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Serum Platinum retention and long-term effects in Testicular cancer survivors

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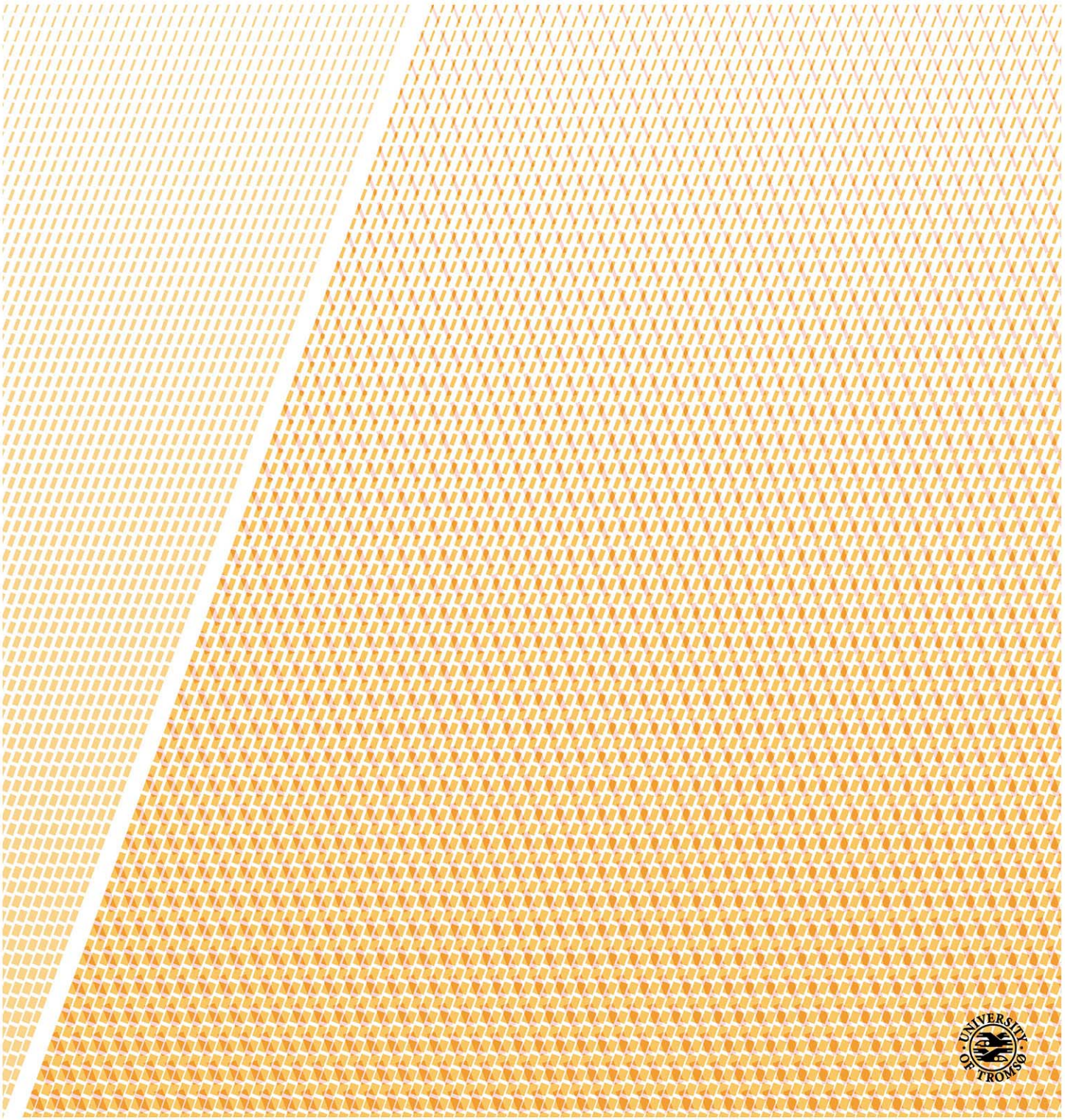

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III. Long-term serum platinum changes and their association with cisplatin-related late effects in testicular cancer survivors

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ABBREVIATIONS

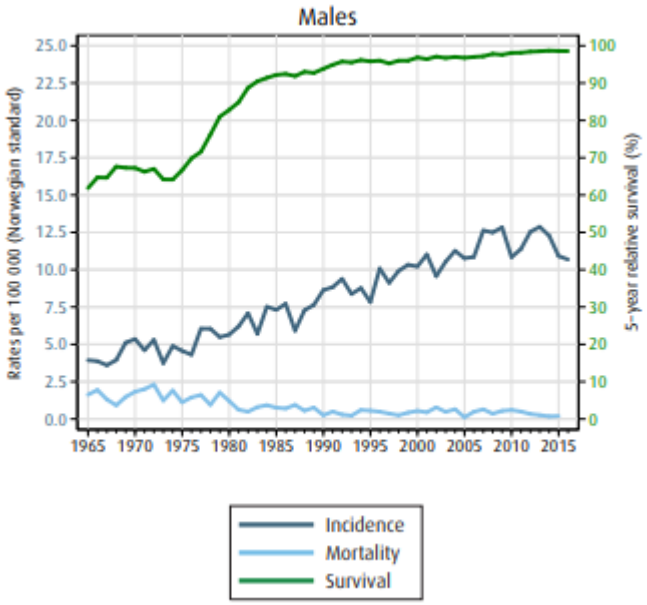
BEP	Bleomycin, etoposide and cisplatin
BIP	Bleomycin-induced pneumonitis
CBCT	Cisplatin-based chemotherapy
CI	Confidence interval
CIPN	Chemotherapy-induced peripheral neuropathy
Cps	Counts per second
CT	Computed tomography
CV	Cardiovascular
CVB	Cisplatin, vinblastine and bleomycin
CVD	Cardiovascular disease
Endocrine-GF	Endocrine gonadal function
EORTC	European Organization for Research and Treatment of Cancer
EP	Cisplatin and etoposide
GCT	Germ cell tumor
GFR	Glomerular filtration rate
GP	General Practitioner
HR	Hazard ratio
ICP-MS	Inductively coupled plasma mass spectrometry
Loq	Level of quantification
LH	Luteinizing hormone
MRI	Magnetic resonance imaging
NCEP	National Cholesterol Education Program
NRH	Norwegian Radium Hospital
NTX	Neuro- and ototoxicity
OLR	Ordinal logistic regression
OR	Odds ratio
PGE	Platinum group elements
Pt	Serum platinum
RR	Relative risk
RPLND	Retroperitoneal lymph node dissection
RT	Radiotherapy
SD	Standard deviation
SI	Survey 1
SII	Survey 2
SCIN	Scale for Chemotherapy-Induced Neurotoxicity
SHBG	Sex hormone-binding globulin
SWENOTECA	The Swedish-Norwegian testicular cancer group
TC	Testicular cancer
TCSs	Testicular cancer survivors
UNN	University Hospital of North Norway
WHO	The World Health Organization

1. INTRODUCTION AND BACKGROUND

1.1 The population of cancer survivors is growing

In Norway, a country with roughly 5.3 million inhabitants, nearly 33 000 new cancer incidents are reported each year, moreover approximately 262 000 prevalent cancer patients were reported alive at the end of 2016[1]. For testicular cancer (TC), the worldwide incidence has doubled during the past four decades, and TC is now the most prevalent solid tumor in men between 15 and 34 years of age[2,3]. The improvement in TC survival increased rapidly during the 1970s due to the introduction of cisplatin therapy for advanced germ cell tumors (GCT), leading to a greatly improved prognosis for testicular cancer. Since we today consider TC as a highly curable malignant disease (Figure 1), the prevalence is rising, and in 2016 close to 7500 Norwegian testicular cancer survivors (TCSs) were registered.

Figure 1. Age-adjusted incidence, mortality and survival rates of testicular cancer, from 1965-2014 in Norway[1]. Adapted from www.kreftregisteret.no; cancer in Norway 2016.



As most TCSs are young at diagnosis, they may live for another 30-50 years after successful treatment for TC. Consequently, the number of long-term TCSs are growing steadily, which in turn has led to an increasing interest in the long-term side-effects of cancer therapy.

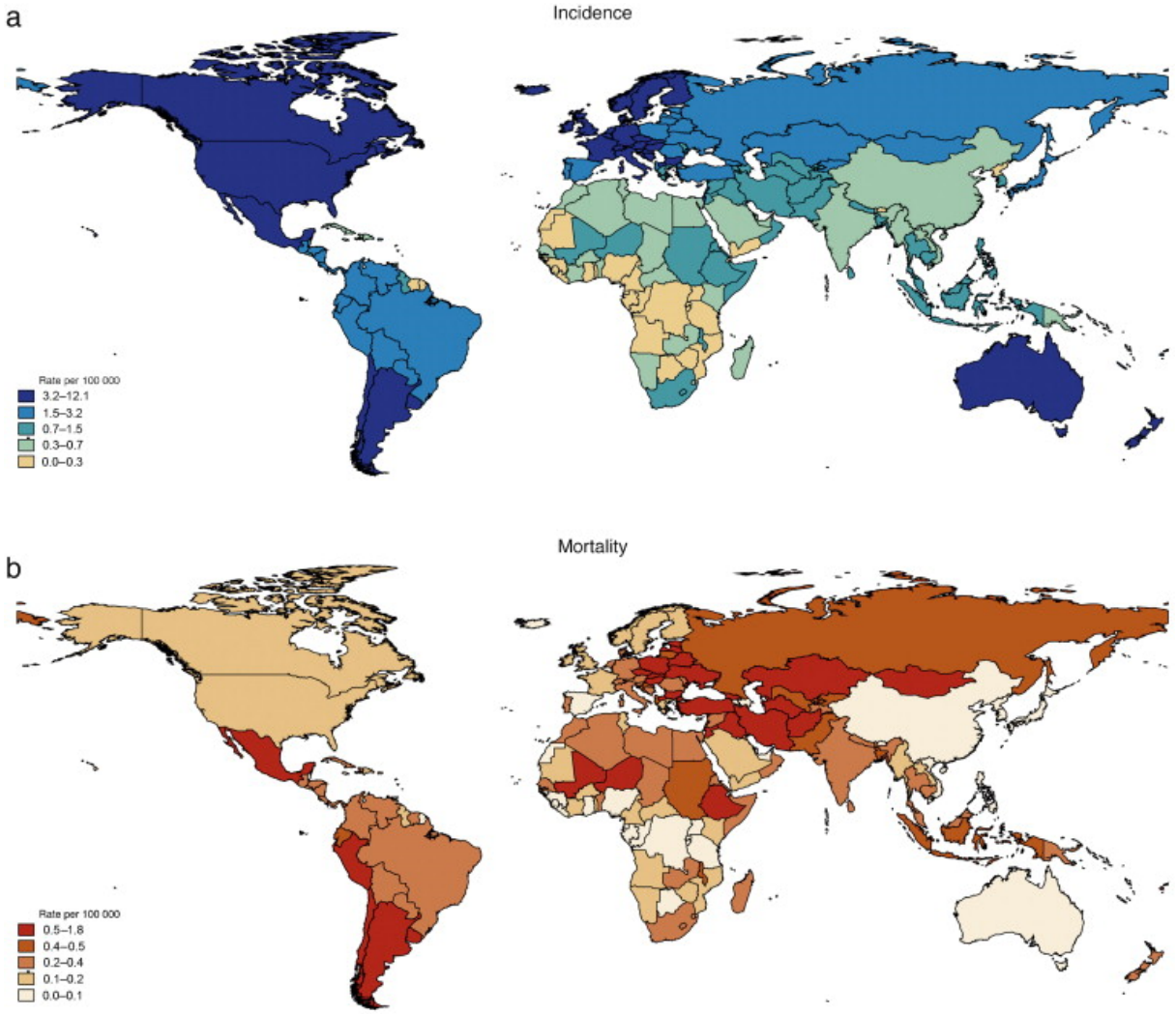
Numerous studies focusing on TCSs have identified increased risks for several long-term and late effects associated with cisplatin-based chemotherapy (CBCT), such as cardiovascular disease (CVD), hypertension (HT), ototoxicity, Raynaud's phenomenon, peripheral neuropathy, decreased renal function, decreased pulmonary function, sexual dysfunction, reduced endocrine gonadal function, obesity and hypercholesterolemia[4-15]. High levels of residual serum platinum (Pt) have been measured in several long-term follow-up studies after CBCT, and up to 10% of the retained Pt species has been demonstrated to remain its activity[16-18]. A relationship between retained Pt and the development of late effects has been hypothesized[16,19-21].

Treatment burden and some genetic polymorphisms[22] are currently the only identified risk factors associated with particularly high risk for long-term effects in TC patients after CBCT. When this study was initiated, a few reports had demonstrated that Pt was measurable in serum several years after treatment with CBCT[17,23]. However, only one study had evaluated the association between Pt and long-term effects (neuro- and ototoxicity)[16]. Further research to clarify associations between long-term Pt and late effects in TCS was recommended[24]. Thus, increased awareness and knowledge regarding long-term CBCT-related toxicity and its related mechanisms was considered essential to prevent and reduce adverse events in future TC survivors.

1.2 Epidemiology and risk factors for testicular cancer

The TC incidence is highest in the Northern parts of Europe and North-America and lowest in Asia and Africa[3,25]. In Denmark and Norway, almost 1% of males are diagnosed with a TC during their life-time[2,3,26], and these countries have the highest worldwide incidence rates. In total, 285 men were diagnosed with TC in Norway in 2016, corresponding to an age-adjusted incidence rate at 10.7 per 100 000[1]. This rate is almost tripled compared to the registered rate during the 1960s. But even though the incidence rates are increasing in most European countries (Figure 2), the mortality rates are declining[3].

Figure 2. Age adjusted TC a) incidence rates and b) mortality rates[3]. Permission obtained from Elsevier.



Although TC is not a frequent malignancy overall, it is the most common cancer among 15-49 year old males. TC has the lowest median age at diagnosis of all cancers among adults (36 years)[1]. Only 11% of Norwegian males diagnosed with TC in the period 2012-2016 were older than 50 years[1].

The overall cancer specific 10-year survival for non-seminomatous germ cell tumor (NSGCT) in Norway is currently 95%, and roughly 67% among poor-prognosis patients[27]. Today, no other malignancies have cure rates which can compete with TC, and TCSs have life expectancies almost similar to healthy age-matched men[28,29].

Since the incidence of TC has increased steadily during the last decades, a possible relationship with increased exposure to carcinogens from the environment has been implied, but the causes and mechanisms of TC development are still not well understood. Yet, the strongest known risk factors for TC are a previously diagnosed TC, a family history of TC and cryptorchidism[30-32].

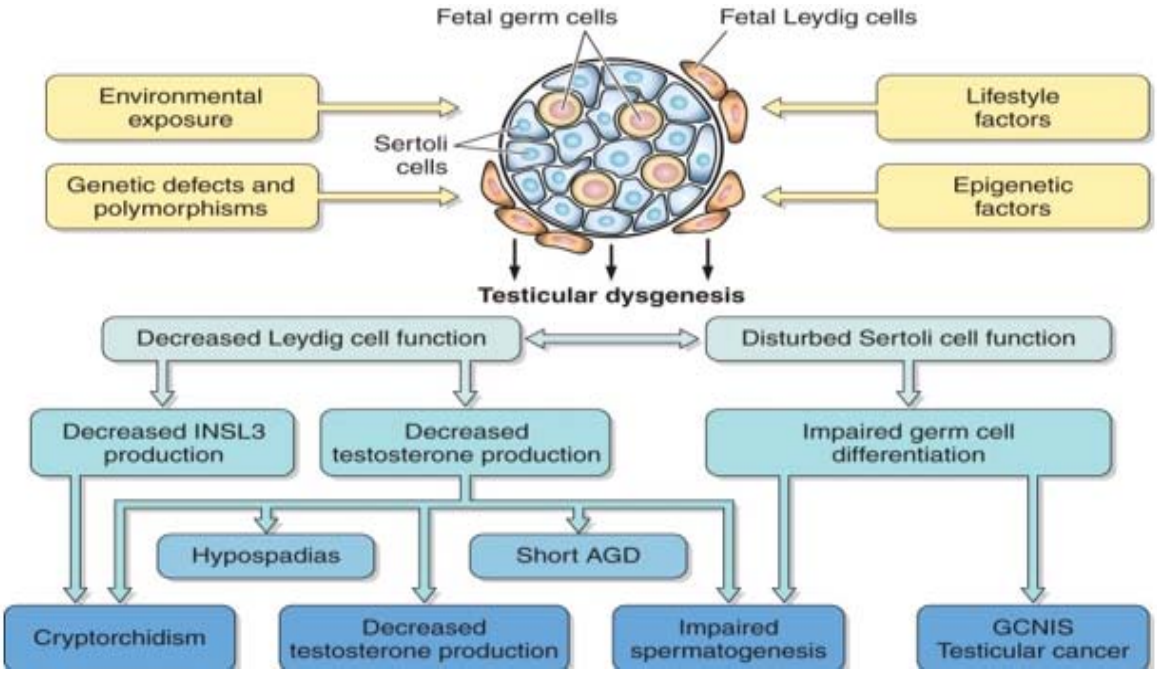
In a Norwegian study with roughly 2000 TCSs treated during 1953-1990, the cumulative risk of developing a second germ cell cancer after 15 years was 5% and 3.4% for non-seminomas and seminomas, respectively[32]. The risk for a second germ cell cancer diagnosis is thus significantly higher than the initial TC risk in the general population, with a cumulative risk of roughly 1%.

Family studies have shown that sons and siblings of TC patients have a 4-6-fold and 8-10-fold increased TC risk, respectively[33]. The remarkably high risk within these families might represent the impact of shared genes or similar childhood environment. The combination of several susceptible genes has been hypothesized to contribute to the development of TC. However, the rapid increase in TC incidence and the fact that sons develop TC at younger age than their TC affected fathers, underscores the added effect from environmental factors, as the genetic composition in the population is not believed to change during a few generations only[34].

The fact that siblings have a greater risk of TC development than sons of TC patients, indicates a possible effect of environmental disruptors in addition to genetic factors.

Increasing adult height is associated with testicular cancer[35], and the lifetime risk of having TC follows a typical birth cohort pattern[36], implying that the causative factors for TC initiate their effect *in utero* or early in life. The TC risk among first-generation immigrants reflects the risk in the country of origin. On the other hand, second-generation immigrants have a risk close to the level observed among natives in their new country[37]. Taken together, environmental influences early in life are believed to increase the TC risk. Other less significant risk factors include testicular atrophy, infertility, inguinal hernia, hydrocele and other disorders of male sexual differentiation[38]. The association between TC risk and testicular developmental problems, such as infertility and testicular maldescent, have led to the theory of a "testicular dysgenesis syndrome" (TDS)[38,39], where TC is the most serious manifestation of this syndrome (Figure 3).

Figure 3. The testicular dysgenesis syndrome[38]. Adapted from Skakkebaek et al.



This feature has been hypothesized to originate *in utero*, and both environmental, genetic and epigenetic factors as well as lifestyle factors are probably involved[40]. Accumulating evidence suggest that changes in the hormonal ambience, and particularly increasing estrogen exposure, are linked to TDS and a rising incidence of TC[41].

1.4 Malignant germ cell tumors (GCTs)

GCTs account for approximately 95% of all malignant tumors in the testes. The remaining tumors are composed of sex-cord tumors, lymphomas or metastases, and will not be further discussed in this thesis. Testicular GCTs are histopathologically classified into two groups, seminomas and non-seminomas[42], both derived from a pre-invasive germ cell neoplasia in situ (GCNIS), which originates from transformed fetal gonocytes. Overall, at the time of diagnosis, about 25% of men with GCT have metastases[43].

Pure seminomas normally affect men in their thirties and forties. Unlike non-seminomas, the majority of men with seminomas have tumors localized to the testis at presentation (about 85%)[44], and rarely have metastasis beyond the retroperitoneal lymph nodes at disease debut[45]. A shift towards a higher proportion of seminomas has been observed during the last decades , and the seminomas are now slightly more common than non-seminomas[46].

Roughly 40-45% of patients with TC are diagnosed with non-seminomas, and of these 40-45% will present with metastases in the lymph nodes, the lungs and/or other organs. Non-seminomas normally affect men in the early-adult life, and are a clinically more aggressive GCT[43]. The histology of non-seminomas are heterogenous, and includes variants of embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. Non-seminomas can consist of a single histopathologic variant, or a mixed variant where also seminoma elements can be included.

In approximately 5% of GCTs the primary site of disease is extra-testicular, i.e. extra-gonadal germ cell tumors (EGGCTs). These tumors are located in the midline of the body, usually in the mediastinum or in the retroperitoneum. The non-seminoumatous EGGCTs have poorer prognosis compared with the other GCTs, and EGGCTs originating in the central nervous system require treatment different from the therapy reported hereein[47].

1.5 Tumor markers

The conventional serum protein biomarkers α-fetoprotein (AFP) and human chorionic gonadotropin (hCG) are used to assist in diagnostics, treatment response evaluation and follow-up assessment of GCTs, but their use is generally restricted to tumors containing the relevant biomarker producing malignant subtypes. At diagnosis, roughly 60% of all GCT patients, regardless of stage, test positive for these markers; hCG may be increased in 30-35% and 10-20% of patients with non-seminomas and seminomas respectively, while AFP is increased in 50-60% of non-seminoma patients[43]. In patients with disseminated disease serum hCG and/or AFP are elevated in 85% of cases. Both AFP and hCG are essential in diagnosis, prognosis and treatment of patients with germ-cell TC, and should be determined both before and after orchiectomy, and during and after further treatment[48]. Elevated markers pre orchiectomy should normalize after orchiectomy in the case of stage I disease, and hCG and AFP have half-lives of 1-3 days and about seven days, respectively[48]. Rising or lack of normalization of markers after orchiectomy indicate the presence of metastatic disease. A tumor markers decline slower than their half-life during chemotherapy, may indicate treatment resistance. Consequently, some collaborative groups recommend intensification of treatment in this situation[27,49].

Serum lactate dehydrogenase (LDH) levels are also used at diagnosis to assist with treatment decisions in patients with metastatic NSGCTs, but this marker lacks sufficient specificity to be useful in diagnosis or monitoring[48]. Importantly, only 3% of the TC patients that relapsed after a diagnosis of stage I seminoma were identified using standard tumor markers, but detection rate was 87% for CT imaging[50].

Current priorities in GCT research include the identification of novel biomarkers for malignant disease, to assist in diagnosis, correct staging and reduce the need for repeated cross-sectional CT imaging in follow-up monitoring, hence reducing the associated radiation burden and risk of second malignancy development[51]. Micro-RNAs represent novel biomarkers for detecting TC, with a high sensitivity of 86% and a specificity of 92% of miR-371a-3p[52,53]. Importantly, miR-371a-3p is expressed both in seminoma and non-seminoma as opposed to the classical GCT markers.

1.6 Staging

TC treatment is based on the histological diagnosis, tumor marker levels including lactate dehydrogenase, and the site(s) of or absence of metastases[42]. In Scandinavia TCSs are staged according to the Royal Marsden Hospital System (RMHS), after orchiectomy (Table 1)[54].

Table 1. Classification of testicular cancer in clinical stages (Royal Marsden)[54].

Stage	**Disease extensiveness**
I	No detected metastases, either clinically, radiologically, or biochemically
IMk+	Pathological values of the serum markers AFP and/or hCG beta, without other signs of metastases
II	Lymph node metastases under the diaphragm. The size is measured in horizontal diameter (A<2cm, B 2-5 cm, C>5 cm)
III	Lymph node metastases above the diaphragm. (A<2cm, B 2-5 cm, C>5 cm)
IV	Extra lymphatic metastases (most often to the lungs) L1 ≤ 3 metastases to the lungs, none > 2 cm L2 > 3- ≤20 metastases to the lungs, none > 2 cm L3< 20 metastases to the lungs, one or more > 2 cm L4 > 20 metastases to the lungs

To decide on the therapy for metastatic TC, three additional prognostic groups were established by The international Germ Cell Consensus Classification Group (IGCCCG) (Table 2)[55].

Table 2. Definition of the Germ Cell Consensus Classification[55].

Classification	**Nonseminoma**	**Seminoma**
Good risk	Gonadal or retroperitoneal primary tumor No non-pulmonary visceral metastases Good tumor markers (AFP<1.000 µg/l and hCG<5.000 IU/l and LDH<1.5 x Normal)	Any primary site No pulmonary visceral metastases Normal AFP, any hCG, and any LDH
Intermediate risk	Gonadal or retroperitoneal primary tumor No non- pulmonary visceral metastases Intermediate tumor markers (AFP 1.000-10.000 µg/l or hCG 5.000-50.000 IU/l and LDH 1.5-10 x Normal)	Any primary site Non-pulmonary visceral metastases Normal AFP, any hCG, and any LDH
Poor risk	Mediastinal primary tumor or Non-pulmonary visceral metastases or poor tumor markers (AFP>10.000 µg/l or hCG>50.000 IU/l or LDH>10 x Normal)	Not applicable

1.7 Treatment principles for TC

1.7.1 How the TC treatment has evolved through the past half century

Half a century ago, limited metastatic TC was treated by surgically removing retroperitoneal lymph nodes with bilateral templates [retroperitoneal lymph node dissection (RPLND)]. 5-Year survival rates were poor, reaching about 50% during the 1950s. The surgical techniques evolved gradually during the 1980s, and today modified nerve-sparing and unilateral surgical techniques are used to reduce side effects[56-58]. Residual vital tumor tissue or teratoma is found in approximately one third of retroperitoneal post-chemotherapy non-seminoma lesions <2 cm in diameter, despite modern CBCT[59]. According to the Swedish–Norwegian testicular cancer (SWENOTECA) project recommendations, post-chemotherapy RPLND remains important for non-seminoma patients with retroperitoneal lesions of 1cm or more, while those under 1 cm will be observed if tumor markers are normal.

Both seminoma and non-seminoma patients with localized disease or retroperitoneal lymph node metastases have been treated with radiotherapy (RT) since the 1950s[60]. Since the 1980s the prescribed dose and target volumes have decreased gradually, and the treatment techniques have improved[61,62]. Seminoma patients with limited retroperitoneal metastases can still benefit from RT today[42,63].

In the 1960s, before cisplatin was introduced as TC treatment, several chemotherapeutic drugs were used against metastatic TC, with survival rates of 10-20% for disseminated disease[64]. The introduction of a combination of vinblastine and bleomycin led to an overall response rate of 75% including partly durable complete remissions in 32% of the patients[65]. The addition of cisplatin to the regimen of vinblastine plus bleomycin, known as the PVB regimen, was introduced by Einhorn and Donohue in the mid-70s. Intriguingly, 5-year survival rates reached 64% in patients with metastatic TC[66]. Aiming to reduce toxicity and increase

efficacy, vinblastine was substituted with etoposide during the 80s (known as the BEP regimen)[64,67]. CBCT is today routinely administered for patients with stage II–IV testicular GCTs according to IGCCCG prognostic criteria[55], and the BEP regimen is still considered as the standard treatment option in first line for disseminated TC[68]. Active surveillance or adjuvant chemotherapy are the typical treatment-options for stage I TC patients in Europe[61,62].

1.7.2 Treatment principles within our study cohort (1980-1994)

When a testicular malignant tumor is suspected, scrotal ultrasound and tumor markers are mandatory. Patients are initially treated with orchiectomy, which is both a diagnostic and therapeutic procedure in stage I disease. During the treatment period (1980-1994), which the follow-up studies this thesis is based upon, all patients had X-ray or CT of the thorax, and CT of the abdomen and pelvis performed after histologically confirmed germ cell TC diagnosis. The clinical staging during the treatment time period was performed according to the Royal Marsden Staging System (Table 1).

All men included in both Norwegian follow-up studies [survey I (SI) and survey II (SII)] were treated according to the SWENOTECA collaboration[69,70] or the European Organization for Research and Treatment of Cancer and Medical Research Council protocols[71-76].

1.7.3 The most common cytotoxic agents used during 1980-1994

In SI and SII, most chemotherapy treated TCSs received an initial regimen with either CVB, BEP, or EP (cisplatin in combination with etoposide), with ifosfamid as first line salvage therapy. Cisplatin was usually administered ad modum Einhorn, i.e. a dose of 100 mg/m^2 over the course of 5 days per cycle (daily dose of 20 mg/m^2). Within specific research protocols cisplatin was given at higher dose intensities (dose-intensive), either with cisplatin above 100

mg/m^2 per cycle or by administering the same cisplatin dose over less days[72,77-79]. A strict hydration regimen was standard for all CBCT regimen.

Cisplatin forms cross-links with the cell's DNA and induces apoptosis[80]. Its major dose-limiting acute toxicity is renal damage, which is ameliorated by prophylaxis in the form of high fluid administration/intake and furosemide administered when needed. Nausea and vomiting represent bothersome side-effects of cisplatin, which are usually avoided by modern antiemetic treatment introduced in the 1990s[81]. Other typical side-effects are neuro- and ototoxicity (NTX)[82].

Bleomycin induces DNA strand scissions by free radical actions eventually inducing cell death. Bleomycin-induced pneumonitis (BIP) represents its major dose-limiting effect[83]. BIP can ultimately lead to lung fibrosis, by endothelial damage of the lung vasculature due to bleomycin-induced cytokines and free radicals. Several studies suggest that the bleomycin administration route, dose, higher age, smoking, thoracic radiotherapy, oxygen rich air (ventilation during surgery etc.), and growth factors might increase the risk of BIP[83].

Etoposide, a topoisomerase inhibitor, induces cell death by preventing DNA strand re-ligation. Its major dose-limiting side-effect is myelosupression[84].

Vinblastine is a vinca-alkaloid which binds to tubulin, thereby inhibiting the assembly of microtubules and DNA repair[85]. Myelosuppression can occur during treatment, and neurotoxicity is a prevalent side-effect[82].

Carboplatin is a second-generation Pt compound, acting similarly to cisplatin by forming reactive Pt complexes that bind to nucleophilic guanine-cytosin-rich sites in DNA, thereby inducing intra- and inter-strand crosslinks. Carboplatin is more chemically stable compared with cisplatin, resulting in a lower reactivity with DNA, therefore the doses needed to receive equivalent clinical effects are four times higher. With regard to toxicity, carboplatin is less nephrotoxic and less emetogenic than cisplatin without relevant neuro- or ototoxicity.

Myelosuppression is considered the major toxic effect of carboplatin, particularly thrombocytopenia with a nadir usually between day 21 and 28[86].

1.7.4 Specific treatment of seminoma patients through 1980-1994

Infradiaphragmatic radiotherapy was typically given to all men with early-stage seminomas (stage I and IIA). Most men received an L-field or dogleg field, involving opposing anterior and posterior fields covering the para-aortic and ipsilateral iliac nodes, while a few patients had para-aortic fields only[87,88]. During the 1980s and 1990s the radiation dose for these stages was gradually reduced from 36–40 Gy to 25.2–27 Gy[89]. TCSs with stage ≥IIB were treated with CBCT. However, some patients received additional radiation or RPLND.

1.7.5 Specific treatment of non-seminoma patients through 1980-1994

Until 1990, men with stage I or IIA were treated with a modified bi- or ipsilateral template RPLND. Nerve-sparing surgery was introduced in 1989. Adjuvant chemotherapy was given if lymph node metastases were present in the pathology specimen[69,90]. After 1990, patients with stage I non-seminomas were either followed closely with radiographic imaging, clinical examination and tumor markers (surveillance) or treated with one to three cycles of adjuvant chemotherapy[70]. Patients with disseminated non-seminomas generally received three or more cycles of CBCT, often followed by RPLND and resection of tumors affecting other organs if possible[74].

2. LATE EFFECTS

2.1 General aspects of cancer survivorship

Today, the current 5-year relative survival rate for all cancers taken together approximates 70%. Given the continuously increasing number of cancer survivors, in-depth investigations of treatment-related toxicities affecting health, quality of life and functional status are particularly important.

Most therapeutic modalities for cancer are associated with a wide range of late complications, from minor and treatable to serious or, occasionally, potentially lethal conditions. Thus, there is today a greater recognition of symptoms that persist after the completion of treatment and those that arise years after primary therapy. *Long-term side effects* generally refer to any side effects or complications of treatment that begin during treatment and continue beyond the end of treatment. *Late effects*, in contrast, appear months to years after the completion of treatment, and refer specifically to toxicities that are absent or sub-clinical at the end of therapy and become manifest at a later time-point[91].

Second cancers and CVD represent the most serious late effects. Furthermore TCSs are at risk of nephrotoxicity, pulmonary toxicity, NTX, hypogonadism, decreased fertility, and psychosocial problems like fatigue and depression[4,10,92,93].The debut time and the risk of these numerous and different adverse effects vary according to treatment type (chemotherapy, RT or both) and intensity. Apart from the treatment burden and some genetic polymorphisms, there is still little knowledge about the mechanisms for late effect evolvement, and it is yet not possible to identify TCSs at high risk for late effects after TC treatment.

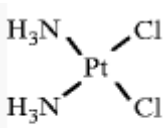
CBCT is associated with several of the known late effects affecting TCSs, and long-term Pt residuals have been suggested as a possible late effect biomarker of interest. Platinum

retention and typical cisplatin related long-term and late effects studied in this thesis will be discussed in detail below.

2.2 Long-term serum Platinum retention after cisplatin treatment

Platinum is a member of the platinum group elements [PGE, (platinum, pallidum and rhodium)] and has six naturally occurring isotopes. It is a very rare metal, occurring mostly in some nickel and copper ores in South-Africa[94]. Pt is considered a noble metal as it is highly inert, even at high temperatures, and therefore used in catalytic converters, electrical and jewelry industry, laboratory and dentistry equipment. Additionally, platinum is an important compound of the platinating cytotoxic agents, such as cisplatin (Figure 4), oxaliplatin and carboplatin.

Figure 4. The chemical structure of Cisplatin



Cisplatin

Of the high cisplatin doses used in TC treatment, only approximately 1% of the cisplatin that enters the cells is hydroxylated and binds to the guanine residue of DNA, leading to interruption of transcription and apoptosis by bending the double helix[95]. The remaining cisplatin (not associated with DNA) can bind to extra- and intracellular proteins. The first day after cisplatin treatment, 30% of cisplatin will be eliminated from the body, while after 5 days only 50% of the cisplatin is eliminated[96]. The elimination half-life of cisplatin may be described by numerous half-lives which increases with longer follow-up periods[23]. Between 120 and 240 months after cisplatin administration, the half-live has been calculated to be 54 months[97].

Several studies have shown that with cisplatin-containing chemotherapy, plasma and tissue Pt levels are still considerably elevated years after chemotherapy[17,23,98]. Long-term Pt levels are related to time since cisplatin administration, age, dose and glomerular filtration rate (GFR). Studies revealed that up to 10% of the retained Pt remains reactive (*ex vivo)*[23]. In 2012 an association between increasing long-term serum Pt levels and increasing severity of neuro- and ototoxicity was described, and the assumption that reactive serum Pt several years after chemotherapy exposition may contribute to vascular and organ damage was then hypothesized for the first time[16].

2.3 Neuro- and ototoxicities

NTX, including peripheral neuropathy (paresthesias), Raynaud's phenomenon, hearing impairment, and tinnitus are well-documented cisplatin-related side effects[4,16,82,99-101].

A typical long-term effect after CBCT is chemotherapy-induced peripheral neuropathy (CIPN), developing during or shortly after treatment[102]. Typically, CIPN presents as a "stocking and glove" distribution in feet and hands, due to the vulnerability of the long nerves[103]. The prevalence of CIPN varies from 10 to 100% depending upon the particular anticancer drug, drug combination administered and/or the dosing regimen[104]. After CBCT the prevalence of peripheral neurotoxicity is 20-30%[82]. The exact pathogenesis of long-term CIPN is largely unknown, but relatively high Pt levels have been found in the dorsal roots in a post-mortem and biopsy study[105]. Also, the retained serum Pt levels have been found to correlate with the administered cisplatin dose[16].

Raynaud's phenomenon is the most frequent NTX symptom reported by up to 39% of TSCs receiving CBCT[82,106]. Typically, it is a well-demarcated discoloration of the fingers and

toes upon exposure to cold, for which bleomycin has been considered the primary causative agent[107,108]. In addition, an association with cisplatin is likely as the incidence of Raynaud-like phenomena following chemotherapy for TC increased after the introduction of cisplatin[109]. Furthermore, the risk of experiencing Raynaud's phenomenon was increased four-fold for TCSs in the highest compared with the lowest Pt quartile for hands (OR, 4.15; 95% CI, 1.60 to 10.76) and feet (OR, 4.46; 95% CI, 1.70 to 11.71), median 12 years after receiving chemotherapy[16].

Cisplatin is one of the most ototoxic drugs in clinical use causing permanent, bilateral, sensorineural, high frequency hearing loss in a substantial number of patients[110]. The reported prevalence of hearing impairment in TCSs varies considerably, probably partly due to a lack of standardized measurement tools[110]. The most comprehensive and recent report on hearing function among TCSs after CBCT reported almost one in five (18%) patients to experience severe to profound hearing loss[111]. Additionally, many develop permanent tinnitus (40%)[82], which is demonstrated to be significantly correlated with reduced hearing at each frequency. Moreover, 50% of patients receiving a cumulative cisplatin dose of >200 mg/m^2 have a significant reduction in their hearing, with a severe to profound hearing loss in both ears[111].

Considerable inter-individual variability in susceptibility to cisplatin ototoxicity has been described. Other known ototoxic risk factors are: Very young or old, renal failure, pre-existing hearing loss, noise exposure[112,113], nutritional deficiency states (including anemia and serum hypoalbuminemia)[114], polymorphism of the GST-P1 gene[115], and radiotherapy affecting the cochlea at doses higher than 48 Gy[113].

2.4 Endocrine-gonadal function

TCSs are often concerned about their sexual and reproductive function. However, the majority of men who have one healthy testicle produce sufficient male hormones and sperm to continue sexual relations and father children[116]. Still, cryopreservation of sperm is recommended prior to treatment and in particular before chemotherapy.

Testicular endocrine dysfunction includes insufficient testosterone production and/or compensatory increased luteinizing hormone (LH) levels, also called *hypoandrogenism*, while the exocrine dysfunction gives inadequate spermatogenesis with increased levels of follicle-stimulating hormone (FSH)[26]. Usually, the first sign of primary or testicular hypogonadism is an elevation of LH level, with subsequent testosterone decline if the LH stimulus is not sufficient. A significant rise in LH levels has, in fact, been detected in TCSs treated with orchiectomy only[117]. Several studies have identified long-term hypogonadism after cancer treatment, and approximately 50% of the TCSs have levels of sex hormones outside the reference range 18 years after treatment[5,118]. The paternity rate median 11 years after TC treatment varied from 81% in the surveillance group to 38% in the high-dose chemotherapy group. Overall, 62% of men receiving ≤ 850 mg cisplatin trying for conception became fathers[119]. Higher cumulative cisplatin doses are associated with higher LH levels, corresponding to premature hormonal aging[5]. The degree of both endocrine and exocrine hypogonadism is related to treatment intensity[120].

Intriguingly, more Pt has been shown to be retained by testicles after chemotherapy than by other hormone producing organs outside the brain[121]. However, the high prevalence of hypoandrogenism in TCSs may be explained by several factors: Orchiectomy, testicular dysgenesis syndrome, aging and post- orchiectomy therapy[26].

2.5 Cardiovascular disease

Several European studies have reported 1.4- to 7-fold higher CVD risk among CBCT-treated TCSs than in either the general population or in TCSs managed with surgery alone[122-125]. CVD in TCSs typically appears several years to decades after treatment[6]. Well-documented CVD related risk factors like hypogonadism, hypertension, obesity and the metabolic syndrome are significantly increased after treatment with CBCT[125-127], but the risk is highest for those treated with a combination of both RT and chemotherapy[125]. Mediastinal RT is especially toxic, but is no longer applied in TCSs[92,125]. CVD may be caused in TCSs by a direct vascular damage, e.g. an injured endothelium, possibly inducing atherosclerotic processes[128]. An indirect effect by increasing the levels of cardiovascular risk factors has been hypothesized[129]. Moreover, exposure to circulating Pt residuals has been suggested to initiate direct endothelial damage[124,130], and was for the first time shown to be associated with several of the most prominent risk factors of CVD in 2015[20].

Men treated with CBCT have a higher risk of coronary artery disease compared with the general population as they age, and should be particularly aware of risk factors such as hyperlipidemia, hypertension, obesity, and smoking[4]. Established risk prediction tools for predicting future CVD risk, like the Framingham or SCORE, do not take cisplatin dose into account and probably underestimate the true CVD risk after CBCT in TCSs[131,132].

2.6 Second cancers

Second cancer is the leading cause of death among long-term TCSs after treatment with either radiotherapy and/or CBCT[4]. Second cancers after RT are typically located in the former radiation field, most often in the stomach, pancreas, kidneys and the urinary bladder[133,134].

Several publications have demonstrated elevated relative risks for solid second cancers after CBCT in most follow-up periods, but particularly with follow-up beyond 20 years[135,136]. Overall, TCSs have a 1.7 to 3.5-fold increased risk of second malignant neoplasms, with a significantly increased 40% excess demonstrated for CBCT treated non-seminoma patients[133,136].

The rare second myeloid neoplasms occur median 5 years after primary TC treatment, and are associated with etoposide dose, with a possible concomitant effect of cisplatin[133,137,138]. Additionally, RT as primary treatment for TC is associated with a 3-fold risk of developing leukemia[139].

Patients diagnosed with stage I TC often choose postoperative surveillance as the risk for second cancers has not been shown to be increased after orchiectomy alone[135]. Nevertheless, these patients may be at an increased risk for developing second cancer induced by the radiation from diagnostic imaging[51,140]. Therefore, low-dose CT scan or even better, magnetic resonance imaging (MRI) has become the standard of surveillance-care in many institutions, and its use is encouraged by most TC specialists.

3. AIMS OF PRESENT THESIS

In 2010 further research to clarify associations between long-term serum Pt and late effects was recommended in an international workshop devoted to TCSs[24]. Longitudinal studies with consecutively assessed data are necessary to understand the associations between CBCT, long-term Pt change and treatment-related side effects as most published studies have had a cross-sectional design, with few exceptions[16,20]. Therefore, the aims of the present thesis were to evaluate the associations between serum Pt levels and long-term adverse effects in TCSs at two consecutive national surveys with up to 28 years of follow-up.

Aim 1) To describe the long-term serum Pt levels at SII, according to treatment groups (carboplatin, cisplatin>850 mg (cis>850 mg), cisplatin<850 mg (cis<850 mg) and orchiectomy), cumulative Pt-based dose and time since therapy in 458 TCSs treated during 1980-1994 (paper I).

Aim 2) To investigate the possible associations between long-term serum Pt levels at SII with NTX, endocrine-gonadal function and CVD risk factors and events, and the possible impact of smoking, in 292 TCSs treated with CBCT received during 1980-1994 (paper II).

Aim 3) To describe the long-term change in serum Pt levels from SI to SII and to evaluate whether the Pt change is associated with second cancers, renal function and NTX in 77 TCSs treated with CBCT (paper III).

4. MATERIAL AND METHODS

4. 1 The study design and study populations

The initiation of an unselected large Norwegian follow-up survey which focused on long-term treatment-related toxicity was motivated by the growing population of TCSs and the need of knowledge regarding their possible side-effects. These two subsequent surveys were conducted as Norwegian Urological Study Group (NUCG) studies, and all five university hospitals in Norway were involved in these studies. All long-term survivors (n=1,814) of unilateral germ-cell TC with the age of 18 to 75 years and treated during 1980-1994 were identified through the Cancer Registry of Norway and invited to participate. Exclusion criteria were bilateral orchiectomy for any reason, extragonadal germ cell cancer, other malignancies except skin cancer, and mental retardation. The patients' medical records were used to find information about all oncological treatment including relapse treatment, staging and histology.

In the first survey, SI (1998-2002), 1463 (81%) consented to participation and had an outpatient visit and blood samples drawn and analyzed at the responsible university hospital. Deep-frozen serum was stored only for patients at the Norwegian Radium Hospital (NRH) for supplementary analyses, including Pt levels.

Overall 1371 of the men from the first survey were invited to a second follow-up study during 2007-2008, SII, where 1093 (80%) participated. A clinical examination was performed and blood samples were drawn at the participants' general practitioner. All the blood samples were sent to the Oslo University Hospital for analyses.

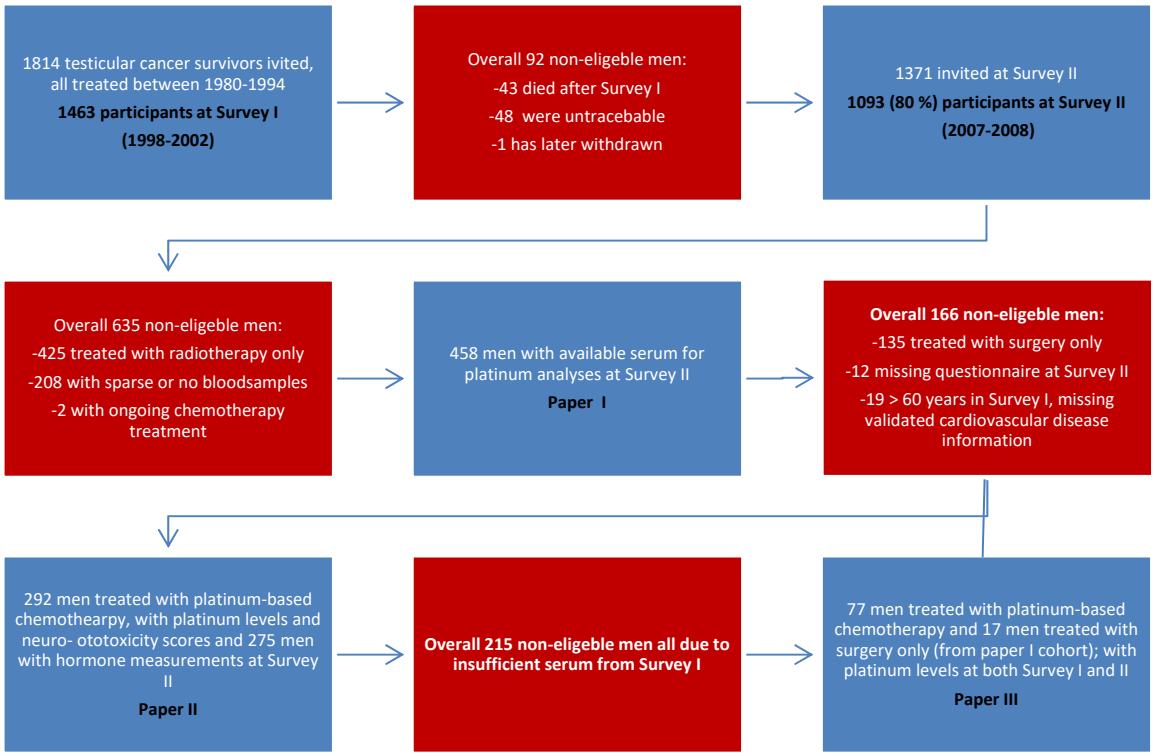
Among the TCSs in SII, 458 men treated with either CBCT or surgery had serum available for Pt levels measurements, giving the study population of paper I (Figure 5). A total

of 635 TCSs were excluded because they either had ongoing treatment, received RT treatment only or they lacked serum for the Pt analyses.

From the cohort that constituted paper I, we excluded men treated with surgery only, leaving 292 TCSs treated with CBCT to define the study population of paper II for investigation of Pt relations with late effects. Additionally, we excluded men >60 years at SI because they did not have validated CVD information[125], and all men lacking questionnaire information addressing problems regarding NTX. Two hundred and seventy-five men were assessable for hormone analyses in paper II, as 17 men who received testosterone substitution were excluded in the analyses of endocrine hypogonadism.

In paper III we wanted to measure serum Pt in samples from both SI and SII, to elucidate the longitudinal serum Pt change in relation with late effects, thus the study size was limited by the amount of frozen serum available at SI. As previous research within our research group had been performed on the plasma from TCSs, only 77 TCSs previously treated with CBCT and 17 controls had Pt measurements available at both SI and SII, thus constituting our study cohort in paper III. Only samples from NRH patients were frozen at -70ºC. Thus, Paper III involves TCSs treated at NRH exclusively.

Figure 5. Selection of the study populations constituting the papers



4.2 The treatment groups

All TCSs with advanced disease within this thesis received chemotherapy. Those treated with RT alone were considered ineligible. Most men had received treatment with CVB, BEP or EP regimens. Overall, two thirds of the 458 men in paper I had RPLND performed, and 41 men experienced a relapse. Twenty-four of the 458 TCSs in the cisplatin treatment groups received dose-intensive therapy. In addition, 19 men investigated in paper I were treated with carboplatin-based chemotherapy within research protocols[74-76], of whom five received both carboplatin-based and cisplatin-based chemotherapy during their treatment period. In paper II and III, 16 and five TCSs, respectively, received carboplatin.

An equivalent amount of carboplatin was throughout this study considered 4-fold less potent than cisplatin, conferring to studies based on treatment of ovarian cancer where these doses achieved a relative clinical equivalence[86,141]. For all men throughout this thesis that received carboplatin alone or in addition to cisplatin, we calculated their corresponding cisplatin dose by dividing their carboplatin dose by four before adding to their cumulative cisplatin dose.

In paper I, the individual treatment including relapse treatment established the categorization of TCSs into treatment groups: Surgery only (n=135, reference group), carboplatin only (n=14), cumulative cisplatin dose ≤850 mg (cis ≤850; n=252) and cumulative cisplatin dose >850 mg (cis >850; n=57). In paper II, only men treated with CBCT were included and no treatment groups were applied. In paper III, we used the following categorization of the TCSs: Controls (surgery only, n=17), and cases (cis≤ 850, n= 52; cis> 850, n= 17).

The cut-off at 850 mg cisplatin was set to separate 1) the TCSs receiving four courses or less of standard-dose CBCT from 2) TCSs receiving higher cumulative cisplatin doses due to a large number of cycles (progression, relapse or poor prognosis) or treatment with dose-intensive regimens. Men with a body surface area up to 2.1 m² with maximum four cycles with cisplatin-containing regimens were then allocated to the lower dose group, and TCSs who received dose-intensive regimens were allocated into the Cis> 850 group, even if they received a maximum of four cycles.

4.3 Serum platinum quantification

From SI and SII, serum samples from 94 and 458 TCSs, respectively, were analyzed for total serum Pt at St. Olav University Hospital in Trondheim, using well-established methods[23,142]. The samples were shipped on dry ice from the Oslo University Hospital, and then kept at -20°C until they were equilibrated for three hours at room temperature prior to analyses.

4.3.1 Inductively coupled plasma mass spectrometry (ICP-MS)

In order to determine the Pt levels, instrumentation with high sensitivity is required. ICP-MS is an instrument (Element 2, Thermo Scientific, Bremen, Germany) that consists of two main parts: An ion source (ICP) coupled to a mass analyzer (MS). The ion source is a partially ionized Argon gas, with very high temperature and electron density. When the sample is exposed to this ion source, the chemical bonds are broken and ions are produced. The sample ions are transported to the mass analyzer where they are separated on the basis of mass and charge. Serum is a complex matrix which makes it necessary to prepare the serum sample prior to the analysis with a weak acid. In order to quantify Pt content in the serum sample, the instrument is calibrated with a standard containing a certified platinum concentration. A relatively simple test and rapid instrumental analysis provide high capacity. ICP-MS has good detection properties and is now the preferred technique for determining metal and other trace elements in clinical trials.

4.3.2 Reagents and standards

We used doubly distilled concentrated HNO3 and HCl (Chem Scan AS, Elverum, Norway) and purified water produced from a MilliQ Element unit (Millipore, France) as reagents and a certified standard Pt solution at 1000mg/L (Spectrapure, Oslo, Norway) for preparation of calibrators. For the preparation of quality controls we applied oxaliplatin (St. Olav Hospital pharmacy, Trondheim, Norway). Both calibrators and controls were prepared by spiking Pt-free plasma samples as further described below.

4.3.3 Sample handling

We chose a simple dilution of 1+9 as sample preparation to reduce matrix effects and maintain detection power. This method is partly adopted from Brouwers et al[142]. Aliquots of 100µL sample were pipetted into clean test tubes (2mL polypropylene, Sarsted, Nűmbrecht, Germany) and diluted with 400µL H_2O and 500 µL dilution reagent [1% (v/v) HNO3, 1% (v/v) HCl and 2,000ng Ir/L in H_2O]. To provide proper mixing, each test tube was inverted five times.

Quality controls and calibrators were prepared by the same method, using Pt-free plasma. For external calibration, three calibrators (25, 250 and 1000 ng/l) were produced by spiking with the certified Pt solution. Quality controls were prepared at two levels by spiking Pt-free plasma with the oxaliplatin solution. A serum sample from a quality management program (QMEQAS, Quebec, Canada) with a known Pt value analyzed in every sequence to determine the accuracy of the method.

4.3.4 Instrumentation

The monitoring of Pt was performed in low resolution. A concentric nebulizer and a cooled (5 °C) cyclonic spray chamber made from PFA-material (ESI, Omaha, USA) and an auto sampler (Omaha, USA) constituted the sample introduction system.

The ^{195}Pt-isotope was monitored due to its lack of possible spectral interferences and high abundance. Internal standardization was used to balance for analytical issues. For this, ^{193}Ir was chosen, and we applied it at a final solution of 1,000 ng/L to all samples and calibrators.

To ensure optimal daily instrument performance, a solution containing 1,000 ng/L of indium, uranium and barium were used. Instrument settings were tuned to give typically readings like ^{115}In: 1.5 x10^6 cps (counts per second), ^{238}U: 2.0 x10^6 cps, and production of BaO^+

less than 0.3% of Ba^+. Plasma settings like nebulizer gas flow rate and torch alignment were adjusted daily.

4.3.5 Method Performance

Limit of quantification (loq) was calculated from 10 times the standard deviation of a series of blanks. Pt was analyzed in batches for SI and SII, with a time interval of approximately four years between the analyses, hence loq was calculated for SI and SII separately. The loq level for this method was 15 ng/l in SII and 13ng/l in SI. Serum Pt below loq was set to zero for both surveys. Linearity was proved for the concentration range from 15 to 10,000 ng/L. Based on quality control samples, inter-sequence precision in low level and high level were estimated to 9.9% and 5.1% in SII and 7.7% and 5.9% in SI, respectively. Intra-sequence precision in low level (100 ng/L) and high level (1,000 ng/L) were estimated to 3.6% and 1.2%, respectively. A serum sample from a quality management program gave mean values corresponding to a consensus value [143].

4.4 The questionnaires and neuro-ototoxicity assessment

In both surveys the questionnaires (see appendix) addressed several aspects of somatic and psychosocial health in long-term TCSs. It contained questions about social status, physical activity, comorbidities, medication use and smoking habits, and the information of such was based on self-report. If questions where left blank, individuals with missing data were categorized as healthy (comorbidities), without treatment (medication use) or missing (physical activity and smoking), respectively. All CVD information was validated[125], and overall eight men had missing NTX information from SI (paper III).

Additionally, the questionnaires included a validated six-item scale for chemotherapy-induced neurotoxicity (SCIN) addressing neuropathy (paresthesias) in hands and feet, Raynaud-like phenomena in hands and feet, tinnitus, and impaired hearing. The symptom scores ranged from zero (not at all), one (a little), two (quite a bit) to three (very much) (Table 3). Adding the six symptoms generated a total SCIN score ranging from zero to 18. The total SCIN score were categorized into four groups of similar size (quartiles), according to increasing symptoms (paper II). In the third paper, change within the six individual SCIN symptoms was categorized into three groups according to if the symptoms were decreasing, stable or increasing during the time-period from SI to SII.

Table 3. Scale for chemotherapy-induced neuro-oto-toxicity (SCIN)

Neurotoxicity	Question	Not at all	A little	Quite a bit	Very much
Paresthesias hands/fingers	Have you suffered from pain and/or tingeling in your hands/fingers?	0	1	2	3
Paresthesias feet/toes	Have you suffered from pain and/or tingeling in your feet/toes?	0	1	2	3
Raynaud's hands/fingers	Have you suffered from numb or cold hands/fingers?	0	1	2	3
Raynaud's feet/toes	Have you suffered from numb or cold feet/toes?	0	1	2	3
Tinnitus	Have you suffered from ringing in your ears?	0	1	2	3
Impaired hearing	Have you suffered from reduced hearing?	0	1	2	3

4.5 Assessments and definitions

In both SI and SII, resting blood pressure was measured with an automatic device or manually. Blood samples were drawn by venipuncture before 11 AM at the university hospital's outpatient clinic or at the TCSs general practitioners office, for SI and SII respectively, for assessments of

blood lipids, glucose, LH, testosterone, creatinine and serum Pt. The blood samples were drawn in a fasting state only in SII. In SII, all routine blood samples were analyzed at Oslo University Hospital to reduce the variation coefficient, since poor reproducibility of steroid hormones measurements has been observed[144]. Total testosterone and LH were determined using a commercial immunoassay.

In paper I, the serum Pt levels were categorized into quartiles to evaluate the risk of being in the highest quartile according to the four different treatment groups mentioned above.

In paper II, the same categorization into quartiles of Pt levels as in paper I was performed, to assess associations with different late effects according to higher Pt levels.

Levels of testosterone and LH from 599 controls were obtained from the Nordic reference interval project, and categorized into one to four with respect to cutoff values for the 25, 50 and 75 percentiles within each decadal age group[145]. To assess associations between Pt and disturbed endocrine gonadal function (endocrine-GF), testosterone and LH levels in 275 TCSs were assigned to one of these four categories, based on the percentiles derived from the reference group.

Also, in paper II CVD was defined as ischemic heart disease [angina and myocardial infarction (MI)], stroke or artery occlusion. CVD risk factors like hypertension, obesity, and metabolic syndrome were defined by the National cholesterol education program criteria (NCEP)[146]. Diabetes was defined as previously diagnosed diabetes based on information retrieved from the questionnaires or a serum glucose ≥ 11 mmol/l. Smoking status was defined as never, previous or current smoker.

In paper III, Pt change was defined as (Pt at SI minus Pt at SII)/ per year. Since most men had a Pt decline, the Pt change was called a Pt decline throughout paper III. All information

about second cancers after SII was retrieved from the Norwegian Cancer Registry updated December 31st, 2015. Only one man with a second cancer (malignant melanoma, diagnosed 1998) prior to SI was excluded from these analyses, as we wanted to address the relationship with the Pt change observed between SI and SII, considering the late effects.

Furthermore, in paper III, in line with a similar long-term Pt retention and late effect study in TCSs, serum creatinine was dichotomized at ≤ or >90 µmol/l[20].

In paper III, the smoking status was defined differently, according to if analyses were in relation with second cancers or NTX. Within the second cancer analyses smoking was defined as never, earlier or current smokers at SII, with never smokers as reference group. For NTX analyses, smoking habits were categorized in four groups; never, earlier, or current smokers (reference group) reported in both surveys (SI and SII), and stopped smoking between SI and SII. Within this paper the physical activity was defined as low, middle or high, with high as reference level, in line with previous publications[19,147].

4.6 Statistical methods

All p-values were two-sided and statistical significance was set at $P< 0.05$. The data were analyzed by using IBM SPSS (SPSS, Chicago, IL) statistics version 21.0 for both paper I and II and version 24.0 for paper III.

Categorical variables were presented as counts and proportions, and continuous variables were presented as median (range). The Mann-Whitney U test was used to compare median values of serum Pt or Pt change across different groups since the Pt levels were not normally distributed. Simple associations between continuous variables were analyzed with either Pearson correlation, Spearman's rank, or simple linear regression. The χ^2 test was used

to test associations between categorical distributions. Additionally, Pt levels were visualized with scatter plots.

Ordinal logistic regression (OLR) models were used to evaluate the risk of having serum Pt in the highest quartile according to treatment group, with the surgery group representing the reference group (paper I). Similarly, in paper II, the risk of having serum Pt in the highest quartile according to intensity of the toxicity of interest (separate symptom scores for NTX and the total SCIN score, or endocrine-GF) was assessed with OLR. OLR models assessed associations between both Pt change and cisplatin dose as the explanatory factors and all six SCIN symptoms in SII or with NTX change observed from SI to SII as dependent variables in paper III. Model assumptions in all the ordinal logistic regression models were checked by a test of parallel lines.

Cox proportional hazard regression models were used for analyzing the associations of serum Pt and cumulative cisplatin with respect to CVD incidence, with the observation time registered from the date of TC diagnosis until the date of first CVD event of interest or until the date of SII (paper II). Cox proportional regression models were also applied to analyze the risk of a second cancer diagnosis after SII according to Pt change from SI to SII and Pt levels at SII, with the observation time registered from the date of orchiectomy until the date of diagnosis of a second cancer, or until December 31st 2015 (paper III). In paper III, the analyses only included two variables because of the rule of ten events per variable in Cox regression models[148]. Visual inspection of log minus log of survival curves was used for model assumption in all Cox regression models.

Overall, data were presented as odds ratios (OR) or Hazard ratios (HR) with 95% confidence intervals (CIs), and both ordinal regression and Cox proportional hazard regression

models included administered cumulative cisplatin and age, as they were considered of high importance clinically.

4.7 Approvals

The Committee for Medical Research Ethics, the Southern Health Region of Norway, approved both of the surveys (S-98094 and S-07305b, for SI and SII, respectively) and the additional Pt studies presented in this thesis (2015/1630). All participants gave informed written consent for attendance in both studies and concession for obtaining relevant medical record data.

5. RESULTS

In SI (N=1463), the non-responders were not different from responders with respect to age at follow-up, histology, stage or treatment. Because of our exclusion criteria (not allowing men treated with RT only and men >60 years at SI) the 458 men participating in paper I had somewhat lower age at disease debut, longer follow-up time, and higher TC stages compared with the 1093 men participating in SII.

5.1 Paper I

Long-term platinum retention after treatment with platinum-based chemotherapy in testicular cancer survivors: A 20-year follow-up study. (Anticancer Research 2015)

This paper describes the serum Pt levels according to treatment and follow-up time in 458 TCSs. The TCSs were categorized into four treatment groups: Surgery (n=135), carboplatin (n=14), cis≤850 mg (n=252) and cis>850 mg (n=57). The observation time was from 16 to 20 years (range 13-28) for all, and the majority of men had non-seminoma (87%). Overall, 51% had metastatic disease at the diagnosis.

The median Pt level for the cis≤850 group 85 ng/L (0-725), the cis>850 group 106 ng/L (21-247), the surgery group was 50 ng/L (range 0-230) and for the carboplatin group 40 ng/L (0-1140). Pt levels were positively associated with cisplatin-treatment groups ($p<0.001$) and cisplatin dose ($p<0.001$), and negatively associated with follow-up time ($p<0.001$). We did not reveal associations with Pt levels and carboplatin treatment ($p=0.18$).

The odds for having Pt in the highest quartile was positively associated with cumulative cisplatin dose (OR 1.29, 95% CI 1.20-1.38 per 100 mg increase in cisplatin dose).

Additionally, the cisplatin treatment groups were associated with an increased risk of having serum Pt in the highest quartile with an OR at 9.4 (cis≤850: 95% CI 3.9-22.5) and an OR at 31.2 (cis>850: 95% CI 11.6-84.1), compared with the surgery group.

In conclusion, this paper documented that TCSs previously treated with CBCT have increased Pt levels up to 28 years after receiving treatment, when compared with controls. Pt was also detectable among some men treated with surgery alone.

5.2 Paper II

Associations between long-term serum platinum and neuro- and ototoxicity, endocrine gonadal function and cardiovascular disease in testicular cancer survivors. (Urologic oncology 2016).

In this paper, 292 CBCT treated TCSs were included to evaluate the serum Pt measured at SII median 19 years after chemotherapy, and its impact on NTX, endocrine gonadal function, and CVD. Approximately 80% of the TCSs received 3-4 cycles of CBCT.

Herein, we documented that increasing serum Pt quartiles was significantly associated with increasing quartiles of total SCIN score (P for trend=.05), increased hearing impairment (P=.04) and increased tinnitus (P<.001). All associations attenuated when cisplatin were added in the OLR-models.

Importantly, current smokers had significantly increased intensity of paresthesias in hands (OR 2.85, 95% CI; 1.60-5.06), feet (OR 1.76, 95% CI; 0.99-3.14), and Raynaud's phenomenon in hands (OR 2.50, 95% CI; 1.43-4.39) and feet (OR 2.42, 95% CI; 1.37-4.28) in multivariable OLR models including cisplatin dose, serum Pt and age .

The OR for being in the highest quartiles of LH increased with an increase in quartiles of serum Pt. The OR for being in a higher LH quartile was 2.50 (95% CI 1.28–4.87) for the third serum Pt quartile. The cumulative cisplatin dose was positively associated with higher LH levels (OR 1.17, 95% CI 1.06-1.30 per 100 mg cisplatin). No significant associations between quartiles of testosterone and serum Pt levels were established.

No significant associations between any of the risk factors for CVD and serum Pt levels were discovered.

In conclusion, increasing quartiles of long-term serum Pt are associated with increasing SCIN score, tinnitus, hearing impairment and increasing LH levels. However, these associations were attenuated when adjusted for cumulative administered cisplatin dose, and persisted only for tinnitus and LH.

5.3 Paper III

Long-term platinum change and its associations with cisplatin-related long-term and late effects in testicular cancer survivors. (Submitted to Acta oncologica, March 2018)

A total of 77 CBCT treated men (cases) and 17 controls (TCSs treated with surgery) had serum Pt levels evaluated at both SI (median 12 years after CBCT) and SII (median 20 years after CBCT) in order to describe the Pt change over time, and to evaluate the associations between serum Pt change between SI and SII and second cancers, renal function and NTX in cases.

While the median Pt levels of the controls were 0 ng/L at both surveys, the median Pt level for all cases was 75 ng/l (0-377) and 64 ng/l (0-725) at SI and SII, respectively. In this paper most men experienced a decline of Pt levels from SI to SII [4.2 ng/l/year (range – 93 to

+27)]. However, 11 (14%) of cases experienced increasing Pt from SI to SII. The cumulative cisplatin dose was associated with a Pt decline ($r = 0.30$, $p = 0.01$).

After SII, 12 cases (15%) had a second cancer diagnosis. At SII, a higher Pt level was associated with an increased risk for a second cancer diagnosis (HR 1.22, 95% CI 1.05-1.42 per 50 ng/L increase in Pt), while a larger Pt decline from SI to SII was associated with decreased risk of a second cancer diagnosis (HR 0.78, 95% CI 0.62-0.99 per 10 ng/L/year). Interestingly, the current smokers, when compared with never smokers, had an increased risk of a second cancer (HR 9.14, 95% CI 1.88-45.0).

The serum Pt levels were higher among cases with creatinine >90µmol/L in SI for the cis>850 treatment group ($p=0.05$), compared with cis>850 with creatinine <90µmol/L. The creatinine level at SI and SII was positively associated with the cumulative cisplatin dose ($r=0.25$, $p=0.03$ and $r= 0.24$, $p=0.04$, respectively. Multivariable analyses with Pt levels, late effects and creatinine did not reveal any significant associations.

All six NTX symptoms had significantly increased severity from SI to SII ($p<0.001$ for all). NTX change analyses showed that men with a larger Pt decline from SI to SII had a significantly higher risk of increasing paresthesias in hands (OR 1.98, CI 1.09-3.59, per 10 ng/l/year) and tinnitus (OR 1.51, CI 1.01-2.27, per 10 ng/L/year). These findings remained significant when adjusting for cisplatin dose. Patients who stopped smoking between SI and SII or never smoked had a lower risk of deteriorating Raynaud's phenomenon, compared to current smokers.

In conclusion, after adjusting for age and administered cumulative cisplatin dose, an increasing Pt decline from SI to SII was associated with a decreased risk for a second cancer, but with worsening of paresthesias and tinnitus from SI to SII.

6. DISCUSSION

6.1 Methodological considerations

6.1.1 General aspects

This study evolves from two cross-sectional follow-up studies, in which outcomes were evaluated between 1998-2002 (SI) and 2007-2008 (SII), whereas the cytotoxic treatment was administered several years before (1980-1994).

Cross-sectional studies, also called prevalence studies, are observational and can be useful to detect differences between groups[149]. As we have used data from two cross-sectional studies performed at different time points, we have the possibility to interpret the associations between Pt levels and late effects longitudinally (paper III). Longitudinal studies are considered highly valid for determining long-term changes, and their primary advantage is to detect patterns that occur over long periods. Thus, the present thesis can be seen to some extent as a retrospective cohort study with regard to the late effect outcomes. Retrospective studies often need large sample sizes for evaluating rare outcomes, and there is a risk of selection bias, information bias and confounding[150].

6.1.2 Internal and external validity

It is important to consider both external and internal validity when interpreting a clinical study[150]. External validity refers to whether the study generates a valid hypothesis applicable to a more general clinical population. For this study, all TCSs treated in Norway during 1980-1994 were retrieved from the Norwegian Cancer Registry and cross-checked with the university hospital databases, and the eligible study population was considered complete. Both studies on

which the present thesis is based had approximately 80% response rates. Moreover, all participants were treated according to international guidelines with limited variety, thus the external validity is considered to be acceptable for this study. The TC treatment has changed since 1980-1994. However, the standard treatment for most men with disseminated TC today is still considered to be 3-4 cycles of BEP. The results presented in this thesis are still valid for current TCSs and the doctors/ health personnel involved in treatment and follow-up of these patients.

The internal validity, random and systematic errors (bias), refers to how a clinical study can produce valid results[150]. The random errors are due to chance and can be minimized by increasing the sample size or reducing measurement variations. Herein we have critically few TCSs for grouping according to treatment for especially the CVD analysis in paper II. CVD occurs late in life, most incidents after the age of 60.Thus our participants with median age of 49 at survey II, would probably need a larger population to be able to demonstrate any relationship between exposure and outcome. Studies with few participants have higher risks for incorrectly accepting the null hypothesis (type II error)[149]. In paper III, only 77 men treated with CBCT had available serum for Pt analyses in both surveys, which hampers the ability to draw reliable conclusions[149].

Herein we have applied numerous statistical tests, with the possibility of incorrectly rejecting the null hypothesis only due to chance (type I error). In exploratory and epidemiological studies where a final conclusion might not be necessary nor possible, corrections for multiple testing are not considered compulsory. In such studies the Bonferroni test may be inappropriate, as it will be highly conservative and analyses may miss real differences[151,152], and we have chosen to not make any corrections.

Any errors influencing the study participation (selection bias) or distortion when collecting information about participants (information bias) are referred to as systematic biases[150]. Such biases reflect any deviations that leads to conclusions which may systematically over- or under-estimate the associations between exposure and outcome.

6.1.3 Selection bias

Selection bias occur when participation is hampered by the selection of either individuals, groups or data for analysis[149]. This may lead to various association between outcome and exposure for responders and non-responders. If some groups of the eligible population is less likely to be included than others it is defined a sampling bias[150]. This type of bias may create a sample which is unrepresentative of the population intended to be analyzed.

In our study, all TCSs treated during 1980-1994 were invited, and participation was voluntarily, with insignificant differences between responders and non-responders according to stage, age, histology or treatment. It can be argued that people participating in medical research are healthier and more motivated compared with those who do not participate[153]. Since we lack information about the non-responders' level of late effects, we can only speculate whether the participants in the study are compared to the non-responders[150]. Nevertheless, the participation rate was high in both surveys, hence minimalizing the risk of selection bias.

In paper II and for late effect analyses in paper III, only TCSs with prior chemotherapy were included. Additionally, the cohorts included in all papers in the current thesis were restricted by available frozen serum, which had been used for several previous studies, thereby introducing a possible selection bias. In paper III, only patients with serum samples frozen at both surveys were eligible, and this was limited to patients treated at only one hospital (the

Norwegian Radium Hospital). During the treatment period, this hospital was main hospital for cancer treatment in Norway, increasing the possibility of including patients with more intensive disease needing more advanced treatment, rendering a possibility of selection bias for more late effects.

6.1.4 Information bias

Information bias (observational bias) occurs when measurement or classification of information about the study participants is incorrect. Non-differential misclassification refers to when an exposure variable has the same probability of being misclassified for all subjects, regardless of outcome. Differential misclassification refers to when the misclassification of exposure differs for study participants according to outcome status[150].

In paper II and III, smoking status and physical activity are based on self-reported information retrieved from the questionnaires. In issues where strong personal feelings can be a source of bias, for example with smoking habits and physical activity, data may be incorrectly reported to reduce a person's feelings of guilt, with a risk of information bias (social desirability bias)[154]. In paper II, only self-reported information about incident CVD in the questionnaire were validated, with a probability of underestimating both the true incidence of CVD and associations between exposure (cisplatin dose, Pt level) and CVD.

Misclassification of symptoms regarding self-reported NTX may also exist. However, a report comparing audiograms with self-report of hearing impairment has shown high correlation, and the SCIN is recommended as a brief screening instrument for chemotherapy induced neuro-oto-toxicity[155]. Additionally, the SCIN score represents a clinical relevant measure, addressing to which extent the symptoms affect quality of life.

Most of the patients had blood samples collected before 11.00 a.m., to assure similar conditions regarding hormonal analyses, due to diurnal variations of testosterone[5]. Measurements of testosterone may differ between laboratories, however, in paper II the variability of testosterone is considered to be acceptable since all hormonal analyses was performed at the same laboratory.

To minimize possible measurement errors when assessing Pt levels, only one laboratory performed all analyses with a method partly adopted from Brouwers et al[142]. For evaluation of the Pt measurement accuracy, a standardized serum sample from a quality management program was analyzed in every sequence. To ensure optimal instrument performance, instrument settings were tuned and adjusted daily.

6.1.5 Confounding

Confounding refers to a variable that influences both the independent and the dependent statistical variable causing a distortion or confusion of effects. Confounding can be statistically reduced by stratification or adjustments in multivariate analyses[149].

The prevalence of most of the late effects which we have studied, increases with age. This includes CVD, neuropathy, tinnitus and hearing impairment as well as cancer and endocrine hypogonadism[156-159]. Since age was a possible confounder it was necessary to adjust all outcome analyses for age. Additionally, in the multivariate analyses concerning late effects and serum Pt levels we adjusted for the cumulative cisplatin dose, since all late effects studied in this thesis are associated with CBCT.

Another possible confounder was smoking, which is a well-known risk factor for CVD, neuropathy and cancer[160-162]. Consequently, we included smoking status when we performed

all ordinal and cox regression models involving these outcomes to explore the effect of smoking.

Of note, when addressing Raynaud's phenomenon, most patients in the study also received bleomycin, which is considered the main cytotoxic causative agent[82]. Hence, confounding of the associations between cisplatin and Raynaud's phenomenon by bleomycin is a possibility in our study.

6.2 Discussion of results

6.2.1 Long-term platinum levels at SII and platinum level change from SI to SII (paper I and paper III)

In paper I, we showed that Pt levels are higher in TCSs treated with cisplatin up to 28 years after chemotherapy compared with patients treated with surgery only. In agreement with previous research, we detected significant association between Pt levels and cumulative cisplatin dose as well as time since treatment[16,17,23]. Besides, as reported in paper III, although most men had a decline of Pt during follow-up, 14% of the TCSs showed a Pt increase.

For Pt level quantification, we utilized ICP-MS, a highly sensitive technique partially adopted from Brouwers et al[142]. The susceptibility of the procedure is due to both the instrument performance and the sample preparation. To avoid interference and minimizing the contamination risk, we diluted the serum specimens to reduce the concentration of organic matrix, hence maintaining a high sensitivity and detection power. For measuring total Pt levels, the signal from the ^{195}Pt isotope can be a subject to interference of signals from hafnium oxides. In ICP-MS conditions, this metal oxide observation is typically insignificant and within our

study the detected signal of hafnium was low in all samples, which made further improvements redundant.

Surprisingly, our surgery treated controls had higher Pt levels compared with data from both Sprauten et al (personal communication), Gietema et al. and Brouwers et al[16,17,23]. This may be the result of different analytical methods and specimens, environmental factors, or incomparable genetic susceptibility, which all theoretically may influence the Pt levels in men not exposed to cisplatin.

The observed increase in Pt levels from SI to SII among 14% of cases in paper III may possibly be explained by Pt exchange between compartments with diverse pharmacokinetics, as Pt residuals has been found in most organs after chemotherapy[121]. This theory is supported by a demonstration of retained Pt pharmacokinetics resembling lead, which stores within bone with the possibility to be released into the circulation[21]. In addition, the observed increase in Pt levels in some cases may in part also be explained by a higher exposure to PGE pollution.

The serum Pt levels in our Norwegian male controls (blood samples drawn 2007-2008) was high compared with blood levels in Italian healthy adolescents (from 2009), with median values at 50ng/L and 9.87 ng/l, respectively[163]. Biomonitoring studies have shown that the body burden levels of PGE reflect the exposure to elevated concentrations of these noble metals, with higher exposure and uptake among urban populations and those working in close proximity with traffic[164]. In a German study, Pt concentrations in airborne particulate matter were found to be six times higher for samples collected in 2008–2010 compared to 2002[165], and inhalation of PGE-containing particulate matter are believed to be the most important exposure route for Pt in humans[166]. Importantly, the worldwide production of PGEs has increased significantly since the 1970s because a more prevalent use of vehicle exhaust catalysts[94]. High levels of PGE in soil bordering heavy trafficked areas are well

documented[167,168]. Pt typically occurs as an insoluble metal and is the least soluble PGE, solubility ranging from 1.4-19% for gasoline-powered engines and from 2-7% for both new and aged diesel powered engines[165]. In Norway, approximately 80% of the population is living in urban communities, where the soluble Pt of roadside dust is high. An explanation for the lower Pt levels reported in earlier studies[23,169] may be that the investigated populations were assesed in a period with less PGE pollution and accumulation.

A genetic difference between the Dutch and the Norwegian cohorts might explain the difference in median Pt levels. Various gene expressions have been linked with chemotherapy-induced toxicities[99,115], and it remains to estimate if genetic polymorphisms can generate heterogeneous pharmacokinetics and chemotherapy tolerance among patients.

From our data, no relationship between Pt levels and long-term follow-up time for carboplatin treated TCSs could be established, probably due to the limited number of patients. Additionally, levels of Pt is shown to be artificially low in carboplatin treated patients after serum storage temperatures at -20º C[170], comparable to our study. To the best of our knowledge, long-term reports on Pt levels after carboplatin treatment are limited.

6.2.2 Long- term platinum levels and changes, and their associations with cisplatin related late effects (paper II and paper III)

In paper II we found that cumulative administered cisplatin doses remained associated with NTX, while associations between long-term Pt levels and NTX symptoms diminished over time[16,19]. Additionally, we found associations with Pt levels at SII and higher LH-levels, but no associations with CVD. In paper III we found that a larger Pt decline from SI to SII was

associated with a decreased risk for second cancer and an increased risk for tinnitus and paresthesias in hands.

Sensory neuropathy, Raynaud's phenomenon, tinnitus and hearing impairment are well-known neurotoxic side effects of cisplatin with a prevalence of 30% to 40% in TCSs, with a potential negative impact on their quality of life[82,108]. These side effects are related to both cumulative cisplatin dose and treatment intensity[171,172]. Our findings in paper II partially corroborated the results demonstrated in 2012 by Sprauten et al[16]. Compared with our study, the Sprauten study, which to some extent was based on the same TCSs cohort as our study, demonstrated a stronger association between all NTX symptoms and retained Pt median 12 years after CBCT. In their study, the cumulative cisplatin dose was not associated with neither total SCIN score nor individual SCIN symptoms in multivariate OLR analyses. Possibly, our seven year longer follow-up with subsequently lower Pt levels, less dose-intensive treatments and differences in ICP-MS methodology can partly explain a diminished association between the Pt levels and NTX when cisplatin dose was included in our statistical models.

The exact pathogenesis of long-term CIPN is largely unknown. Results of several post-mortem studies show that Pt is retained and stored in essentially all organs, such as lungs, kidneys, liver, muscle, bone and skin[121,173,174]. Furthermore, Pt levels measured within nerves are typically highest in dorsal root ganglia and lowest in the brain[105]. Whether the cumulative amount of cisplatin correlates with Pt levels in the dorsal roots is, however, not known. It has been hypothesized that continuous exposure to low-level serum Pt on neural tissue contributes to ongoing damage[16]. In paper II, the diminished association between serum Pt levels and SCIN symptoms, when cisplatin was added to our multivariable OLR models, suggests that the treatment burden has a stronger effect on NTX development than the Pt residuals. In paper III, we demonstrated that a larger Pt decline from SI to SII correlated positively with higher

cumulative cisplatin doses, and was additionally associated with a higher intensity of paresthesia (hands). Taken together, since cisplatin-induced peripheral neuropathy (CIPN) typically develops during or shortly after treatment[102], we hypothesize that it is more likely that CIPN are associated with the administered cisplatin dose rather than the long-term Pt exposure or Pt decline.

In paper II, tinnitus remained significantly associated with long-term Pt when adjusting for cisplatin dose. Additionally, in paper III, we found that a larger Pt decline was associated with an increase in tinnitus from SI to SII. Previous studies have shown that 40–80% of adults and at least 50% of children are left with permanent hearing loss after receiving CBCT, when including frequencies outside normal speaking range[111,175]. Chemotherapy-induced ototoxicity is mainly ascribed to cisplatin, which is believed to cause inner ear damage trough loss of outer hair cells in the organ of Corti, leading to tinnitus and hearing impairment[176]. If Pt stored in nerves is related to ear function and/or the cisplatin-induced initial damage during treatment is responsible for outer hair cell dysfunction, are yet to be investigated. Further knowledge was recently proposed by showing that cisplatin accumulation in mice and human cochlea is consistently high in the stria vascularis, the region of the cochlea that maintains the ionic composition of endolymph. Moreover, the authors demonstrated prominent amounts of cisplatin levels in the long bones[21]. Similar to lead, Pt can be distributed into bone and be exchanged back into the blood, with a half-life of years-to-decades[177]. The major protein component of bone, type I collagen, binds to Pt, from which it slowly dissociates[178]. Hence, the cochlear bone is suggested to function as a reservoir for Pt, leading the long-term destruction of cochlear and bone cells, a possible premise for the ototoxicity caused by cisplatin[21]. Whether the prolonged release of Pt from bone can mediate the late toxicities of cisplatin, needs further

investigation. As far as we know, there is still no documented substance that may relieve the neurotoxicity of platinating agents [179,180].

Hypogonadism can cause a diversity of complications for TCSs, such as fertility problems, muscle weakness, reduced sexual functioning and psychological problems[116,181-183]. It is also associated with conditions like decreased bone mineral density, obesity, CVD development and the metabolic syndrome[125,126,129,184]. Corresponding with our results, an increased risk of premature hormonal aging with higher LH levels has been significantly associated with administered cumulative cisplatin dose[5,120]. Additionally, in paper II, increased Pt levels were associated with increasing LH levels after CBCT, supporting previous findings[20]. In a post-mortem study, testicles retained more Pt after CBCT compared with other endocrine organs outside the brain[121]. Hypothetically, the endocrine hypogonadism observed in long-term TCSs can be due to ongoing damage of the testicles, possibly due to continuous exposure to residual Pt.

The increased risk of potentially life-threatening CVD in TCSs is a major complication of CBCT, mediastinal radiotherapy and even subdiaphragmatic radiotherapy[122-125,185,186], with an increased risk for CVD several years after treatment termination[6]. Inflammation and endothelial dysfunction are essential components in the development of atherosclerosis, on both short- and long-term. CBCT has been demonstrated to activate the atherosclerotic process[128,187,188]. Pt residuals have been measured in TCSs up to median 20 years after CBCT[17,18], additionally 10% of the serum Pt remain reactive median 41 months after treatment[23]. Hence, CVD after CBCT is hypothesized to partially be the result of ongoing endothelium damage caused by the raised long-term Pt levels, as well as increased CVD risk factor levels. Recently. Boer et al. demonstrated associations between Pt exposure and both CVD risk factors, paresthesias and hypogonadism. They assessed a pharmacokinetic model for

Pt exposure which included cisplatin dose, age, weight, and height along with Pt levels[20], but their subsequent statistical models did not include cisplatin dose. Thus, elucidation of the effect of cisplatin dose is still lacking. In paper II, we demonstrated an association between CVD and cumulative cisplatin dose only, but statistical power was hampered by few CVD events in our cohort.

The most prominent cause of death among long-term TCSs after cytotoxic treatment is second cancers[4]. Numerous studies have shown an elevated relative risk for solid second cancers, especially with follow-up beyond 20 years[133,135,136]. The cancer sites registered in our cohort corroborates with a Danish study reporting increased risks for cancers in the lung and bladder among others. However, our cohort is not large enough to calculate relative risks for further comparison[135]. Nevertheless, in paper III, we are the first to show a relationship between a larger decline in Pt levels and a reduced risk of having a second cancer, whereas the cumulative cisplatin dose was not associated with the risk of second cancer. We hypothesize that Pt storage and pharmacokinetics might be just as important as the cisplatin dose itself for very late effects after cancer treatment, such as second cancers.

Decreased renal function after TC treatment is closely related to an increased number of BEP cycles and the accumulated doses of cisplatin, but the reported changes in GFR are partly reversible and have no impact on CVD risk or associated death[189-191]. Nevertheless, renal function, both prior to and shortly after CBCT, was found to be associated with long-term exposure to circulating Pt in the study of Boer et al[20]. In paper III, we demonstrate a significant association between Pt levels at SI and creatinine at SI. However, no association between Pt decline and creatinine levels was demonstrated, probably due to our limited study population.

Smoking has been shown to cause damage in most organs[192,193], and is a considerable risk factor for different cancers[194,195]. In paper II we found a strong association between smoking and neurotoxicity in TCSs, similar to previous studies performed after CBCT[82]. In paper III we demonstrated that current smokers at SII, when compared with never smokers, had a major increased risk of developing a second solid cancer. Additionally, we saw that men who never smoked and men who quit smoking between SI and SII had a lower risk of Raynaud's symptoms increasing, confirming earlier studies which report smoking to be an important causative factor for developing Raynaud's phenomenon[196].

7. CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

In paper I, we were the first to document that TCSs previously treated with CBCT have increased Pt levels up to 28 years after CBCT, compared with those treated with surgery only (control group). Their Pt levels were positively associated with the cisplatin dose and inversely associated with follow-up time. Additionally, we found that our controls had relatively high levels of platinum, when compared with healthy controls in PGE biomonitoring studies. In paper II, we present the longest follow-up time published so far for Pt retention in CBCT treated TCSs and associations with NTX, endocrine–GF and CVD. Tinnitus and increasing LH-levels were positively associated with higher Pt levels after adjusting for cisplatin dose. In paper III, we found that the Pt decline from SI to SII in 77 TCSs previously treated with CBCT, was associated with worsening of NTX and a reduced risk of second cancer. 14% of TCSs had increasing Pt levels from SI to SII.

Further studies with respect to late effects are needed to clarify underlying mechanisms and to explore associations with serum Pt. We suggest larger prospective studies including evaluation of Pt elimination rates, storage and excretion, to elucidate their consequences for long-term effects in TCSs. Of note, the relationship between residual long-term Pt and the more life threatening toxicities, like second cancers and CVD, needs to be prioritized in larger studies with follow-up periods beyond 20 years.

Prophylaxis studies have not been able to document any substances that prevent the neurotoxicity of platinating agents[179,180]. We hope that future studies with focus on detoxifying agents will be performed, which hypothetically can prevent all possible late effects associated with Pt exposure.

Genes associated with Pt detoxification should be elucidated to further understand the individual differences observed with respect to late toxicity. Knowledge about the inter-individual vulnerability after CBCT may be clinically important in risk-adapted follow-up of TCSs in the future. We suggest a further exploration of the relationship between cisplatin related late effects and genetics.

The high Pt levels in surgery treated TCSs (paper I), along with the observed increasing Pt levels for some of our TCSs (paper III), and possible disease associations, especially second cancers, should be investigated further. Airborne particulate matter, which is associated with PGEs, has been associated with an increased incidence of morbidity and mortality in exposed urban populations[197,198]. Whether environmental Pt exposure contributes to the associations between Pt levels and the medical problems included in this thesis remains to be evaluated.

Regarding clinical relevance, we interpret the associations between late effects and smoking to be helpful in the follow-up of all TCSs treated with CBCT, with smoking cessation as a high priority. Careful follow-up of TCSs is necessary to quantify and possibly prevent the long-term risks of these survivors. We suggest focusing on improving unfavorable life style factors to possibly prevent late effects.

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APPENDIX I

Questionnaire Survey I, 1998-2002

Etterundersøkelse av pasienter behandlet for testikkelkreft

REGIONSYKEHUSET I TROMSØ

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	Antall år _____	2
c.	Samboene	Antall år _____	3
d.	Enkemann	Antall år _____	4
e.	Separert	Antall år _____	5
f.	Skilt	Antall år _____	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	☐ Ja 1	☐ Nei 2
Jeg er blitt separert	☐ Ja 1	☐ Nei 2
Jeg er blitt skilt	☐ Ja 1	☐ Nei 2
Jeg er blitt enkemann	☐ Ja 1	☐ Nei 2
Jeg har startet en nytt fast forhold	☐ Ja 1	☐ Nei 2
Jeg har avsluttet et fast forhold	☐ Ja 1	☐ Nei 2
Ingen forandring av partnerforholdet	☐ Ja 1	☐ Nei 2

3. Tror du at diagnosen og behandlingen for testikkelkreft har hatt innflytelse på ditt nåværende forhold til partneren din? ☐ Ja 1 ☐ Nei 2

Hvis «ja», på hvilken måte? _____

_____

_____

BOFORHOLD

4. Hvem bor du sammen med? (Sett ett kryss for hver linje, og oppgi hvor mange du bor sammen med.)

	Ja	Nei	Antall
Ektefelle/samboer	☐ 1	☐ 2	
Andre personer over 18 år	☐ 1	☐ 2	_____
Personer under 18 år	☐ 1	☐ 2	_____

ARBEID/UTDANNING

5. Hvilken utdanning er den høyeste du har fullført?

- ☐ Grunnskole 7-10 år, framhaldskole, folkehøgskole 1
- ☐ Realskole, middelskole, yrkesskole, 1-2 årig videregående skole 2
- ☐ Artium, økonomisk gymnas, allmennfaglig retning i videregående skole 3
- ☐ Høgskole/universitet, mindre enn 4 år 4
- ☐ Høgskole/universitet, 4 år eller mer 5

6. Hva er din nåværende arbeidssituasjon? (Sett ring rundt det svaret som passer.)

1.	Arbeidsledig/permittert	1
2.	Ikke i stand til å arbeide	
	a) sykemeldt	2
	b) attføring	3
	c) uføretrygdet	4
3.	Delvis i arbeid	5
4.	I fullt arbeid	6
5.	Alderspensjonist	7
6.	Student/skoleelev	8

<u>Hvis du for tiden ikke har inntektsgivende arbeid eller du ikke har heltids husarbeid: Gå til spørsmål nr. 11.</u>

7. Har du i løpet av de siste 12 månedene hatt sykefravær:

	Ja	Nei
med egenmelding?	☐ 1	☐ 2
med sykemelding fra lege?	☐ 2	☐ 2

8. Hvis «ja»; hvor lenge til sammen?

☐ 2 uker 1 ☐ 2 - 8 uker 2 ☐ Mer enn 8 uker 3 eller mindre

9. Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag?

☐ Ja, nesten alltid 4 ☐ Ganske sjelden 2
☐ Ganske ofte 3 ☐ Aldri, eller nesten aldri 1

10. Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag?

☐ Ja, nesten alltid 4 ☐ Ganske sjelden 2
☐ Ganske ofte 3 ☐ Aldri, eller nesten aldri 1

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

☐ Ja 1 ☐ Nei 2

Hvis «ja», på hvilken måte? _____

_____

_____

_____

12. Har du hatt noen vanskeligheter vedrørende arbeid, forsikring og/eller lån, eller innenfor andre praktiske områder av ditt liv, etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

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 ytelser?

Sykepenger/sykelønn/ rehabiliteringspenger	☐ Ja [1]	☐ Nei [2]
Ytelser under yrkesrettet attføring	☐ Ja [1]	☐ Nei [2]
Uførepensjon	☐ Ja [1]	☐ Nei [2]
Alderspensjon	☐ Ja [1]	☐ Nei [2]
Sosialstøtte	☐ Ja [1]	☐ Nei [2]
Arbeidsledighetstrygd	☐ Ja [1]	☐ Nei [2]
Overgangsstønad	☐ Ja [1]	☐ Nei [2]
Etterlattepensjon	☐ Ja [1]	☐ Nei [2]
Andre ytelser	☐ Ja [1]	☐ Nei [2]

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

☐ Ja, ofte [4] ☐ Ja, en sjelden gang [2]
☐ Ja, av og til [3] ☐ Nei, aldri [1]

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?
☐ Ja [1] ☐ Nei [2]

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

☐ Aldri, eller noen få ganger i året [4]
☐ 1-2 ganger i måneden [3]
☐ Omtrent en gang i uken [2]
☐ Mer enn en gang i uken [1]

Generell helsetilstand/livsstil

KREFT/ALVORLIG SYKDOM

18. Har du fått en annen kreftdiagnose etter din testikkelkreft-behandling? (Kryss av for det svaret som passer og angi mnd./år for diagnose.)
☐ Ja [1] ☐ Nei [2]
Hvis «ja», angi type og tidspunkt: _____

_____

_____

19. Har du hatt noen andre alvorlige sykdommer/ operasjoner? ☐ Ja [1] ☐ Nei [2]
Hvis «ja», angi type og tidspunkt: _____

_____

_____

20. Har noen i din familie fått testikkelkreft eller en annen form for kreft? ☐ Ja [1] ☐ Nei [2]
Hvis «ja», angi type, slektsforhold, eventuelt navn, krefttype og sykehus (f.eks.: Morbror Peder Ås, magekreftoperert i 1997 på Aker Sykehus.)

_____

_____

FØR/ETTER BEHANDLING FOR TESTIKKELKREFT

21. Brukte du noen ganger nervemedisiner før du fikk behandling for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

22. Har du noen gang brukt nervemedisiner etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

23. Brukte du noen gang narkotika før du fikk behandling for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

24. Har du noen gang brukt narkotika etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

25. Oppsøkte du noen gang en psykolog/psykiater før du fikk behandling for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

26. Har du noen gang oppsøkt en psykolog/psykiater etter behandlingen for testikkelkreft? ☐ Ja [1] ☐ Nei [2]

27. Har du noen gang tenkt på/ forsøkt selvmord? ☐ Ja [1] ☐ Nei [2]

ALKOHOLBRUK

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

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

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 omgjengelig 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

RØYKING

32. Røyker du	Ja	Nei
- sigaretter til daglig?	☐ 1	☐ 2
- sigarer/sigarillos til daglig?	☐ 1	☐ 2
- pipe til daglig?	☐ 1	☐ 2
- kun til fest?	☐ 1	☐ 2

Aldri røykt daglig (Sett kryss) ☐

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 sigaretter: _____

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 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.

37. Har du, eller har du hatt:

	Ja	Nei	Alder første gang
Hjerteinfarkt	☐ 1	☐ 2	_____ år
Angina pectoris (hjertekrampe)	☐ 1	☐ 2	_____ år
Hjerneslag/hjerneblødning	☐ 1	☐ 2	_____ år
Diabetes (sukkersyke)	☐ 1	☐ 2	_____ år

38. Hva ble resultatet siste gang du målte blodtrykket ditt?

- ☐ Begynne med/fortsette med blodtrykksmedisin 4
- ☐ Komme til kontroll, men ikke ta blodtrykksmedisin 3
- ☐ Ingen kontroll og ingen medisin nødvendig 2
- ☐ Har aldri fått målt blodtrykket 1

39. Har legen din noen gang sagt at du har/har hatt noen av disse sykdommene?

	Ja	Nei
Beinskjørhet (osteoporose)	☐ 1	☐ 2
Fibromyalgi (fibrositt/kronisk smertesyndrom)	☐ 1	☐ 2
Leddgikt (reumatoid artritt)	☐ 1	☐ 2
Slitasjegikt (artrose)	☐ 1	☐ 2
Bechterews sykdom	☐ 1	☐ 2
Andre langvarige skjelett- eller muskelsykdommer	☐ 1	☐ 2

40. Har du eller har du hatt smerter eller kramper i bena som begrenser deg når du går eller som gjør at du våkner om natten?
☐ Ja 1 ☐ Nei 2
Hvis «ja», angi når smertene/krampene begynte:
_____

41. I hvilken grad har du hatt disse plagene det siste året?

	Ikke plaget	Litt plaget	Mye plaget
Kvalme	☐ 1	☐ 2	☐ 3
Brystbrann/ sure oppstøt	☐ 1	☐ 2	☐ 3
Diaré	☐ 1	☐ 2	☐ 3
Treg mage	☐ 1	☐ 2	☐ 3
Hjertebank	☐ 1	☐ 2	☐ 3
Åndenød	☐ 1	☐ 2	☐ 3

42. 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?
☐ 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	Nei
Nakke	☐ 1	☐ 2
Skuldre (aksler)	☐ 1	☐ 2
Albuer	☐ 1	☐ 2
Håndledd, hender	☐ 1	☐ 2
Bryst/mage	☐ 1	☐ 2
Øvre del av rygg	☐ 1	☐ 2
Korsrygg	☐ 1	☐ 2
Hofter	☐ 1	☐ 2
Knær	☐ 1	☐ 2
Ankler, føtter	☐ 1	☐ 2

(Hvis du har hatt plager i flere områder i minst 3 måneder det siste året, sett ring rundt det ja-krysset hvor plagene har vart lengst.)

44. Har plagene redusert din arbeidsevne det siste året? (Gjelder også hjemmearbeidende.)

☐ Nei/ubetydelig [1] ☐ I betydelig grad [3]
☐ I noen grad [2] ☐ Vet ikke [4]

45. Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ☐ Ja [1] ☐ Nei [2]
(Langvarig = Minst ett år)

Hvis «nei», gå til spørsmål nr. 47.

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

	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. kroppslig sykdom	☐ [1]	☐ [2]	☐ [3]
Hemmet pga. psykiske plager	☐ [1]	☐ [2]	☐ [3]
Andre plager, beskriv: _____	☐ [1]	☐ [2]	☐ [3]

MEDISINBRUK

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

☐ Ja [1] ☐ Nei [2]

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

	Antall måneder
Smertestillende	_____ mnd.
Sovemedisin	_____ mnd.
Beroligende medisin	_____ mnd.
Medisin mot depresjon	_____ mnd.
Allergimedisin	_____ mnd.
Astmamedisin	_____ mnd.
Hjertemedisin	_____ mnd.
Blodtrykksmedisin	_____ mnd.
Jerntabletter	_____ mnd.
Vitamintilskudd	_____ mnd.
Tran/fiskeoljer	_____ mnd.
Annen medisin, spesifiser navn og antall mnd.: _____	_____ mnd.

49. Hvor ofte har du brukt avslappende/beroligende medisiner eller sovemedisiner den siste måneden?

☐ Daglig [4] ☐ Sjeldnere enn hver uke [2]
☐ Hver uke, men ikke hver dag [3] ☐ Aldri [1]

BRUK AV HELSETJENESTER

50. Har du i løpet av de siste 12 månedene vært hos:

(Sett ett kryss for hver linje.)	Ja	Nei
Allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat)	☐ [1]	☐ [2]
Bedriftslege	☐ [1]	☐ [2]
Lege ved sykehus (uten innleggelse)	☐ [1]	☐ [2]
Annen lege	☐ [1]	☐ [2]
Fysioterapeut	☐ [1]	☐ [2]
Kiropraktor	☐ [1]	☐ [2]
Homøopat	☐ [1]	☐ [2]
Annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, «healer», «synsk» e.l.)	☐ [1]	☐ [2]

51. Har du vært innlagt på sykehus de siste 5 årene?

☐ Ja [1] ☐ Nei [2]

Hvis «ja», vennligst spesifiser hvilke sykehus (utenom RiTø) og hvorfor du var innlagt? _____

FRITID

52. Hvordan har din fysiske aktivitet i fritida vært det siste året? (Tenk deg et ukentlig gjennomsnitt for året. Arbeidsvei regnes som fritid.)

	Ingen	Timer pr uke: Under 1	1-2	3 og mer
Lett aktivitet (ikke svett/andpusten)	☐ [4]	☐ [3]	☐ [2]	☐ [1]
Hard fysisk aktivitet (svett/andpusten)	☐ [4]	☐ [3]	☐ [2]	☐ [1]

HVORDAN DU FØLER DEG

Under følger noen flere spørsmål om hvordan du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret - de spontane svarene er best.

53. Jeg er nervøs eller anspent.

☐ For det meste [4] ☐ Noen ganger [2]
☐ Ofte [3] ☐ Ikke i det hele tatt [1]

54. Jeg gleder meg fortsatt over ting slik jeg pleide før.

☐ Avgjort like mye [1] ☐ Bare lite grann [3]
☐ Ikke fullt så mye [2] ☐ Ikke i det hele tatt [4]

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 som før [2] ☐ Ikke i det hele tatt [4]

57. Jeg har hodet fullt av bekymringer.
- ☐ Veldig ofte 4
- ☐ Ganske ofte 3
- ☐ Av og til 2
- ☐ En gang i blant 1

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

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

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

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

62. Jeg bryr meg ikke lenger om hvordan jeg ser ut.
- ☐ Ja, jeg har sluttet å bry meg 4
- ☐ Ikke som jeg burde 3
- ☐ Kan hende ikke nok 2
- ☐ Bryr meg som før 1

63. Jeg er rastløs som om jeg stadig må være aktiv.
- ☐ Uten tvil svært mye 4
- ☐ Ganske mye 3
- ☐ Ikke så veldig mye 2
- ☐ Ikke i det hele tatt 1

64. Jeg ser med glede fram til hendelser og ting.
- ☐ Like mye som før 1
- ☐ Heller mindre enn før 2
- ☐ Avgjort mindre enn før 3
- ☐ Nesten ikke i det hele tatt 4

65. Jeg kan plutselig få en følelse av panikk.
- ☐ Uten tvil svært ofte 4
- ☐ Ganske ofte 3
- ☐ Ikke så veldig ofte 2
- ☐ Ikke i det hele tatt 1

66. Jeg kan glede meg over gode bøker, radio og TV.
- ☐ Ofte 1
- ☐ Fra tid til annen 2
- ☐ Ikke så ofte 3
- ☐ Svært sjelden 4

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Vennligst kryss av for hvert utsagn hvor enig eller uenig du er.

	Svært enig	Enig	Uenig	Svært uenig
67. Jeg har en positiv holdning til meg selv.	☐ 1	☐ 2	☐ 3	☐ 4
68. Jeg føler meg virkelig ubrukelig til tider.	☐ 4	☐ 3	☐ 2	☐ 1
69. Jeg føler at jeg ikke har mye å være stolt av.	☐ 4	☐ 3	☐ 2	☐ 1
70. Jeg føler at jeg er en verdifull person, i alle fall på lik linje med andre.	☐ 1	☐ 2	☐ 3	☐ 4

HVORDAN DU FØLER DEG NÅ

Vennligst kryss av for det svaret som best beskriver dine følelser i den siste uken. Sett bare ett kryss.

71. Er du vanligvis glad eller nedstemt?
- ☐ Svært nedstemt 7
- ☐ Nedstemt 6
- ☐ Nokså nedstemt 5
- ☐ Både - og 4
- ☐ Nokså glad 3
- ☐ Glad 2
- ☐ Svært glad 1

72. Føler du deg stort sett sterk og opplagt, eller trøtt og sliten?
- ☐ Meget sterk og opplagt 1
- ☐ Sterk og opplagt 2
- ☐ Ganske sterk og opplagt 3
- ☐ Både - og 4
- ☐ Ganske trøtt og sliten 5
- ☐ Trøtt og sliten 6
- ☐ Svært trøtt og sliten 7

73. Når du tenker på hvordan du har det for tiden, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
- ☐ Svært fornøyd 1
- ☐ Meget fornøyd 2
- ☐ Ganske fornøyd 3
- ☐ Både/og 4
- ☐ Nokså misfornøyd 5
- ☐ Meget misfornøyd 6
- ☐ Svært misfornøyd 7

Fertilitet, sex og samliv

FERTILITET (FRUKTBARHET)

74. a. Ble 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. Hadde du egne barn? ☐ Ja 1 ☐ Nei 2

Antall barn: _____

Barnas fødselsår: _____

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

79. Frosset du ned sæd før du ble behandlet for testikkelkreft? ☐ Ja 1 ☐ Nei 2

ETTER behandling for testikkelkreft:

80. Har du prøvd å bli far? ❑ Ja [1] ❑ Nei [2]

81. Har du fått egne barn? ❑ Ja [1] ❑ Nei [2]
Antall barn: _____
Barnas fødselsår: _____

82. Har din partner hatt aborter etter at hun ble gravid med deg? ❑ Ja [1] ❑ Nei [2]

83. Trengte dere hjelp av en medisinsk spesialist for at partneren din skulle bli gravid? ❑ Ja [1] ❑ Nei [2]

a. Hvis «ja», ble din partner gravid med sæd som du selv produserte etter behandlingen? ❑ Ja [1] ❑ Nei [2]

b. Hvis «ja», ble nedfrosset sæd fra før behandlingen benyttet? ❑ Ja [1] ❑ Nei [2]

84. Ble noen av dine barn født med alvorlige sykdommer? ❑ Ja [1] ❑ Nei [2]
Hvis «ja», spesifiser hvilke sykdommer:
_____
_____

85. Har du adoptert barn? ❑ Ja [1] ❑ Nei [2]
Hvis «ja», angi årstall for adopsjon:_____

86. Eventuelt 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 ring rundt det svaret som passer.)

Ingen dager	Bare noen få dager	Noen dager	De fleste dagene	Nesten hver dag
1	2	3	4	5

88. Hvordan vurderer du nivået på seksualdriften din de siste 30 dagene?

Ingen drift	Lav drift	Middels drift	Middels sterk drift	Sterk drift
1	2	3	4	5

REISNING

89. Hvis du er blitt seksuelt stimulert på noen måte de siste 30 dagene; hvor ofte har du hatt delvis eller full reisning?

Aldri	Noen få ganger	Ganske ofte	Vanligvis	Alltid
1	2	3	4	5

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

Aldri	Noen få ganger	Ganske ofte	Vanligvis	Alltid
1	2	3	4	5

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

Har ikke fått reisning	Store vansker	Noen vansker	Få vansker	Ingen vansker
1	2	3	4	5

SÆDUTTØMMING

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

Har ikke hatt noen seksuell stimulering de siste 30 dagene	Store vansker	Noen vansker	Få vansker	Ingen vansker
1	2	3	4	5

93. I hvilken grad har du over de siste 30 dagene sett på mengden sæd ved uttømming som et problem for deg?

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

94. Har sæduttømmingen blitt helt borte etter behandlingen for testikkelkreft? ❑ Ja [1] ❑ Nei [2]

PROBLEMVURDERING

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

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

96. I hvilken grad har du over de 30 siste dagene vurdert din evne til å få og beholde reisning som et problem?

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

97. I hvilken grad har du over de 30 siste dagene sett på din sæduttømming som et problem?

Stort problem	Middels problem	Lite problem	Ganske lite problem	Ikke noe problem
1	2	3	4	5

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

Veldig utilfreds	For det meste utilfreds	Omtrent like tilfreds som utilfreds	For det meste tilfreds	Svært tilfreds
1	2	3	4	5

Livshendelser

Vennligst 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 spørsmålene, 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:			Angi grad av belastning fra 0-100
99. Egen alvorlig sykdom/ ulykke/sykehusinnleggelse?	❑ Nei [2]	❑ Ja [1]	_____
100. Skilsmisse/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/sykehusinnleggelse hos familie eller nære venner?	❑ Nei [2]	❑ Ja [1]	_____
105. Andre vansker hos nær familie (skilsmisse, 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 bomessige problemer?	❑ Nei [2]	❑ Ja [1]	_____
110. Har du selv eller noen i din nære familie vært utsatt for eller innblandet i alvorlig lovbrudd?	❑ Nei [2]	❑ Ja [1]	_____

Livskvalitet

HELSE

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:

Utmerket	Meget god	God	Nokså god	Dårlig
1	2	3	4	5

112. Sammenlignet med for ett 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 ett 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.)

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
113. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett.	1	2	3
114. Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid.	1	2	3
115. Løfte eller bære en handlekurv.	1	2	3
116. Gå opp trappen flere etasjer.	1	2	3
117. Gå opp trappen en etasje.	1	2	3
118. Bøye deg eller sitte på huk.	1	2	3
119. Gå mer enn to kilometer.	1	2	3
120. Gå noen hundre meter.	1	2	3

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
121. Gå hundre meter.	1	2	3
122. Vaske deg eller kle på deg.	1	2	3

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.)

	Ja	Nei
123. Har du redusert tiden du har brukt på arbeidet ditt eller på andre aktiviteter pga. din fysiske helse?	1	2
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 krevde ekstra anstrengelser)?	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 deprimert eller engstelig? (Sett ring rundt ett tall.)

	Ja	Nei
127. Har du redusert tiden du har brukt på arbeidet ditt eller på andre aktiviteter pga. følelsesmessige problemer?	1	2
128. Har du utrettet mindre enn du hadde ønsket pga. følelsesmessige problemer?	1	2
129. Har du ikke arbeidet eller utført andre aktiviteter like nøye 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.)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
1	2	3	4	5

131. Hvor sterke kroppslige smerter har du hatt i løpet av de siste fire ukene? (Sett ring rundt ett tall.)

Ingen	Meget svake	Svake	Moderate	Sterke	Meget sterke
1	2	3		5	6

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.)

Ikke i det hele tatt	Litt	Endel	Mye	Svært mye
1	2	3	4	5

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?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

134. - følt deg veldig nervøs?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

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

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

136. - følt deg rolig og harmonisk?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

137. - hatt mye overskudd?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

138. - følt deg nedfor og trist?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

139. - følt deg sliten?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

140. - følt deg glad?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

141. - følt deg trett?

Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5	6

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 hele tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
1	2	3	4	5

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 riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

144. Jeg er like frisk som de fleste jeg kjenner.

Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

145. Jeg forventer at min helse vil bli dårligere.

Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

146. Min helse er utmerket.

Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
1	2	3	4	5

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
Svært dårlig						Helt utmerket

148. Hvordan har livskvaliteten din vært i løpet av den siste uken?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

SMERTER/PLAGER

Sett ring rundt det tallet som best beskriver din tilstand.

	Ikke i det hele tatt	Litt	Endel	Svært mye
149. Er du plaget av smerter, stikninger eller nummenhet i hendene/ fingrene?	1	2	3	4
150. Er du plaget av smerter, stikninger eller nummenhet i føttene/tærne?	1	2	3	4
151. Er du plaget av hvite/ kalde hender/fingre når det er kaldt?	1	2	3	4
152. Er du plaget av hvite/ kalde føtter/tær når det er kaldt?	1	2	3	4
153. Er du plaget av øresus?	1	2	3	4
154. Er du plaget av nedsatt hørsel?	1	2	3	4

BEKYMRINGER

155. Har du lite hår i forhold til jevnaldrende?

❑ Ja [1] ❑ Nei [2] ❑ Vet ikke [3]

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

❑ Ja [1] ❑ Nei [2]

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 tatt	Litt	Endel	Svært mye
1	2	3	4

I løpet av den siste uken:

Sett ring rundt det tallet som best beskriver din tilstand.

	Ikke i det hele tatt	Litt	Endel	Svært mye
157. Har ditt egenbilde som mann vært nedsatt som følge av din sykdom eller behandling?	1	2	3	4

	Ikke i det hele tatt	Litt	Endel	Svært mye
158. Har du vært plaget av bekymringer for ikke å kunne få barn?	1	2	3	4
159. Har du vært redd for tilbakefall av din sykdom?	1	2	3	4
160. Har du vært fornøyd med måten sykehus(ene) har foretatt undersøkelsene/ kontrollene av deg?	1	2	3	4
161. Har du følt at de avgjørelser som er foretatt med henblikk på din behandling har vært riktig for deg?	1	2	3	4

Mestring av plager/problemer

Utsagnene nedenfor handler om hvordan du opplever og mestrer de plagene/problemene du har. Utsagnene er skrevet i jeg-form og du setter kun ett kryss i den ruten som passer best i forhold til hvordan du opplever deg selv.

	Helt enig	Nokså enig	Både og	Nokså uenig	Svært uenig
162. Jeg sier fra når jeg er sint eller trist.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
163. Jeg snakker gjerne med noen utvalgte mennesker når det røyner på.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
164. Å gjøre nye ting er ofte vanskelig for meg.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
165. Jeg går aktivt inn for å finne en løsning på problemene mine.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
166. Fysisk aktivitet er viktig for meg.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
167. Jeg prøver å glemme plagene mine.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
168. Jeg legger problemene mine bak meg ved å konsentrere meg om noe annet.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
169. Jeg tror det kan komme noe positivt ut av plagene/ problemene mine.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
170. Jeg har god tro på at plagene mine vil bli bedre.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
171. Jeg graver meg ned i arbeid for å holde plagene/ problemene på avstand.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
172. Jeg føler langt på vei at jeg har gitt opp.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
173. Jeg trekker meg tilbake fra andre når jeg har det vanskelig.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

FØLELSER

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

174. Jeg har hatt perioder med sterke følelser omkring sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

175. Ting jeg har sett og hørt minnet meg plutselig om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

176. Tanker om sykdommen har trengt seg på også når jeg ikke har villet.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

177. Bilder fra sykdommen har plutselig dukket opp i tankene mine.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

178. Enhver påminnelse har gjenopplivet følelser knyttet til sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

179. Jeg har hatt vanskelig for å sove på grunn av tanker og bilder om sykdommen.

I høy grad	Ganske mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

180. Jeg har hatt vonde drømmer om sykdommen.

I høy grad	Ganske mye	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 mye	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 mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

183. Jeg har ønsket å bli kvitt minner om sykdommen.

I høy grad	Ganske mye	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 mye	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 mye	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 mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

187. Mine følelser rundt sykdommen er nærmest lammet.

I høy grad	Ganske mye	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 mye	Middels	Noe	Litt	Aldri
6	5	4	3	2	1

Tretthet

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste tiden. Vi spør om hvordan du har følt deg i det siste, dvs. de tre siste månedene, og ikke hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge, ber vi om at du sammenligner deg med hvordan du følte deg sist du var bra. Sett kun ett kryss for hvert spørsmål.

189. Har du problemer med at du føler deg sliten?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

190. Trenger du mye hvile?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

191. Føler du deg søvnig eller døsig?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

192. Har du problemer med å komme i gang med ting?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

193. Mangler du overskudd?

❑ Ikke i [1] det hele tatt	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

194. Har du redusert styrke i musklene dine?

❑ Ikke i [1] det hele tatt	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

195. Føler du deg svak?

❑ Mindre [1] enn vanlig	❑ Som [2] vanlig.	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

196. Har du vansker med å konsentrere deg?

❑ Mindre [1] enn vanlig	❑ Som [2] vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

197. Forsnakker du deg i samtaler?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

198. Er det vanskelig å finne de rette ordene?

❑ Mindre [1] enn vanlig	❑ Ikke mer [2] enn vanlig	❑ Mer [3] enn vanlig	❑ Mye mer [4] enn vanlig

199. Hvordan er hukommelsen din?

❑ Bedre [1] enn vanlig	❑ Ikke verre [2] enn vanlig	❑ Verre [3] enn vanlig	❑ Mye verre [4] enn vanlig

200. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Sett kun ett kryss.)

- ❑ Mindre enn en uke 1
- ❑ Mindre enn tre måneder 2
- ❑ Mellom tre og seks måneder 3
- ❑ Seks måneder eller mer 4

201. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det?

- ❑ 25 % av tiden 1
- ❑ 50 % av tiden 2
- ❑ 75 % av tiden 3
- ❑ Hele tiden 4

Personlighet

Spørsmålene nedenfor dreier seg om hvordan du vanligvis opptrer, føler og handler. Vennligst kryss av for enten «ja» eller «nei» for hvert spørsmål. Svar hurtig og ikke tenk for lenge over den nøyaktige meningen med hvert spørsmål.

202. Er du forholdsvis livlig?	❑ Ja 1	❑ Nei 2
203. Ville du bli oppskaket av å se et barn eller et dyr lide?	❑ Ja 1	❑ Nei 2
204. Liker du å treffe nye mennesker?	❑ Ja 1	❑ Nei 2
205. Blir dine følelser lett såret?	❑ Ja 1	❑ Nei 2
206. Hender det ofte at du "går trøtt"?	❑ Ja 1	❑ Nei 2
207. Liker du å spille andre et puss som av og til kan såre dem?	❑ Ja 1	❑ Nei 2
208. Er du ofte bekymret?	❑ Ja 1	❑ Nei 2
209. Er gode manerer og renslighet viktig for deg?	❑ Ja 1	❑ Nei 2
210. Bekymrer du deg for at fryktelige ting kan skje?	❑ Ja 1	❑ Nei 2
211. Tar du vanligvis selv det første skrittet for å få nye venner?	❑ Ja 1	❑ Nei 2
212. Er du for det meste stille når du er sammen med andre?	❑ Ja 1	❑ Nei 2
213. Liker du å komme til avtaler i god tid?	❑ Ja 1	❑ Nei 2
214. Har du ofte følt deg trøtt og giddeløs uten grunn?	❑ Ja 1	❑ Nei 2
215. Er det mange mennesker som forsøker å unngå deg?	❑ Ja 1	❑ Nei 2
216. Klarer du holde fart i et selskap?	❑ Ja 1	❑ Nei 2
217. Bekymrer du deg lenge etter en pinlig opplevelse?	❑ Ja 1	❑ Nei 2
218. Liker du å ha masse liv og røre rundt deg?	❑ Ja 1	❑ Nei 2
219. Forteller folk deg en masse løgner?	❑ Ja 1	❑ Nei 2

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

Tusen takk for hjelpen!

RiTø

REGIONSYKEHUSET
I TROMSØ

APPENDIX II

Questionnaire Survey II, 2007-2008

29834

Pasient nr.: ☐☐☐☐

Etterundersøkelse av pasienter behandlet for testikkelkreft

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: ☐☐.☐☐.☐☐☐☐ (dag . måned . år)

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
☐ Ja, hovedsakelig

Hvis nei, oppgi alternativ grunn: ☐

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)

☐ Grunnskoleutdanning (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 kreften 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 kreften 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?

	Ikke i det hele tatt	I noen grad	I stor grad
Ufrivillig overflytting til andre oppgaver	☐	☐	☐
Trussel om tvangspermittering	☐	☐	☐
Trussel om oppsigelse	☐	☐	☐
Arbeidsledighet	☐	☐	☐
Uføretrygd	☐	☐	☐

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

10. La oss gå ut fra at arbeidsevnen din på sitt beste ville fått 10 poeng. Hvor mange poeng vil du da gi din nåværende arbeidsevne? (0 innebærer at du i dag ikke er i stand til å arbeide i det hele tatt. Sett kryss ved det tallet som du mener best tilsvarer din nåværende arbeidsevne).

☐ 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/utdanningssituasjon?

☐ 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?

	Litt	Middels	Mye
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 følesesmessige 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:

	Ja	Nei
Fastlege/allmennlege	☐	☐
Annen legespesialist utenfor sykehus	☐	☐
Konsultasjon uten innleggelse		
- ved psykiatrisk poliklinikk	☐	☐
- ved annen sykehus poliklinikk	☐	☐
Fysioterapeut	☐	☐
Kiropraktor	☐	☐
Homøopat, 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

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

b) Røyker du for tiden av og til?

☐ Ja ☐ Nei

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

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

22. Hvordan har din fysiske aktivitet i fritida vært det siste året? Tenk deg et ukentlig gjennomsnitt for året. Arbeidsvei regnes som fritid.

	Timer per uke			
	ingen	under 1	1-2	3
Lett aktivitet (ikke svett/andpusten):	☐	☐	☐	☐
Hardere fysisk aktivitet (svett/andpusten):	☐	☐	☐	☐

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 hjerteoperert 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

Snu arket!

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:

	Ja	Nei	Hvis JA, alder første gang
Astma	☐	☐	☐☐
Kronisk bronkitt, emfysem eller KOLS	☐	☐	☐☐
Slitasjegikt (artrose)	☐	☐	☐☐
Leddgikt (reumatoid artritt)	☐	☐	☐☐
Bechterews sykdom	☐	☐	☐☐
Ny kreftsykdom ETTER testikkelkreften (dvs evnt. ny kreft etter 1994)	☐	☐	☐☐
Sarkoidose	☐	☐	☐☐
Beinskjørhet (osteoporose)	☐	☐	☐☐
Epilepsi	☐	☐	☐☐
Psoriasis	☐	☐	☐☐
Eksem	☐	☐	☐☐

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?

	Liten grad		Middels		Stor grad
a) Hull i tennene - nedslitte tenner	☐	☐	☐	☐	☐
b) Sykdommer i tannkjøtt og slimhinner	☐	☐	☐	☐	☐
c) Munntørrhet	☐	☐	☐	☐	☐

41. Hvordan vurderer du din munn-og tannhelse?

Meget dårlig	Dårlig	Verken god eller dårlig	God	Meget god
☐	☐	☐	☐	☐

SMERTER/PLAGER (i løpe av den siste måneden)

(sett et kryss X ved det som passer)

	Ikke i det hele tatt	Litt	En del	Svært mye
42. Er du plaget av smerter, stikninger eller nummenhet i hender/fingre?	☐	☐	☐	☐
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 diaré/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 uroføelse 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 humør
   - ☐ 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 utseendet like mye som jeg alltid 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 alltid 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 TVprogram
    - ☐ Ofte
    - ☐ Fra tid til annen
    - ☐ Ikke så ofte
    - ☐ Svært sjelden

29834

Fatigue (tretthet)

Pasient nr.: | | | | |

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måneden. Vennligst besvar ALLE spørsmålene ved å krysse av x for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Vi spør om hvordan du har følt deg i det siste og ikke om hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra.

(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 konsentrere 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!

PAPER I

PAPER II

PAPER III