograde ejaculation. Also, fewer men now undergo RT, and target volumes and target doses have gradually been reduced since the start of our study period. Nevertheless, cryo-preservation of sperm should routinely be offered to better ensure the patients’ possibility of future paternity.

### 2.6 Fatigue

Fatigue can be described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest. Whenever discussing fatigue in this thesis we refer to the definition of Chronic Fatigue (CF) by Fukuda et al, who restricted the term to fatigue of a specified level persisting for more than 6 months. The general male population in Norway previously reported a CF rate of 10%, with just a slight increase with age. CF has repeatedly been reported to be associated with anxiety and depression in the literature, and associations with comorbidity, low educational level, not living in a relationship, being female, and with increasing age have also been described. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist have been reported to occur more frequent in TCSs with CF, indicating a possible association between CF and a low-grade inflammatory response. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs median 12 years after treatment for TC when compared with the age-matched Norwegian population (10%). Apart from this, treatment-related fatigue in TCSs has rarely been addressed. At present, there is no gold standard on how to treat cancer related fatigue, however, several randomized trials suggest that physical activity, mindfulness-based cognitive therapy, and psychosocial interventions might be beneficial.
2.7 Psychosocial aspects and Health Related Quality of Life

In a Norwegian study, Hospital Anxiety and Depression Scale (HADS)-defined anxiety disorder was significantly more prevalent in TCSs mean 11.3 years after diagnosis compared with controls, whereas the prevalence of HADS-defined depression did not differ from the general population.\textsuperscript{114} However, results regarding depression in TCSs are conflicting, as another study did find a significantly increased prevalence of depression compared with the general population.\textsuperscript{115} The HADS-defined anxiety disorder is significantly associated with younger age, fear of recurrence, economic concerns, alcohol abuse, sexual difficulties, peripheral neuropathy, and a history of treatment for mental problems. The risk of suicide in TCSs is 20\% higher than for the general population.\textsuperscript{116} TCSs have been reported to be more likely to engage in problem drinking and current smoking than age-matched relative controls, and to have a lower intake of fruits and vegetables. However, compared with their relative controls, they were more likely to engage in regular exercise.\textsuperscript{117} Levels of work engagement are similar to the age-matched males in the general population, although data on work engagement extending 10 years follow-up have so far not been published.\textsuperscript{118}

Several studies of Health Related Quality of Life (HRQoL) in TCSs, assessed by validated questionnaires, conclude that their HRQoL is comparable to that of age-matched males.\textsuperscript{86,119} Even if this may be an accurate observation it could also be due to a response-shift after having experienced a potentially life threatening disease. It may also be that the used questionnaires are insufficient in evaluating the HRQoL issues experienced by TCSs.

2.8 Cardiovascular disease and the metabolic syndrome

Long-term survivors after treatment for TC with RT and/or CT have an increased risk of cardiovascular disease (CVD) as demonstrated by Haugnes et al, with the risk being highest
for those treated with a combination of both chemotherapy and RT.\textsuperscript{120} Mediastinal RT, which was applied for some in this period, is considered particularly harmful, buts no longer applied in TCSs.\textsuperscript{121,122} Nevertheless, the scattered dose from infra-diaphragmatic RT still represents an increased risk factor for subsequent CVD.\textsuperscript{123,124} Well-known risk-factors for CVD may be optimized through life style counselling and the early detection of conditions that can be treated by antihypertensive and lipid-lowering medications, thereby hopefully preventing or delaying the increased cardio-vascular morbidity seen in TCSs. In addition to well-known risk-factors like hypertension and hyperlipidemia, it has been suggested that direct endothelial toxicity from circulating residual serum platinum after cisplatin-based therapy may be essential in driving the atherosclerotic process.\textsuperscript{72-74} Elevated levels of high sensitivity-C-reactive protein in TCSs after RT have also been suggested as a possible mechanism for development of atherosclerotic changes through a continuous process of low-grade inflammation.\textsuperscript{125}

The metabolic syndrome (MetS) is characterized by a group of metabolic risk factors occurring in one person. These risk factors include abdominal obesity, dyslipidemia, hypertension, and insulin resistance. There are several reports of MetS in studies of TCSs, and the syndrome has been suggested to be associated with the cumulative doses of chemotherapy.\textsuperscript{73,74,126-128} Endocrinological disturbances have also been hypothesized to be associated with the MetS and the dyslipidemia.\textsuperscript{99,129}

2.9 Pulmonary toxicity

The potential for life-threatening pulmonary toxicity is regarded as the major dose-limiting effect of bleomycin-based therapy. Bleomycin is an antibiotic agent that acts by inducing double-strand breaks in DNA. The enzyme bleomycin hydrolase may deacivate bleomycin, however, due to the lack of this enzyme in the lungs and skin, bleomycin-related toxicity is
typically expressed in these organs. Pneumonitis is regarded the most threatening side-effect of bleomycin, and may progress to pulmonary fibrosis. De Haas et al recently reported that variation in the bleomycin hydrolase gene is associated with reduced survival after chemotherapy for testicular germ cell cancer, however not due to pulmonary toxicity, but as a result of a higher prevalence of early relapses in TC patients treated with bleomycin-containing chemotherapy. Exposure of high concentrations of oxygen during surgical procedures like RPLND has been suggested to provoke endothelial damage of the pulmonary vasculature by increasing the free radical formation in the lungs. Although, findings are conflicting, the general advice still remains oxygen restriction during surgery at least the first months after chemotherapy, however, avoiding fluid overload and perioperative pulmonary edema may be of greater importance. Should bleomycin-induced lung injury develop, steroids are the treatment of choice, however, novel targeted drugs developed on other indications may offer therapeutic potentials against the bleomycin-induced lung injury. The development of bleomycin-induced pneumonitis is typically described to occur during treatment and up to 6 months after bleomycin based therapy, and any further development of long-term effects after this are poorly described, and only as case reports.

2.10 Second Cancers

Second cancers after successful treatment for TC may represent a price for cure, and can be induced by CT and/or RT. The largest study reporting second cancers in TCSs followed more than 7800 TCSs for 20 years and almost 2100 TCSs for 30 years. The risk of developing a second malignancy after treatment for TC has been reported to be up to 2-3 times higher than for the general population. These solid cancers typically present from ten years or more after their primary treatment and are primarily associated with RT.
For TCSs treated with RT alone, second cancers are typically located within the former radiation field, most often in the kidney, urinary bladder, pancreas and stomach.\textsuperscript{135}

Cisplatin-based regimens have also been reported to be associated with a statistically significantly increased hazard ratio of solid tumors of roughly 2.0.\textsuperscript{135,138}

Males undergoing chemotherapy for TC are at increased risk of developing secondary myeloid neoplasms, with the effects from etoposide-based therapy well described.\textsuperscript{135,139-141} Leukemias induced by etoposide, typically present two to three years after treatment, and an additional synergistic effect from cisplatin on the development of leukemia has been suggested.\textsuperscript{139}

TCSs with second primary malignancies have similar outcomes for cancer-related mortality or all-cause mortality when compared to a control population.\textsuperscript{142}

\textbf{2.11 Status quo at the start of this thesis}

Status quo at the start of this thesis was mainly dominated by results from cross-sectional studies on treatment-related late toxicities in TCSs.

I. The long-term retention of platinum after platinum-based therapy was well documented by Gietema et al in 2000, but its clinical impact had not assessed, yet Brouwers et al. showed in 2008 that approximately 10\% of the platinum remain reactive long-term after treatment.\textsuperscript{69,143}

II. Biochemical hypogonadism in TCSs had been described by several researchers. Most of these results, however, were cross-sectional, thereby not providing clues for a hypothesized accelerated hormonal ageing in TCSs compared with controls.\textsuperscript{90,144}

III. Low levels of testosterone are more prevalent in TCSs. As men with low testosterone may present with symptoms of fatigue, and an increased prevalence of CF in TCSs had
recently been described, we wanted to explore this possible association in a longitudinal manner.\textsuperscript{90,98,111}

3. Aims of this thesis

The overall objective of this thesis was to look further into the long-term effects after treatment, investigating the possible association between neurotoxicity and measured long-term serum levels of platinum after platinum-based therapy, and also to study the longitudinal course of male sex hormones and CF in a population-based sample of long-term survivors of TC. The aim was to add further knowledge into the survivorship field, and hopefully revealing some factors that might be prevented, ameliorated, or treated in TCSs today, and TCSs to come. We specifically wanted to address the following:

I. Whether levels of long-term total serum-platinum are associated with the development and severity of the most common platinum-related toxicities like peripheral paresthesias, Raynaud’s phenomenon and ototoxicity in TCSs treated with platinum-based chemotherapy (Paper I).

II. To investigate whether long-term TCSs have a higher risk of biochemical hypogonadism than males from a healthy control group. Further, to evaluate if TCSs are more vulnerable to ageing-related deterioration of sex hormones than controls when assessing them in a longitudinal manner after adjusting for age. We also wanted to explore whether type of treatment has any impact on the “hormonal deterioration rate” (Paper II).
III. To describe the prevalence of CF in TCSs median 12 and 19 years after treatment. Further, to assess the relationship between CF and possible risk factors including serum levels of testosterone and LH, treatment, long-term toxicities and comorbidity. We also wanted to assess the impact of having more than one risk factor associated with CF (Paper III).

4. Materials and Methods

4.1 Study populations

Between 1998 through April 2002, a national follow-up survey (SI) was performed at all Norwegian University hospitals to assess somatic and psychosocial morbidity in long-term TCSs, including a questionnaire, clinical examination, blood samples and semen analysis. All TCSs treated for unilateral germ cell TC between 1980 and 1994 with the age of 18 to 75 years were identified both through the Cancer Registry of Norway and at all regional University hospitals. In total 1814 men were invited to participate. Overall 1463 (81%) of the eligible men consented. Non-responders did not differ from the responders with regard to age at follow-up, stage, histology or treatment based on the information on from their medical charts from the time of treatment (results not shown). The 217-item questionnaire was completed by 1438 men, while 1289 of the men underwent a clinical examination at the five outpatient clinics including laboratory tests. A total of 356 men provided semen analyses. Patients with extragonadal germ cell tumors, bilateral orchiectomy for any reason, secondary malignancy except skin cancer, or those mentally disabled were excluded.

Blood samples drawn during Survey I were all analyzed at The Norwegian Radium Hospital (NRH), but only samples from NRH patients were also frozen. Consequently, as the platinum analyses performed in 2009 were based on these frozen samples, Paper I is restricted
to TCSs treated at the NRH. A total of 308 of the men treated at the NRH had received platinum-based therapy. However, as frozen blood samples had also been used in prior research projects, sufficient material only remained for 169 of the previously cisplatin-exposed TCSs. (Figure 2).

A second follow-up study (SII) was performed in 2007 and 2008, median eight years (range, 7-9 years) after SI. SII consisted of a questionnaire and blood samples drawn at the patients’ primary care physician’s office. Of the 169 TCSs with platinum measurements from Survey I, 127 (75%) participated in SII, when they completed a questionnaire, including the Scale for Chemotherapy-Induced Neurotoxicity (SCIN, Table 2, see questionnaire section). Levels of testosterone, LH and FSH were measured at baseline (after orchiectomy, but prior to other treatment), at SI, and at SII (Paper II). As the NRH was the only Norwegian hospital routinely measuring hormone levels in TC patients in the early eighties, our study sample was based on NRH patients only (Figure 2).

Levels of testosterone and LH, the HADS, and Fatigue Questionnaire (FQ) were available for 812 men at both SI and SII median 12 and 19 years after treatment (Paper III) (Figure 2).
Figure 2. Study populations

1,814 TCSs invited to SI

1,463 participated (81%)
- 774 treated at the NRH
- 689 treated at other Hospitals

308 of the 774 men treated at the NRH received platinum-based chemotherapy

238 of the platinum-treated TCSs had complete SCIN

774 TCSs treated at NRH
- 470 with hormone levels at base-line and SI, but not at SII

307 of the TCSs had male sex hormone levels at base-line, SI, and SII

1,463 accepting invitation SI
- 256 excluded

The 1207 TCSs eligible for SI were considered for SII
- 49 diseased
- 18 emigrated

1140 considered for study
- 328 excluded

169 platinum-treated TCSs had complete SCIN and available blood samples at SI

127 of the 169 TCSs had complete SCIN at SII

812 TCSs had male sex hormone levels and complete HADS and FQ at both SI and SII

*Exclusion criteria were: irradiated scrotum, hyperprolactinoma, substitution of testosterone, removal of contralateral testicle, missing questionnaire data and missing blood samples.

Abbreviations:
FQ - Fatigue Questionnaires
HADS - Hospital Anxiety and Depression Scale
NRH - Norwegian Radium Hospital
SCIN - Scale for Chemotherapy-Induced Neurotoxicity
SI - Survey I
SII - Survey II
TCSs - Testicular Cancer Survivors
4.2 Methods

4.2.1 Platinum measurement (Paper I)

In 2009, at the Biometals Laboratory of the University of Massachusetts-Boston, serum samples from 169 TCSs were analyzed for total serum platinum using established methods.\textsuperscript{146,147} Samples were kept frozen on dry ice during shipment from Norway to Boston and stored in a freezer at -70°C upon arrival. Prior to analyses, samples were equilibrated at room temperature for 4 hours, followed by gentle agitation with a Global Spec Laboratory slow shaker for 30 minutes to re-homogenize the fluid. Of each serum sample 0.1mL was volumetrically pipetted into a trace metal clean test tube and verified gravimetrically with ±0.001g. Samples were diluted by using 18.2 MΩ·cm\textsuperscript{-1} resistance water and acidified using ultra-pure (12.4 mol L\textsuperscript{-1}) hydrochloric acid. Known quantities of indium, bismuth, and iridium used to correct for instrumental drift, were added to the serum samples.

The platinum concentrations were determined by the average of 10 duplicate analyses for each sample using external calibration analogously to the methods previously reported for the analysis of metals in other biological tissues.\textsuperscript{59,146,148} Detection of serum platinum levels was performed according to Brouwers et al.\textsuperscript{146,147} Limits of platinum-detection, quantification and method detection limit calculated according to Long and Winefordner were 0.010 pmol/g, 0.035 pmol/g, and 0.097 pmol/g, respectively.\textsuperscript{149}

4.2.2 Laboratory tests- Hormone analyses (Paper II and III)

Sex hormones were measured by routine immunoassays. For FSH and testosterone, the correlations between the different assays used during the actual time period were within biologic variations, and reference values were left unchanged because of methodological
adaptations. However, methodological changes did have consequences for some of the baseline measurements of LH in Paper II due to differences in cross-reactivity of hCG. From 1980 until January 1986, LH radioimmunoassay methods with 100% cross-reactivity for hCG were applied, consequently as some men presented with elevated hCG levels at baseline, this could interfere with the measured LH levels. AutoDelfia assays with minimal cross reactivity for hCG were used from 1986 until September 1999. The baseline samples described in paper II, were collected after orchiectomy, but prior to any further treatment like surgery, radiotherapy, chemotherapy or a combination by any of these.

### 4.3 The questionnaires- Subjective symptom assessment

At both surveys the questionnaire responses provided detailed information with regard to tobacco use, co-morbidities, medication use and civil status (Appendix with questionnaires at both surveys). Males reporting substitution of testosterone were excluded (N= 10, Paper II and N= 62 Paper III). The validated instruments SCIN, FQ, and HADS were included at both surveys (Paper I, and III).145,150-152

Presence of comorbidities was recorded based on self-reported medical conditions or the reported use of medication for diabetes, cardiac disease (having or having had angina or having had a heart attack) and pulmonary disease (at SI use of asthma medication ≥ three months during the year before the survey, whereas at SII use of asthma medication for ≥ three months during the last year or reporting asthma/chronic bronchitis/chronic obstructive pulmonary disease or emphysema).

Levels of physical activity were categorized into three categories (inactive, moderately active, highly active) as previously published.153
Neurotoxicity was assessed by the SCIN, which is part of a TC specific module by Fosså et al.\textsuperscript{154} The SCIN has undergone psychometrical validation in terms of correlation with audiogram data.\textsuperscript{145} In this questionnaire, the TCSs scored the relevant questions as to how bothered they were by neuropathy, Raynaud’s phenomenon, and ototoxicity, regarding the extent of symptom bother as: 0-“not at all”, 1-“a little”, 2-“quite a bit”, to 3-“very much” (Paper I and III) (Table 3). Summation of the six symptom scores yielded the possible total SCIN score from 0 to 18. Categorization of the total SCIN score into quartiles yielded roughly similar-sized groups with increasing symptoms (Paper I).

Table 3. SCIN= Scale for Chemotherapy-Induced Neurotoxicity\textsuperscript{145}

<table>
<thead>
<tr>
<th>Subscales</th>
<th>Items</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias hands/fingers</td>
<td>1a Have you suffered from pain and tingling in your feet/toes?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesias feet/toes</td>
<td>1b Have you suffered from pain and tingling in your hands/fingers?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Raynaud’s hands/fingers</td>
<td>2a Have you suffered from numb or cold feet or toes?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Raynaud’s feet/toes</td>
<td>2b Have you suffered from numb or cold hands or fingers?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>3a Have you suffered from ringing in your ears?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Impaired hearing</td>
<td>3b Have you suffered from reduced hearing?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

The validated FQ includes 11 items, of which 7 items cover physical fatigue and 4 items cover mental fatigue.\textsuperscript{150,152} Items-scores in this Likert scale range from 0-3. Summation of the 11 item scores yields a possible total fatigue score ranging from 0 to 33, with higher scores indicating higher levels of fatigue. Two additional items address the extent and
duration of fatigue. For case definition, the 11 item scores were dichotomized (0 and 1 = 0 and 2 and 3 = 1), and summarized, with a sum score of $\geq 4$ and duration of symptoms $\geq 6$ months defining CF (Paper III).

The HADS questionnaire consists of 7 items covering anxiety (HADS-A) and 7 items covering depression (HADS-D), with item-scores of 0-3. Summation of the 7 item scores yields a total sum score between 0 and 21, with higher scores implying higher levels of anxiety or depression (Paper III).

4.4 Controls from the Nordic Reference Interval Project

The Nordic Reference Interval Project was performed at 102 laboratories in the five Nordic countries to obtain reference values for the most common biochemical properties measured in serum and plasma. The control material referred to in both Paper II and Paper III was obtained from this study. Inclusion of all individuals between 18 and 91 years old, collection of blood samples and protocol for analyses and questionnaires, were all according to a common protocol. Approximately 75% of the hormone samples were collected between 07.00 am and 09.00 am. The calculation of reference intervals and exclusion of study subjects and data, were performed centrally.

4.5 Statistical analysis

All tests were two-sided, and p-values $\leq 0.05$ were considered statistically significant. Analyses were performed using SPSS software for PC, version 17.0 (Paper I), 18.0 (Paper II) and 19.0 (Paper III) (SPSS, Chicago, IL).

Continuous variables were described with median and range, and categorical ones with counts and proportions. Means of age, HADS, and fatigue scores were compared by t-tests,
and the $\chi^2$-test of trend assessed crude associations between pairs of ordered categorical variables.

Ordinal Logistic Regression (OLR) was used to model total SCIN score and ordered individual SCIN symptoms as a function of administered cisplatin dose, dose-intensive versus standard chemotherapy, age at survey and quartiles of serum platinum levels. Variables considered to be of high clinical relevance or those reaching $p<0.2$ in univariate analyses were included in OLR with Odds ratios (OR) for any dichotomization of the four ordered outcome levels reported for each independent predictor, along with 95% Confidence Interval (CI). A test of parallel lines checked the proportional odds assumption that the OR for each predictor was similar for all three possible dichotomizations of the outcome. OR represent a comparison of higher to lower grouped ordered outcomes (i.e., symptoms of “a little” or more vs. “not at all”; “very much” or “quite a bit” vs. “a little” or “not at all”; and “very much” vs. “quite a bit” or less). For tinnitus and hearing impairment, the two highest toxicity groups were pooled to remedy violations of this assumption; however, results were nearly identical without pooling. (Paper I).

The testosterone, LH, and FSH levels from the reference range for decadal age from 599 controls (based on a Nordic reference material), were categorized into six scores (range, 1 to 6), according to cut-off values of 2.5, 25, 50, 75, and 97.5 percentiles for each decadal age group (the reference range defined as being between 2.5 to 97.5). Levels of testosterone, LH, and FSH in TCSs were then allocated to one of these six scores based on their percentile derived from the reference range and grouped according to treatment (S, RT, and CT).

OLR was performed to assess the risk of decreased gonadal function in TCSs according to treatment compared with controls. The risk was expressed as ORs for higher (LH, FSH) or lower (testosterone) levels (Paper II).
Multivariate logistic regression analyses were performed to investigate the association between CF at SI and SII and hormone levels, treatment, age, neurotoxicity and comorbidity. Surgery, the state of having no comorbidity, no symptoms in the SCIN score, a high testosterone-, education-, and physical activity level were all set as referents in the logistic regression analyses. As the association between depression and anxiety and CF is well known, HADS was not included in the multivariate analyses (Paper III).

To calculate the impact of having 0-1 versus 2, 3 or 4-5 of the variables significantly associated with CF from the multivariate analyses, a total score (The “CF risk score”) ranging from 0 to 5 was constructed. The presence of one of the five significant risk factors for CF (low testosterone levels, low physical activity, cardiac disease, neuropathy and Raynaud’s phenomenon), would give a score of 1, while having two of such risk factors would give a score of 2, etcetera. This CF risk score (variable) was then entered into logistic regression to calculate the impact from 2, 3 or 4-5 risk factors on the risk of CF compared with having only 0-1 risk factors (reference group) (Paper III).

### 4.6 Approvals

All participants provided written informed consent to participate in the studies, including permission for retrieval of relevant data from their medical records. The studies were approved by the Regional committee for Medical Research Ethics of Southern Norway and data processing performed according to the requirements of the Norwegian Data Inspectorate.
5. Main Findings

5.1 Paper I

Impact of Long-Term Serum Platinum Concentrations on Neuro- and Ototoxicity in Cisplatin-Treated Survivors of Testicular Cancer.

In this paper we measured long-term serum levels of platinum in blood samples drawn from 169 TCSs median 12 years (range 4.0- 19.0) after platinum-based chemotherapy and assessed whether these serum levels were associated with the severity of common long-term side effects after platinum-based CT.

Levels of paresthesias, Raynaud’s phenomenon and ototoxicity had previously been recorded with the SCIN at both SI and SII, with a total of 127 of the 169 TCSs from SI also completing the SCIN questionnaire at SII.

At Survey I, we demonstrated a significant four- to five-fold association between the total SCIN score and the highest compared with the lowest serum platinum quartile (OR 4.69; 95% CI, 1.82 to 12.08) (multivariate analyses). Also, paresthesias and Raynaud’s syndrome (hands and feet) had a significant two- to four-fold increased associations with the highest platinum quartile compared with the lowest quartile. Dose-intensive therapy had a significant impact on tinnitus and hearing impairment (OR, 2.63; 95% CI, 1.08 to 6.25 and OR, 4.00; 95% CI, 1.61 to 10.00, respectively). Total SCIN score (OR, 1.71; 95% CI, 1.25 to 2.32), paresthesias in the hands and feet (OR, 1.44; 95% CI, 1.06 to 1.96 and OR, 1.86; 95% CI, 1.36 to 2.54, respectively), tinnitus and hearing impairment (OR, 1.44; 95% CI, 1.05 to 1.98 and OR, 1.89; 95% CI, 1.35 to 2.64, respectively) were all significantly associated with increasing age. No significant associations between cumulative cisplatin dose and total SCIN score or individual SCIN symptoms emerged in the multivariate analyses.
At Survey II, a significant association for the total SCIN score emerged for the highest platinum quartile versus the lowest quartile (OR, 4.28; 95% CI, 1.36 to 13.48), while risks for paresthesias (hands and feet) and tinnitus were significantly three- to four-fold increased for patients in the highest platinum quartile. No significant associations were found between neither cumulative cisplatin dose nor dose intensive therapy and the total SCIN score or individual SCIN symptoms in the multivariate analyses. Age impacted on the total SCIN score with an OR per decade of 1.43 (95% CI, 1.03 to 1.99). At Survey II, paresthesias in the feet (OR, 1.44; 95% CI, 1.06 to 1.96) and hearing impairment were also significantly associated with increasing age (OR, 1.86; 95% CI, 1.36 to 2.54).

In conclusion, there was a significant association between the measured long-term serum platinum levels and overall severity of neurotoxicity and most individual symptoms of neurotoxicity after platinum-based chemotherapy, even after adjusting for cumulative platinum dose. No significant associations emerged between the cumulative cisplatin dose and severity of total neurotoxicity or individual symptoms in the SCIN. However, having received dose-intensive therapy impacted significantly on both hearing and tinnitus at SI.

### 5.2 Paper II

**Longitudinal serum testosterone, LH and FSH levels in a population-based sample of long-term testicular cancer survivors.**

This paper describes longitudinal sex hormone serum levels (testosterone, LH and FSH) in TCSs measured at three time points: 1) After orchiectomy, but prior to subsequent management with either observation/S, RT or CT, 2) At SI, median 12 years after treatment, 3) At SII, median 18 years after treatment.

In this paper we document that the risk of lower testosterone and higher LH and FSH levels was significantly increased for TCSs compared with controls at all time points after RT.
and CT. Importantly, as many as 50% of the TCSs had at least one of the three hormones measured outside the reference range at a median of 18 years after treatment.

To calculate the impact of the cumulative platinum dose, this variable was entered as continuous into OLR. The cumulative platinum dose was not significantly associated with testosterone at SI or SII, or with FSH at SII, but a significant association emerged for LH at SI and SII and FSH at SI. For each cycle of platinum-based CT, the risk of having a higher LH level increased with ORs of 1.3 (95% CI, 1.0 to 1.6) at SI and 1.4 (95% CI, 1.1 to 1.8) at SII. For FSH at SI, the OR was 1.5 (95% CI, 1.0 to 2.0).

When adjusted for age and compared with controls, we documented an accelerated hormonal ageing in TCSs.

In conclusion, after adjusting for age, the risk of having lower testosterone and higher LH and FSH levels was increased for TCSs when compared with controls at all time points for all treatment groups reaching statistical significance for all hormones except for LH at SI after surgery only. TCSs were found to have an accelerated hormonal ageing when compared to controls.

5.3 Paper III

Chronic Fatigue in 812 testicular cancer survivors during long-term follow up: increasing prevalence and risk factors.

This paper describes the course of CF in 812 TCSs and the relationship between CF and testosterone, LH, age, treatment, long-term toxicities and comorbidity in these men.

In total 164 males (20%) were treated by S alone (orchiectomy (77) or orchiectomy and RPLND (87)), while 343 men (42%) received RT and 305 (38%) received CT after orchiectomy. In the CT group 32 males also received RT.
Serum levels of testosterone and LH were recorded at two time points, at SI and SII, median 12 and 19 years after treatment, respectively. In addition to serum hormone analyses, the TCSs also responded to questionnaires addressing comorbidities, medication, tobacco use, and educational and marital status. The FQ, HADS and SCIN were part of the questionnaires at both surveys.

In paper III we found that the prevalence of self-reported CF in TCSs increased with time from 15% at SI to 27% at SII. This increase was higher than for the general Norwegian male population previously reported by Loge et al, who found a prevalence of 10% in a cross-sectional study of the general male population with only a slight increase with age.\textsuperscript{110} Two thirds of those reporting CF at SI also reported CF at SII, and these TCSs had significantly higher mean score at SII for total fatigue (21.0, p=0.005) and HADS-A (7.4, p=0.012), than TCSs only having CF at SII. CF at SII was significantly associated with lower quartiles of testosterone, cardiac disease, physical inactivity, neuropathy and Raynaud’s’ phenomenon. There was a stepwise increase in the risk of CF with increasing levels of neuropathy (OR 5.1, 95%CI; 2.7- 9.9) for the highest level compared with no neuropathy. CF was not significantly associated with level of education, smoking, diabetes, pulmonary disease, age, or treatment.

To calculate the impact of having an increasing number of factors influencing on CF, we composed the “CF risk score” ranging from 0 to 5, comprising the five items significantly associated with CF in the multivariate analyses. A total of 233 (29%), 249 (31%), 216 (27%), and 94 (12%) men had 0-1, 2, 3, and 4-5 risk factors, respectively. In the analysis of the “CF risk score” at SII, the presence of 2 risk factors conferred a significantly increased OR of 3.4 (95%CI; 2.0- 5.7) compared with 0- 1 risk factors (reference). Presence of 3 or 4- 5 risk factors increased the OR for CF to 6.1 (3.6- 10.3) and 12.0 (95%CI; 6.5- 21.9), respectively.

In conclusion, prevalence of CF in TCSs continues to increase with time after treatment, and much more than one would expect after time alone. There seems to be a
considerable impact on CF from long-term adverse effects like hypogonadism, neurotoxicity, and comorbidity.

6. Discussion

6.1 Methodological Considerations

6.1.1 General aspects

Findings in this thesis are based on data from two population-based follow-up studies performed on TCSs. Treatment was administered several years before the studies were performed (range 4-28). The study design was retrospective, with details regarding treatment (exposure) and outcome variables collected simultaneously like most other studies on late effects. This thesis report on late effects related to standard treatment strategies in 1980-1994. Although therapy has been modified since 1994 the principle treatment with 3-4 cycles of BEP for metastatic TC with subsequent removal of remaining non-seminomatous lesions (for some) is still valid, such that these findings are of interest for “today’s patients and oncologists”.

Due to the removal of one testicle in TCSs, and also the hypothesis of a dysfunction in the remaining testis, hormone levels might be better assessed by comparing sex hormone levels of TCSs with those of men with a single testis due to other reasons (trauma etc.). However, to assemble a group large enough to be representative of males who have lost one testicle due to non-cancer reasons proved not feasible in Norway. Consequently, the control group in our study consists of healthy men, and to the best of our knowledge, with both testicles in place.
6.1.2 Selection bias

Any inaccuracy in the recruitment of study participants and/or factors influencing study participation may lead to selection bias. This type of systematic error occurs when the association between exposure and outcome differs between those who were included in the study (responders) and those who did not participate in the study (non-responders).

Both surveys described in this thesis recruited unselected TCSs. All eligible Norwegian men (Chapter 4.1) were invited to the studies, with an overall 81% participation rate in the first follow-up, and 80% participation at SII. The high participation rates support the validity of our findings. Lost to follow-up bias was close to zero. Non-responders did not differ from the responders with regard to age at follow-up, stage, histology or treatment based on the information on from their medical charts from the time of treatment, minimizing the risk of greater impact on the validity of these studies by selection bias (own analyses).

Paper I included only previous NRH patients as this was the only hospital storing frozen samples at SI and SII. Only TCSs with previous platinum-based CT and complete SCIN was included (238 TCSs), however, as blood samples had been used in prior research projects, sufficient material remained for only 169 previously cisplatin-exposed TCSs, rendering this a possible selection bias. However, as the research projects in question also wanted to look at all CT treated TCSs, there was no selection as to which samples were left for us to analyze, but simply a question of which TCSs had any frozen serum left.

Paper II; The sample size of 307 TCSs is critically small for grouping according to prior treatment and further categorization according to decadal age and percentiles. Also, the rigorous selection of TCSs with complete hormone samples at all three time-points limited the number of eligible patients, despite high participation rates at SI and II of 81% and 80%, to roughly 50% of those with hormone samples at baseline, Figure 2. The eligible patients at each of the three time points (618 males at baseline, 470 males at SI and the 307 males at SII)
were, however, homogenous when comparing distribution of age at orchiectomy, surveys, stages, and type of treatment (Table 4).

Table 4. Characteristics of males with hormone samples available at different time points, Paper II.

<table>
<thead>
<tr>
<th></th>
<th>Baseline N=616*</th>
<th>Survey I N=470*</th>
<th>Survey II N=307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>31 (16-65)</td>
<td>32 (16-65)</td>
<td>32 (16-64)</td>
</tr>
<tr>
<td>Age at Survey I, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>42 (22-75)</td>
<td>42 (23-75)</td>
<td>42 (23-73)</td>
</tr>
<tr>
<td>Age at Survey II, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>50 (31-85)</td>
<td>50 (31-84)</td>
<td>50 (31-81)</td>
</tr>
<tr>
<td>Royal Marsden stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>463 (75.2)</td>
<td>357 (76.0)</td>
<td>233 (75.9)</td>
</tr>
<tr>
<td>Stage IM</td>
<td>5 (0.8)</td>
<td>4 (0.9)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Stage II</td>
<td>100 (16.2)</td>
<td>76 (16.2)</td>
<td>53 (17.3)</td>
</tr>
<tr>
<td>Stage III</td>
<td>14 (2.3)</td>
<td>9 (2.0)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>34 (5.5)</td>
<td>24 (5.1)</td>
<td>16 (5.2)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>315 (51)</td>
<td>241 (51)</td>
<td>153 (50)</td>
</tr>
<tr>
<td>Non-seminoma</td>
<td>301 (49)</td>
<td>229 (49)</td>
<td>154 (50)</td>
</tr>
<tr>
<td>Treatment group, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>130 (21)</td>
<td>99 (21)</td>
<td>69 (22)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>265 (43)</td>
<td>206 (44)</td>
<td>130 (42)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>221 (36)</td>
<td>165 (35)</td>
<td>108 (35)</td>
</tr>
</tbody>
</table>

*Age for the 616 men at SI and SII and 470 men at SII was calculated from the median date for SI and SII for those included in the study (307).

6.1.3 Information bias

Information bias may occur if measurement or classification of information obtained from or about study participants is incorrect.\textsuperscript{157}

Misclassification of symptoms with regards to the SCIN, HADS and FQ may occur. Further, one could argue that reliance on self-report without objective measurements represent
a serious limitation, with the risk of both over- and under-reporting in paper I and III. However, ototoxicity as measured by SCIN was previously validated in these patients by comparing self-reported hearing problems with findings from the audiogram, showing a high correlation between the self-reported hearing impairment and the audiogram. The FQ has been found to be both reliable and valid with a high degree of internal consistency in a previous study.\textsuperscript{150}

Misclassification could also occur when retrieving the subjects’ treatment parameters. However, as their treatment was recorded in detail, and thereby by a number of variables, any systematic error in this respect is not considered likely.

Under-reporting of testosterone substitution in SI and SII, may represent a misclassification bias in paper II and III as a handful of subjects failed to report substitution of testosterone even though medical charts confirmed that they received testosterone therapy regularly. Substituted males were identified by self-report or information from the medical records and removed from all analyses in Paper II and Paper III. Due to the fact that some failed to report substitution of testosterone, and not all medical charts documented complete follow up to the date of SII, we cannot rule out the possibility of some males receiving this treatment from their primary care physician. However, as substitution therapy is preferably left to the specialists in this field, the probability of a bias due to this is considered small.

Blood samples should be collected at the same time of the day for all participants and according to laboratory procedures, preferably between 0800 and 0900 due to the diurnal variation of testosterone. Most TCSs had their blood samples drawn before 1100 a.m., when the testosterone levels are highest.\textsuperscript{158} Measurements of sex steroids may vary between laboratories, thus posing a possible information bias, however, in general, the total variability of testosterone is considered to be within acceptable limits.
6.1.4 Confounding

Confounding can be explained as a mixing, or confusion of effects which may occur if the estimated association between the exposure variable and outcome variable is interfered by one or several other variables. Confounding may be adjusted for in multivariable analyses. The prevalence of hypogonadism and CF both increase with age, and as there were differences in age between our treatment groups, age is a possible confounder of our results. Consequently, the multivariate analyses in Paper II and III were adjusted for age.

A history of previous noise exposure might be a confounder for ototoxicity. However, this factor was not likely to interfere with the administered treatment or platinum levels, which were the key variables explored in Paper I.

6.1.5 Internal and external validity

The internal validity reflects to which extent the findings are associated with the effects that are studied in the actual/specific study population or whether they can be a product of selection bias, information bias or confounding. Comparison of responders and non-responders in the papers showed negligible differences between groups (own analyses, not shown), and with low possibility for systematic errors as discussed above. We thus regard the internal validity of the surveys to be satisfactory.

External validity stands for the extent the results of a study can be generalized to the general population. Our papers were based on the results from two population-based studies with the subjects identified through the Norwegian Cancer Registry and the Regional Hospitals. The completeness of identifying all TCSs is considered high. Further, the studies had high response rates of roughly 80% at both surveys. Treatments applied during the period 1980-1994 adhered to research trials or international guidelines, with only minor variations within hospitals, and external validity is considered to be representative for this time period.
Importantly, generalization to TCSs of today must be done with caution, as treatment modifications introduced since the time period studied, represent a less toxic treatment for TCSs in general. The typical retrospective design of long-term research represent a challenge as researchers will continuously search for better therapy or reduced toxicity, consequently leaving cancer treatment perpetually changing. As a result, most research on long-term effects will represent conclusions representative for those treated similarly during the same time period, while these conclusions may not be fully representative for subsequent cancer survivors. Nevertheless, careful extrapolation of such results may provide guidance on the early prevention of adverse events, treatment of adverse events and the long-term follow-up of metastatic TC.

6.2 Discussion of main findings

6.2.1 Introduction

This thesis is based on two population-based studies, designed to cover physical, psychosocial, biochemical health issues, and quality of life in TCSs. The aim of this thesis was to 1) evaluate the relationship between long-term serum levels of platinum and neurotoxicity, 2) describe longitudinal changes in testosterone, LH and FSH and the hormonal ageing process in TCSs, 3) describe the longitudinal course of fatigue and 4) explore which factors impacted on the prevalence of fatigue. Except from biochemical samples of sex hormones and serum-platinum, our results were based on the completed questionnaires of TCSs and data on treatment retrieved from their medical journals. Our overall objective was to assess the prevalence, degree, and pathogenesis of long-term complications in TCSs. Hopefully, these results may lead to better ways to prevent or manage the long-term toxicity from cancer treatment in future patients.
The findings in paper I-III are based on a study population treated according to international guidelines during the time period 1980-1994. Although several modifications have been introduced since this time, the main treatment principles are relatively unchanged for those with metastatic disease.

6.2.2 Long-Term retention of Serum Platinum Concentrations and Neuro- and Ototoxicity (Paper I)

In this paper (Paper I), long-term total serum platinum levels in TCSs were measured from serum samples collected median 12 years after treatment. To the best of our knowledge, this is the first study documenting elevated long-term serum platinum levels to be significantly associated with the severity of neurotoxicity 5 to 20 years after platinum-based chemotherapy. Importantly, this relationship remained significant after adjustment for initial cisplatin dose.

In accordance with prior studies, we could demonstrate a significant relationship between initial dose and platinum levels and an inverse relationship between time since administration and platinum levels.\textsuperscript{69,143,159} Unlike Gietema et al, who demonstrated that long-term platinum levels in cisplatin-treated TCSs were significantly higher than for cisplatin-naive patients, we did not compare our TCSs with a group of unexposed TCSs, which may be considered a weakness. Brouwers concluded that approximately 10% of the reactivity of the platinum species was retained median 41 months after cisplatin-based therapy.\textsuperscript{69} As such analyses would require more serum than we had available for the 169 TCSs, this was not feasible in our study.

At the ASCO meeting 2014, Hjelle et al presented data on a subgroup from the Norwegian population-based study described in this thesis.\textsuperscript{160} They performed measurements on serum platinum at a median of 20 years after treatment in 292 platinum-treated TCSs. Confirming our findings, they could report an association between the highest serum platinum
levels and the severity of neurotoxicity. Further, they also documented an association between the highest levels of platinum and the most elevated levels of LH, but not for testosterone. No significant association emerged between serum platinum levels and CVD.

Brouwers et al assessed neuropathy up to 6 years after treatment with cisplatin (n=20) or oxaliplatin (n=25).\textsuperscript{161} Neuropathy was assessed by questionnaire, neurological tests, and vibration threshold measurements. In accordance with our findings, severity of neuropathy was related to cumulative cisplatin dose. Unlike our study, no significant relationship between neuropathy and long-term platinum levels emerged, possibly explained by limited statistical power due to a small sample size. Unlike our study of TCSs, they included a heterogeneous group of cancer survivors (TC, lung- and head and neck cancer). As cancer of the lung, head and neck generally presents at a higher age than TC, and is associated with higher comorbidity, smoking and/or alcohol, this may have confounded their analyses of determinants on persisting neuropathy. Neuropathy was transformed to a dichotomous scale (yes/no), which did not allow for OLR analyses. The inclusion rate of 54% may represent a selection bias as a potentially higher symptom burden in the non-responders may have resulted in underestimation of the neurotoxicity in this group of cancer survivors.

Dose intensive therapy impacted significantly on tinnitus and hearing impairment at SI, but not at SII. Results at Survey I concur with previous studies, describing substantial ototoxicity in men receiving dose-intensive regimen.\textsuperscript{25,49} The lack of a significant relationship at Survey II, could be due to a much greater impact from dose-intensive chemotherapy on ototoxicity shortly after chemotherapy, and that with time, other factors like age and possibly residual platinum levels impose an impact.

All 169 participants had received cisplatin-based chemotherapy and most also received either etoposide or vinblastin, both of which produce a sensory or sensorimotor polyneuropathy. Consequently, the neuropathy reported may not be cardinal features of
cisplatin alone. Although the CVB regimen traditionally has been considered to be associated with more acute neurotoxicity and Raynaud’s phenomenon than BEP, Brydøy et al in a study on 1409 TCSs from Survey I, found no statistically significant differences in any of the assessed symptoms between men exposed to etoposide (as in BEP) and those exposed to vinblastine (as in CVB). As for Raynaud’s phenomenon, it has been considered to be a common side effect after treatment with Bleomycin. However, it has also been documented that there was an increase in the incidence of Raynaud’s phenomenon after the introduction of cisplatin.

Previous data have suggested that both the incidence and severity of neurotoxicity are mainly determined by the cumulative cisplatin dose, and for ototoxicity also dose-intensive regimen. Observational case series suggest that most peripheral nervous system toxicity develops sub acutely, occurring over weeks, followed by long-term improvement with resolution or plateau. However, in our study, the highest long-term serum platinum levels were most strongly correlated with the severity of SCIN, even when adjusted for initial cisplatin dose. A possible explanation for this finding is that after the acute toxicity, mainly determined by the cumulative cisplatin dose, the persistent exposure to low-level platinum levels in neural tissue, may prevent resolution of the initial and dose-dependent toxic neuropathy, hypothetically also contributing to ongoing damage.

Importantly, Brouwers et al showed that approximately 10% of platinum remains reactive long-term. Long-term circulating platinum is believed to occur as a dissolved platinum salt in serum. Ionic platinum species and associated platinum salts are found to be biologically reactive and comparable in toxicity to cadmium, hexavalent chromium, and mercury, and even more toxic than nickel. Ionic platinum acts as a strong oxidizing agent disturbing cellular equilibrium, replacing essential trace metals in protein reactions and interferes with the functional groups of biomolecules, including proteins, enzymes, DNA, and
An in vitro study on the effects of exposure to ionic platinum and platinum salts on human bronchial epithelial cells, yielded dose-dependent, deleterious effects on cell viability and the generation of reactive oxygen species. Whether these intracellular concentrations are comparable to serum platinum remains unclear, but platinum concentrations as low as 100 nmol/L produce a ~150% increase in the reactive oxygen species. By comparison, the serum platinum of our patients 5-20 years after treatment ranged between 0.031-12.710 nmol/L.

Unfortunately, serum platinum levels were available for Survey I only, precluding calculation of platinum elimination rates. Also, our findings and conclusions would be stronger if the time course of symptom measurement and the measurement of platinum levels were performed in a matched fashion at both surveys. However, serum samples from one time point was what we had available when planning the study. Our results need to be confirmed in an independent large cohort of platinum treated survivors of cancer.

Reliance on self-reported symptoms without objective measurements represents a limitation of our study. Ototoxicity as reported in the SCIN was nevertheless previously tested among a subgroup of these patients through objective measurements with good psychometric properties. Neurological tests were, however, unfortunately not performed in this study. Another study observed that, compared with self-report, prevalence of side-effects may actually be higher when measured objectively.

As cisplatin-based therapy is extensively used for several cancer diagnoses, its frequent side effects are widely described in the literature. Although many studies have been carried out with the intention to explain the mechanisms involved in platinum-induced neuropathy, they have so far not been fully elucidated. Platinum agents seem to target a variety of structures and functions in the peripheral nervous system. The dorsal root ganglion appears to be the primary site at which neural damage occurs. For cisplatin, it was shown that
platinum was retained in the dorsal root ganglia of patients who were analyzed post mortem.\textsuperscript{61} The fact that platinum is retained in tissues and circulation long-term after chemotherapy, has also been described in several papers.\textsuperscript{143} During the last two decades, reports of circulating elevated long-term levels of partly reactive platinum have concurred with several reports of long-term, toxicity in TCSs like secondary cancer, increased risk of CVD, MetS, hypogonadism, neurotoxicity etcetera.\textsuperscript{69,91,120,135,143,166} As a consequence, an expert consensus recommended further characterization of long-term serum levels of platinum and its correlation with late effects after TC treatment a priority research item.\textsuperscript{167}

While the SCIN may reflect neurotoxicity in general, we did unfortunately not have any baseline levels of these symptoms before treatment for TC, nor did we have a control group of healthy and age adjusted subjects. Consequently, it was impossible to distinguish whether the toxicity recorded in the SCIN resulted from chemotherapy-induced neurotoxicity or other neurologic conditions. To elucidate the underlying mechanisms of toxicities related to the effect of reactive platinum and to validate our findings, we emphasize the importance of further studies on the impact of residual platinum in an independent large cohort of platinum-treated cancer survivors, preferably with base line levels of a symptom score and a control group.

### 6.2.3 Longitudinal serum levels of testosterone, LH and FSH (Paper II)

In paper II, the longitudinal course of testosterone, LH and FSH in 307 TCSs was described and compared with a reference material of 599 controls.\textsuperscript{100} The risk of having lower testosterone and higher levels of LH and FSH was significantly increased for all treatment groups when compared with controls at all time points except for LH at SI for those receiving surgery only. Importantly, the fact that an increasing proportion of TCSs reached testosterone levels below the 2.5 percentile and LH and FSH levels above the 97.5 percentile for controls
at SII after age adjustment was interpreted as an accelerated hormonal ageing in TCSs. No significant differences emerged between the treatment groups, however, proportions of TCSs treated with radiotherapy and chemotherapy and displaying hormone levels in the hypogonadal range were numerically higher than for the surgery group.

As a TC diagnosis itself irrespective of administered treatment is associated with an increased risk of hypogonadism due to orchiectomy and the TDS, it is important to compare the results on hormone levels and the impact from cancer therapy with controls representing the general population.¹⁴⁴

The impact of ageing on hormone levels is also well described in the literature, and already from the age of 30 years, males can expect an annual decrease in testosterone levels of approximately 1%, with a concomitant increase in plasma levels of SHBG by approximately 1.2% annually.¹⁶⁸ The combined changes in the levels of testosterone and SHBG result in a relatively steep decline in free testosterone levels, which is what is considered the biologically active testosterone. As the “normal range” of T, LH and FSH depends on age, it should be adjusted for accordingly as recommended by Bjerner et al.¹⁰⁰

As some men presented with elevated hCG after orchiectomy, interpretation of baseline levels of LH was restricted, due to the cross reactivity between hCG and LH in the immunoassays used in the early 1980s. Also, independent of LH levels, testosterone levels were probably increased for some, due to metastatic disease at baseline. The absence of elevated hCG in the surgery group at baseline might to some extent explain the low testosterone observed in this group. Due to the potentially confounding effects of hCG on both testosterone and LH, baseline hormone levels in our study must be considered with caution. Consequently, the following discussion of findings in paper II, will mainly address findings at Survey I and Survey II.
In a study investigating the pituitary-Leydig cell axis in stage I patients treated by orchiectomy only, all hCG-negative patients had T levels within the normal range at baseline and one year after orchiectomy. Bandak et al could demonstrate a significant increase in LH between baseline and follow-up with a growing proportion of TCSs outside the 97.5 percentile in a bivariate LH/T chart suggesting subtle disturbances of the pituitary-Leydig cell axis already present at the time of diagnosis. Comparison of our baseline samples with the findings of Bandak et al, pose limitations, however, due to the potentially confounding effects of hCG on testosterone and LH in our data set, and the much longer time span between baseline and the first follow-up. Nevertheless, in concordance with Bandak et al, we conclude that TCSs carry an increased risk of developing primary hypogonadism rendering LH measurements clinically meaningful.

Our data suggested an isolated correlation of the cisplatin dose with LH elevation, but not for lowered testosterone levels, however, increased LH levels may be interpreted as limited Leydig cell capacity, predicting subsequently declining testosterone levels. Even if we could not demonstrate a significant relationship with the cumulative dose of platinum based therapy and testosterone levels, risk for lower testosterone levels in the chemotherapy group was significantly increased compared with the surgery group at SII, with ORs 5.2 (95%CI; 3.5-7.9) and 2.0 (95%CI; 1.3-3.2) in the groups respectively, (p-value 0.004). Further, the proportion of TCSs in the lower quartile of the normal range for testosterone was higher for males with platinum-based doses above median (760 mg/m2) when compared with those with doses below median at SII, suggesting a trend towards an association between cisplatin dose and declining testosterone levels, in accordance with previous findings.102
The TCS’s levels of testosterone were allocated to one of 4 groups derived from cut-off values of 25-, 50- and 75 percentiles from healthy controls for each decadal age group.

Associations between serious long-term effects like MetS, CVD and decreased testosterone levels has previously been reported in TCSs. So far, there is no evidence that testosterone substitution improves the metabolic profile or prevents CVD in these hypogonadal cancer survivors. To the best of our knowledge, no proof exists that substitution of T induces prostate cancer, although a meta-analysis of adverse events associated with T substitution in randomized trials in middle-aged and older men, found rates of prostate events (prostate cancer, PSA levels > 4 ng/ml or PSA increment ≥ 1.5 ng/ml during treatment, prostate biopsies and increases in International Prostate Symptom Score) to be numerically, although
not significantly higher among substituted men compared with placebo. Hematocrit levels were more than 50%, in four times as many of the substituted men, suggesting increased risk of thromboembolic complications. Although there are few evidence-based recommendations for testosterone substitution in young men; most clinicians agree that hypogonadism in TCSs should be treated, at least for those with consistently low testosterone levels and clinical symptoms of hypogonadism. The high prevalence of hypogonadism in this cohort underlines the importance of prolonged follow-up of TCSs, including assessment of risk factors of CVD, MetS, lifestyle factors, and hypogonadism.

### 6.2.4 Chronic Fatigue in 812 testicular cancer survivors during long-term follow up: increasing prevalence and risk factors (Paper III)

In this paper (Paper III), we could document an increasing prevalence of CF in TCSs from 15% after 12 years follow-up to 27% 19 years after treatment. Two thirds of those with CF at SI also had CF at SII. The total fatigue score and anxiety levels were significantly higher in those with CF at both surveys compared with those only having CF at SII. At SII, inactivity, cardiac disease, testosterone levels, increasing levels of neuropathy and Raynaud’s phenomenon were all significantly associated with CF in the multivariate analysis.

On the background of a 10% prevalence of CF in the Norwegian general male population, who only express a slight increase with age, the increase from 15% to 27% in TCSs is remarkable, and has to our knowledge not been reported before. The prevalence at SII is comparable with what is found in many studies on lymphoma survivors, and consistent with these findings, there is a lack of significant associations between CF and type of treatment. Importantly, we could demonstrate a significant association between several treatment-related toxicities and also self-reported comorbidity, which is also in accordance with the majority of studies on CF in cancer survivors.170-173
We found testosterone levels to be significantly associated with CF at SII. This contrasts with the report from Huddart et al, who found no significant relationship between testosterone and fatigue in TCSs. This inconsistency might possibly be due to their shorter follow-up time of median 10 years. The varying results might also be explained by different categorizations of testosterone in the two studies (levels below 10 nmol/l versus ordinal categorization according to quartile thresholds for decadal age groups). Importantly, we do not imply the implementation of testosterone substitution to treat chronic fatigued in general, but rather that high testosterone levels are associated with the absence of CF. However, as testosterone replacement in a study of severely hypogonadal males yielded increased energy levels, one may consider such treatment in fatigued TCSs with repeatedly low testosterone levels.

For the physically inactive men, the risk of CF was increased 2.7-fold, however, it was also slightly increased for those moderately active when compared with the highly active at SII. It is still not clear whether CF give rise to inactivity, and/or inactivity contributes to the development of fatigue. However, several meta-analyses, systematic reviews, and randomized trials conclude that fatigue after cancer treatment may be reduced by initiating or maintaining adequate levels of physical activity. Importantly, before intervening through physical activity programs it is advised that all contributing factors (e.g. medical and substance-induced) should be assessed and treated in cancer survivors with moderate to severe fatigue.

For TCSs suffering from several of the “risk factors” identified for CF, we observed significant differences between TCSs having 0-1 versus 2, 3 or 4-5 of the risk factors. Joly et al reported that cases with high levels of chronic fatigue had low scores on the functional scale and high levels of symptoms (pain, dyspnea, sleep disturbance) in addition to lower incomes and more changes in their sex lives (mostly due to impairment of fertility). These
observations demonstrate that fatigue is complex, including social, psychological, physical, and biologic dimensions. We suggest that while many TCSs may manage to cope with the stress induced by one such risk factor, the effects of having 2 or more of these factors in addition to ageing itself, become increasingly difficult to compensate.

7. Conclusions and implications for future research

In paper I we described increased platinum levels in TCSs at a median of 12 years after chemotherapy. Further, we documented an association with elevated long-term serum levels of platinum in TCSs and the severity of neurotoxicity many years after platinum-based therapy. Whether chronically raised and circulating serum platinum levels in TCSs increase other toxicities than reported in paper I, like the more life threatening toxicities like CVD and secondary malignancies is not known. Further studies are needed to define the role of platinum retention in the late sequelae of cancer treatment, and to find possible ways to circumvent these effects. In order to achieve these aims, prospective collection of larger sample volumes to determine the pharmacologically and toxicologically active species of platinum should be performed. Detoxification approaches to help speed up the platinum elimination process might be considered, especially if our findings are confirmed in an independent large cohort of TCSs, as this might hypothetically not only reduce neurotoxicity long-term, but even the more serious long-term effects like CVD and second cancers in TCSs.

In paper II, we concluded that TCSs are at risk of an accelerated and premature hormonal ageing. Median 18 years after treatment, as many as 50% of the TCSs had levels of at least one of three sex hormones studied outside the reference range, consequently at risk of developing hypogonadism. These findings underline the importance of life-long follow-up of these men, as implemented systematically for TCSs treated in Sweden and Norway. At cessation of their follow-up at the hospital, both TCSs and their general practitioner now
receive written information of the most common long-term adverse effects after TC treatment in addition to general advice regarding further follow-up. Due to the loss of one testicle and TDS, TCSs are particularly prone to the development of hypogonadism. Nevertheless, according to our results, treatment with RT and CT also impacted on the accelerated and premature hormonal ageing reported in paper II. Consequently our findings may apply for cancer patients in general, and be of particular interest in future long-term studies on survivors of childhood and adolescent cancer as many of them may live for decades after treatment.

In paper III we reported a substantial increase in the prevalence of CF from 15% median 12 years after treatment to 27% median 19 years after treatment. Moreover, the demonstrated association between CF and comorbidities like hypogonadism, cardiac disease and neurotoxicity, all well described side-effects after treatment for TC, as well as physical inactivity, may suggest that early intervention through life style interventions and early detection, treatment and follow-up of comorbid conditions can reduce the risk of CF.

In conclusion, our data underline the importance of continued long-term assessments of TCSs beyond the standard follow-up time of 10 years.
8. REFERENCES


13. Skakkebæk NE, Rajpert-De Meyts E, Main KM: Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 16:972-978, 2001
16. Ioachim HL, Medeiros LJ: Ioachim's Lymph Node Pathology, in, Lippincott, Williams & Wilkins., 2009


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APPENDIX 1

Questionnaire Survey I – 1998 - 2002
Etterundersøkelse av pasienter behandlet for testikkelkreft

Vi ber deg om å fylle ut dette spørreskjemaet så godt du kan, enten ved å krysse av eller sette ring rundt det svaret som passer, eller ved å skrive ned dine kommentarer. Alle svar behandles konfidensielt.

Dato for utfylling: ____________________________

Navn: ____________________________

Født: ____________________________

Høyde: ___________ cm Vekt: ___________ kg

Blodtrykk (hvis kjent): ____________________________

Sosial og økonomisk situasjon

**Sivil status**

1. Hva er din nåværende sivilstatus? (Sett ring rundt det svaret som passer.)
   a. Aldri vært gift 1
   b. Gift 2
   c. Samboene 3
   d. Enkemann 4
   e. Separert 5
   f. Skilt 6

2. Har ditt partnerforhold forandret seg etter at du ble behandlet for testikkelkreft? (Sett kryss ved det svaret som passer. Flere svaralternativer er mulig.)
   Jeg er blitt gift 1
   Jeg er blitt separert 2
   Jeg er blitt skilt 3
   Jeg er blitt enkemann 4
   Jeg har startet en nytt fast forhold 5
   Jeg har avsluttet et fast forhold 6
   Ingen forandring av partnerforholdet 7

3. Tror du at diagnosen og behandlingen for testikkelkreft har hatt innflytelse på ditt nåværende forhold til partneren din? 1
   Hvis «ja», på hvilken måte? ____________________________

**Bøforhold**

4. Hjem bor du sammen med? (Sett ett kryss for hver linje, og oppgi hvor mange du bor sammen med.)
   Ektefelle/samboer 1
   Andre personer over 18 år 2
   Personer under 18 år 3

ARBEID/UTDANNING

5. Hvilken utdanning er den høyeste du har fullført?
   a. Grunnskole-7-10 år, framhaldskole, folkehøgskole 1
   b. Realskole, middelskole, yrkesskole, 1-2 årig videregående skole 2
   c. Artium, økonomisk gymnas, allmennfaglig retning 3
      i videregående skole 4
   d. Høgskole/universitet, mindre enn 4 år 4
   e. Høgskole/universitet, 4 år eller mer 5

6. Hva er din nåværende arbeidssituasjon? (Sett ring rundt det svaret som passer.)
   a. Arbeidsledig/permittert 1
   b. Ikke i stand til å arbeide 2
      a) sykemeldt 2
      b) attføring 3
      c) utførettrygdet 4
   c. Delvis i arbeid 5
   d. I fullt arbeid 6
   e. Alderspensjonist 7
   f. Student/skoleeleve 8

Hvis du for tiden ikke har innfølgende arbeid eller du ikke har heltids husarbeid: Gå til spørsmål nr. 11.

7. Har du i løpet av de siste 12 månedene hatt syk- fravær:
   a. med egenmelding? 1
   b. med sykemelding fra lege? 2

8. Hvis «ja»; hvor lenge til sammen?
   a. 2 uker 1
   b. 2-8 uker 2
   c. Mer enn 8 uker 3
       eller mindre

9. Er arbeidet ditt så fysisk anstrengende at du ofte
   er sliten i kroppen etter en arbeidsdag?
   a. Ja, nesten alltid 4
   b. Ganske sjelden 5
   c. Aldri, eller nesten aldri 6

10. Krever arbeidet ditt så mye konsentrasjon og
    oppmerksomhet at du ofte føler deg utsatt etter
    en arbeidsdag?
    a. Ja, nesten alltid 4
    b. Ganske sjelden 5
    c. Aldri, eller nesten aldri 6

11. Tror du diagnosen og behandlingen av testikkel-
    kreft har hatt negativ innflytelse på din nåværende
    arbeids situasjon/utdannings situasjon?
    a. Ja 1
    b. Nei 2

Hvis «ja», på hvilken måte? ____________________________


Vennligst angi de organisasjoner/institusjoner som har vært involvert i vanskelighetene, og beskriv hva problemene bestod i:

a) Arbeid: 

b) Forsikring: 

c) Lån: 

d) Andre forhold: 

**ØKONOMI**

13. Mottar du noen av følgende offentlige ytelsel?  

<table>
<thead>
<tr>
<th>Ytelse</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sykepenger/sykelsønn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehabiliteringspenger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ytelse under yrkesrettet atføring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uførepensjon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alderspensjon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sosialstøtte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arbeidsledighetstrygd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overgangsstønad</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etterlattepensjon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre ytelser</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14. Har det i løpet av det siste året hendt at utholdningen har hatt vansker med å klare de løpende utgifter til mat, transport, bolig og liknende?  

<table>
<thead>
<tr>
<th>Bedriftstilstand</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ja, ofte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ja, av og til</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**VENNER**

15. Hvor mange gode venner har du?  

(Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det. Tell ikke med de du bor sammen med, men regn med andre slektninger.)

Antall: 

16. Føler du at du har mange nok gode venner?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

17. Hvor ofte tar du vanligvis del i foreningsvirksomhet, som f.eks. idrettslag, politiske lag, religiøse møter eller andre foreninger?  

<table>
<thead>
<tr>
<th>Foreningsvirksomhet</th>
<th>Aldri, eller noen få ganger i året</th>
<th>1-2 ganger i måneden</th>
<th>Omtrent en gang i uken</th>
<th>Mer enn en gang i uken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldri, eller noen</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>få ganger i året</td>
<td>1-2 ganger i måneden</td>
<td>Omtrent en gang i uken</td>
<td>Mer enn en gang i uken</td>
<td></td>
</tr>
</tbody>
</table>

**Generell helsetilstand/livsstil**

18. Har du fått en annen kreftdiagnose etter din testikkelfkreft-behandling?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krass av for det svaret som passer og angii mund./år for diagnose.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hvis «ja», angi type og tidspunkt:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

19. Har du hatt noen andre alvorlige sykdommer/operasjoner?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvis «ja», angi type og tidspunkt:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

20. Har noen i din familie fått testikkelfkreft eller en annen form for kreft?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hvis «ja», angi type, slektforhold, eventuelt navn, krefttype og sykehus (f.eks.: Morbror Peder Ås, magekreftoperert i 1997 på Aker Sykehus):</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FØR/ETTER BEHANDLING FOR TESTIKKELKREFT**

21. Brukte du noen ganger nervermedisiner før du fikk behandling for testikkelfkreft?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

22. Har du noen gang brukt nerve- medisiner etter behandlingen for testikkelfkreft?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

23. Brukte du noen gang narkotika før du fikk behandling for testikkelfkreft?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

24. Har du noen gang brukt narkotika etter behandlingen for testikkelfkreft?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

25. Oppskøkte du noen gang en psykolog/psykiater før du fikk behandling for testikkelfkreft?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

26. Har du noen gang oppsøkt en psykolog/psykiater etter behandlingen for testikkelfkreft?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

27. Har du noen gang tenkt på/ forsøkt selvmord?  

<table>
<thead>
<tr>
<th></th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
</table>

**ALKOHOLBRUK**

28. Hvor ofte er du beruset flere dager i strek på grunn av alkohol? (Sett ring rundt det svaret som passer best.)

|   | Aldri | Sjøldnere enn månedlig | Noen ganger i måneden | Noen ganger i uken | Daglig eller nesten daglig |
|   | 1    | 2                      | 3                     | 4                  | 5                      |

2
29. Hvor ofte hopper du over måltider på grunn av alkohol?
   Aldri 1
   Sjeldnere enn månedlig 2
   Noen ganger i måneden 3
   Noen ganger i uken 4
   Daglig eller nesten daglig 5

30. Hvor ofte har du blitt mer vennlig og omgjenge-
lig etter å ha drukket siste år?
   Aldri 1
   Sjeldnere enn månedlig 2
   Noen ganger i måneden 3
   Noen ganger i uken 4
   Daglig eller nesten daglig 5

31. Hvor ofte trenger du en drink om morgenen etter å ha drukket kvelden før?
   Aldri 1
   Sjeldnere enn månedlig 2
   Noen ganger i måneden 3
   Noen ganger i uken 4
   Daglig eller nesten daglig 5

ROYKING
32. Røyker du
   Ja 1
   Nei 2
   - sigaretter til daglig? 1
   - sigarer/sigarillos til daglig? 1
   - pipe til daglig? 1
   - kun til fest? 1
   Aldri røykt daglig (Sett kryss) 2

33. Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? Antall år: __________

34. Hvis du røyker daglig nå eller har røykt tidligere; hvor mange sigaretter røyker eller røykte du vanligvis daglig? Antall sigareter: __________

35. Hvor gammel var du da du begynte å røyke daglig? Alder: __________ år

36. Hvor mange år til sammen har du røykt daglig? Antall år: __________

SYKDOM/PLAGER
I noen av de følgende spørsmål ber vi deg oppgi alderen din da eventuelt sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt. Kryss av for det svaret som passer, og sett kun ett kryss.

37. Har du, eller har du hatt:
   Ja 1
   Nei 2
   Alder første gang
   Hjerteinfarkt
   Angina pectoris (hjertekrampe)
   Hjerneslag/hjernebloeding
   Diabetes (sukkersykje)

38. Hva ble resultatet siste gang du måtte blodtrykket ditt?
   Begynne med/fortsette med blodtrykksmedisin 1
   Komme til kontroll, men ikke ta blodtrykksmedisin 1
   Ingen kontrol og ingen medisin nødvendig 1
   Aldri fått målt blodtrykket 1

39. Har legen din noen gang sagt at du har/har hatt noen av disse sykdommene?
   Ja 1
   Nei 2
   Beinskjøtethet (ostoporose) 1
   Fibromyalgi (fibrosis/kronisisk smertesyringdom) 1
   Leddgifkt (reumatoid artritt) 1
   Slitasje-miglet (artrose) 1
   Bechterews sykdom 1
   Andre langvarige skjelett- eller muskelsykdommer 1

40. Har du eller har du hatt smertens eller kranper i bena som begynner deg når du går eller som gjør at du våkner om natten?
   Ja 1
   Nei 2
   Hvis «ja», angi når smertene/krampen begynte:

41. I hvilken grad har du hatt disse plagene det siste året?
   Ikke plaget 1
   Litt plaget 2
   Mye plaget 3
   Kvalme 1
   Brystbrann/ sure oppusset 1
   Diaré 1
   Treg mage 1
   Hjertebank 1
   Åndenød 1

42. Har du i løpet av det siste året vært plaget med smerters og/eller stivhet i muskler og ledd som har vært i minst 3 måneder sammenhengende?
   Ja 1
   Nei 2
   Hvis «nei», gå videre til spørsmål nr. 45. Hvis «ja», svar på følgende:

43. Hvor har du hatt disse plagene?
   Ja 1
   Nei 2
   Nakke 1
   Skuldrer (aksler) 1
   Albufer 1
   Håndled, hender 1
   Bryst/mage 1
   Øvre del av rygg 1
   Korsrygg 1
   Hooter 1
   Kneer 1
   Anklar / Titter 1

(Hvis du har hatt plager i flere områder i minst 3 måneder det siste året, sett ring rundt det ja-krysset hvor plagene har vært lengst.)
44. Har plagene redusert din arbeidsevne det siste året? (Gjelder også hjemmearbeidinge.)
☐ Nei/unbeteglig   ☐ I betydelig grad
☐ I noen grad    ☐ Vet ikke

45. Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ☐ Ja  ☐ Nei
(Langvarig = Minst ett år)

Hvis «nei», gå til spørsmålet nr. 47.

46. Hvis «ja»; hvor mye vil du si at dine funksjoner er nedsett?

Litt nedsatt  Middels nedsatt  Mye nedsatt
Er bevegelseshemmet    1  2  3
Har nedsatt syn        1  2  3
Har nedsatt hørsel      1  2  3
Hemmet pga. kropplig sykdom  1  2  3
Hemmet pga. psykiske plager  1  2  3
Andre plager, beskriv:

47. Har du i deler av det siste året brukt noen medisiner daglig eller nesten daglig?
☐ Ja  ☐ Nei

48. Hvis «ja»; angi hvor mange måneder du brukte følgende medisiner/kosttilskudd. (Sett 0 hvis du ikke har brukt medisinene.)

Smertestillende  Antall måneder
Sovemedisin
Beroligende medisin
Medisin mot depresjon
Allergimedisin
Asthamedisin
Hjertemedisin
Blodtrykksmedisin
Jernetabletter
Vitamintilskudd
Tran/fiskeoljer
Annem medisin, spesifiser navn og antall måneder:

49. Hvor ofte har du brukt avslappende/beroligende medisiner eller sovemedisiner den siste måneden?
☐ Daglig  4  ☐ Sjeldnere enn hver uke  3
☐ Hver uke, men ikke hver dag  2
☐ Aldri  1

50. Har du i løpet av de siste 12 månedene vært hos: (Sett et kryss for hver linje.)
Ja  ☐ Nei
Allmennpraktiserende lege  1  2
Kommunelege, privatpraktiserende lege, turnuskandidat  1  2
Bedriftslege  1  2
Lege ved sykehus (uten innleggsle)  1  2
Annen lege  1  2
Fysioterapeut  1  2
Kiropraktor  1  2
Homöopath  1  2
Annen behandler (naturmedisiner, fotsoneterapeut, håndspåleger, «healer», «synsk» e.l.)  1  2

51. Har du vært innlagt på sykehus de siste 5 årene?
☐ Ja  ☐ Nei
Hvis «ja», venligst spesifiser hvilke sykehus (utenom RiTø) og hvorfor du var innlagt?

52. Hvordan har din fysiske aktivitet i fritida vært det siste året? (Tenk deg et ukentlig gjennomsnitt for året. Arbeidsevne regnes som fritid.)
Ingen  ☐ Timer pr uke:
Under 1  2  3 og mer
Lett aktivitet  4  3  2  1
Hard fysisk aktivitet  4  3  2  1

53. Jeg er nervøs eller ansynet.
☐ For det meste  4  ☐ Noen ganger  3
☐ Ofte  3  ☐ Ikke i det hele tatt  1

54. Jeg gleder meg fortsatt over ting slik jeg pleide før.
☐ Avgjort ikke mye  1  ☐ Bare lite grann  3
☐ Ikke fullt så mye  2  ☐ Ikke i det hele tatt  1

55. Jeg har en urofølelse som om noe forferdelig vil skje.
☐ Ja, og noe svært ille  4  ☐ Litt, bekymrer meg lite  2
☐ Ja, ikke så veldig ille  3  ☐ Ikke i det hele tatt  1

56. Jeg kan le og se det morsomme i situasjoner.
☐ Like mye nå som før  1  ☐ Avgjort ikke som før  3
☐ Ikke like mye nå  2  ☐ Ikke i det hele tatt  4

57. Jeg har en urofølelse som om noe forferdelig vil skje.
☐ Ja, og noe svært ille  4  ☐ Litt, bekymrer meg lite  2
☐ Ja, ikke så veldig ille  3  ☐ Ikke i det hele tatt  1

58. Jeg kan le og se det morsomme i situasjoner.
☐ Like mye nå som før  1  ☐ Avgjort ikke som før  3
☐ Ikke like mye nå  2  ☐ Ikke i det hele tatt  4

59. Jeg har en urofølelse som om noe forferdelig vil skje.
☐ Ja, og noe svært ille  4  ☐ Litt, bekymrer meg lite  2
☐ Ja, ikke så veldig ille  3  ☐ Ikke i det hele tatt  1

60. Jeg kan le og se det morsomme i situasjoner.
☐ Like mye nå som før  1  ☐ Avgjort ikke som før  3
☐ Ikke like mye nå  2  ☐ Ikke i det hele tatt  4

61. Jeg har en urofølelse som om noe forferdelig vil skje.
☐ Ja, og noe svært ille  4  ☐ Litt, bekymrer meg lite  2
☐ Ja, ikke så veldig ille  3  ☐ Ikke i det hele tatt  1

62. Jeg kan le og se det morsomme i situasjoner.
☐ Like mye nå som før  1  ☐ Avgjort ikke som før  3
☐ Ikke like mye nå  2  ☐ Ikke i det hele tatt  4

63. Jeg har en urofølelse som om noe forferdelig vil skje.
☐ Ja, og noe svært ille  4  ☐ Litt, bekymrer meg lite  2
☐ Ja, ikke så veldig ille  3  ☐ Ikke i det hele tatt  1

64. Jeg kan le og se det morsomme i situasjoner.
☐ Like mye nå som før  1  ☐ Avgjort ikke som før  3
☐ Ikke like mye nå  2  ☐ Ikke i det hele tatt  4

65. Jeg har en urofølelse som om noe forferdelig vil skje.
☐ Ja, og noe svært ille  4  ☐ Litt, bekymrer meg lite  2
☐ Ja, ikke så veldig ille  3  ☐ Ikke i det hele tatt  1

66. Jeg kan le og se det morsomme i situasjoner.
☐ Like mye nå som før  1  ☐ Avgjort ikke som før  3
☐ Ikke like mye nå  2  ☐ Ikne i det hele tatt  4

67. Jeg har en urofølelse som om noe forferdelig vil skje.
☐ Ja, og noe svært ille  4  ☐ Litt, bekymrer meg lite  2
☐ Ja, ikke så veldig ille  3  ☐ Ikne i det hele tatt  1

68. Jeg kan le og se det morsomme i situasjoner.
☐ Like mye nå som før  1  ☐ Avgjort ikke som før  3
☐ Ikne like mye nå  2  ☐ Ikne i det hele tatt  4
57. Jeg har hodet fullt av bekymringer.
☐ Veldig ofte 4
☐ Av og til 2
☐ Ganske ofte 3
☐ En gang i blant 1

58. Jeg er i godt humør.
☐ Aldri 4
☐ Ganske ofte 2
☐ Noen ganger 3
☐ For det meste 1

59. Jeg kan sitte i fred og ro og kjenne meg avslappet.
☐ Ja, helt klart 1
☐ Ikke så ofte 3
☐ Vanligvis 2
☐ Ikke i det hele tatt 4

60. Jeg føler meg som om alt går langsommere.
☐ Nesten hele tiden 4
☐ Fra tid til annen 2
☐ Så ofte 3
☐ Ikke i det hele tatt 1

61. Jeg føler meg urolig som om jeg har sommerfugler i magen.
☐ Ikke i det hele tatt 1
☐ Ganske ofte 3
☐ Fra tid til annen 2
☐ Så ofte 4

☐ Ja, jeg har sluttt å bry meg 2
☐ Ganske ofte 3
☐ Ikke i det hele tatt 4
☐ Ikke som jeg burde 1

63. Jeg er rasist som om jeg stadig må være aktiv.
☐ En gang i hvert fjerde 1
☐ Ikke så veldig også 2
☐ Ganske mye 3
☐ Ikke i det hele tatt 4

64. Jeg ser med glede fram til hendelser og ting.
☐ Ikke mye som før 4
☐ Avgjort mindre enn før 3
☐ Hvis det er et eneste 2
☐ Nesten ikke i det hele tatt 1

65. Jeg kan plutselig få en følelse av panikk.
☐ Ikke så ofte 1
☐ Ikke i det hele tatt 2
☐ Ganske ofte 3
☐ Så ofte 4

66. Jeg kan glede meg over gode bøker, radio og TV.
☐ Ikke så ofte 1
☐ Ikke ofte 2
☐ Ganske ofte 3
☐ Så ofte 4

---

Fertilitet, sex og samliv

**FERTILITET (FRUKTBARHET)**

74. a. Bli du født med begge testikler i pungen? ☐ Ja 1 ☐ Nei 2
b. Hvis nei, er du blitt operert? ☐ Ja 1 ☐ Nei 2
Årstall for operasjon: __________

75. Har du hatt kusma med hevelse av en eller begge testiklene? ☐ Ja 1 ☐ Nei 2

---

**FØR diagnosen for testikkelkreft:**

76. Prøvde du å bli far? ☐ Ja 1 ☐ Nei 2

77. Haddde du egne barn? ☐ Ja 1 ☐ Nei 2
Antall barn: __________
Barnas fødselsår: __________

78. Oppskrte du eller din partner en lege på grunn av problemer med å få barn? ☐ Ja 1 ☐ Nei 2

79. Froaset du ned med før du ble behandlet for testikkelkreft? ☐ Ja 1 ☐ Nei 2
ETTER behandling for testikkelkreft:

80. Har du prøvd å bli far? □ Ja □ Nei

81. Har du fått egne barn? □ Ja □ Nei
Antall barn: ____________________________

Barnas fødselsår: ______________________

82. Har din partner hatt aborter etter at hun ble gravid med deg? □ Ja □ Nei

83. Trengte dere hjelp av en medisinsk spesialist for at partnerein din skulle bli gravid?
□ Ja □ Nei

a. Hvis «ja», ble din partner gravid med sød som du selv produserte etter behandlingen?
□ Ja □ Nei

b. Hvis «ja», ble nedfrosset sød fra før behandlingen benyttet?
□ Ja □ Nei

84. Ble noen av dine barn født med alvorlige sykdommer?
□ Ja □ Nei
Hvis «ja», spesifiser hvilke sykdommer:

85. Har du adoptert barn? □ Ja □ Nei
Hvis «ja», angi årstall for adopsjon:

86. Eventuelle andre opplysninger angående svangerskap, barn, etc.

SEKSUALDRIFT

La oss definere seksualdrift som en følelse som kan omfatte ønske om seksuell aktivitet (onani eller samleie), tanken på å ha sex eller frustrasjon som følge av mangel på sex.

87. Hvor mange dager har du følt seksualdrift de siste 30 dagene? (Sett langt rundt det svaret som passer.)
Ingen Bare noen Noen De fleste Nesten få dager dager dagene hver dag
1 2 3 4 5

88. Hvordan vurderer du nivået på seksualdriften din de siste 30 dagene?
Ingen Lav drift Middels Middels Sterk drift drift
1 2 3 4 5

REI NS NING

89. Hvis du er blitt seksuelt stimulert på noen måte de siste 30 dagene; hvor ofte har du hatt delvis eller full rei nsk?
Aldri Noen få ganger Ganske ofte Vanligvis Altid
1 2 3 4 5

90. Hvis du har hatt rei nsk de siste 30 dagene; hvor ofte var penis stiv nok til at du kunne ha samleie?

<table>
<thead>
<tr>
<th>Aldri</th>
<th>Noen få ganger</th>
<th>Ganske ofte</th>
<th>Vanligvis</th>
<th>Altid</th>
</tr>
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</table>

91. Hvor store vansker har du hatt med å få rei nsk de siste 30 dagene?

<table>
<thead>
<tr>
<th>Har ikke fått rei nsk</th>
<th>Vansker vansker vansker</th>
<th>Ingen vansker</th>
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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SÆDUTTØMMING

92. Hvor store vansker har du hatt med å få sæddømming når du er blitt seksuelt stimulert de siste 30 dagene?

<table>
<thead>
<tr>
<th>Har ikke</th>
<th>Store</th>
<th>Noen</th>
<th>Få</th>
<th>Ingen</th>
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93. I hvilken grad har du over de siste 30 dagene sett på mengden sød ved uttømming som et problem for deg?

<table>
<thead>
<tr>
<th>Stort</th>
<th>Middels</th>
<th>Lite</th>
<th>Ganske</th>
<th>Ikke noe</th>
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</table>

94. Har sæddømmingen blitt helt borte etter behandlingen for testikkelkreft? □ Ja □ Nei

PROBLEMVURDERING

95. I hvilken grad har du over de siste 30 dagene sett på manglende seksualdrift som et problem?

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<th>Stort</th>
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<th>Ganske</th>
<th>Ikke noe</th>
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96. I hvilken grad har du over de 30 siste dagene vurdert din evne til å få og beholde rei nsk som et problem?

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<tr>
<th>Stort</th>
<th>Middels</th>
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97. I hvilken grad har du over de 30 siste dagene sett på din sæddømming som et problem?

<table>
<thead>
<tr>
<th>Stort</th>
<th>Middels</th>
<th>Lite</th>
<th>Ganske</th>
<th>Ikke noe</th>
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</table>

98. Hvor tilfreds har du samlet sett vært med ditt seksualliv de siste 30 dagene?

<table>
<thead>
<tr>
<th>Veldig</th>
<th>For det utilfreds</th>
<th>Omtrent like tilfreds</th>
<th>For det svært tilfreds</th>
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</thead>
<tbody>
<tr>
<td>problem</td>
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<td>problem</td>
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Livshendelser

Venligst kryss av for det svaralternativet som passer best, og angi med et tall fra 0-100 hvor stor påkjenning/belastning du syntes ulike hendelser eventuelt har medført for deg. 0 betyr ingen belastning, mens 100 betyr stor belastning. Har du krysset av for «ja» under ett eller flere av sørsmålene, pass på at du også har skrevet ned et tall fra 0-100 som best beskriver hvor stor påkjenning/belastning hendelsen førte til.

Har du i løpet av de siste 12 månedene opplevd noe av det følgende:

99. Egen alvorlig sykdom/ulykke/sykehusinleggelse?
   - Nei 2  Ja 1

100. Skilsmisses/separasjon/brudd med samboer?
   - Nei 2  Ja 1

101. Giftet deg/flyttet sammen med samboer?
   - Nei 2  Ja 1

102. Fått barn?
   - Nei 2  Ja 1

103. Opplevd dødsfall i familie/nære venner?
   - Nei 2  Ja 1

104. Alvorlig sykdom/ulykke/sykehusinleggelse hos familie eller nære venner?
   - Nei 2  Ja 1

105. Andre vansker hos nær familie (skilsmisser, alkoholproblemer, nerveproblemer osv.)?
   - Nei 2  Ja 1

106. Vært arbeidsløs/permittert?
   - Nei 2  Ja 1

107. Ektefelle/samboer har vært arbeidsløs/permittert?
   - Nei 2  Ja 1

108. Alvorlige økonomiske problemer?
   - Nei 2  Ja 1

109. Alvorlige bone-messige problemer?
   - Nei 2  Ja 1

110. Har du selv eller noen i din nære familie vært utsatt for eller inblandet i alvorlig lovbudd?
   - Nei 2  Ja 1

Angi grad av belastning fra 0-100

Livskvalitet

HELESE

Spørsmålene under dreier seg om hvordan du ser på din egen helse. Sett en ring rundt det tallet som best beskriver din tilstand.

111. Stort sett, vil du si at din helse er:
   - Ut- Meget God Nokså Dårlig
   - god 3
   - Dårlig 5

112. Sammenlignet med for et år siden; hvordan vil du si at din helse stort sett er nå?
   - Mye bedre nå enn for ett år siden 1
   - Litt bedre nå enn for ett år siden 2
   - Omtrent den samme som for ett år siden 3
   - Litt dårligere nå enn for ett år siden 4
   - Mye dårligere nå enn for et år siden 5

AKTIVITETER

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå, og eventuelt i hvor stor grad? (Sett ring rundt ett tall på hver linje.)

113. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett.
   - Ja, begrenser meg mye 1
   - Ja, begrenser meg litt 2
   - Nei, begrenser meg ikke i det hele tatt 3

114. Moderate aktiviteter som å flytte et bord, støvse, gå en tur eller drive med hagearbeid.
   - 1

115. Løfte eller bære en handlekurv.
   - 1

   - 1

117. Gå opp trappen en etasje.
   - 1

118. Bøye deg eller sitte på huk.
   - 1

119. Gå mer enn to kilometer.
   - 1

120. Gå noen hundre meter.
   - 1
121. Gå hundre meter. | Ja | Nei | Nei, be- | Nei, be- | Nei, be- |
<table>
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</table>

122. Vaske deg eller kle på deg.

**FYSISKE PROBLEMER**

I løpet av de siste fire ukene; har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse? (Sett ring rundt ett tall.)

123. Har du redusert tiden du har brukt på arbeidet ditt eller på andre aktiviteter pga. din fysiske helse?

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
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<tbody>
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</table>

124. Har du utrettet mindre enn du hadde ønsket pga. din fysiske helse?

| 1 | 2 |

125. Har du vært hindret i visse typer arbeid eller andre aktiviteter pga. din fysiske helse?

| 1 | 2 |

126. Har du hatt vanskeligheter med å utføre arbeidet ditt eller andre aktiviteter (f.eks. fordi det krevede ekstra anstrengelser) pga. din fysiske helse?

| 1 | 2 |

**FØLELSESMESSIGE PROBLEMER**

I løpet av de siste fire ukene; har du hatt følelsesmessige problemer som har ført til vanskeligheter i arbeidet ditt eller i andre av dine daglige gjøremål, f.eks. fordi du har følt deg deprimeret eller engstelig? (Sett ring rundt ett tall.)

127. Har du redusert tiden du har brukt på arbeidet ditt eller på andre aktiviteter pga. følelsesmessige problemer?

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
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128. Har du utrettet mindre enn du hadde ønsket pga. følelsesmessige problemer?

| 1 | 2 |

129. Har du ikke arbeidet eller utført andre aktiviteter like noye som vanlig pga. følelsesmessige problemer?

| 1 | 2 |

130. I løpet av de siste fire ukene; i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger? (Sett ring rundt ett tall.)

<table>
<thead>
<tr>
<th>Ikke i det hele tatt</th>
<th>Litt</th>
<th>Endel</th>
<th>Mye</th>
<th>Svært mye</th>
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131. Hvor sterke kroppslige smerter har du hatt i løpet av de siste fire ukene? (Sett ring rundt ett tall.)

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Nå</th>
<th>Sakte</th>
<th>Moderate</th>
<th>Sterke</th>
<th>Meget sterke</th>
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132. I løpet av de siste fire ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)? (Sett ring rundt ett tall.)

<table>
<thead>
<tr>
<th>Ikke i det</th>
<th>Litt</th>
<th>Endel</th>
<th>Mye</th>
<th>Svært mye</th>
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</table>

De neste spørsmålene dreier seg om hvordan du har følt deg og hvordan du har hatt det de siste fire ukene. For hvert spørsmål, vennligst sett ring rundt det tallet som best beskriver hvordan du har hatt det.

**Hvor ofte i løpet av de siste fire ukene har du:**

133. - følt deg full av tiltakslyst?

<table>
<thead>
<tr>
<th>Hele tiden</th>
<th>Neste</th>
<th>Mye</th>
<th>En del</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
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</thead>
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<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

134. - følt deg veldig nervøs?

<table>
<thead>
<tr>
<th>Hele tiden</th>
<th>Neste</th>
<th>Mye</th>
<th>En del</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
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<td>6</td>
</tr>
</tbody>
</table>

135. - vært så langt nede at ingenting har kunnet munter deg opp?

<table>
<thead>
<tr>
<th>Hele tiden</th>
<th>Neste</th>
<th>Mye</th>
<th>En del</th>
<th>Litt av tiden</th>
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136. - følt deg rolig og harmonisk?

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<tr>
<th>Hele tiden</th>
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137. - hatt mye overskudd?

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<tr>
<th>Hele tiden</th>
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138. - følt deg nedfor og trist?

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<tr>
<th>Hele tiden</th>
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<td>139. - følt deg sliten?</td>
<td>140. - følt deg glad?</td>
<td>141. - følt deg trett?</td>
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<tr>
<td><strong>6</strong></td>
<td><strong>6</strong></td>
<td><strong>tatt</strong></td>
<td></td>
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</tr>
</tbody>
</table>

| 142. I løpet av de siste fire ukene: hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)? (Sett ring rundt ett tall.) |
|----------------------------------|----------------------------------|
| **Hele tiden**                   | **Nesten**                       |
| **En del**                       | **av**                            |
| **Litt av**                      | **av**                            |
| **Ikke i det hele**              | **tiden**                         |
| **tatt**                         | **en del**                        |
| **3**                             | **4**                             |
| **5**                             | **6**                             |

Hvor riktig eller gal er hver av de følgende påstander for deg? (Sett ring rundt det tallet som passer.)

| 143. Det virker som om jeg blir lettere syk enn andre. |
|----------------------------------|----------------------------------|
| **Helt**                         | **Delvis**                       |
| **tatt**                         | **Vet**                           |
| **riktig**                       | **Delvis**                       |
| **riklig**                       | **Helt**                          |
| **ikke**                         | **gal**                           |
| **gal**                          | **gal**                           |
| **1**                             | **2**                             |
| **3**                             | **4**                             |
| **5**                             | **6**                             |

| 144. Jeg er ikke frisk som de fleste jeg kjenner. |
|----------------------------------|----------------------------------|
| **Helt**                         | **Delvis**                       |
| **tatt**                         | **Vet**                           |
| **riktig**                       | **Delvis**                       |
| **riklig**                       | **Helt**                          |
| **ikke**                         | **gal**                           |
| **gal**                          | **gal**                           |
| **1**                             | **2**                             |
| **3**                             | **4**                             |
| **5**                             | **6**                             |

| 145. Jeg forventer at min helse vil bli dårligere. |
|----------------------------------|----------------------------------|
| **Helt**                         | **Delvis**                       |
| **tatt**                         | **Vet**                           |
| **riktig**                       | **Delvis**                       |
| **riklig**                       | **Helt**                          |
| **ikke**                         | **gal**                           |
| **gal**                          | **gal**                           |
| **1**                             | **2**                             |
| **3**                             | **4**                             |
| **5**                             | **6**                             |

| 146. Min helse er utmerket. |
|----------------------------------|----------------------------------|
| **Helt**                         | **Delvis**                       |
| **tatt**                         | **Vet**                           |
| **riktig**                       | **Delvis**                       |
| **riklig**                       | **Helt**                          |
| **ikke**                         | **gal**                           |
| **gal**                          | **gal**                           |
| **1**                             | **2**                             |
| **3**                             | **4**                             |
| **5**                             | **6**                             |

| 147. Hvordan har din helse vært i løpet av den siste uken? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |
| **5**                             | **6**                             |
| **7**                             | **7**                             |

| 148. Hvordan har livskvaliteten din vært i løpet av den siste uken? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |
| **5**                             | **6**                             |
| **7**                             | **7**                             |

| **Svært**                         | **Helt**                          |
| **dårlig**                        | **utmerket**                      |

**SMERTER/PLAGER**
Søtt ring rundt det tallet som best beskriver din tilstand.

| 149. Er du plaget av smerter, stikkninger eller nummenhet i hendene/fingrene? |
|----------------------------------|----------------------------------|
| **Ikke i det hele**              | **Litt**                         |
| **Endel**                        | **Svært**                        |
| **mye**                          | **tatt**                         |
| **1**                             | **2**                             |
| **3**                             | **4**                             |

| 150. Er du plaget av smerter, stikkninger eller nummenhet i fottene/tærne? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |

| 151. Er du plaget av hvite/kalte hender/fingre når det er kaldt? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |

| 152. Er du plaget av hvite/kalte føtter/tær når det er kaldt? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |

| 153. Er du plaget av sresus? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |

| 154. Er du plaget av nedsatt hørsel? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |

**BEMYRINGER**

| 155. Har du lite hår i forhold til jevnaldrende? |
|----------------------------------|----------------------------------|
| **Ja**                           | **Nei**                          |
| **1**                             | **2**                             |
| **3**                             | **4**                             |

Hvis «ja», tror du dette er en følge av din behandling? |

<table>
<thead>
<tr>
<th><strong>Ja</strong></th>
<th><strong>Nei</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

| 156. Hvis du mener du har lite hår i forhold til jevnaldrende; har du vært bekymret for dette? (Sett ring rundt det tallet som best beskriver din tilstand.) |
|----------------------------------|----------------------------------|
| **Ikke i det hele**              | **Endel**                        |
| **Svært**                        | **mye**                          |
| **tatt**                         | **en del**                       |
| **2**                             | **3**                             |
| **4**                             | **5**                             |

I løpet av den siste uken: |

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Ikke i det hele</strong></td>
<td><strong>Endel</strong></td>
</tr>
<tr>
<td><strong>Svært</strong></td>
<td><strong>mye</strong></td>
</tr>
<tr>
<td><strong>tatt</strong></td>
<td><strong>en del</strong></td>
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<tr>
<td><strong>1</strong></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

| 157. Har ditte egenbilde som man vært nedsatt som følge av din sykdom eller behandling? |
|----------------------------------|----------------------------------|
| **1**                             | **2**                             |
| **3**                             | **4**                             |

| **ALT I ALT** |
|----------------------------------|----------------------------------|
| **Som svar på de neste spørsmålene, sett en ring rundt det tallet fra 1 til 7 som best beskriver din tilstand.** |
|----------------------------------|----------------------------------|
| **147. Hvordan har din helse vært i løpet av den siste uken?** |
| **1**                             | **2**                             |
| **3**                             | **4**                             |
| **5**                             | **6**                             |
| **7**                             | **7**                             |
| **Svært**                         | **Helt**                          |
| **dårlig**                        | **utmerket**                      |
### Mestring av plager/problemer


<table>
<thead>
<tr>
<th>Ikke i det hele tatt</th>
<th>Litt</th>
<th>Endel</th>
<th>Svært mye</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

158. Har du vært plaget av bekymringer for ikke å kunne få barn?

159. Har du vært redd for tilbakefall av din sykdom?

160. Har du vært fornøyd med måten sykehus(ene) har foretatt undersøkelsene/kontrollene av deg?

161. Har du følt at de avgjørelser som er foretatt med henblikk på din behandling har vært riktig for deg?

### FØLERER

Vennligst beskriv hvordan du har hatt det de siste syv dagene ved å sette en ring rundt det tallet som best beskriver din tilstand.

162. Jeg sier fra når jeg er sint eller trist.

Helt | Nokså | Både | Nokså | Svært
enig | enig | og | enig | uenig

163. Jeg snakker gjerne med noen utvalgte mennesker når det røyner på.

164. Å gjøre nye ting er ofte vanskelig for meg.

165. Jeg går aktivt inn for å finne en løsning på problemene mine.

166. Fysisk aktivitet er viktig for meg.

167. Jeg prøver å glemme plagene mine.

168. Jeg legger probleemene mine bak meg ved å konsentrere meg om noe annet.

169. Jeg tror det kan komme noe positivt ut av plagene/problemmene mine.

170. Jeg har godt tro på at plagene mine vil bli bedre.

171. Jeg graver meg ned i arbeid for å holde plagene/problemmene på avstand.

172. Jeg føler langt på vei at jeg har gitt opp.

173. Jeg trekker meg tilbake fra andre når jeg har det vanskelig.
### Tretthet

| 179. Jeg har hatt vanskelig for å sove på grunn av tanker og bilder om sykdommen. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 180. Jeg har hatt vondre drømmer om sykdommen. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 181. Jeg vet mange uforløste følelser er der, men jeg har skjøvet dem bort. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 182. Jeg har ikke tillatt meg å bli følelsesmessig berørt når jeg tenker på sykdommen eller blir minnet om den. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 183. Jeg har ønsket å bli kvitt minner om sykdommen. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 184. Jeg har forsøkt å la være å snakke om sykdommen. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 185. Jeg har opplevd det uvirkelig, som om sykdommen ikke var hendt eller ikke var virkelig. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 186. Jeg har holdt meg unna ting eller situasjoner som kan minne meg om sykdommen. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 187. Mine følelser rundt sykdommen er nærmest lammet. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 188. Jeg har ikke tillatt meg selv å ha tanker om sykdommen. |
| I høy grad | Ganske | Middels | Noe | Litt | Aldri |
| 6 5 4 3 2 1 |

| 189. Har du problemer med å fylle deg sliten? |
| Minde 1 | Ikke mer 3 | Mer 2 | Mye mer 4 | enn vanlig | enn vanlig | enn vanlig |

| 190. Trenger du mye hvile? |
| Minde 1 | Ikke mer 2 | Mer 3 | Mye mer 4 | enn vanlig | enn vanlig | enn vanlig |

| 191. Føler du deg savnlig eller døsigg? |
| Minde 1 | Ikke mer 2 | Mer 3 | Mye mer 4 | enn vanlig | enn vanlig | enn vanlig |

| 192. Har du problemer med å komme i gang med ting? |
| Minde 1 | Ikke mer 2 | Mer 3 | Mye mer 4 | enn vanlig | enn vanlig | enn vanlig |

| 193. Mangler du overskudd? |
| Ikke i 1 | Ikke mer 2 | Mer 3 | Mye mer 4 | det hele tatt | enn vanlig | enn vanlig |

| 194. Har du redusert styrke i musklene dine? |
| Ikke i 1 | Ikke mer 2 | Mer 3 | Mye mer 4 | det hele tatt | enn vanlig | enn vanlig |

| 195. Føler du deg svak? |
| Minde 1 | Som 2 | Mer 3 | Mye mer 4 | enn vanlig | vanlig |

| 196. Har du vansker med å konsentrere deg? |
| Minde 1 | Som 2 | Mer 3 | Mye mer 4 | enn vanlig | vanlig |

| 197. Forsnakker du deg i samtaler? |
| Minde 1 | Ikke mer 2 | Mer 3 | Mye mer 4 | enn vanlig | vanlig |

| 198. Er det vanskelig å finne de rette ordene? |
| Minde 1 | Ikke mer 2 | Mer 3 | Mye mer 4 | enn vanlig | vanlig |

| 199. Hvordan er hukommelsen din? |
| Bedre 1 | Ikke verre 2 | Verre 3 | Mye verre 4 | enn vanlig | vanlig | vanlig | vanlig |
### Personlighet


<table>
<thead>
<tr>
<th>Spørsmål</th>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>202. Er du forholdsvis livlig?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>203. Ville du bli oppskaket av å se et barn eller et dyr lede?</td>
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</tr>
<tr>
<td>204. Liker du å treffe nye mennesker?</td>
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<tr>
<td>205. Blir dine følelser lett såret?</td>
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</tr>
<tr>
<td>206. Hender det ofte at du &quot;går trystt&quot;?</td>
<td></td>
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</tr>
<tr>
<td>207. Liker du å spille andre et puss som av og til kan såre dem?</td>
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</tr>
</tbody>
</table>

208. Er du ofte bekymret?  
209. Er gode manøver og renlighet viktig for deg?  
210. Bekymrer du deg for at fryktelige ting kan skje?  
211. Tar du vanligvis selv det første skrittet for å få nye venner?  
212. Er du for det meste stille når du er sammen med andre?  
213. Liker du å komme til avtaler i god tid?  
214. Har du ofte følt deg trøtt og gliddels uten grunn?  
215. Er det mange mennesker som forsøker å unngå deg?  
216. Klarer du holde fart i et selskap?  
217. Bekymrer du deg lenge etter en pinlig opplevelse?  
218. Liker du å ha masse liv og røre rundt deg?  
219. Forteller folk deg en masse løgner?  

Vennligst legg det ferdig utfylte spørreskjemaet i vedlagte svarkonvolutt. Porto er allerede betalt av oss.

Tusen takk for hjelen!
APPENDIX 2

Questionnaire Survey II – 2007 - 2008
Etterundersøkelse av pasienter behandlet for testikkkelkreft

Vi ber deg om å fylle ut dette spørreskjemaet så godt du kan ved å krysse av det svaret som passer. Svar på alle spørsmål, selv om det noen gang kan virke slik at vi spør om det samme i flere spørsmål. Alle svar behandles konfidensielt.

Dato for utfylling: [__], [__], [__]

Høyde: [__] cm Vekt: [__] kg

ARBEID OG UTDANNING

1. a) Hva er din nåværende arbeidssituasjon? (sett kun ett kryss X ved det svaret som passer)
   
   - Inntektsgivende arbeid heltid
   - Inntektsgivende arbeid deltid
   - Selvstendig næringsdrivende
   - Alderspensjonist
   - For tiden arbeidsledig/arbeidstrygd
   - Attføring
   - Uføretrygdet
   - Langtidssykemeldt (>8 uker)
   - Elev, student
   - Hjemmeværende/husarbeid i hjemmet
   - Annet

   b) Hvis arbeidsledig, sykemeldt, eller pensjonist, er kreftsykdommen årsak for at du for tiden ikke er i arbeid?
   
   - Nei
   - Ja, delvis [oppgi alternativ grunn: ____________]
   - Ja, hovedsakelig

2. Sett kryss ved det yrkesområdet som best beskriver arbeidet ditt. Dersom du for tiden ikke er yrkesaktiv, oppgi det yrkesområdet du sist har hatt. (sett kun ett kryss X)
   
   - Grunnskoleutdannin (10-årlig grunnskole -tidl. 9-årig, 7-årig folkeskole eller lignende)
   - Videregående utdanning (Allmennfag, yrkesskole eller annet)
   - Fagutdanning / yrkesutdanning / fagbrev / videregående yrkesfaglig utdanning
   - Universitets-/høgskoleutdanning med inntil 4 års varighet
   - Universitets-/høgskoleutdanning med mer enn 4 års varighet

Snu arket!
3. Har kreftsykdommen hatt innvirkning på dine muligheter til å få den utdanning som du ønsket eller planla før du fikk kreft?
   □ Ja   □ Nei

4. a) Har du noen gang skiftet arbeidsplass?
   □ Ja   □ Nei   Hvis Ja, antall ganger: [□□□□]
   b) Hvis Ja: Var kreftens noen gang årsak til at du skiftet arbeidsplass?
      □ Nei    □ Ja, delvis    □ Ja, i hovedsak
      Hvis Ja: Kan du spesifisere hvorfor/hvordan kreften førte til at du skiftet arbeidsplass?

5. a) Har du noen gang skiftet yrke?
      □ Ja   □ Nei   Hvis Ja, antall ganger: [□□□□]
      b) Var kreftens årsak til at du skiftet yrke/ny yrkesutdannelse?
         □ Nei    □ Ja, delvis    □ Ja, i hovedsak
         Hvis Ja: Kan du spesifisere hvorfor/hvordan kreften førte til at du skiftet yrke?

6. Har kreftsykdommen virket inn på din mulighet for å delta i opplæring knyttet til yrkesfaglig utvikling som arbeidsplassen har arrangert?
   □ Ikke aktuelt    □ Ikke i det hele tatt    □ I noen grad    □ I stor grad

7. Har kreftsykdommen hatt innvirkning på dine muligheter til å oppnå en forbedret situasjon på jobben?
   □ Ikke aktuelt    □ Ikke i det hele tatt    □ I noen grad    □ I stor grad
8. Har kreftsykdommen noen gang ført til at du har blitt utsatt for noen av disse hendelsene?

<table>
<thead>
<tr>
<th>Hendelse</th>
<th>Ikke i det hele tatt</th>
<th>I noen grad</th>
<th>I stor grad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ufrivillig overflytting til andre oppgaver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trussel om tvangspermittering</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trussel om oppsigelse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arbeidsledighet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uføretrygd</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Mener du at din arbeidsevne er blitt nedsatt på grunn av kreftsykdommen?

☐ Ikke i det hele tatt
☐ Nokså lite
☐ I noen grad
☐ Ganske mye
☐ Svært mye


☐ 0  ☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5  ☐ 6  ☐ 7  ☐ 8  ☐ 9  ☐ 10

11. Tror du diagnosen og behandlingen av testikkelkreft har hatt negativ innflytelse på din nåværende arbeidssituasjon/utdannings situasjon?

☐ Ja  ☐ Nei

Hvis Ja, på hvilken måte?

HELSE OG DAGLIGLIV

12. Hvordan er helsen din nå?

☐ Dårlig  ☐ Ikke helt god  ☐ God  ☐ Svært god

Snu arket!
13. Har du noen langvarig (minst 1 år) sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter din funksjon i ditt daglige liv?

☐ Ja  ☐ Nei

**Hvis Ja**, hvor mye vil du si at dine funksjoner er nedsatt?

<table>
<thead>
<tr>
<th>Litt</th>
<th>Middels</th>
<th>Mye</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

- Er bevegelseshemmet
- Har nedsatt syn
- Har nedsatt hørsel
- Hemmet pga kroppslig sykdom
- Hemmet pga psykisk sykdom

14. I hvilken grad har din fysiske helse eller eventuelle følgesmessig problemer begrenset deg i din vanlige sosiale omgang med familie eller venner i løpet av de siste 4 uker?

☐ Ikke i det hele tatt  ☐ En del  ☐ Litt  ☐ Mye

---

**HELSETJENESTER**

15. Har du i løpet av de siste 12 måneder vært hos:

<table>
<thead>
<tr>
<th>Ja</th>
<th>Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

- Fastlege/allmennlege
- Annen legespesialist utenfor sykehus
- Konsultasjon uten innleggelse
  - ved psykiatrisk poliklinikk
  - ved annen sykehus poliklinikk
- Fysioterapeut
- Kiropraktor
- Homørøpat, akupunktør, soneterapeut, håndspålegger, eller annen alternativ behandler

16. Har du vært innlagt på sykehus i løpet av de siste 12 måneder:

☐ Ja  ☐ Nei

Årsak og hvilket sykehus:
17. Har du i løpet av de siste 5 år vært hos psykolog/psykiater?
   □ Ja □ Nei

18. Har noen av disse kontakt med helsevesenet hatt relasjon med din testikkelkreft sykdom?
   □ Ja □ Nei □ Ikke aktuelt

---

**RØYKING**

Her ønsker vi å kartlegge all din bruk av tobakk. Vi har derfor delt inn i et hovedspørsmål om daglig røyking, og et spørsmål om "røyking av og til".

19. a) Har du noen gang røykt daglig?
   □ Ja □ Nei  **HVIS NEI - GÅ TIL SPØRSMÅL 20**

19. b) Røyker du for tiden daglig?
   □ Ja □ Nei

c) Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?
   □ Antall år

d) Hvis du røyker daglig nå eller har røykt daglig tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis daglig?
   □ Antall sigaretter

e) Hvor mange år til sammen har du røykt daglig?
   □ Antall år

20. a) Har du noen gang røykt av og til?
   □ Ja □ Nei  **HVIS NEI - GÅ TIL SPØRSMÅL 21**

20. b) Røyker du for tiden av og til?
   □ Ja □ Nei

20. c) Hvis du røyker av og til eller har røykt av og til tidligere: Hvor mange sigaretter røyker eller røykte du vanligvis i løpet av en måned?
   □ Antall sigaretter

20. d) Hvor mange år til sammen har du røykt av og til?
   □ Antall år

21. Røyker du pipe/sigar?
   □ Ja □ Nei

   **Hvis Ja:** Pakker pipetobakk per måned:
   □ □ □ □

   eller: Antall sigarer per måned:
   □ □ □ □

---

Snu arket!
AKTIVITET


<table>
<thead>
<tr>
<th>Timer per uke</th>
<th>ingen</th>
<th>under 1</th>
<th>1-2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lett aktivitet (ikke svett/andpusten):</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Hardere fysisk aktivitet (svett/andpusten):</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

SYKDOMMER OG PLAGER

I noen av de følgende spørsmål ber vi deg oppgi alderen din da eventuell sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt. Kryss av for det svaret som passer, og sett kun ett kryss.

DIABETES

23. Har du fått påvist diabetes (sukkersyke)?
   ☐ Ja ☐ Nei
   a) Hvis Ja: Hvor gammel var du da din diabetes ble oppdaget? ☐ ☐ år
   b) Hvis Ja: Bruker du insulin (sprøyter, penn) mot din diabetes nå? ☐ Ja ☐ Nei
   c) Hvis Ja: Bruker du tabletter mot din diabetes? ☐ Ja ☐ Nei

BLODTRYKK

24. Har du brukt eller bruker du blodtrykksmedisin?
   ☐ Ja, nå ☐ Ja, tidligere ☐ Nei, aldri
   Hvis Ja: Hvor gammel var du første gang du begynte med slik medisin? ☐ ☐ år

HJERTE/KAR-SYKDOMMER

25. Har du hatt hjerteinfarkt?
   ☐ Ja ☐ Nei
   a) Hvis Ja: Hvor gammel var du første gang du fikk hjerteinfarkt? ☐ ☐ år
   b) Hvis Ja: Hvor mange ganger har du hatt hjerteinfarkt? Antall ganger
26. Har du eller har du hatt angina pectoris (hjertekrampe)?

☐ Ja  ☐ Nei

a) Hvis Ja: Hvor gammel var du da du merket slike hjertekramper første gang?  ____ år

b) Hvis Ja: Hvor mange ganger per uke har du merket slike smerter i løpet av den siste måneden?  ____ Antall ganger

c) Ved anstrengelse:  ____ ganger/uke

d) Når du er i ro om dagen:  ____ ganger/uke

e) Om natten:  ____ ganger/uke

27. a) Har du fått behandling for angina pectoris med tabletter?

☐ Ja  ☐ Nei

Navn på tabletter og hvilken lege / evt. sykehus startet behandlingen?

b) Har du blitt hjenteoperert med nye blodårer til hjertet (bypass-ACB)?

☐ Ja  ☐ Nei

Hvilket sykehus?

c) Har du blitt blokket/fått innsatt stent i blodårene på hjertet?

☐ Ja  ☐ Nei

Hvilket sykehus?

28. Har legen sagt at du har hjerteflimmer (atrieflimmer)?

☐ Ja  ☐ Nei

29. Har legen sagt at du har hjertesvikt (svakt hjerte, vann på lungene, hovne ben)?

☐ Ja  ☐ Nei

30. Har du noen gang fått påvist forsnevring på hovedpulsåren i hals eller mage, eller fått påvist trange blodårer i bena?

☐ Ja  ☐ Nei

Hvis Ja, spesifiser hvor forsnevringen satt

Hvilket årstall ble dette påvist?  ____

31. Har du noen gang hatt blodpropp i bein eller lunge?

☐ Ja  ☐ Nei

Hvis Ja, vennligst spesifiser hvor

Hvor gammel var du første gang?  ____ år
HJERNESLAG / HJERNEBLØDNING

32. a) Har du hatt TIA ("drypp") eller symptomer på hjerneslag som gikk fullstendig tilbake innen 24 timer?
   ☐ Ja  ☐ Nei
   Hvis Ja: Hvor gammel var du da du hadde det første gang?   ☐  år
   Hvis Ja: Hvor mange ganger har du hatt det?   ☐  Antall ganger

b) Har du noen gang hatt hjerneslag (blodpropp eller blødning i hjernen)?
   ☐ Ja  ☐ Nei
   Hvis Ja: Hvor gammel var du da du hadde hjerneslag første gang?   ☐  år
   Hvis Ja: Hvor mange ganger har du hatt hjerneslag?   ☐  Antall ganger

NYRESYKDOMMER

33. Har det noen gang blitt påvist nedsatt nyrefunksjon hos deg?
   ☐ Ja  ☐ Nei
   Hvis Ja: Hvor gammel var du da dette ble påvist første gang?   ☐  år
   Hvis Ja, spesifiser på hvilken måte den nedsatte nyrefunksjonen ble oppdaget (egghvite eller blod i urinen, blodprøve)

ANDRE SYKDOMMER

34. Har du, eller har du hatt:

<table>
<thead>
<tr>
<th>Sykdom</th>
<th>Ja</th>
<th>Nei</th>
<th>Hvis JA, alder første gang</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astma</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Kronisk bronkitt, emfysem eller KOLS</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Slitasjegikt (artrose)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Leddgikt (reumatoid artritt)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Bechterews sykdom</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Ny kreftsykdom ETTER testikkelkreften (dvs evnt. ny kreft etter 1994)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Sarkoidose</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Beinskjørhet (osteoporose)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Epilepsi</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Eksem</td>
<td>☐</td>
<td>☐</td>
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</tr>
</tbody>
</table>
TANNHELSE

35. Når var du sist hos tannlegen?
- 6 måneder siden eller mindre
- 7-12 måneder siden
- 13-24 måneder siden
- 25-35 måneder siden
- 3-4 år siden
- 5-6 år siden
- Mer enn 6 år siden
- Aldri

36. Har du vært hos tannlegen regelmessig (minst 1 gang i året) de siste 5 år?
- Ja
- Nei

37. Hvor mye har du til sammen betalt hos tannlegen i løpet av de siste 12 månedene?
- Ingenting (har ikke vært hos tannlegen)
- Ingenting (har fått kostnadene dekket)
- Mindre enn 500 kroner
- 501 - 1000 kroner
- 1001 - 3000 kroner
- 3001 - 5000 kroner
- 5001 - 15000 kroner
- Mer enn 15000 kroner

38. Har du fått refundert noen av dine tannlegeutgifter pga munntørrhet etter kreftbehandlingen?
- Ja
- Nei

39. Hva har du fått utført hos tannlegen etter kreftbehandlingen? (sett eventuelt flere kryss X)
- Undersøkt tenner (med ellen uten røntgenbilder)
- Renset tenner/fjernet tannsten
- Plombert/fylt hull i tenner
- Satt inn krone eller bro i tennene
- Rotfylt tann
- Trukket tann
- Satt inn protese
- Tannregulering
- Fått implantat
- Fått råd om renhold av tenner
- Tannkjøttbehandling

Snu arket!
40. Har du hatt noen av de følgende problemer med munnhulen ETTER kreftbehandlingen?

a) Hull i tennene - nedslitte tenner
   Liten grad □ □ □ □ □
   Middels □ □ □ □ □
   Stor grad □ □ □ □ □

b) Sykdommer i tannkjøtt og slimhinner
   □ □ □ □ □

c) Munntørrhet
   □ □ □ □ □

41. Hvordan vurderer du din munn-og tannhelse?

<table>
<thead>
<tr>
<th>Meget dårlig</th>
<th>Dårlig</th>
<th>Verken god eller dårlig</th>
<th>God</th>
<th>Meget god</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

SMERTER/PLAGER (i løpe av den siste måneden)

(sett et kryss X ved det som passer)

42. Er du plaget av smerter, stikninger eller nummenhet i hender/fingre?
   Ikke i det hele tatt □ □ □ □ □
   Litt □ □ □ □ □
   En del □ □ □ □ □
   Svært mye □ □ □ □ □

43. Er du plaget av smerter, stikninger eller nummenhet i føtter/tær?
   □ □ □ □ □

44. Er du plaget av hvite/kalde hender/fingre når det er kaldt?
   □ □ □ □ □

45. Er du plaget av hvite/kalde føtter/tær når det er kaldt?
   □ □ □ □ □

46. Er du plaget av øresus?
   □ □ □ □ □

47. Er du plaget av nedsatt hørsel?
   □ □ □ □ □

48. Er du plaget med smerter i muskler og ledd?
   □ □ □ □ □

49. Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?
   □ □ □ □ □

50. Er du plaget av kvalme?
   □ □ □ □ □

51. Er du plaget av brystbrann/sure oppstøt?
   □ □ □ □ □

52. Er du plaget av diarré/løs mage?
   □ □ □ □ □
MEDISINBRUK

53. Har du i deler av det siste året brukt noen medisiner/behandlinger daglig eller nesten daglig?  

[ ] Ja  [ ] Nei  

Hvis Ja, angi hvor mange måneder i løpet av det siste året.  

Antall måneder i løpet av det siste året  
(Sett 0 hvis du ikke har brukt medisinene)

Smertestillende  [ ]  
Sovemedisin  [ ]  
Beroligende medisin  [ ]  
Medisin mot depresjon  [ ]  
Allergimedisin  [ ]  
Astmamedisin  [ ]  
Hjertemedisin  [ ]  
Kolesterolnedsettende medisin  [ ]  
Mannlige kjønnshormoner  [ ]  
Annen medisin, spesifiser antall mnd  [ ]  
Navn: _________________________

Behandling for impotens, spesifiser antall mnd  [ ]  
Navn: _________________________

SOSIAL OG ØKONOMISK SITUASJON

54. Hva er din nåværende sivilstatus? (sett et kryss X ved det som passer)  

[ ] Ugift  
[ ] Gift/samboende  
[ ] Enkemann  
[ ] Separert/skilt

55. Antall barn under 18 år i din husstand:  [ ]  

Hvorav under 7 år:  [ ]  

56. Hva er for tiden husstandens forventede årsinntekt før skatt (inntekt fra selvstendig og næringsvirksomhet, lønn og pensjon)? (forventet beløp for 2007)  

[ ] Ingen inntekt  500.000-599.900  
[ ] 100-99.900  600.000-699.900  
[ ] 100.000-199.900  700.000-799.900  
[ ] 200.000-299.900  800.000-899.900  
[ ] 300.000-399.900  900.000-999.900  
[ ] 400.000-499.900  1.000.000 eller mer

Snu arket!
HADS

Pasient nr.:

Dette spørreskjemaet er utformet for å hjelpe oss til å forstå hvordan du føler deg. Les hvert utsagn og sett kryss x i ruten som best beskriver dine følelser den siste uka. Fundér ikke for lenge på ditt svar; din umiddelbare reaksjon på hvert spørsmål er sannsynligvis riktigere enn et svar som du har tenkt lenge på.

1. Jeg er nervøs eller anspent
   □ For det meste
   □ Ofte
   □ Noen ganger
   □ ikke i det hele tatt

2. Jeg gleder meg fremdeles over ting jeg pleide å glede meg over
   □ Avgjort like mye
   □ Ikke fullt så mye
   □ Bare lite grann
   □ Ikke i det hele tatt

3. Jeg har en urofølelse som om noe forferdelig kommer til å skje
   □ Helt sikkert og svært ille
   □ Ja, men ikke så veldig ille
   □ Litt ille, men det bekymrer meg ikke så mye
   □ Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner
   □ Like mye som jeg alltid har gjort
   □ Ikke like mye nå som før
   □ Avgjort ikke så mye nå som før
   □ Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer
   □ Veldig ofte
   □ Ganske ofte
   □ Av og til
   □ En gang i blant

6. Jeg er i godt humor
   □ Aldri
   □ Noen ganger
   □ Ganske ofte
   □ For det meste

7. Jeg kan sitte i fred og ro og kjenne meg avslappet
   □ Ja, helt klart
   □ Vanligvis
   □ Ikke så ofte
   □ Ikke i det hele tatt

8. Jeg føler meg som om alt går langsommere
   □ Nesten hele tiden
   □ Svært ofte
   □ Fra tid til annen
   □ Ikke i det hele tatt

9. Jeg føler meg urolig liksom jeg har sommerfugler i magen
   □ Ikke i det hele tatt
   □ Fra tid til annen
   □ Ganske ofte
   □ Svært ofte

10. Jeg har sluttet å bry meg om hvordan jeg ser ut
    □ Ja, helt klart
    □ Jeg bryr meg ikke så mye som jeg burde
    □ Det kan nok hende jeg ikke bryr meg nok
    □ Jeg bryr meg om at utseendet like mye som jeg altid har gjort

11. Jeg føler meg rastløs som om jeg stadig må være i aktivitet
    □ Uten tvil svært mye
    □ Ganske mye
    □ Ikke så veldig mye
    □ Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting
    □ Like mye som jeg altid har gjort
    □ Heller mindre enn jeg pleier
    □ Avgjort mindre enn jeg pleier
    □ Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk
    □ Uten tvil svært ofte
    □ Svært ofte
    □ Ikke så veldig ofte
    □ Ikke i det hele tatt

14. Jeg kan glede meg over en god bok eller et radio eller et TV-program
    □ Ofte
    □ Fra tid til annen
    □ Ikke så ofte
    □ Svært sjelden

(Ett kryss på hver linje)

1. Har du problemer med at du føler deg sliten?  
   □ Mindre enn vanlig  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

2. Trenger du mer hvile?  
   □ Nei, mindre enn vanlig  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

3. Føler du deg søvnig eller døsig?  
   □ Mindre enn vanlig  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

4. Har du problemer med å komme igang med ting?  
   □ Mindre enn vanlig  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

5. Mangler du overskudd?  
   □ Ikke i det hele tatt  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

6. Har du redusert styrke i musklene dine?  
   □ Ikke i det hele tatt  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

7. Føler du deg svak?  
   □ Mindre enn vanlig  □ Som vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

8. Har du vansker med å konsentriere deg?  
   □ Mindre enn vanlig  □ Som vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

9. Forsnakker du deg i samtaler?  
   □ Mindre enn vanlig  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

10. Er det vanskeligere å finne det rette ordet?  
    □ Mindre enn vanlig  □ Ikke mer enn vanlig  □ Mer enn vanlig  □ Mye mer enn vanlig

11. Hvordan er hukommelsen din?  
    □ Bedre enn vanlig  □ Ikke verre enn vanlig  □ Verre enn vanlig  □ Mye verre enn vanlig

12. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart?  
    □ Mindre enn en uke  □ Mindre enn tre måneder  □ Mellom tre og seks måneder  □ Seks måneder eller mer

13. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det?  
    □ 25% av tiden  □ 50% av tiden  □ 75% av tiden  □ Hele tiden

TAKK FOR HJELPEN!
# ERRATA

Cor – correction

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<td>Cor</td>
<td>anti</td>
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PAPERS