Cognitive function in testicular cancer patients: prospective studies of self-reported and neuropsychological function

Tone Skaali

Department of Oncology, Oslo University Hospital,
The Norwegian Radium Hospital
and
Institute of Clinical Medicine, Faculty of Medicine,
University of Oslo

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Oslo, September 2010

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List of papers

Paper I (The 1990'ies study)

A prospective study of cognitive complaints in testicular cancer patients treated in the pre "chemo brain" era

Skaali T, Fosså SD, Dahl AA

Submitted, 2010

Paper II (The distress paper)

Is psychological distress in men recently diagnosed with testicular cancer associated with their neuropsychological test performance?

Skaali T, Fosså SD, Andersson S, Langberg CW, Lehne G, Dahl AA

Psycho-Oncology 2010, published online June 28, 2010, DOI: 10.1002/pon.1737

Paper III (The neuropsychological paper)

A prospective study of neuropsychological functioning in testicular cancer patients

Skaali T, Fosså SD, Andersson S, Cvancarova M, Langberg CW, Lehne G, Dahl AA

Annals of Oncology, in press 2010

Paper IV (The self-report paper)

Self-reported cognitive problems in testicular cancer patients: Relation to neuropsychological performance, fatigue and mental distress

Skaali T, Fosså SD, Andersson S, Cvancarova M, Langberg CW, Lehne G, Dahl AA

Submitted, 2010

SYNOPSIS OF THE THESIS

Due to concern about possible negative effects of systemic chemotherapy on cognitive function (i.e. memory and concentration), these functions in cancer patients after such treatment have received increasing clinical and public attention. However, in 2005, at the onset of the research project leading to this thesis, no neuropsychological studies had been published on cognitive function in testicular cancer patients (TCPs) after systemic chemotherapy. TCPs in general are young and have a favorable prognosis. Hence, most patients have a long life expectancy after their malignancy, and they are expected to resume a regular professional and familial life after treatment. Cisplatin, the cornerstone of chemotherapy for testicular cancer, has well-known toxic effects on the peripheral nervous system. Therefore we considered systematic assessment of cognitive function in TCPs treated with chemotherapy to be of considerable importance, both for the patients and for future clinical work.

The main aim of this thesis was to explore cognitive function in TCPs. In the period from 2006 to 2009 we therefore conducted a prospective study of cognitive function in TCPs evaluated and treated at the Norwegian Radium Hospital and the Ullevaal University Hospital (now both parts of the Oslo University Hospital). This thesis also includes a prospective study on self-reported cognitive complaints in TCPs included in three European Organization of Research and Treatment of Cancer Organization (EORTC) / Medical Research Council (MRC) treatment studies done during the 1990'ies, before the associations between chemotherapy and reduced cognitive function became a public concern.

In *paper I (the 1990'ies study)* self-reported cognitive complaints in TCPs treated with chemotherapy or radiotherapy during the 1990'ies are prospectively explored. We found no significant difference between the chemotherapy and the radiotherapy group in prevalence of cognitive complaints at one-year follow-up. Treatment modality was not significantly associated with cognitive complaints at any time point after adjustment for QoL domains such as emotional function and fatigue.

Paper II-IV reports results from our prospective study of cognitive function in TCPs, conducted at the Oslo University Hospital ("*The Oslo-study"*). In *paper II (the distress paper)* we explored the level of emotional distress shortly after the diagnosis of TC (at the baseline evaluation of our study), and investigated whether current level of distress had any impact on the neuropsychological test results at that time-point. About one-fourth of the

TCPs had clinically significant distress at baseline. However, we found that the majority of neuropsychological test scores (14 out of 18) were *not* significantly associated with levels of emotional distress.

In *paper III (the neuropsychological paper)* we compared the proportions of TCPs in three treatment groups (no chemotherapy, one cycle of chemotherapy, and multiple cycles of chemotherapy) with changes in neuropsychological test performance from baseline (pre-treatment) to one year follow-up. No significant group differences in proportions of TCPs with a decline in neuropsychological test performance from baseline to follow-up were observed.

In *paper IV (the self-report paper)* we prospectively explored self-reported cognitive complaints in TCPs. Increase of cognitive complaints from baseline to one-year follow-up was significantly associated with levels of emotional distress and fatigue and treatment with chemotherapy, but not with a decline in neuropsychological test performance.

From the findings presented in this thesis we conclude that cisplatin-based chemotherapy does not seem to have a negative impact on neuropsychological test performance in TCPs at one year follow-up. However, this finding should be confirmed in larger prospective studies before definite conclusions can be made. Self-reported cognitive complaints were not associated with neuropsychological test performance in our study, but were related to current emotional distress and fatigue. For TCPs treated in the 1990'ies, chemotherapy was not a significant predictor of post-treatment cognitive complaints after adjustment for emotional function and fatigue.

Abbreviations and definitions

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BEP	Bleomycin, Etopside and Cisplatin
CAGE	Instrument to assess alcohol problems (acronym)
CHEM group	Group of patients treated with chemotherapy
CI	Confidence interval
EORTC	European Organization for Research and Treatment of Cancer
EPQ	Eysenck Personality Questionnaire
FQ	Fatigue Questionnaire
HADS	Hospital Anxiety and Depression Scale
IES	Impact of Event Scale
MRC	Medical Research Council
MULTIPLE-CHEMO group	Group of patients treated with multiple cycles of chemotherapy
NART	National Adult Reading Test
NO-CHEMO group	Group of patients who have received no chemotherapy
NRH	Norwegian Radium Hospital
ONE-CHEMO group	Group of patients treated with one cycle of chemotherapy
OR	Odds ratio
PANAS	Positive and Negative Affect Scale
RPLND	Retroperitoneal lymph node dissection
SCIN	Scale for Chemotherapy-Induced Neurotoxicity
RAD group	Group of patients treated with radiotherapy
SD	Standard deviation
SRB model	Standardized regression-based model
TC	Testicular cancer
TCP	Testicular cancer patient
QLQ-C30	Quality of Life Questionnaire C30
QoL	Quality of life
UUS	Ullevål University Hospital

1. BACKGROUND

1.1. Oncological aspects of testicular cancer

1.1.1. Incidence and etiology

Testicular cancer (TC) is the most common malignancy in males aged between 15 and 40 years in the Western countries. During the past 50 years the incidence of TC has been rising steadily with a doubling of the incidence-rate during this period (Richiardi *et al.* 2004). Today, Norway and Denmark have the highest incidences of TC worldwide (Bray *et al.* 2006; Richiardi *et al.* 2004). In Norway, the age-adjusted incidence-rate of TC in Norway was 12.3 per 100.000 person-years in 2008, and 296 Norwegian males were diagnosed with TC in that year (Cancer Registry of Norway, 2009).

Research indicates that both genetic and environmental factors acting on the primordial gonocytes (germ cells) during foetal life may be involved in the etiology and pathogenesis of testicular tumors (Krausz and Looijenga, 2008; McGlynn and Cook, 2009). There is an increased risk of TC in brothers and sons of affected males supporting an eventual genetic factor (Heimdal *et al.* 1996; Krausz and Looijenga, 2008), however a major gene associated with TC has not been identified so far.

Peri-natal environmental factors are suspected to influence the development of TC (McGlynn and Cook, 2009). In particular, exposure of the male foetus to endocrine-disrupting chemicals (i.e. chemicals with a hormone-like effect used in industrial and household products) have been proposed as a possible risk factor. Post-natal environmental factors such as testicular trauma and factors in work life have also been considered (McGlynn and Cook, 2009). Overall, the etiology and pathogenesis of TC seem to be multi-factorial, and the exact mechanisms involved are far from clear (Krausz and Looijenga, 2008; McGlynn and Cook, 2009). Skakkebæk and colleagues have proposed that TC may be a part of a *testicular dysgenesis syndrome*, in which conditions like cryptorchidism (non-descended testis), impaired spermatogenesis, hypospadias (birth defect of urethra) and TC are risk factors for each other, and share a common biology of early dysgenesis in the foetal testis (Wohlfahrt-Veje *et al.* 2009).

1.1.2. Tumor staging and treatment principles

If TC is suspected (lump or changes in a testicle), the diagnosis is usually verified by unilateral orchidectomy (surgical removing of the affected testicle) and a subsequent histologic examination of the tumour. Ninety-eight percent of TCs are malignant germ cell

tumours with a histological diagnosis of seminoma (50-60%) or non-seminoma (40-50%) (Horwich *et al.* 2006). The incidence of seminoma peaks at 35 years of age, while the incidence of non-seminoma peaks ten years earlier (McGlynn and Cook, 2009).

After the orchidectomy, further medical examinations are performed to evaluate the stage of the disease and the eventual need for chemotherapy or radiotherapy. These examinations usually include analyses of biochemical markers (human chorionic gonadotropin, α-foetoprotein and lactate dehydogenase) and radiologic examinations of the chest, abdomen and pelvis in order to detect metastases. Scanning of the brain is performed only if there are clinical signs of brain metastases or in high-risk patients (Horwich *et al.* 2006).

In Norway, the Royal Marsden Index (Peckham, 1988) is used for clinical staging of TC at the time of diagnosis. TC stage I indicates non-metastatic disease, whereas stage II, III and IV indicate metatstatic disease at increasing levels of severity. For seminoma, approximately 80% of patients have clinical stage I at the time of diagnosis, while for non-seminoma around 50% have stage I at that time (Oldenburg *et al.* 2008b).

Risk-adapted post-orchidectomy treatment of TC is planned based on histology, stage and biochemical markers (Horwich *et al.* 2006), and the current treatment strategies for TC in Norway are as follows: *Seminoma stage I* is managed with surveillance (no additional treatment but frequent follow-up examinations), or treated with one dose of carboplatin chemotherapy. Traditionally, radiotherapy was used in stage I seminoma, however this is not practice today. *Seminoma stage II-IV* is treated with radiotherapy (only stage II), or more commonly with cisplatin-based (bleomycin, etoposide and cisplatin – BEP) chemotherapy.

Non-seminoma stage I is managed with surveillance (low risk) or with one or two BEP-cycles (high risk). *Non-seminoma stage II-IV* is treated with 3 or 4 BEP-cycles and additional chemotherapy if needed. Surgical removing of retroperitoneal lymph nodes (Retroperitoneal lymph node dissection - RPLND) are performed in patients with metastatic non-seminoma if retroperitoneal lymph node masses persist after end of chemotherapy.

1.1.3. Prognosis of TC

After cisplatin was introduced in treatment during the 1980-ies, the prognosis of TC has improved quite significantly compared to earlier on, and the overall age-adjusted five years survival rate of TC in the European countries has reached 97% (Verdecchia *et al.* 2007). Non-metastatic (stage I) TC has a five years survival rate of almost 99% (Horwich *et al.*

2006). For metastatic TC three prognostic groups have been defined by the International Germ Cell Cancer Collaborative Group (International Germ Cell Cancer Collaborative Group, 1997), and the 5 years survival rate ranges from 48% (poor prognosis group) to 91% (good prognosis group). Relapse of TC is usually diagnosed within the first year after primary treatment, and occurs rarely more than two years later (Oldenburg *et al.* 2006b).

1.1.4. Short- and long-term health and morbidity after TC

Due to the high cure rate, long-term adverse effects of the disease and/or the treatment have received considerable clinical attention (Fossa *et al.* 2009; Travis *et al.* 2010). Adverse effects after cancer can be divided into short-term effects (<1 year post-diagnosis), medium-term (1-4 years post-diagnosis) and long-term ones (≥5 year post-diagnosis). In this thesis, long-term TC survivors are defined as testicular cancer patients (TCPs) alive and tumour-free ≥5 post-diagnosis. In 2008 about 5,700 Norwegian men lived with a prior diagnosis of TC, and around 4,400 (77%) of these men were long-term TC survivors (Cancer Registry of Norway, 2009).

Only a few studies on *acute emotional distress* related to the orchidectomy and the TC-diagnosis have been published. As expected, TCPs frequently report emotional distress shortly after the diagnosis (Fossa *et al.* 2003; Trask *et al.* 2003; Tuinman *et al.* 2007; van Basten *et al.* 1996).

Physical health problems during the first year after diagnosis are mostly related to *acute side-effects of surgery, radiotherapy or chemotherapy* (Fossa *et al.* 2009). Acute toxicity of the BEP chemotherapy may affect the gastrointestinal (nausea), the hematological (anemia/infections), the renal (nephrotoxicity), or the neurological (peripheral neurotoxicity) organ systems (Brydoy *et al.* 2009). Nausea and fatigue are reported as acute side-effects of abdominal radiotherapy in TCPs (Fossa *et al.* 2009).

Patients with non-metastatic disease receiving *surveillance only* have no somatic side-effects other treatments, but must cope with the psychological distress associated with having TC and frequent follow-up examinations (Jones and Payne, 2000). Long-term TC survivors have demonstrated increased levels of *anxiety and fatigue* compared to normative male population samples (Dahl *et al.* 2005; Orre *et al.* 2008) and *fear of cancer recurrence* is not uncommon among TC survivors (Skaali *et al.* 2009). In contrast, long-term health related quality of life (QoL) (Mykletun *et al.* 2005; Vidrine *et al.* 2010) have not been found different to the normative population. Also, the *work ability* of long-term TC survivors has been found similar as in the general population (Gudbergsson *et al.* 2008).

Studies have shown that about 20% of TCPs have *clinical or sub-clinical hypogonadism* (low levels of testosterone) already at diagnosis, while some TCPs develop hypogonadism after treatment (Fossa *et al.* 2009; Travis *et al.* 2010). Post-treatment endocrine hypogonadism is usually related to a decrease of testosterone production after removal of the diseased testicle, and occurs until a compensatory increase of the production is achieved by the non-affected testicle (Eberhard *et al.* 2008). If hypogonadism persists, medical substitution with testosterone may be a therapeutic option.

As to *sexual function* after TC, research findings have been ambiguous. Wiechno et al (Wiechno *et al.* 2007) reported that survivors with abnormal hormone levels had more sexual complaints compared with survivors with normal hormone levels. However, in a study by Dahl et al (Dahl *et al.* 2007) no difference in overall sexual satisfaction between long-term TC-survivors and a normative sample was found.

Knowledge about *long-term toxic effects after cisplatin-based (BEP) chemotherapy* in TCPs are emerging (Horwich *et al.* 2006). Reduced fertility due to gonadal toxicity, long-term cardiovascular morbidity and persistent peripheral neurotoxic symptoms are major side effects (Fossa *et al.* 2009). The neurotoxic effects of the chemotherapeutic agents used in treatment of TC are discussed in detail below. Second cancers are rare but represent serious late effects after radiotherapy and chemotherapy for TC (Fossa *et al.* 2009; Travis *et al.* 2010).

1.1.5. Neurotoxicity of cytotoxic agents used in treatment of TC

Cisplatin is a platinum compound with cytotoxic and antitumor effects, mostly exerting its effect by producing cross-links on the DNA (Wang and Lippard, 2005). Cisplatin has a well-known neurotoxic effect, mostly affecting the peripheral nervous system. Among TCPs treated with cisplatin, 10-30% develop persisting peripheral neuropathy (numbness / reduced sensation in fingers or toes) due to the accumulation of cisplatin in the dorsal root ganglia and/or to axonal damage of the sensory peripheral nerves (Fossa *et al.* 2009). Further, about 20% of long-term TC survivors treated with cisplatin complain about hearing loss or tinnitus (Brydoy *et al.* 2009). Such ototoxic symptoms are most probably due to cisplatin-induced damage of the outer hair cells of the inner ear. Genetic polymorphisms involved in the metabolism of cisplatin and possibly protective of ototoxicity have been described (Oldenburg *et al.* 2008a).

Cisplatin is supposed to have poor penetration of an intact blood-brain barrier (in patients without brain metastases), and low penetration of systemically administrated

cisplatin has been shown in an animal study (Jacobs *et al.* 2005). However, reports of post-mortem histo-pathological damage in the central nervous system (CNS) after cisplatin infusion have been published (Troy *et al.* 2000). Further, there exist case reports of cerebral symptoms (seizures, encephalopathy and visual disturbances) in patients after systemically administrated cisplatin (Hartmann and Lipp, 2003; Troy *et al.* 2000). Hence, systemically administrated cisplatin could possibly have a direct toxic effect on the CNS in some cases.

Carboplatin is a platinum compound resembling cisplatin, but is less effective on tumor cells. In routine treatment of TC, carboplatin is used only as adjuvant treatment for seminoma stage I patients. Carboplatin has less nephrotoxic and neurotoxic effects compared to cisplatin (Hartmann and Lipp, 2003). *Bleomycin* and *etopside* have little or no neurotoxic effects (Dahl O *et al.* 2009).

1.2. Cognitive function in adult cancer patients

1.2.1. Cognitive function

Cognitive function refers to the mental activities of information processing in the brain, and involves functions like perception, memory, thinking, reasoning and expression. In everyday language cognitive function is usually referred to as concentration and memory. Information processing in the brain is based on complex neural activity involving schematically four "classes" of cognitive functions (Lezak *et al.* 2004). Processing starts with the perception of incoming sensory stimulus (*receptive functions*), followed by storage and retrieval of information (*learning and memory*), then reaching a "higher level" of processing involving functions like abstraction, reasoning, planning and executive functions[1] (*thinking*), and finally the level by which information or thoughts are communicated or acted upon (*expressive functions*). These four "classes" of cognitive functions are visualized in the following model of information processing (Figure 1), modified from Vanderploeg (Vanderploeg, 2000). In this figure, the different "classes" of cognitive functions are marked with different colors: *receptive functions* (green), *learning and memory* functions (blue), *thinking* (orange) and *expressive functions* (yellow).

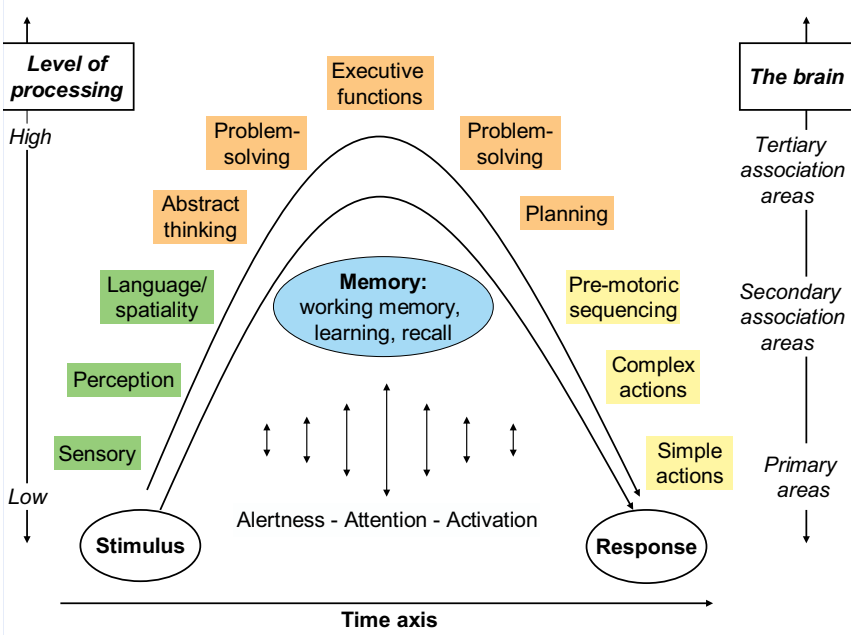

Figure 1. Schematic model of cognitive information processing, modified from Vanderploeg (Vanderploeg, 2000)

[1] executive functions refer to "higher order" mental functions such as rule acquisition, initiating appropriate actions and inhibiting inappropriate actions

As visualized in Figure 1, cognitive information processing from stimulus to response (via memory and thinking) represents mental activities at different levels of complexity in the brain. By cognitive dysfunction we usually mean disturbances at any level of information processing. Basic mental functions such as alertness /attention /activation are the "gateway" for all subsequent information processing. If these basic functions are disturbed, for example in a person who is preoccupied by anxiety or fatigue, further information processing such as learning and memory may be disturbed. Dysfunctions at the highest level of processing, involving abstraction, reasoning, planning and executive functions, can reduce an individual's ability to function in complex settings (multi-tasking), even though the more basic functions such as learning and memory seem to be intact (Vanderploeg, 2000).

Earlier models of cognitive information processing were based on the assumption that different cognitive functions were located in discrete anatomical areas of the brain. In contrast, current models emphasize that cognitive functions are based on activity in complex neural circuits involving large parts of the brain, comprising both cortical and sub-cortical structures (Vanderploeg, 2000). However, some basic anatomic localization of cognitive functions is recognized, for example that the left cerebral hemisphere predominantly processes verbal information, whereas the right one mostly processes visuo-spatial information. Complex "higher order" cognitive functions such as abstraction, logical thinking, planning and executive functions are based on neuronal circuits in the prefrontal cortex in conjunction with sub-cortical structures (fronto-subcortical circuits).

1.2.2. Assessment of cognitive function

Neuropsychological testing represents the gold standard for assessment of an individual's cognitive function (Lezak *et al.* 2004; Reitan and Wolfson, 1993; Vanderploeg, 2000). A neuropsychological test battery consists of a set of tasks designed to measure different aspects of cognitive function, i.e. different *cognitive domains*. The neuropsychological tasks are administrated in a standardized manner by trained personnel. Comprehensive neuropsychological test batteries usually include evaluation of the following *cognitive domains* (Lezak *et al.* 2004):

- Attention / concentration / working memory
- Verbal and visual learning and memory
- Speed of information processing

- Executive functions including verbal fluency
- Motor function

These cognitive domains do not represent totally separate functional constructs however, and many neuropsychological tests require involvement of several cognitive domains. Examples of neuropsychological tests are to memorize a word list, to draw a line alternating between ascending and letters numbers as fast as possible, or to copy a construction using as few moves as possible. In addition to traditional "paper and pencil" neuropsychological tests, also newer computer-based neuropsychological tests have been developed (Levaux *et al.* 2007; Sahakian and Owen, 1992). Computerized tests may be particularly useful for evaluation of attention and speed of information processing.

Age, level of basic education, and level of intellectual capacity (IQ) are factors that have an impact on neuropsychological test performance. Normative data for neuropsychological tests are regularly customized for gender and age, and preferably also for level of education and intellectual capacity. Hence, neuropsychological test results can usually be controlled for these variables. High levels of education and intellectual capacity have been suggested as protective factors to reduced cognitive function after brain trauma, explained by a larger "cognitive reserve" (Stern, 2009).

The neuropsychological test method is generally sensitive for detecting reduced cognitive function; however, the method is not specific concerning the *cause* of cognitive reduction (Vanderploeg, 2000). In the case of non-focal (diffuse) cognitive reduction, the same pattern of reduced test performance can be observed with different neurological etiologies. Neuropsychological test performance can also be reduced secondary to emotional distress, fatigue or low motivation for testing, and controlling for these variables may be difficult (Vardy and Tannock, 2007).

A general problem with neuropsychological testing is the low *ecological validity* of many tests, referring to the fact that the tests do not adequately mirror task performances of everyday life, but rather assess performances in a standardized test situation (Lezak *et al.* 2004; Spooner and Pachana, 2006). Currently, work is going on to develop new neuropsychological tests which better represent the cognitive challenges of everyday life, thereby increasing the ecological validity. There are also some problems when neuropsychological testing is performed in a sample of individuals with good cognitive capacity. Many traditional neuropsychological tests were developed to detect major cognitive deficits rather than subtle changes in cognitive function, hence *ceiling effects* of test performance may occur. Finally, "higher order" cognitive functions such as planning,

multi-tasking and executive functions are *per definition* difficult to evaluate by standardized testing, since such functions describe how the person cope with "non-standardized" cognitive demands. However, executive tests do measure some aspects of these functions.

In addition to neuropsychological testing, cognitive function can also be studied by *functional* brain scanning [e.g. functional MRI or positron emission tomography (PET)], which implies that the test person is performing a cognitive task while the brain activity is registered. Such cognitive imaging techniques are an emerging field, however beyond the scope of this thesis, and will therefore not be presented further. Neurophysiologic registration of brain activity during cognitive tasks [e.g. event-related potentials (ERP)] also represents an opportunity for assessment that will not be covered further here.

1.2.3. Cognitive function in cancer patients

Malignant disease affecting the CNS and/or cancer treatment with direct involvement of the CNS may have a detrimental effect on brain functioning including cognitive function. This has been well documented (Correa, 2010; Platta *et al.* 2010; Ricard *et al.* 2009), and is not a theme of this thesis.

Complaints about reduced concentration and memory are, however, frequent also in cancer patients with no obvious CNS involvement of the tumor or treatment (Kohli S *et al.* 2007). During the last decade there has therefore been an increasing attention and research on cognitive functioning among patients with non-CNS cancers (Vardy *et al.* 2008; Vardy and Tannock, 2007), particularly so after treatment for breast cancer (Shilling and Jenkins, 2007; Vardy and Tannock, 2007; Vodermaier, 2009).

Patients and oncologists are concerned that systemic chemotherapy may have a negative effect on cognitive function, and reduced cognitive function in (breast) cancer patients after chemotherapy has popularly been called "chemo brain" or "chemo fog". However, based on systematic research so far, significant associations between systemic chemotherapy and reduced cognitive function in cancer patients are still only partially documented.

At the onset of the studies of this thesis, no neuropsychological study exploring cognitive function in TCPs after systemic chemotherapy had been published.

1.2.4. History of "chemo brain"

One of the first reports of to mention cognitive dysfunction in relation to chemotherapy was published in 1974 (Weiss *et al.* 1974a; Weiss *et al.* 1974b). A few small scale

neuropsychological studies (Cull *et al.* 1996; Meyers *et al.* 1995; Oxman and Silberfarb, 1980; Silberfarb *et al.* 1980; Wieneke M and Dienst E, 1995) evaluating cognitive function in patients after chemotherapy for non-CNS solid tumors (lymphoma, lung cancer, breast cancer or mixed cancers) were published in the subsequent 20 years, including a Norwegian study by Kaasa et al on lung cancer patients (Kaasa *et al.* 1988). Conflicting results concerning reduced cognitive function after chemotherapy were presented.

Neuropsychological studies with larger sample sizes conducted in breast cancer patients have been published during the last 15 years. Among them, the earlier cross-sectional studies (Ahles *et al.* 2002; Brezden *et al.* 2000; Castellon *et al.* 2004; Schagen *et al.* 1999; Tchen *et al.* 2003; van Dam *et al.* 1998) all demonstrated that a subgroup of the breast cancer patients showed reduced cognitive function after chemotherapy. In contrast, newer prospective studies in breast cancer patients, including a pre-treatment assessment (Bender *et al.* 2006; Debess *et al.* 2010; Jenkins *et al.* 2006; Mehlsen *et al.* 2008; Quesnel *et al.* 2009; Schagen *et al.* 2006; Stewart *et al.* 2008; Tager *et al.* 2009; Wefel *et al.* 2004b; Wefel *et al.* 2010), have reported more divergent findings regarding significant associations between systemic chemotherapy and reduced cognitive function.

1.2.5. Hypothetical mechanisms for reduced cognitive function after non-CNS malignancies

In addition to a possible direct effect of systemic chemotherapy on the brain, several other factors could hypothetically affect short- and/or long-term cognitive function in patients with non-CNS malignancies. These factors (including systemic chemotherapy) are shown in Figure 2 and presented in some detail below.

Systemic chemotherapy

It is generally assumed that only a few cytotoxic agents (e.g. 5-fluoruracil, methotrexate and ifophosphamide) cross an intact blood-brain barrier, while most cytotoxic agents do not (Ahles and Saykin, 2007). However, sporadic reports about encephalopathic and cerebellar symptoms after systemic chemotherapy with commonly used cytotoxic agents have been published (Troy *et al.* 2000; Verstappen *et al.* 2003). Hypothetically, patients may be genetically more or less susceptible for cytotoxic agents crossing the blood-brain barrier (Ahles and Saykin, 2007). In the brain, the cytotoxic agents may exert a *direct* toxic effect by damage of neurons or their supportive cells, or interfere with the level or function of neurotransmitters.

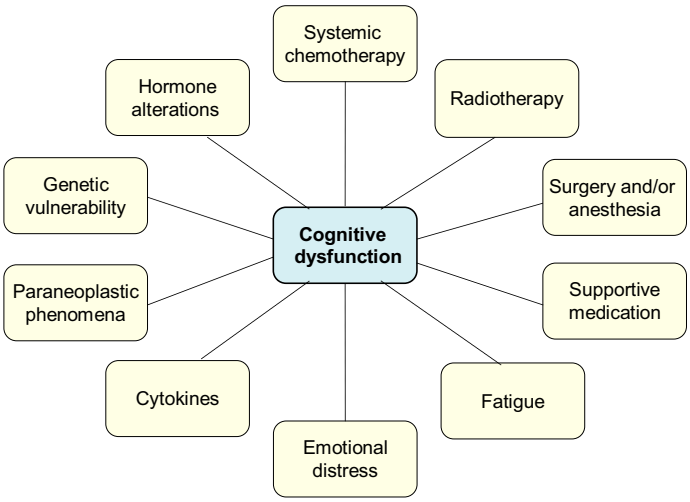

Figure 2. Overview of factors that hypothetically could impact on cognitive function in cancer patients with non-CNS malignancies (direct or indirect effects)

In a preclinical study by Noble and colleagues (Dietrich *et al.* 2006), cytotoxic agents (carmustine or cisplatin) administered systemically in mice were associated with an increased cell death and decreased cell division in the hippocampus and the corpus callosum regions of the brains, several weeks after the drug administration. In a later study by the same research group (Han *et al.* 2008), altered transcriptional regulation in oligodendrocytes and damage to myelin was found in adult mice brains 56 days after the administration of 5-fluoruracil in clinically relevant doses. This later study may indicate a particular toxic effect of cytotoxic agents on the myelin in the CNS, eventually resulting in axonal damage of neuronal networks ("white matter").

In a recent clinical study by de Ruiter et al (de Ruiter *et al.* 2010) using functional MRI, brain activation during an executive (planning) task and a memory task was registered in 16 breast cancer patients treated with high dose chemotherapy 10 years earlier (chemotherapy group) and in 15 controls (breast cancer patients not treated with chemotherapy). The chemotherapy group showed significantly lower activation in parts of the prefrontal cortex (dorsolateral prefrontal cortex) during the executive task and in parts of the hippocampus (parahippocampal gyrus) during the memory task compared to the control group, indicating functional changes in the brain associated with chemotherapy. Further, the chemotherapy group showed a general lower activation of parts of the parietal cortex (lateral posterior parietal cortex) during both the executive and the memory tasks compared to the

control group, indicating a disturbance in attentional processing among the patients treated with chemotherapy.

In addition to a direct toxic effect, several *indirect* mechanisms by which cytotoxic agents could affect the brain have been proposed (Vardy *et al.* 2008). *Cytokines* are released during chemotherapy, and some cytokines could have direct or indirect negative effects on brain cells. Further, some cytotoxic agents may cause endothelial disruption, and brain cells could be affected indirectly due to vascular damage leading to insufficient oxygenation. Toxic effects to the bone marrow resulting in anemia and low oxygen levels could also be a contributing factor. Cytotoxic agents may also have a damaging effect on gonadal function and hormone production, thereby indirectly causing hypogonadism (low levels of sex hormones) in both sexes and premature menopause in women. Hormone receptors are widely distributed in the brain (Luine, 2008; Ulubaev *et al.* 2009), and changes in circulating hormone levels could have an impact on cognitive function.

Hormonal changes

In addition to the indirect hormonal effects of chemotherapy described above, some malignancies (such as ovarial cancer and TC) directly involve the gonads and may therefore interfere with hormone production. Also, anti-hormonal treatment is commonly used in the treatment of for example breast cancer (anti-estrogens) and prostate cancer (testosterone blockade).

Paraneoplastic phenomena

These are induced by the malignancy itself and involve inflammation processes with the release of cytokines that could have an effect on brain function (as described above) (Foster and Caplan, 2009).

Cytokines

In addition to the release of cytokines in response to the malignancy or its treatment, some cytokines are used directly as therapeutic agents in treatment of certain malignancies (immunotherapy) (Fry and Lankester, 2010). Such agents could possibly have an adverse effects on cognitive function.

Supportive agents

Among these are anti-emetics, corticosteroids, analgesics and anxiolytics/hypnotics that are commonly used during or after treatment of malignancies. These agents may have adverse effects on cognitive function.

Radiotherapy

Radiotherapy may hypothetically have an indirect effect on cognitive function via secondary vascular effects (endothelial damage) (Jurado *et al.* 2008) affecting the brain cells, or via radiotherapy-induced fatigue which is common after such treatment for malignancies (Wang, 2008).

Surgery and anesthesia

Particularly in older cancer patients there is a risk of post-operative cognitive dysfunction due to the anesthetic agents or to insufficient cerebral oxygenation.

Genetic susceptibility

Individual variability in genetic predisposition (genetic polymorphisms) for cognitive dysfunction (e.g. apolipoprotein E), or for an increased permeability of cytotoxic agents over the blood-brain barrier may lead to an increased risk for cancer-related cognitive dysfunction in some patients (Ahles and Saykin, 2007).

Fatigue

Clinically significant fatigue of long duration is common during and after malignancies and includes both physical and mental symptoms (Wang, 2008). Mental fatigue is characterized by subjective cognitive symptoms such as concentration problems, word finding problems and memory problems.

Emotional distress

Symptoms of reduced concentration and memory function are prevalent in individuals with anxiety disorders and/or depressive disorders. Such cognitive symptoms may also be a consequence of cancer-related emotional distress. Dysregulation of the glucocorticoid hormones pathway (cortisol) are observed in patients with major depression, and altered cortisol metabolism may eventually be a contributing factor in distress-related cognitive dysfunction (Sierksma *et al.* 2010).

1.2.6. Neuropsychological functioning in breast cancer patients

Since nearly all research studies on cognitive function after treatment of non-CNS malignancies so far have been performed in breast cancer patients, a summary of the findings in this patient group is given. As referred above (Section 1.2.4), the majority of the early cross-sectional neuropsychological studies in such patients demonstrated that more patients exposed to chemotherapy had reduced cognitive function compared to controls (no chemotherapy) or published norm data (Ahles *et al.* 2002; Brezden *et al.* 2000; Castellon *et al.* 2004; Schagen *et al.* 1999; Tchen *et al.* 2003; van Dam *et al.* 1998; Wieneke M and Dienst E, 1995). However, the proportions of patients showing reduced cognitive function after chemotherapy ranged widely, from 17% to 75% across the studies (Correa and Ahles, 2008). Cognitive domains possibly affected by chemotherapy included attention/working memory, processing speed, and verbal and visual memory (Correa and Ahles, 2008) (Vardy and Tannock, 2007). Notably, two more recent cross-sectional studies (Donovan *et al.* 2005; Scherwath *et al.* 2006) did not find group differences in neuropsychological performance between breast cancer patients exposed or non-exposed to chemotherapy.

Newer prospective neuropsychological studies in breast cancer patients, with the inclusion of a pre-chemotherapy evaluation, have shown variable findings concerning the relation between chemotherapy and cognitive function. Interestingly, some of these studies reported that a subgroup of the patients showed reduced neuropsychological performance in several cognitive domains (verbal memory and reaction time) at *pre-treatment* (before chemotherapy) compared to healthy controls or published age-adjusted norm data (Ahles *et al.* 2008; Wefel *et al.* 2004a; Wefel *et al.* 2010). The authors explain these findings by paraneoplastic phenomena which may trigger release of inflammatory cytokines affecting cognitive function. Another explanation could be that the neuropsychological performance is reduced due to high levels of emotional distress shortly after the cancer diagnosis. Alternatively the study samples studied could lack representativeness in relation to relevant populations as to level of cognitive capacity due to selection biases.

As to post-treatment cognitive function, several prospective studies have documented that a subset of breast cancer patients exposed to chemotherapy had decline in neuropsychological test performance from baseline (pre-treatment) to *short-term* follow-up (1-6 months post-treatment) (Quesnel *et al.* 2009; Schagen *et al.* 2006; Shilling *et al.* 2005; Stewart *et al.* 2008). Among the cognitive domains affected were attention and verbal memory. However, other prospective studies with short-term follow-up assessments did not find an overall decline in cognitive function from pre- to post-chemotherapy (Debess

et al. 2010; Hermelink *et al.* 2007; Mehlsen *et al.* 2008; Tager *et al.* 2009), hence discrepant results have been reported.

Notably, most prospective studies with longer follow-up intervals (12-18 months after chemotherapy) found that neuropsychological performance was unchanged or had improved compared to pre-treatment levels (Collins *et al.* 2009; Jenkins *et al.* 2006). These results suggest that a possible negative effect of chemotherapy on cognitive function is resolved over time. However, in a recent prospective study by Wefel et al (Wefel *et al.* 2010), a subgroup of breast cancer patients exhibited decline in neuropsychological performance from pre-chemotherapy to 12-months follow-up; again conflicting findings have been observed.

The majority of breast cancer patients also receive *hormonal therapy* (anti-estrogens) and/or experience hormonal changes due to chemotherapy-induced menopause. The level of estrogens may possibly influence on cognitive functioning (Maki and Dumas, 2009), and hormonal therapy after breast cancer is associated with reduced cognitive function in some patients (Schilder *et al.* 2010). Castellon et al found that breast cancer patients who were exposed to both chemotherapy and hormonal therapy were more likely to show reduced cognitive function compared to patients treated with chemotherapy only (Castellon *et al.* 2004).

Based on these findings there is an ongoing debate whether any reduced cognitive function after treatment for breast cancer should be attributed mainly to chemotherapy or to hormonal changes (Vodermaier, 2009). Finally, *radiotherapy* is regularly given for breast cancer and may hypothetically have an indirectly negative effect on cognitive functioning due to related fatigue.

No consistent patterns of affected cognitive domains have been described after chemotherapy in breast cancer patients. Cognitive reductions are generally mild and non-focal (diffuse), and seem particularly to involve attention, processing speed and memory. Such cognitive reductions are mostly consistent with fronto-subcortical abnormalities, involving neural circuits between prefrontal cortex and subcortical structures (Vardy *et al.* 2008). Patients with fronto-subcortical abnormalities are characterized by slow mental processing with difficulties concerning attention, encoding and retrieval of information (Bonelli and Cummings, 2008).

1.2.7. Neuropsychological functioning in other cancer groups including males

Hardly any neuropsychological studies of cognitive function in other malignancies than breast cancer have been published. This implies that cognitive function rarely has been explored in male cancer patients. Exceptions are studies of cognitive function in patients treated for prostate cancer. However, the agenda in these studies were to explore if medically induced castration was associated with cognitive dysfunction (Nelson *et al.* 2008), and chemotherapy-related cognitive function was not an issue. Recently, however, two cross-sectional neuropsychological studies in TCPs were published (Pedersen *et al.* 2009; Schagen *et al.* 2008) and they are described fully in Section 1.3.

Hormonal factors may be related to the post-treatment cognitive dysfunction described in cancer patients, with possible differences across the genders. Future studies involving both male and female cancer patients could possibly illuminate any cognitive side-effects of systemic chemotherapy.

1.2.8. Methodological issues in neuropsychological studies of cancer-related cognitive function

Methodological issues concerning the neuropsychological studies reported above are covered here. First, the majority of studies has relatively small sample sizes, and thereby will only report significance for big differences due to type II statistical errors. Studies reporting no significant differences may therefore show significant differences in larger samples. Further, most of the early studies were cross-sectional without pre-treatment baseline data; hence individual changes in cognitive function over time could not be assessed.

This state of affairs called for prospective studies which are now gradually emerging, but until now such studies of patients with other malignancies than breast cancer are few. As stated in the preceding section, it is difficult distinguish between cognitive effects of chemotherapy and hormonal changes in breast cancer patients. Prospective neuropsychological studies have their own limitations, however, since pre-treatment evaluation is performed shortly after the cancer diagnosis when the patients may experience high levels of emotional distress due to their recent diagnosis. Increased level of emotional distress might have an impact on neuropsychological test performance (Vardy *et al.* 2008).

The neuropsychological test batteries used for assessing cognitive function have varied across studies, both in the numbers and selections of tests. Also, time points for the assessments vary considerably between studies. Lastly, various definitions of reduced or

decline in cognitive function have been used across studies (Shilling *et al.* 2006) (Vardy *et al.* 2007).

In sum, based on neuropsychological studies conducted so far, the relation between systemic chemotherapy and cognitive function is still mostly unsettled.

1.2.9. Self-reported cognitive function

The basis for the neuropsychological research described above has been cancer patients' complaints about impaired memory and concentration during and after treatment (Clegg, 2009). Hence, assessment of self-reported ("subjective") cognitive function is important in this field, as a supplement to the more "objective" neuropsychological test studies. Self-reported cognitive problems are often referred to as *cognitive complaints* (this term will be used in this thesis), in contrast to *cognitive dysfunction* as measured by neuropsychological tests.

Cognitive complaints in cancer patients can be assessed by interviews, by specific cognitive questionnaires such as the Functional Assessment of Cancer Therapy-cognitive function (FACT-COG) questionnaire (Lai *et al.* 2009; Vardy *et al.* 2006), or by QoL questionnaires which include items on cognitive function. For example, the EORTC Quality of Life Questionnaire (QLQ)-C30 (Aaronson *et al.* 1993) includes two items on memory and concentration.

Several of the neuropsychological studies in breast cancer patients mentioned in Section 1.2.6. also included assessment of cognitive complaints (Hermelink *et al.* 2010; Mehnert *et al.* 2007; Shilling and Jenkins, 2007). In these studies more than half of the patients had some post-treatment cognitive complaints, however such complaints were not restricted to patients exposed to chemotherapy. A recent systematic review on cognitive complaints in breast cancer patients (Pullens *et al.* 2009) reported that the prevalence of post-treatment cognitive complaints ranged widely across studies, from 21% to 90% of the patients.

Noteworthy, a low correlation between self-reported cognitive complaints and cognitive dysfunction found by neuropsychological testing has been repeatedly documented in breast cancer patients (Hermelink *et al.* 2010; Mehnert *et al.* 2007; Shilling and Jenkins, 2007). This discrepancy was already described in a small study of lymphoma patients from 1996 (Cull *et al.* 1996). Low correlations between self-reported and test-assessed cognitive function have been found also in other medical conditions associated with subtle cognitive dysfunction (Vardy and Tannock, 2007).

In contrast, cognitive complaints in breast cancer patients are reported to be significantly associated with symptoms of emotional distress and fatigue (Hermelink *et al.* 2010; Jenkins *et al.* 2006; Mehnert *et al.* 2007), and such complaints may actually reflect emotional status more than neurocognitive dysfunction. However, there are some data from non-cancer populations suggesting that self-reported cognitive complaints may be associated with brain-imaging parameters, in spite of normal neuropsychological test performance. In a study by Saykin et al (Saykin *et al.* 2006), 40 healthy older adults with cognitive complaints and normal neuropsychological test performance were examined with structural brain MRI. The results were compared with brain MRI's from a group of adults with mild dementia (amnestic mild cognitive impairment). The group with cognitive complaints showed grey matter abnormality in the temporal lobes of the brain comparable to the group with mild dementia, suggesting that neuropsychological testing was not sensitive to detect subtle cognitive impairment among these persons with cognitive complaints.

In 2007, Kohli et al. published a prospective study on self-reported memory and concentration complaints among 595 cancer patients with various malignancies (34% male patients) and treated with chemotherapy and/or radiotherapy (Kohli S *et al.* 2007). The patients filled in questionnaires at pre-treatment (T1), within 2 weeks after end of therapy (T2), and then at 6 months post-treatment (T3). Memory and concentration complaints were reported by nearly half of the study sample at baseline (T1) and these rates had significantly increased at T2 (shortly after end of treatment). At 6-months follow-up (T3) the rates of complaints were lower than at T2 but had not returned to baseline levels. Patients exposed to chemotherapy had significantly higher prevalence of concentration and memory complaints at T2 and T3 compared with patients treated with radiotherapy only. Compared to females, the male patients had significantly lower prevalence of cognitive complaints both at T2 and T3.

During the last decade there has been an increasing public attention about "chemo brain" or "chemo fog" in the media and on the Internet. Hence *expectation bias* (see Section 6.1.3) may be a problem in current studies of subjective cognitive complaints among patients treated with chemotherapy. In a study by Schagen and colleagues (Schagen *et al.* 2009), breast cancer patients with pre-existing knowledge about chemotherapy-related cognitive problems reported significantly more cognitive complaints compared with patients without such knowledge. In another study on cognitive complaints in breast cancer patients (Shilling and Jenkins, 2007), the authors stated: "self-report [of cognitive complaints] may

be high, simply because we asked patients to take part in a study investigating the potential effects of treatment on their memory".

1.3. Neuropsychological functioning and cognitive complaints in TCPs

Before the onset of the studies comprising this thesis, only one published study had described aspects of cognitive function in TCPs. In a prospective QoL study published in 2003, Fossa et al (Fossa *et al.* 2003) described subjective cognitive complaints (memory and concentration problems) as assessed by the EORTC QLQ-C30 questionnaire (Aaronson *et al.* 1993) in 666 TCPs treated with 3 or 4 BEP cycles. Nineteen percent of the TCPs had an increase of cognitive complaints from baseline (pre-treatment) to 2 years follow-up. This study gave the impetus for planning of the prospective study of cognitive function in TCPs presented in this thesis, including both neuropsychological and self-report evaluations.

Two cross-sectional studies of cognitive function in TCPs including neuropsychological evaluation were published during our period of data collection (see Section 3.2). In 2008, Schagen et al (Schagen *et al.* 2008) presented study of neuropsychological functioning and cognitive complaints in 182 TCPs at a mean follow-up time of 3 years post-treatment. Their sample consisted of 70 TCPs treated with 4 cycles of BEP-chemotherapy after orchidectomy (*chemotherapy group*), 57 TCPs treated with abdominal radiotherapy (20-30 Gy) after orchidectomy (*radiotherapy group*), and 55 TCPs treated with orchidectomy only (*surveillance group*). These TCPs were tested once with a neuropsychological battery consisting of 10 tests (24 sub-test measures) at a minimum of 6 months after end of treatment. Concerning mean raw neuropsychological scores, no significant differences were observed across the three treatment groups.

The authors also performed *individual analyses* using the following approach: The raw neuropsychological scores were converted to z-scores using the surveillance group as the reference group. If a patient scored ≤ 2 SD below the mean of the surveillance group on a test then he was considered as impaired on that test. Based on the fifth-percentile of the surveillance group a person was classified as showing reduced neuropsychological performance if he had deviant scores on at least 3 of the 24 test measures (corresponding to 12.5% of the test measures). Significantly higher proportions of patients in the chemotherapy and the radiotherapy groups had reduced neuropsychological performance (14% and 18% respectively) compared to the surveillance group (6%). No significant difference in proportions with reduced performance was observed between the chemotherapy and the radiotherapy group. However, after adjustment for age and level of

intellectual functioning, the chemotherapy group had significantly higher risk for showing reduced neuropsychological performance compared to the surveillance group (OR 4.6, 95% CI 1.1 – 19.7, p=0.04), but not if compared to the combined radiotherapy and surveillance group (OR 0.8, 95% CI 0.3 – 2.4, p=0.70).

The TCPs were also interviewed about cognitive problems, and the responses were rated on 5-point scales ranging from 1 (never) to 5 (always). A score of 3 or more defined the category of having *cognitive complaint*. Further, the patients were asked to indicate the extent they were *bothered* by eventual cognitive problems, also this question rated on a 5-point scale ranging from 1 (not) to 5 (extremely), and with a score of 3 or more defining as being *bothered* by the problems. Thirty-two percent of both the chemotherapy and the radiotherapy groups reported cognitive complaints, while for the surveillance groups the corresponding percentage was 27. Hence no significant between-groups differences in prevalence of cognitive complaints were observed. Approximately half of all TCPs with cognitive complaints indicated that they were bothered by these problems. Further, the study found no significant association between cognitive complaints and reduced neuropsychological performance. As previously reported in breast cancer patients, cognitive complaints in the TCPs were significantly associated with symptoms of fatigue and emotional distress, while being classified as cognitively impaired on neuropsychological tests did not show significant associations with these variables (Schagen *et al.* 2008).

Schagen et al concluded that regarding the possible effects of BEP chemotherapy on neuropsychological functioning in TCPs, their results were inconclusive and further research, in particular prospective studies, were needed. The strengths of the study by Schagen et al was a high inclusion rate (89%) and well powered group samples of TCPs that had received three different treatment modalities. The surveillance group served as an ideal control group and the authors report that the mean neuropsychological scores in the surveillance group were in line with published norm data. Complete data on neuropsychological test performance and self-reported cognitive complaints were obtained. However, a limitation was cross-sectional design with lack of pre-treatment assessment; hence individual change over time in neuropsychological test performance or cognitive complaints could not be assessed.

In 2009, Pedersen and colleagues (Pedersen *et al.* 2009) published a cross-sectional study on neuropsychological functioning in 72 TCPs at a mean of 4 years after end of treatment. In their study, 36 TCPs had received chemotherapy (3 or 4 BEP-cycles) after orchidectomy (*chemotherapy group*) and 36 patients had not received chemotherapy (23

TCPs had orchidectomy only and 13 received radiotherapy; *no chemotherapy group*). These patients were tested with a neuropsychological test battery of 21 test measures. Cognitive complaints were not assessed.

In line with Schagen et al, these authors did not find any differences in mean raw neuropsychological test scores between the treatment groups. Pedersen et al used the same method as Schagen et al for the classification of individually reduced neuropsychological performance. However, based on the fifth percentile of this control group (the no chemotherapy group), patients were defined as showing reduced neuropsychological performance if they had test scores ≤ 2 SD below the mean of the no chemotherapy group on at least 4 of the 21 test measures (corresponding to 19% of the test measures). Six percent of patients in the chemotherapy group and 8% of patients in the no chemotherapy group were classified with reduced neuropsychological performance, and this difference was not statistically different. The authors concluded that BEP-chemotherapy did not have a long-term negative effect on cognitive function in TCPs.

Limitations of this study are a rather small sample size with a risk for type II statistical error, and that the control-group consisted of TCPs who had received either surveillance or radiotherapy. As mentioned in Section 1.2.5, radiotherapy could hypothetically affect cognitive function indirectly through fatigue. The inclusion rate of the study is not given. Finally, this study also lacks pre-treatment neuropsychological evaluation.

1.4. Implications of cancer-related cognitive problems

Reduced cognitive function after cancer may have considerable consequences for patients' QoL and daily functioning. In Norway about 50% of cancer patients are older than 70 years (Cancer Registry of Norway, 2009). Cancer-related cognitive problems may eventually aggravate existing age-related cognitive reduction in such patients. For younger patients, cognitive problems may interfere with educational and occupational tasks. Studies in breast cancer patients have documented that perceived cognitive problems had substantial negative impact on the patients' professional life (Boykoff *et al.* 2009; Downie *et al.* 2006; Oberst *et al.* 2010).

Knowledge about cognitive problems after cancer is important for health care workers, both as to inform the patients about potential side-effects before treatment, but also for securing adequate interventions if such problems should arise. In a pilot study, cognitive

rehabilitation techniques were shown to be effective in alleviating treatment-related cognitive problems in breast cancer patients (Ferguson *et al.* 2007a).

To facilitate for further information and research on cancer-related cognitive problems, an international working group of clinicians and researchers [the International Cancer and Cognition Task Force (ICCTF)] was established in 2006 (ref http://www.icctf.com/ retrieved August 21, 2010) (Vardy *et al.* 2008).

1.5. Status on the relation between systemic chemotherapy and cognitive function at the onset of this thesis

When the studies of this thesis were planned in 2005, the QoL-study by Fosså et al (Fossa *et al.* 2003) was the only published study that included aspects of cognitive function in TCPs. Among breast cancer patients, several cross-sectional neuropsychological studies had been published at that time, and most of these reported that systemic chemotherapy seemed to have a negative impact on cognitive function in subgroups of patients. Until 2005, only one small-scale prospective neuropsychological study in breast cancer patients had been published (Wefel *et al.* 2004b). Results from this study also indicated negative cognitive effects of chemotherapy in a subgroup of the patients.

Reviews and meta-analyses of cognitive function after systemic chemotherapy conducted until 2006 (Anderson-Hanley *et al.* 2003; Falleti *et al.* 2005; Jansen *et al.* 2005; Minisini *et al.* 2004; Stewart *et al.* 2006; Tannock *et al.* 2004) found evidence for the conclusion that systemic chemotherapy exerted a small to moderate negative effect on neuropsychological test performance in a subgroup of breast cancer patients. However, the majority of studies included in these reviews had cross-sectional designs and comprised only breast cancer patients.

More studies on cognitive function also in other groups of cancer patients were requested, in particular prospective studies including a pre-treatment assessment (Tannock *et al.* 2004). Further, recommendations were given to consider the use of computer-based neuropsychological tests, since such tests possibly were more sensitive to subtle changes in cognitive processing speed than traditional tests (Tannock *et al.* 2004). The intriguing findings of low correlations between subjective cognitive complaints and cognitive dysfunction (as assessed with neuropsychological tests) in breast cancer patients also warranted further exploration. Studies of treatment and patient-related variables associated with cognitive complaints or cognitive dysfunction were requested, in order to elucidate possible etiological and pathogenetic mechanisms.

Due to the excellent cure rate of TC, in part established by highly effective chemotherapy, TCPs have a long life-expectancy after their disease and are expected to resume their regular professional and familial life after treatment. Based on the findings by Fosså et al (Fossa *et al.* 2003) further exploration of cognitive adverse effects of BEP-chemotherapy in TCPs seemed necessary, since such adverse effects could have serious consequences for QoL as well as for future career and employment of TC survivors.

On this background, we found it timely and of clinical importance to initiate a prospective study of cognitive function in TCPs with the assessment of both neuropscyhological and self-reported function, and with the aim to study eventual differences in cognitive function from baseline (pre-treatment) to 12 months follow-up in various treatment groups. In addition, due to the general knowledge of "chemo brain", we decided to prospectively compare cognitive complaints in TCPs treated with or without chemotherapy during the 1990-ies, when that concept was virtually unknown to the public.

2. THIS THESIS

2.1. Research setting

During the last twenty years much research on different aspects of TC has been conducted at the Norwegian Radium Hospital (NRH) under the leadership of professor Sophie D. Fosså at the National Resource Center for Long-term Effects after Cancer. Based on previous findings by Fosså et al on cognitive complaints after TC treatment (Fossa *et al.* 2003), it was a natural next step for the research group to initiate further studies of cognitive function in TCPs. Collaboration with chief psychologist Stein Andersson at the Neuropsychological laboratory at Department of Neuropsychiatry and Psychosomatic Medicine at Rikshospitalet was established for implementation of this research. When the studies of this thesis were planned in 2005, both the NRH and the Ullevaal University Hospital (UUS) were responsible for the treatment of TC in the Southern and Eastern parts of Norway. Cooperation with the oncological department of UUS, represented by uro-oncologist Carl W. Langberg, was initiated in order to recruit TCPs from both hospitals. Systematic neuropsychological assessment of cancer patients was a new procedure at both hospitals.

The research fellow and principal investigator on the studies of this thesis (Tone Skaali) is a medical doctor trained in psychiatry. She has clinical experience from consultation/liaison psychiatry at the Department of Oncology, Oslo University Hospital (NRH).

2.2. Aims of the studies

Based on the Background section and the research setting described above, the following studies were initiated, with the aims described here.

Paper I. A prospective study of cognitive complaints in TCPs treated in the pre "chemo brain" era (The 1990'ies study)

Background: During the last decade there has been an increasing attention among patients and oncologists on whether systemic chemotherapy has cognitive side-effects. After this concern has become public, there is a risk of expectation bias in current studies of self-reported cognitive complaints (Schagen *et al.* 2009). We therefore decided to explore cognitive complaints in TCPs treated during the 1990'ies, prior to today's increased awareness of this adverse effect. Our study sample were TCPs enrolled in three EORTC / MRC treatment studies during the 1990-ies who had had completed the EORTC QLQ-C30

before and after treatment with chemotherapy or radiotherapy. The QLQ-C30 includes two items on cognitive function (memory and concentration).

Purpose: To examine if TCPs treated with chemotherapy (CHEM group) had more cognitive complaints during the first year after the diagnosis compared with TCPs treated with radiotherapy (RAD group), and to explore variables associated with such cognitive complaints.

Aims: 1) To study the prevalence of self-reported cognitive complaints and its changes from before treatment (baseline) to 3 and 12-month follow-up among TCPs treated with either chemotherapy or radiotherapy, and to identify variables associated with such cognitive complaints; and 2) To identify self-reported QoL dimensions before treatment that were predictive for cognitive complaints at 12-month follow-up.

Hypotheses: Based on previous studies of cognitive complaints in breast cancer patients and a mixed cancer sample (Kohli S *et al.* 2007), we hypothesized that 1) The CHEM group had higher prevalence of cognitive complaints at 3 and 12 months follow-up compared to the RAD group, and that post-treatment cognitive complaints were significantly associated with treatment modality, current fatigue and emotional function. 2) Emotional function and fatigue symptoms before treatment were predictors for cognitive complaints at 12 month follow-up.

Paper II. Is psychological distress in men recently diagnosed with testicular cancer associated with their neuropsychological test performance? (The distress paper)

Background: Prospective neuropsychological studies of cancer patients, including a pre-treatment assessment, have been requested in the field. We therefore initiated a prospective neuropsychological study in TCPs. However, such studies imply that the baseline neuropsychological assessment is performed shortly after the patients have got their cancer diagnosis, when the patients may experience high levels of emotional distress due to this negative life event. The level of distress could hypothetically have an impact on neuropsychological test performance, but research-based knowledge on such distress in TCPs at that time point was lacking at the onset of our study. At follow-up evaluation one year after end of treatment, we expected the level of emotional distress to be lower compared to baseline, since treatment was finished and a good prognosis was regularly expected. If current distress has an impact on neuropsychological test performance, then *change* in distress-levels from baseline to follow-up assessments could confound the interpretation of changes in neuropsychological test results between the two time-points.

Purpose: To explore the level of cancer-related emotional distress in TCPs shortly after the cancer diagnosis, and to study if level of emotional distress had an impact on neuropsychological test performance at this time point (at baseline).

Aims: To study the following aspects: 1) What proportion of the recently diagnosed TCPs reports clinically significant cancer-related distress? 2) Which variables are significantly associated with increased level of cancer-related distress? 3) (*Main aim*) Does the current level of emotional distress significantly affect the results on any of the neuropsychological tests at the baseline evaluation?

Hypotheses: 1) A considerable proportion of TCPs has clinically significant distress shortly after the diagnosis; 2) The level of cancer-related distress at baseline is associated with both patient-related variables and with stage of TC; 3) The current level of emotional distress is significantly associated with some of the neuropsychological test scores.

Paper III. A prospective study of neuropsychological functioning in testicular cancer patients (The neuropsychological paper)

Background: Based on cross-sectional studies, ambiguous findings concerning the effect of cisplatin-based chemotherapy on neuropsychological test performance in TCPs have been reported. Prospective neuropsychological studies in TCPs, with the inclusion of a pre-treatment evaluation, were requested in order to elucidate an eventual causal relationship.

Purpose: To prospectively study neuropsychological test performance in TCPs treated with or without chemotherapy.

Aims: 1) To compare *changes* from baseline to one year follow-up of neuropsychological test performance in TCPs exposed to three different treatment modalities: no chemotherapy, one cycle of chemotherapy, and multiple cycles of chemotherapy; 2) To study *variables* associated with a decline in neuropsychological test performance from baseline to one-year follow-up.

Hypotheses: 1) A significantly larger proportion of TCPs treated with multiple cycles of chemotherapy exhibit a decline in neuropsychological test performance compared to TCPs treated with no or only one cycle of chemotherapy; 2) A decline in neuropsychological test performance from baseline to one year follow-up is significantly associated with chemotherapy.

Paper IV. Self-reported cognitive problems in testicular cancer patients: Relation to neuropsychological performance, fatigue and mental distress (The self-report paper)

Background: In studies of breast cancer patients, low correlations between reduced neuropsychological performance and self-reported cognitive complaints have been observed. In a cross-sectional study of cognitive complaints in TCPs (Schagen *et al.* 2008), approximately 1/3 of all patients had such complaints at a mean of three years after end of treatment. In this study, cognitive complaints were associated with emotional distress and fatigue, but not with treatment modality or with neuropsychological test performance. The relation between cognitive complaints, neuropsychological test performance, fatigue and emotional distress had not been studied *prospectively* in TCPs.

Purpose: To assess the proportion of TCPs who report an increase of cognitive complaints from baseline to one-year follow-up and to explore variables associated with such an increase.

Aims: 1) To compare the proportions of TCPs with an *increase of self-reported cognitive problems from baseline to one-year follow-up* among patients treated with no chemotherapy, one cycle of chemotherapy and multiple cycles of chemotherapy; and 2) To study *variables associated* with an increase of self-reported cognitive problems from baseline to one-year follow-up.

Hypotheses: 1) A larger proportion of TCPs treated with multiple cycles report increase of cognitive problems from baseline to one year follow-up compared with TCPs treated with no or with one cycle of chemotherapy. 2) An increase of self-reported cognitive problems from baseline to one year follow-up is significantly associated with treatment with chemotherapy and emotional distress and fatigue at follow-up, but not with a decline in neuropsychological test performance.

3. STUDY SAMPLES AND PROCEDURES

3.1. Paper I: The 1990'ies study (TCPs enrolled in three EORTC / MRC trials)

In paper I, we wanted to prospectively compare cognitive complaints during the first year after diagnosis in TCPs treated with or without chemotherapy in the 1990'ies, before "chemo brain" was publicly known, in order to reduce possible expectation bias.

Patients relevant for this study were identified from the electronic records of three randomized treatment-studies of testicular cancer (TC) organized by the EORTC / MRC during the 1990-ies (Figure 3). The *chemotherapy group* consisted of TCPs with metastatic disease included in trial 30941/TE20 (de Wit *et al.* 2001) which evaluated treatment with four different schedules of bleomycin, etoposide and cisplatin (BEP) chemotherapy (3 or 4 cycles given over 5 or 3 days). From the TE20 trial we had access to the data on 791 patients from several countries. This is the same study in which Fossa et al studied QoL in 2003 (Fossa *et al.* 2003).

The *radiotherapy group* (the controls in relation to chemotherapy) consisted of irradiated non-metastatic seminoma patients included in trial 30942 /TE18 (Jones *et al.* 2005) and trial 30982 /TE19 (Oliver *et al.* 2005). The TE18 study compared the effects of 20 Grey versus 30 Grey abdominal radiotherapy, while the TE19 study evaluated radiotherapy (20 or 30 Grey) versus a single-dose of carboplatin chemotherapy. From the TE18/TE19 studies we only had access to the data on the 126 Norwegian patients.

According to the study protocols, the QLQ-C30 and a TC-module were to be completed by the patients at pre-treatment (baseline), approximately 3 months and 12 months after baseline. In the TE20 study the 3-month assessment was done shortly after end of chemotherapy.

The time windows for accepted questionnaires in our study were established as follows: The data files on the Norwegian *radiotherapy patients* in the TE18/TE19 trials were provided to us by the MRC Clinical Trial Unit. For these files, the time-windows for accepted questionnaires had been defined by the MRC, and were: baseline: 0-28 days before treatment start, 3-months: 9-18 weeks after baseline, and 12-months: 9-15 months after baseline. For the TE20 trial (the *chemotherapy patients*) the situation was different as our research group had access to data on *all* TCPs included in that trial. We chose to define accepted time-windows in the TE20 trial according to those used in the TE18/TE19 trials, with some modifications due to the slight uncertainty related of the date of chemotherapy start. Our defined time-windows for accepted questionnaires in the TE20 trial were:

baseline: +/-30 days from randomization, 3-months: 9-20 weeks after baseline, and 12-months: 9-18 months after baseline. Only patients who delivered questionnaires in accepted time-windows and who had filled in both cognitive items of the QLQ-C30 at all three time points were included in our study. Further, we only included TCPs in the age between 15 and 59 years old. The study sample therefore consisted of 347 TCPs: 276 TCPs treated with chemotherapy (CHEM group) and 71 TCPs treated with radiotherapy (RAD group) (Figure 3).

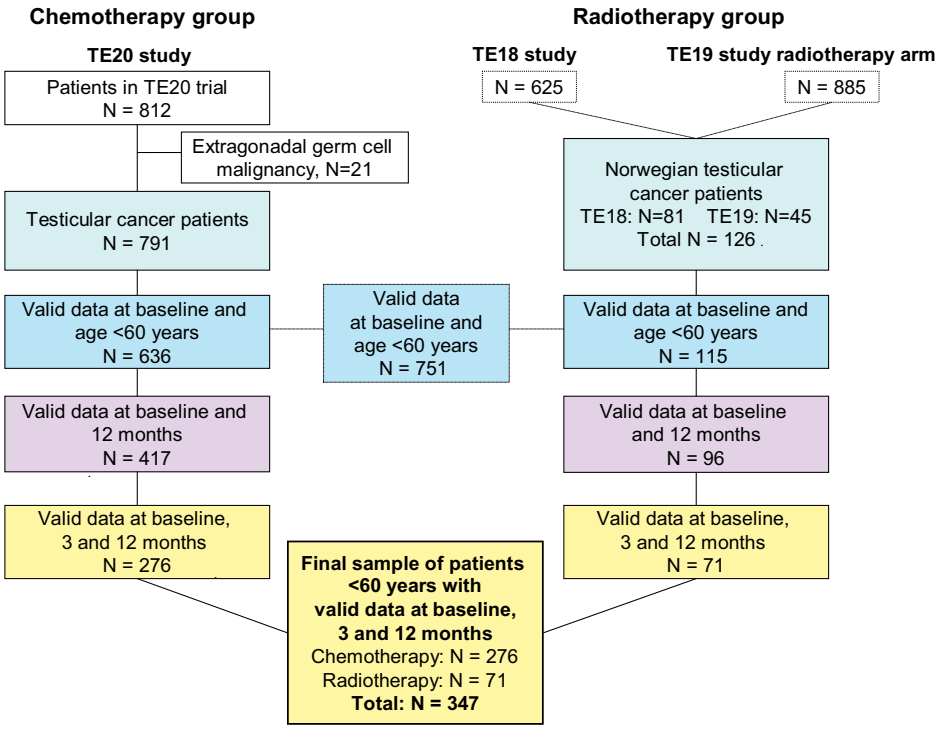

Figure 3. Study sample in paper I

Valid data: Patients who delivered questionnaire in defined time-window and had filled in both cognitive items (#20 and #25) of the EORTC QLQ-C30

3.2. Paper II-IV: The Oslo-study

In 2006 we initiated a prospective study of cognitive function in TCPs evaluated at two university hospitals (the NRH and the UUS) in Oslo. This study was the basis for paper II-IV and is referred to as "the Oslo-study" in this thesis. The main purpose of the Oslo-study was to investigate if cisplatin-based chemotherapy had a negative impact on cognitive function in TCPs. Baseline evaluations in the study were to be completed before the start of any adjuvant treatment with chemotherapy (or radiotherapy), and follow-up evaluation were scheduled 12-months after end of treatment / start of surveillance period. All evaluations consisted of an interview, neuropsychological testing and some questionnaires (Appendix A-D). For this study we wanted to include newly diagnosed TCPs who had not yet started any adjuvant treatment after orchidectomy.

In Norway, TCPs are usually orchidectomized and receive their cancer diagnosis at their local hospital. The patients are then referred to a university hospital for staging and evaluation of further treatment. Until ultimo 2009, newly diagnosed TCPs in South-Eastern Norway (2,600.000 individuals) were referred for evaluation at the NRH or at the UUS.

The inclusion procedure for the Oslo-study was as follows: TCPs aged 18 to 60 years referred to the above mentioned hospitals in the period August 2006 (NRH) / January 2007 (UUS) to September 2008 (both hospitals) were screened by the responsible clinician for eligibility in the study. The exclusion criteria were: 1) Severe mental disorders like psychoses or substance dependence disorders; 2) Degenerative brain disease or previous severe brain trauma; 3) Brain metastases or severe somatic dysfunction; or 4) Lacking proficiency of Norwegian language.

Eligible patients were informed about the study by a written information letter and by oral presentation from a medical doctor or nurse at the clinic. Some patients gave their decision about participation in the study directly to the doctor/nurse, while others gave their decision to the principal investigator (Tone Skaali) after she contacted them and asked for their decision concerning participation.

Among 202 eligible TCPs, 135 accepted to join the study and filled in baseline questionnaires; however, due to administrative reasons, only 131 of these TCPs were interviewed and 129 TCPs (64% of the 202 eligible patients) were tested with a neuropsychological battery (Figure 4). Among the 73 eligible TCPs not included or tested at baseline, approximately 45 patients declined to participate while the rest were not included due to administrative reasons.

At follow-up examination at a median of 12 months after end of chemotherapy / start of the surveillance period, 122 tumour-free TCPs (95% of the 129 with complete baseline evaluation) were re-evaluated (Figure 4). Seven TCPs with complete baseline evaluation were lost to follow-up: three patients declined re-evaluation, one patient had moved abroad and three patients were excluded due to development of mental disorders or somatic diseases.

Among the 122 TCPs re-evaluated at follow-up, 31 TCPs had received no chemotherapy (30 TCPs had surveillance and 1 had radiotherapy; *NO CHEMO group*), 38 TCPs had received one cycle of chemotherapy (34 TCPs had one course of carboplatin and 4 had one cycle of BEP; *ONE CHEMO group*) and 53 TCPs had received two or more (B)EP-cycles (*MULTIPLE CHEMO* group). Among the patients in the MULTIPLE CHEMO group, 17 TCPs had received 2 cycles of BEP or EP (etoposide and cisplatin), 33 had received 3 or 4 BEP-cycles, and 3 had received 4 BEP-cycles plus additional chemotherapy. Seven of the 122 TCPs evaluated at follow-up were initially assigned for surveillance, but developed a relapse during the follow-up period and were therefore treated with chemotherapy instead. Fore these patients, the follow-up evaluation was done approximately 12 months after end of chemotherapy.

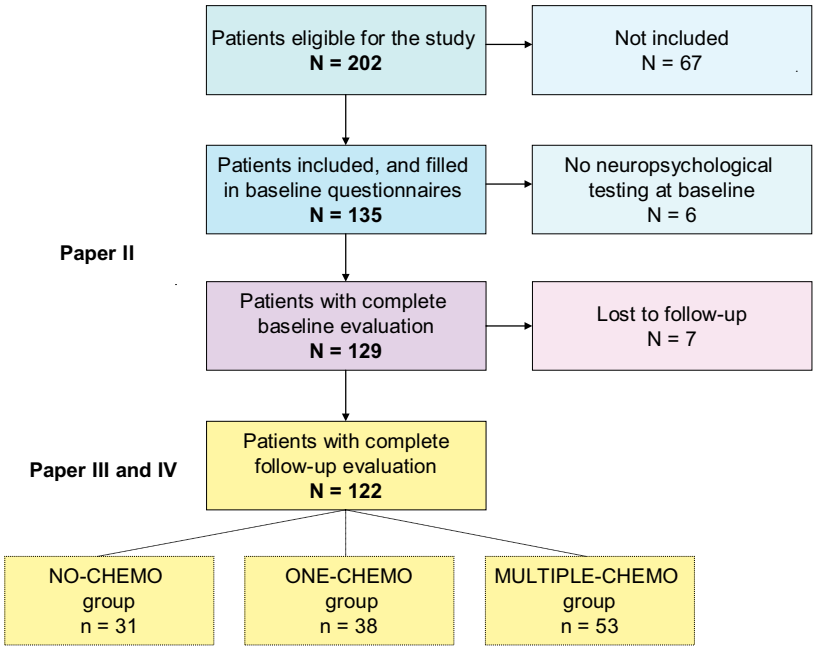

Figure 4. Study sample in the Oslo-study (paper II, III and IV)

4. METHODS

4.1. Questionnaires

European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30 (Paper I)

The EORTC QLQ-C30 is a widely used questionnaire for assessing health-related quality of life in cancer patients (Aaronson *et al.* 1993; Sprangers *et al.* 1993). The development of this questionnaire by the EORTC dates back to 1986, and the QLQ-C30 was validated by Aaronson and colleagues in 1993 (Aaronson *et al.* 1993). The QLQ-C30 has shown satisfactory internal consistency (Hjermstad *et al.* 1998) and good test-retest reliability (Hjermstad *et al.* 1995). Several versions of the QLQ-C30 exist, and currently version 3.0 is standard. In our study, comprising patients included in three randomized studies during the 1990-ies, version QLQ-C33 and version 2.0 were used.

The QLQ-C30 assesses five functional domains: *physical function*, *emotional function*, *social function*, *role function* and *cognitive function*, as well as *global QoL*, and nine symptom scales including *fatigue*, *pain* and *insomnia*. By established algorithms (Aaronson *et al.* 1993) the QLQ-C30 items were transformed to function scales with scores from 0 (worst) to 100 (best), and fatigue, pain and insomnia from 0 (no symptoms) to 100 (worst symptoms). The cognitive outcome measures (cognitive complaints) from the QLQ-C30 are described in detail below (Section 4.4).

As explanatory variables in paper I we selected the functions and symptoms from QLQ-C30 which from a clinician's point of view were most likely to be associated with cognitive complaints: emotional function, role function, social function, fatigue, and insomnia. Pain was excluded due to high correlation with fatigue. Considering the mean scores in a Norwegian population sample (Hjermstad *et al.* 1998), we defined the cut-off for good function at a score of ≥75 and <75 for reduced function, and the symptoms as *absent* by scores ≤16.67 and *present* as scores >16.67.

TC-module (paper I)

A TC-module developed by Fossa and colleagues (Fossa *et al.* 1996; Fossa *et al.* 2003) evaluate specific physical chemotherapy-related symptoms and emotional and sexual symptoms frequently reported by TCPs. From the TC-module we used the items covering peripheral neuropathy, Raynaud's phenomenon and reduced hearing/tinnitus, summarized as *neurotoxic symptoms*, and transformed to a score from 0 (no symptoms) to 100 (worst

symptoms) (Aaronson *et al.* 1993; Fossa *et al.* 2003). The transformed score was then dichotomized into neurotoxicity symptoms *absent* (score≤16.67) or *present* (score >16.67).

Impact of Event Scale (paper II, III and IV)

The Impact of Event Scale (IES) (Horowitz *et al.* 1979; Sundin and Horowitz, 2002) assesses the psychological response to a trauma which in our study was getting TC. The IES evaluates symptoms of intrusion (7 items) and avoidance (8 items) within the past week. Each item is rated from 0 (not at all) to 5 (often), with higher scores denoting more emotional distress. The Norwegian version of the IES has shown satisfactory psychometric properties (Eid *et al.* 2009), and the IES has been validated to measure *cancer-related distress* (Thewes *et al.* 2001). An IES-total score of >26 was used as a cut-off for clinically significant cancer-related distress in the Oslo-study (Tuinman *et al.* 2007).

Hospital Anxiety and Depression Scale (paper II)

The Hospital Anxiety and Depression scale (HADS) (Zigmond and Snaith, 1983) measures symptoms of anxiety and depression during the past week, and consists of two subscales: anxiety (HADS-A; 7 items) and depression (HADS-D; 7 items), summed up as HADS total score. Each item is scored from 0 (minimally present) to 3 (maximally present) and the subscale scores range from 0 to 21 with higher scores representing more symptoms. The psychometric properties of the HADS have been found good both in somatic patients and in the general population (Bjelland *et al.* 2002).

Positive and Negative Affect Scale, state version (paper II)

The Positive and Negative Affect Schedule (PANAS) state version (Watson *et al.* 1988) measures current affects, and contains 20 mood-descriptive adjectives; 10 on positive affects (PA) and 10 on negative affects (NA). Ratings are on 5-point Likert scales ranging from 1 ("not at all/very little") to 5 ("very much"). Higher sum-scores indicate increasing level of current affect. The PANAS has shown good validity and reliability in the general adult population (Crawford and Henry, 2004).

Eysenck Personality Questionnaire, neuroticism scale (paper II, III and IV)

Neuroticism is a basic personality trait and represents the tendency to be nervous and to experience negative emotions. In our study neuroticism was rated at baseline with 6 items from an 18-items version of the Eysenck Personality Questionnaire (EPQ) (Eysenck, 1975;

Tambs K, 2004). Each item is rated as yes (1) or no (0), and the sum-score for neuroticism ranges from 0 (low) to 6 (high). The EPQ has showed satisfactory psychometric properties in a Norwegian twin sample (Eysenck and Tambs K, 1990).

CAGE questionnaire (paper II, III and IV)

Possibly hazardous alcohol-use was assessed at baseline in our study with a 4-items version of the CAGE questionnaire (Ewing, 1984), a well-validated screening measure for alcohol problems (Dhalla and Kopec, 2007). Each item is rated as yes (1) or no (0), and the sum-score ranges from 0 (low) to 4 (high). As recommended, a sum-score of ≥2 defined a possibly hazardous alcohol in our study; however, the clinical value of this cut-off value has been debated (Aertgeerts *et al.* 2004).

Scale for Chemotherapy-Induced Neurotoxicity (paper III and IV)

Scale for Chemotherapy-Induced Neurotoxicity (SCIN) was derived from the *TC-module* (Fossa *et al.* 2003) described previously, and was validated by Oldenburg and colleagues in 2006 (Oldenburg *et al.* 2006a). The SCIN assesses symptoms of peripheral neuropathy (paresthesias in hands or feet), Raynauds phenomenon (white fingers or cold feet) and ototoxicity (tinnitus or hearing loss) on 4-point scales from 1 (no symptoms) to 4 (much symptoms). In the Oslo-study, the item-scores of SCIN were dichotomized into "symptoms" (score 3 or 4) vs. "no symptoms" (score 1 or 2).

Fatigue Questionnaire (paper III and IV)

The Fatigue Questionnaire (FQ) vas developed and validated by Chalder and colleagues in 1993 (Chalder *et al.* 1993). The FQ provides scores for 7 physical and 4 mental fatigue items that are summed up as total fatigue. Each item is rated from 0 (less) to 3 (much more), hence total fatigue score ranges from 0 (low) to 33 (high). The FQ has shown good psychometric properties in the general population (Loge *et al.* 1998; Pawlikowska *et al.* 1994).

In our study we defined that an increase of fatigue symptoms from baseline to follow-up was present if the total fatigue score at follow-up was ≥3 points higher than the baseline score. This represents approximately 10% change on the total fatigue scale.

4.2. Semi-structured interviews

4.2.1. Background data (paper II, III and IV)

In a semi-structured interview **at baseline**, data on socio-demography, previous somatic and mental health, current medication, smoking and sleeping habits were collected. Further, the perceived satisfaction by the patient concerning information about TC at the local hospital was recorded by the interviewer as "*satisfied*" or "*not satisfied*". The patients were also classified by the interviewer as being generally *well informed about TC* or not.

At interviews at **follow-up**, data on current socio-demograhy, medication and somatic and mental health after the TC-diagnosis were collected. All interviews at baseline and follow-up were performed by Tone Skaali. The baseline and follow-up interview manuals are presented in Appendix B.

4.2.2. Cognitive complaints (Paper IV)

In the semi-structured interviews at baseline and follow-up, TCPs were also asked to describe their general concentration and memory function with the response alternatives *very good*, *good*, *not so good*, or *poor* (see Appendix B). The responses to both concentration and memory function were then dichotomized into "no complaints" (*very good/good*) and "complaints" (*not so good/poor*). A change of category in the dichotomized function-scores from baseline to follow-up was noted. If a patient changed category from *no complaints* to *complaints* in either the dichotomized concentration and/or the memory score, then he was defined as reporting an *increase of cognitive complaints* from baseline to follow-up.

4.3. Neuropsychological evaluation

4.3.1. Measure of estimated intellectual functioning (paper II, III and IV)

An estimate of intellectual functioning was measured at baseline of our study by the Norwegian version of the National Adult Reading Test (NART) (Nelson and Willison, 1991; Vaskinn and Sundet, 2001). The scores from this oral reading test are highly correlated with standard IQ-scores from the Wechsler Adult Intelligence Scale (WAIS) (Nelson and Willison, 1991), and this has been shown also a Norwegian sample of healthy adults (Sundet K and Vaskinn A, 2008). The NART-scores range from 0 to 50, and a lower score indicates better intellectual functioning.

4.3.2. Neuropsychological test battery (paper II, III and IV)

A neuropsychological test battery comprising of both computer-based and traditional neuropsychological tests was set up for our study in collaboration with Stein Andersson, an experienced neuropsychologist. The computer tests were selected from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 2005; Sahakian and Owen, 1992), which mostly comprises visuo-spatial tasks. Traditional tests were used to assess verbal and motor tasks. The battery was designed to assess five major cognitive domains listed in Section 1.2.2. The neuropsychological tests covering these domains are presented below, with specification if a *computer* or a *traditional* test. The tests were performed in a pre-defined order, with a few exceptions due to administrative reasons.

Attention, concentration and working memory: The *Spatial Working Memory* test (*computer*) (Cambridge Cognition, 2005) assessed visuo-spatial working memory, while the *Choice Reaction Time* test (*computer*) (Cambridge Cognition, 2005) measured speed of choice response.

Learning and memory: The *Hopkins Verbal Learning Test-Revised* (*traditional*) (Brandt and Benedict, 2001) was used to assess verbal learning and memory, while the *Paired Associates Learning* test (*computer*) (Cambridge Cognition, 2005) assessed visual learning and memory.

Speed of information processing: The *Trail Making Test* part A (*traditional*) (Reitan and Wolfson, 1993) and the *Color-Word Interference Test* part 1 and 2 (*traditional*) *(Delis et al. 2000)* were used to measure psychomotor speed.

Executive functions: The *Color-Word Interference Test* part 3 and 4 (*traditional*) (Delis *et al.* 2000) were used to assess response inhibition and shifting and the *Trail Making Test B* (*traditional*) (Reitan and Wolfson, 1993) assessed set-shifting ability. Verbal fluency was tested with the *Word fluency (FAS)* test (*traditional*) (Ruff *et al.* 1996).

Two supplementary *computer* tests of executive functions were included in the battery at baseline if time allowed for it and the patients were motivated. They were the *Stockings of Cambridge* test (Cambridge Cognition, 2005) which assessed spatial planning and motor control and the *Intra-Extra Dimensional Set Shift* test (Cambridge Cognition, 2005) which evaluated rule acquisition and set-shifting. If any of the supplementary tests were completed at baseline then the patient completed the same tests at follow-up.

***Motor function*:** The *Grooved Pegboard* test (*traditional*) (Reitan and Wolfson, 1993) was used to assess visual-motor coordination and speed, using both dominant and non-dominant hand.

The *basic neuropsychological test battery* comprised 8 tests which yielded 15 sub-test measures. The two supplementary executive tests gave an additional three sub-test measures. Hence, the *total test battery* comprising all 10 tests gave a total of 18 sub-test measures. All neuropsychological tests and sub-test measures reported are listed in Appendix C.

4.4. Definitions of main outcome measures

4.4.1. Cognitive complaints (Paper I: The 1990'ies study)

Cognitive complaints were assessed by responses to the two cognitive questions of the QLQ-C30: "Have you had difficulty in concentrating on things, like reading a newspaper or watching television?" (item #20) and "Have you had difficulty remembering things?" (item #25). There were four response-alternatives: "not at all"(1), "a little"(2), "quite a bit"(3) and "very much"(4), and the time frame were the past week. We defined three separate outcome measures: the scores of item #20 (concentration), the scores of item #25 (memory) and the *cognitive function* (CF) scores defined according to the QLQ-C30 (Aaronson *et al.* 1993) as a combination of the memory and concentration scores transformed to a scale from 0 (worst) to 100 (best), with intervals of 16.67 points.

A representative sample of Norwegian men aged 20 to 59 years had mean CF scores between 86.5 and 91.6 according to 10 year age groups (Hjermstad *et al.* 1998). On this background and due to skewed distributions of scores, the three outcome variables of cognitive complaints were defined as follows: *concentration* and *memory problems* absent ("not at all") or present ("a little"/"quite a bit"/"very much"), and *CF problems* absent (score 100) or present (score ≤83.33).

4.4.2. Strength of associations between distress and neuropsychological test results (Paper II: The distress paper)

The main purpose of paper II was to explore the associations between current levels of emotional distress and the neuropsychological test scores at the baseline evaluation. Hence *the strength of associations* (standardized beta values and p-values) between the IES-total score / the HADS-total score / the PANAS negative score and each of the 18 neuropsychological test scores were the main "outcome measures" in this study.

4.4.3. Changes in neuropsychological test performance (Paper III: The neuropsychological paper)

In paper III exploring eventual changes in neuropsychological functioning in TCPs from baseline to follow-up in our study, both group and individual analyses were performed. For the group analyses, the outcome measures were the *differences* (between baseline and follow-up) in neuropsychological raw-scores for each of the 18 test measures.

As to the individual analyses, we classified each patient as showing *decline* or no decline in neuropsychological test performance from baseline to follow-up. This categorical variable was the main outcome variable for the individual analyses. The method for classification of individual decline in neuropsychological test performance is presented below under *statistical procedures* in Section 4.6.3.

4.4.4. Increase of cognitive complaints (Paper IV: The self-report paper)

Based the responses at the baseline and follow-up interviews concerning the patients' self-rating of memory and concentration function, we constructed a categorical variable defining an *increase* versus no increase of cognitive complaints from baseline to follow-up. This categorical variable represented the main outcome variable in paper IV. The procedure for categorization of this variable has been described previously in Section 4.2.2.

4.5. Data management

4.5.1. Paper I

The selected data (see selection procedure in Section 3.1) was merged into one data file for the statistical analyses. No imputation of missing data was performed, neither for the outcome (cognitive complaints) or the explanatory variables.

4.5.2. Paper II-IV

Interview-data and neuropsychological test results were manually entered into data files. Completed questionnaires were scanned, and added to the data files. Data files were carefully checked for coding errors and prepared for the analyses. No imputation of missing data was performed.

4.6. Statistical procedures

4.6.1. General

Different versions of the statistical software program SPSS (Statistical Package for the Social Sciences), after 2009 changed to PASW Statistics (Predictive Analytics SoftWare), were used for the statistical analyses (SPSS Inc, Chicago IL). All statistical tests were two-sided, and p-values $p<0.05$ were considered as statistical significant except in paper I where the significance level was set at $p<0.01$ due to multiple testing.

Descriptive statistics and group comparisons were performed with parametric or non-parametric tests as appropriate. For continuous variables Students t-test or Mann-Whitney Wilcoxon test were used if two groups were compared, and analysis of variance (ANOVA) or Kruskall Wallis test were used if three groups were compared. For categorical variables Pearson's chi-square test or Fisher's exact test were used. Correlations were assessed with Pearson's correlation coefficient (parametric data) or Spearman's coefficient rho (non-parametric data). Internal consistency was described by Cronbach's coefficient alpha.

4.6.2. Paper I (The 1990'ies study)

Changes over time and inter-group differences (CHEM vs. RAD group) in the proportions of patients with cognitive complaints (concentration problems, memory problems and CF-problems) were analyzed with 2x2 contingency tables and Fisher's exact test.

At each time-point, bivariate and multivariate logistic regression analyses examined the associations between cognitive complaints (dependent variable) and independent variables (treatment group [RAD group as reference] and the self-reported QoL function/symptoms). The strength of the associations were expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). Age was not entered as independent variable in the multivariate analyses since it did not show significant bivariate associations with any of the outcome variables at any time point.

With bivariate and multivariate logistic regression analyses we then explored if any of the pre-treatment QoL variables were predictors of cognitive complaints at 12 months.

4.6.2. Paper II (The distress paper)

Univariate and multivariate linear regression analyses explored the association between the IES-total score (dependent variable) and relevant independent variables. Independent

variables were entered in a multivariate linear regression analysis if they showed p-values <0.10 in the bivariate ones.

Stepwise multivariate linear regression analyses were performed to explore the association between current distress-scores and neuropsychological test-results. In these analyses the score of the IES-total, the HADS-total or the PANAS-NA was independent variable, and each of the 18 neuropsychological test-scores was dependent variables. Some of the neuropsychological test scores were logarithmic or square-root transformed in order to achieve a better model fit. From these stepwise analyses, the p-values are reported, both crude and after adjustment for NART, level of education and age.

4.6.3. Paper III (The neuropsychological paper)

***Group analyses**:* Raw-scores on the neuropsychological test-measures at baseline and follow-up were compared across treatment groups with the Kruskall-Wallis test. Changes in raw-scores (follow-up score subtracted from baseline score) were compared with analyses of covariance (ANCOVAs) with *age at baseline* and *follow-up time* as covariates.

***Individual analyses**:* From prospective studies of breast cancer patients, only a *subset* of the patients (if any) showed decline in neuropsychological test performance from baseline to follow-up. Hence, group analyses comparing the mean group change-scores may obscure individual changes in test performance. To account for such individual changes, *individual* analyses assessing the change in test performance from baseline to follow-up *in each person* have been recommended in this field (Vardy *et al.* 2007).

Several statistical methods for the assessment of individual change have been proposed (Vardy *et al.* 2007) including the reliable change index (RCI) and the standardized regression-based (SRB) models. The SRB-model has the advantage of allowing adjustment of the neuropsychological test results for relevant covariates, and may possibly be more sensitive for individual change than the RCI (Ouimet *et al.* 2009). We therefore chose the SRB-model for assessing individual change in test performance in our study.

The SRB-model utilizes the baseline and follow-up scores of a control group (in our study the NO-CHEMO group) to derive regression equations that predict an individual's follow-up score on a test-measure, based on this person's baseline-score and some selected covariates. Due to limited group sizes, only age and estimated intellectual functioning

(NART score) were used as covariates in our study. Again, some of the neuropsychological test scores were logarithmic or square-root transformed to achieve better model fit.

Applying the SRB-model a predicted follow-up score on each test-measure for each individual was obtained. An individual *z-score of change* was then obtained *for each test-measure* by subtracting the person's actual follow-up score from the predicted score, and dividing the difference by the standard error of estimate (derived from the control group). The obtained z-score of change represents the standardized magnitude and direction of the difference between the expected and actual follow-up score. In our study, a z-score of change outside ±1.64 SD was defined as a *reliable decline* or *improvement from baseline to follow-up* on the reported test-measure.

No established cut-off values exist in the literature concerning the proportion of declined or improved test-measures needed in order to define a relevant individual *change* in neuropsychological performance over time. Based on prospective studies conducted in breast cancer patients (Jenkins *et al.* 2006; Stewart *et al.* 2008), we defined that individual *decline* had occurred with reliable decline on ≥10 % of our test-measures, and individual *improvement* correspondingly. To examine the consequences of our chosen proportions, we also assessed individual changes using 15 % as a cut-off. Finally, we explored the relationship between the proportion of test-measures with decline and improvement for each individual. If the proportion of test-measures with decline was ≥10 % larger than the proportion of measures with improvement, the individual was defined as showing *overall decline* in neuropsychological test performance.

The proportions of patients with individual *decline*, *improvement* and *overall decline* with the various definitions described above were compared across the treatment groups.

Finally, we assessed *cognitive domain z-scores of change* by averaging the z-scores of change for all test-measures of a given cognitive domain in each individual (the test-measures representing each cognitive domain are presented in Appendix C). These *cognitive domain z-scores of change* were compared across the three treatment group by analyses of variance (ANOVAs).

4.6.4. Paper IV (The self-report paper)

Pearson's chi-square test was used to explore differences across the three treatment groups in proportions of TCPs with an increase of cognitive complaints from baseline to follow-up. Descriptive statistics were used for the characterization of TCPs with an increase of cognitive complaints.

4.7. Ethical considerations

4.7.1. Paper I

The EORTC / MRC trials were approved by the local research ethical committees of each participating center. All patients provided written informed consent.

4.7.2. Paper II-IV

The Oslo-study was approved by the Ethical Committee of the Southern Health Region of Norway (ref. S-05362) and the National Data Inspectorate. All patients delivered a written informed consent.

5. RESULTS

5.1. Main findings of Paper I (The 1990'ies study)

5.1.1. Characteristics of the sample

Attrition analyses showed no significant differences in age or in proportions of patients with concentration or memory problems before treatment between the examined sample of 347 TCPs fulfilling the selection criteria and the 404 TCPs with valid baseline data but excluded due to missing data at 3 or 12 months. However, a larger proportion of the excluded patients had non-seminoma compared to the included patients (70% vs. 61%, p=0.005).

Among the 347 included TCPs, the mean age of patients at baseline was significantly lower in the CHEM group (33.0 years ±8.8) compared to the RAD group (38.2 years ±8.0). At 3 month follow-up, the CHEM group had significantly higher proportions with reduced function on *emotional function*, *social function*, *role function* and higher proportions of patients with *fatigue* and *neurotoxic symptoms* compared to the RAD group. None of these functions or symptoms showed significant inter-group differences at baseline (before treatment) or at 12 month follow-up except that the CHEM group had significantly more neurotoxic symptoms at 12 months compared to the RAD group.

5.1.2. Changes in cognitive complaints over time, intergroup differences and variables associated cognitive complaints (*Aim 1*)

At baseline, in the CHEM group 23% had concentration problems, 23% had memory problems, and 37% had CF-problems. The corresponding proportions in the RAD group were 21%, 20% and 27%. At 3 months, the proportions of patients with concentration problems were 39% (CHEM group) / 20% (RAD group), memory problems 38% / 31% and CF-problems 52% / 34%. At 12 months the equivalent proportions were: 15% / 15%, 29% / 28 % and 33% / 33%.

These proportions implied that significantly more patients in the CHEM group had *concentrations problems* and *CF-problems* at 3 months compared to baseline and at 12 months. Further, the proportions of patients with concentration problems and CF-problems were significantly higher in the CHEM than in the RAD group at 3 months. This contrasts with the findings at baseline and 12 month, where no significant intergroup differences in prevalence of concentration problems and CF-problems were observed. For *memory problems,* no significant changes over time were found for any of the treatment groups and no significant inter-group differences were observed at any time point.

In bivariate analyses, belonging to the CHEM rather than the RAD group was significantly associated with *concentration problems* and *CF-problems* at 3-months (OR 2.6 and 2.1 respectively), while this was not the case at baseline or 12 months. However, in multivariate analyses with adjustment for relevant QoL domains no significant associations were observed between *treatment type* and cognitive complaints at any time point. In these multivariate analyses we found that current fatigue was significantly associated with cognitive complaints in six out of the nine analyses (3 outcome measures x 3 time points). Correspondingly, insomnia and reduced social function were significantly associated with cognitive complaints in four analyses, and reduced emotional function in three analyses. Reduced role function and neurotoxic symptoms showed no significant associations with cognitive complaints at any time point.

5.1.3. Pre-treatment variables associated with cognitive complaints at 12 months (Aim 2)
In bivariate analyses exploring the relation between pre-treatment QoL functions and symptoms and cognitive complaints at 12 months, reduced emotional and social functions, as well as more fatigue and neurotoxic symptoms before treatment were significantly associated with *concentration problems* at 12 month follow-up. For *memory problems* no significant predictors before treatment were identified, and for *CF-problems* only reduced emotional function was significant in bivariate analyses. In multivariate logistic regression analyses none of the pre-treatment variables significantly predicted the presence of cognitive complaints at 12 month follow-up.

5.2. Paper II-IV - The Oslo-study: Description of the sample
In the Oslo-study, attrition analyses showed no significant differences between 129 included and the 73 non-included TCPs concerning age or stage of TC at diagnosis, whereas a significantly larger proportion of the included patients had non-seminoma compared to the non-included (49% vs. 29%, p=0.005).

Among the 122 TCPs re-evaluated at follow-up, 89 (73%) were tested with one or two of the supplementary tests. The distribution of the 122 TCPs in the three treatment groups were as follows: NO-CHEMO group (N=31), ONE-CHEMO group (N=38) and MULTIPLE-CHEMO group (N=53).

As expected, a significantly larger proportion of TCPs in the MULTIPLE-CHEMO group had metastatic disease and non-seminoma compared to the NO and the ONE-CHEMO groups. Age at baseline was significantly higher in the ONE-CHEMO group

(median 35 years) compared to the NO-CHEMO (median 32 years) and the MULTIPLE-CHEMO group (median 30 years). No statistically significant group differences were found for follow-up time, NART-score, level of education or other demographic variables.

The two chemotherapy groups had statistically significantly higher total-fatigue scores than the NO-CHEMO group both at baseline and follow-up (mean total-fatigue scores: NO-CHEMO group 12.2 (baseline) / 11.4 (follow-up); ONE-CHEMO group 14.8 / 14.0; and MULTIPLE-CHEMO group 13.8 / 14.3), while no significant group differences were observed concerning level of emotional distress (IES score) at baseline or at follow-up. The presence of self-reported peripheral neurotoxic symptoms did not differ significantly across treatment groups at baseline, while at follow-up a significantly larger proportion in the MULTIPLE-CHEMO group had Raynaud-like symptoms compared to the two other groups (NO-CHEMO group 3%; ONE-CHEMO group 13%; MULTIPLE-CHEMO group 48 %).

5.3. Main findings of Paper II (The distress paper)

5.3.1. Cancer-related distress (Aims 1 and 2)

Clinically significant cancer-related distress, defined by an IES-total score >26, was observed in 24% (95%CI 17%-31%) of the sample at baseline.

None of the demographic, cancer-related variables, or the perceived level of information about TC were significantly associated with level of cancer-related distress (IES-total score) in bivariate linear regression analyses. In contrast, daily smoking, hazardous alcohol use, previous mental problems, sleeping problems and higher level of neuroticism displayed significant bivariate associations. In multivariate regression analysis, higher level of neuroticism, daily smoking and hazardous alcohol-use remained significantly associated with the level of cancer-related distress.

5.3.2. Associations between current emotional distress and neuropsychological test-results (Aim 3 - main study aim)

The 18 baseline neuropsychological sub-test scores (Appendix C) were tested for associations with the baseline sum-scores of the IES-total, the HADS-total, and the PANAS-Negative Affects (NA) emotional distress scales. After adjusting for NART score, education level and age, four out of the 18 test scores were significantly associated with at least one of the three distress scale scores: The *total errors* on Spatial Working Memory test was significantly associated with the scores of the HADS-total and the PANAS-NA; the

latency time on Choice Reaction Time test was significantly associated with the scores of the IES-total and the PANAS-NA; and the *time used* on Color-Word Interference test part 1 and 3 were significantly associated with the IES-total score. All significant associations were inversely correlated, which implies that higher distress scores were associated with lower achievements on these tests.

The remaining 14 neuropsychological sub-test scores were not significantly associated with any of the distress scale scores after adjustment for NART, education level and age.

5.4. Main findings of Paper III (The neuropsychological paper)

5.4.1. Changes in neuropsychological test performance from baseline to follow-up (Aim 1)

Group analyses: There were no significant group differences on raw-scores at baseline or follow-up on any of the 18 test-measures, except that the NO-CHEMO group had significantly fewer errors on the Spatial Working Memory test at baseline compared with the two other groups. No significant group differences were found for *change* in raw-scores from baseline to follow-up (adjusted for age and follow-up time) for any of the 18 neuropsychological measures.

Individual analyses: Applying the SRB-analyses, we found that the proportions of TCPs that exhibited reliable *decline* on any of the 18 test-measures ranged from 0% to 23% while the proportions of patients that exhibited reliable *improvement* ranged from 0% to 39%.

Using the pre-defined definitions of *individual change* in neuropsychological test performance, no statistically significant group differences in proportions of TCPs with individual *decline* on ≥10% of the test-measures or *overall decline* were observed. However, significantly larger proportions of TCPs in the ONE- and the MULTIPLE-CHEMO groups showed *improvement* on ≥10% of the tests compared to the NO-CHEMO group.

Employing a 15% cut-off did not significantly change these results, except that no significant difference between the NO- and the ONE-CHEMO groups in proportions of TCPs with improvement was found.

Finally, we found no significant differences across the three groups concerning *cognitive domain z-scores of change* for any of the five cognitive domains studied.

5.4.2. Variables associated with a decline in neuropsychological test performance (Aim 2)

Decline in neuropsychological test performance (decline on ≥10% of the neuropsychological test-measures) was not significantly associated with any of the demographic variables (age, education or NART score) or the cancer-related variables (treatment with chemotherapy, metastatic disease or follow-up time), and neither with the scores (or change-scores) of emotional distress or fatigue. In contrast, decline in neuropsychological test performance was significantly associated with worsening of ototoxic symptoms (tinnitus/hearing loss), while no such association was found for worsening of peripheral neuropathy or Raynaud-like symptoms.

5.5. Main findings of Paper IV (The self-report paper)

5.5.1. Proportions of TCPs with an increase of cognitive complaints from baseline to follow-up (Aim 1)

Twenty-five TCPs (20%) had an *increase of cognitive complaints* from baseline to follow-up. There was a significant (p=0.02) difference across the three treatment groups in proportions of TCPs with an increase of cognitive complaints: larger proportions in the ONE-CHEMO group (29%) and the MULTIPLE-CHEMO group (25%) had an increase of complaints compared to the NO-CHEMO group. However, no significant difference appeared between the ONE and the MULTIPLE-CHEMO group.

5.5.2. Variables associated with an increase of cognitive complaints (Aim 2)

Among the 25 TCPs with an increase of cognitive complaints from baseline to follow-up, a significantly larger proportion of patients had received chemotherapy (96% vs.69%), had worsening of fatigue score (50% vs.22%) and of Raynaud-like symptoms (42% vs.16%), had lower level of education (68% vs.44%) and reported mental problems before TC (48% vs.19%) compared to those without an increase of cognitive complaints. Further, TCPs with an increase of cognitive complaints had significantly higher follow-up scores of emotional distress (median IES-total score 15.5 vs.10) and fatigue (median total-fatigue score 16 vs.11) compared to those with no such increase of complaints.

No statistically significant association was found between an increase of cognitive complaints and a decline in neuropsychological test performance from baseline to follow-up (p=0.82).

6. DISCUSSION

6.1 Methodological considerations

6.1.1. Study design considerations

Clinical studies may have cross-sectional or prospective (longitudinal) designs. In cross-sectional studies, patients are evaluated at one time-point and changes over time cannot be assessed. No causal conclusions can be drawn from cross-sectional studies, only associations between the variables. In prospective (longitudinal) studies, a group of individuals (cohort) who are similar in many ways (e.g. by having TC), but differ by certain characteristics (e.g. by receiving surveillance or various number of cycles with chemotherapy) are followed over time, and an outcome measure and its changes can be studied over time (such as the development of side-effects like cognitive complaints). Prospectively designed studies are well suited to identify possible predictors for an outcome.

In this thesis paper II is a cross-sectional study, while paper I, III and IV concern prospective ones for the following reasons: In general, large inter-individual variations in neuropsychological test performance are expected, and eventual negative cognitive effects of cancer treatment may affect only a subgroup of individuals. Based on these considerations prospective studies, including a pre-treatment evaluation with the patient serving as his/her own control, have been considered as the optimal design (Tannock *et al.* 2004). We therefore chose this design in the two studies of this thesis. However, *the 1990'ies study* (paper I) was "retrospective" in the sense that the data had already been collected in previous EORTC-trials, but we used these prospectively collected data to assess a secondary outcome (cognitive complaints) not focused on in the primary studies. Our aim in that paper was to study if exposure to chemotherapy was followed by significantly more cognitive complaints compared to radiotherapy.

The Oslo-study (paper II-IV) was clearly a prospective cohort study, where we followed a defined cohort over time in order to explore if there was a causal relationship between chemotherapy and changes in cognitive function. Such a design was obvious, since our main aim was to study if exposure to chemotherapy was followed by reduction in neuropsychological test results and increase in cognitive complaints compared to contrast groups.

6.1.2. Statistical power considerations

In clinical studies, an adequate sample size is needed so that group differences of relevant size can be discovered with confidence. This methodological demand is usually called "adequate statistical power" of the study. If the groups compared are (too) small, only big differences can become significant, and there is a risk that study is under-powered (type II statistical errors). In type I errors the sample sizes are so big that clinically meaningless differences become statistically significant. In the Oslo-study, a risk of type II errors (relevant in paper III and IV) will be discussed further in Section 6.1.4.

6.1.3. Bias considerations

Systematic error in the design or the conduct of a study is called *bias*. *Biases* may occur due to flaws in the methods of selection of study participants, or in the procedures for gathering relevant data. As a consequence, the observed study results of the sample will tend to differ from the true results of the population (Szklo N and Nieto FJ, 2004). Bias (systematic error) should be distinguished from *random variability* which is the fact that when something is studied in a *sample* drawn from the population of interest; the sample estimates may differ from the true parameters in the population (Szklo N and Nieto FJ, 2004). *Biases* possibly relevant for the studies of this thesis are presented below.

S*election bias* may occur if the included study sample is not representative of the population approached. Attrition analyses are usually performed to explore if the included and non-included samples differ significantly, hence exploring the external validity of the studied sample. However, regularly only limited information about patients not included in the study can be retrieved for ethical reasons. Attrition analyses can therefore usually be performed only on available "register data", such as stage of disease, histology and age.

In the Oslo-study, attrition analyses showed no significant differences between included and the non-included TCPs concerning age or stage of TC at baseline. In contrast, significantly larger proportion of included patients had non-seminoma compared to those not included, indicating a possible selection bias. However, among the included TCPs the proportions of patients with non-seminoma vs. seminoma were 49% and 51% respectively, and this is in line with the distributions found in population-based large samples of TCPs (Horwich *et al.* 2006). As the main study aim was to explore individual changes in cognitive function in TCPs treated with different modalities, we hardly believe that a difference in histology between included and non-included patients represents a serious concern to the validity of the study.

In prospective studies, selection bias may also occur if patients with specific characteristics withdraw from the study, e.g. if cancer patients with advanced disease more often are lost to follow-up than patients with localized disease. In the Oslo-study only seven patients (5%) of the patients were lost to follow-up. However, four out of these seven patients had received multiple cycles of chemotherapy, so withdrawal was not equally distributed between the three treatment groups.

Information bias involves errors that may occur if the methods (measures) for data assessment are inappropriate, leading to erroneous information or data. For example, in neuropsychological testing it is important that test instructions are given in a standardized manner, as was done in the Oslo-study. However, since the same person (Tone Skaali) conducted both the testing and the interviews, *expectation bias* (see below) on her part in the interviews could possibly have been a problem. A standardized interview manual (Appendix B) and coding of the responses was used, however, and this probably reduced the risk for such bias.

All measures used in a study should show appropriate psychometric properties – i.e. being reliable (precise) and valid (capturing the true information about a concept) – in order to avoid *measurement bias*. In the Oslo-study, possible *ceiling effects* on the neuropsychological tests could have threatened the validity of the neuropsychological test results. However, most of the test results from our study had relatively broad distributions in the range of scores, indicating that ceiling effects rarely occurred.

Other types of information bias are *expectation bias* [when the patient reports (or the observer classify) data toward the expected or wished outcome] or *memory bias* (when the patients selectively recall past events). In the Oslo-study, both expectation and memory biases could theoretically be operating during self-report of cognitive complaints in the interviews (paper IV). A main aim of the 1990'ies study (paper I) was to prevent expectation bias concerning cognitive complains caused by public knowledge of such effects ("chemo brain") after chemotherapy. The self-report data were collected before "chemo brain" was publicly known, and cognitive function was not a focus of the original studies.

6.1.4. Study samples

In *the 1990-ies study (paper I)*, we aimed to prospectively compare cognitive complaints during the 12 months after diagnosis between TCPs treated and not treated with chemotherapy. Since we did not have access to data from TCPs who had received

surveillance only, TCPs treated with radiotherapy was used as the control group. This is a limitation of the study, since radiotherapy hypothetically could affect cognitive function; however due to anatomy we hardly believe that abdominal radiotherapy could have a substantial long-term negative effect on cognitive function in TCPs. Secondly, we included only TCPs <60 years old at baseline who had delivered questionnaires in the accepted time-windows and had filled in both cognitive items at all three time-points. In order to study changes over time in cognitive complaints in a relevant study sample (not including men with cognitive decline due to age) during the 12-months study period, this selection procedure was necessary. However, by this selection procedure the study sample included only 46% of the patients with valid baseline data. We considered imputation of missing concentration and memory scores in the EORTC QLQ-C30, but with only two cognitive items, we regarded imputation as contraindicated. The high "attrition" rate is a limitation of paper I. With the smallest group size of 71 patients, the 1990-ies study was powered to detect group differences of moderate and large effect sizes (estimated Cohens d ≥0.48)(Murphy K.R. and Myors B, 2004).

In *the Oslo-study (paper II-IV)*, 202 patients with TC were admitted to the two participating hospitals during the sampling period. Among them, 129 were recruited and examined at baseline (64%) and 122 re-examined at follow-up (95% of those examined at baseline). A practical challenge was that all baseline evaluations of this study had to be done during or after the medical evaluation at the NRH/UUS, but *before* the start of any chemotherapy. This time-window was quite short in many cases, and some patients were lost for inclusion due to time constraints.

Some selection bias may have occurred without our intent. Possibly some of the most well-functioning and "busiest" patients, with no time to spare for our study, declined to participate. Also, some of the most distressed patients may possibly have declined study participation, as they felt they had enough just dealing with their current stressful life situation. Also, TCPs with very advanced disease needing immediate treatment with chemotherapy were not eligible for inclusion.

This study introduced cognitive dysfunction as a "new" eventual adverse effect of chemotherapy to the TCPs, and we were worried if this would induce concerns in some of the patients. However, we took the outmost care by cautiously presenting the study aims to the patients. Anyhow, some patients may have been provoked or scared by the cognitive testing part, and therefore declined to participate. Altogether, we regard an inclusion rate of 64% to be fairly good, taken into account that the study was quite effort-demanding and

time-consuming for the patients included. A considerable strength of the study is the high follow-up rate (95%).

As to the sample size, and the power to detect group differences, we admit that our sample sizes were mostly small, with a define risk for type II statistical error. However, for the sampling practical matters were a constraint, since the recruitment of patients and the baseline and follow-up testing had to be done within a three year PhD-period.

As our study had consecutive design, and since many TCPs in Norway receive only one course of chemotherapy, a division into three treatment groups was natural in relation to our study aims. However, by comparing three instead of two groups, more included patients were needed in order to obtain adequate power for the statistical analyses. With a follow-up sample size of 122 patients divided on three groups, we were able to detect group differences of medium and large of effect size (estimated Cohen's d $\geq$0.56) (Murphy K.R. and Myors B, 2004). Our study was therefore not powered to detect small differences in effect size, and a certain risk of type II error is acknowledged in paper III and IV. However, group differences with small effect sizes may not necessarily be clinically significant in relation to cognitive function.

6.1.5. Time points for the evaluations

In *the 1990'ies study (paper I)*, evaluations at pre-treatment, at short term, and at longer term follow-up were of interest. In the QoL-study by Fosså et al (Fossa *et al.* 2003), hardly any changes in function and symptom scores were observed from 12 and 24 months follow-up. Due to this finding and the considerable attrition between the 12 and 24 month evaluations in the EORTC-studies, we chose 12-months as the time point for longer term follow-up in order to keep the sample size as large as possible.

In *the Oslo-study (paper II-IV)*, practical reasons hindered a 3-month evaluation, as the research fellow (Tone Skaali) performed all evaluations both at baseline and follow-up. From a clinical perspective we were mostly interested in any *longer term* effects of chemotherapy on cognitive function. We therefore decided that follow-up evaluations were to be performed 12 months after end of chemotherapy or start of the surveillance period. However, this implicated that the test-retest interval differed between patients treated with chemotherapy and with surveillance. Anyhow, we chose this time-point for follow-up, however, due to correspondence with the regular 12-month follow-up visits for the TCPs. Many of our patients lived far from the Clinics, and we assumed that if the follow-up

examination in our study was done the same day as their visit, compliance would be benefited. The high follow-up rate indicates that this was a reasonable procedure.

6.1.6. The measures used

In *the 1990'ies study (paper I)* we used pre-collected data, and both the outcome variable (cognitive complaints) and the explanatory variables were assessed with the EORTC QLQ-C30 and TC-module used in these studies. The QLQ-C30 has two items on cognitive function (concentration and memory) that can be combined to "cognitive function". Of course, to use an instrument with just two items provided only a rough measure of cognitive complaints. However, the QLQ-C30 is in common use in oncology, and the instrument has well-documented psychometric properties (Aaronson *et al.* 1993).

As to *the Oslo-study (paper II-IV)*, some considerations regarding the measures used will be presented.

Neuropsychological test methods (outcome variable): We chose a combination of traditional "paper and pen" and computer-based tests. The traditional tests are regularly used by Norwegian neuropsychologists, and they are regarded as valid and reliable instruments. The computer tests were, however, new to our research group but were included since they may be more sensitive to small cognitive changes compared to traditional tests, and since computer-based tests were recommended in the field (Tannock *et al.* 2004).

After study start, we realized that the total test battery with 10 tests (including 18 test-measures) was too time-consuming and demanding for the TCPs at the baseline evaluation. We therefore decided that two time-consuming computerized tests of executive functions were done as optional, both since we had several executive tests, and since these computer-based tests were the least commonly used ones. Ideally, we should have performed a feasibility study of the test battery before study start, in order to establish a realistic and adequate size. However, time constraints did not allow for this.

A general problem of the neuropsychological studies previously presented in this thesis is the variation in the selection and the number of tests used. This critique may be raised to our study as well, since we included some computer-based tests not commonly used. The International Cancer and Cognition Task Force (ICCTF) group has initiated work to develop a standardized neuropsychological test-battery to be used in future studies of cognitive function in cancer patients (Vardy *et al.* 2008). This initiative will allow for better opportunities for comparison across studies, and will facilitate meta-analyses.

Evaluation of cognitive complaints (outcome variable): Cognitive complaints were assessed by interviews of the patients only, as no reports from partners or close other was obtained. As mentioned previously, expectation or memory bias could have been a problem in the self-evaluation. Further, the research fellow (Tone Skaali) performed both the interviews and neuropsychological testing, and expectation bias on her part could hypothetically have arisen as described in Section 6.1.3. However, from the patients' point of view, to be evaluated by the same professional probably was a positive factor. Finally, inclusion of a validated questionnaire assessing broader aspects of self-assessed cognitive functioning could have been beneficial for our study. However, such questionnaires are quite comprehensive and time consuming, and no such instrument was included.

Questionnaires (explanatory variables): Questionnaires well-known in our research group and with good psychometric properties were chosen to assess clinically relevant explanatory variables such as emotional distress, fatigue, neuroticism, alcohol-use and symptoms of peripheral neurotoxicity.

The IES was our measure for the assessment of cancer-related emotional distress. However, several cut-off values for clinical significant distress on the IES-total score with a possible range from 0-75 exist in the literature. We used a cut-off score of 26, since this score had been used in a previous study on emotional distress in TCPs (Tuinman *et al.* 2007). In paper II we also included the distress-scale scores of the HADS and the PANAS-NA, in order to explore the associations between several distress-scale scores and neuropsychological test results. The correlation coefficients between the three distress scale scores ranged from 0.63-0.67 (explaining 40-45% of the common variance between the measures), indicating that these measures captured partly different dimensions of distress.

Finally, it could have been of value if the EORTC QLQ-C30 questionnaire had been included in the Oslo-study, since that questionnaire was used in the QoL-study that made basis for our study (Fossa *et al.* 2003) and in paper I. However, due to time constraints we had to limit the number of questionnaires and this questionnaire was not included.

6.1.7. Statistical issues

6.1.7.1. General

Confounder effects are factors that influence the relationship between the independent and the dependent variables. As mentioned in the Introduction, Section 1.2.2, level of emotional distress may possibly be confounder when interpreting neuropsychological test results in relation to treatment groups.

In the Oslo-study we were concerned if high levels of emotional distress shortly after the TC-diagnosis would confound the neuropsychological test results at baseline, and this concern was the basis for the study in paper II. As mentioned in the Results, Section 5.3.2 on paper II, this influence was limited to four out of 18 test measures. Consequently we concluded that the neuropsychological test battery was relatively robust for the influence of current level of emotional distress.

6.1.7.2. Paper I (The 1990'ies study)

In order to assess the prevalence of cognitive complaints in the TCPs we dichotomized the QLQ-C30 cognitive function scores. The cognitive complaints variables *concentration* (range 1-4), *memory* (range 1-4) and *summary cognitive function scores* (range 0-100) were all significantly skewed; the cognitive function scores had a median value of 100 at all time-points. We therefore considered "not at all" to be reference and other scores to be *problems*. This decision implied that a score of "a little" difficulty on concentration and memory, as well as a score of 83.33 on a scale from 100 (best) to 0 (worst) were to be considered as cognitive complaints. Our definitions thus implied that any deviance from perfect score on the three complaint variables implied complaint present. By this strict definition, we may have overestimated the prevalence of cognitive complaints of practical relevance among the TCPs.

6.1.7.3. Paper II (The distress paper)

We performed multiple analyses exploring the associations between three distress-scores and 18 neuropsychological test-scores with a significance level set at 0.05. This implies that one out of 20 significant findings may have occurred by chance alone, and our results should therefore be interpreted with caution. The reason for our choice was that we preferred false positive associations rather than false negatives, since this was an exploratory and hypothesis generating study on the influence of distress on neuropsychological test results.

6.1.7.4. Paper III (The neuropsychological paper)

For the *group analyses* we regarded that *raw test-scores* were the most relevant parameters to analyze, since we did not have published norms for some of the computer tests, and since our control group was relatively small for deriving standardized scores.

As to the *individual analyses,* we chose the SRB-method since it implied an opportunity to adjust for relevant covariates. Since age differed significantly across the treatment groups, such adjustments were important. In general, when performing such individual analyses, the test performance of a control group is used for the prediction of individual achievement in other groups of patients. Hence, the control group should be representative for the population studied. In our study the control group was relatively small, and there was a certain risk that this has influenced on the results, making the results less reliable. Also, since current distress possibly may be a confounder as to the neuropsychological test results, a group size permitting the inclusion of additional co-variates such as levels of distress was preferable.

We defined that a *z-score of change* outside *±1.64 SD* represented a reliable change on the individual test-scores from baseline to follow-up, as proposed by Ouimet et al (Ouimet *et al.* 2009). However, a more strict cut-off (z-scores of change outside *±1.96 SD)* has been used in some studies (Stewart *et al.* 2008).

As to individual analyses, it is a problem that no established definitions of meaningful individual *changes* over time in neuropsychological test performance exist in the literature. Several studies, inclusive those by Jenkins et al. (Jenkins *et al.* 2006) and Stewart et al. (Stewart *et al.* 2008) have defined decline/improvement as present when reliable change appeared on two or more test-measures. However, in these studies the total number of measures varied from 14 to 23, so such a definition implies variable proportions of the total number of test-measures applied (15% and 8%, respectively). Since our sample of TCPs had completed different numbers of tests, we had to define individual decline and improvement in performance by proportions of tests, and not by absolute numbers. To compensate for the uncertainty inherent in our defined proportional cut-off levels, we analyzed the data using two different cut-off levels (10% and 15%). Finally, all these analyses were performed on both the *total* and the *basic* test battery.

6.1.7.5. Paper IV (The self-report paper)

Dichotomizing the responses from self-reported concentration and memory and then constructing an overall change-score (*increase* vs. *no increase of cognitive complaints from baseline to follow-up*) reduced the variability of the data. However, such a categorization was necessary in order to achieve adequate group sizes for the statistical comparisons between TCPs with and without such an increase. A multivariate analysis exploring the strength of association between background variables and an increase of cognitive

complaints could have been preferable in this study. However, the small group size of TCPs with an increase of complaints (n=25) precluded such an analysis. Hence, only descriptive (bivariate) analyses were performed.

6.2. Discussion of the specific results

6.2.1. Paper I (The 1990'ies study)

In paper I, prospectively exploring cognitive complaints in TCPs treated with chemotherapy (CHEM group) or radiotherapy (RAD group) in the 1990-ies, we only partly confirmed our hypotheses (stated in Section 2.2). We *did* find that compared to the RAD group, the CHEM group had significantly higher prevalence of concentration problems and cognitive function (CF) problems at 3 months, while no significant group difference was found for memory problems at this time point. However, contrary to our first hypothesis, no intergroup differences in prevalence of any of the three cognitive complaints measures were found at 12 months. In multivariate analyses with adjustment for self-reported QoL functions and symptoms, treatment modality was not significantly associated with cognitive complaints at any time point, while more current fatigue, presence of insomnia, as well as reduced emotional and social function were significantly associated with cognitive complaints at least two out of three time points, thus confirming parts of our first hypothesis. As to our second hypothesis we found that poorer emotional function and increased level of fatigue before treatment were significantly associated with cognitive complaints (concentration or CF-problems) at 12 months in bivariate analysis, while these associations were not significant in multivariate analyses.

Our results are partly in line with the findings in the mixed cancer sample studied by Kohli et al (Kohli S *et al.* 2007) confirming an increase in prevalence of cognitive complaints from baseline to short-term follow-up among chemotherapy patients not observed in the radiotherapy group. However, in our study, this increased rate had returned to baseline levels at longer-term follow-up while this was not the case in Kohli et al study. However, Kohli et al had shorter follow-up time compared to ours (6 months vs. 12 months in our study), and this may explain the divergent longer-term results.

One-third of our TCPs in both the CHEM and the RAD group had cognitive complaints (CF-problems) at 12 month follow-up and this prevalence is in agreement with the findings by Schagen et al (Schagen *et al.* 2008). We do not know how this prevalence corresponds with the prevalence of cognitive complaints in age-matched men in the general population. However, the mean CF-scores of the TCPs in our study were at the same level

as the CF-scores of Norwegian men aged 30-39 in the general population (Fossa *et al.* 2007), indicating no large difference in self-reported cognitive complaints between TCPs one year after the cancer diagnosis and young men in the general population. The prevalence of long-term cognitive complaints found in TCPs has overall been lower than the corresponding prevalence observed in breast cancer patients (Jenkins *et al.* 2006; Shilling and Jenkins, 2007) and in Kohli et al's mixed cancer sample (Kohli S *et al.* 2007). However, since different instruments for the assessment of cognitive complaints have been used across these studies, such comparisons must be interpreted with caution.

In our study we confirmed the association between cognitive complaints and increased fatigue / lower emotional function (i.e. increased anxiety/depression) observed in other groups of cancer patients (Cull *et al.* 1996; Hermelink *et al.* 2010) and also reported by Schagen et al in their cross-sectional study of TCPs (Schagen *et al.* 2008). In the multivariate analyses of our study, increased current fatigue was significantly associated with cognitive complaints at all time points. Mental fatigue and cognitive complaints may represent similar constructs since both phenomena include symptoms of reduced concentration and memory (Hermelink *et al.* 2010).

There may be a risk of expectation bias in today's studies of self-reported cognitive complaints after chemotherapy (Schagen *et al.* 2009). Among the TCPs treated during the 1990'ies we expect that no such bias was present. Hence, we conclude from this study that chemotherapy does not seem to exert a longer-term negative effect on cognitive complaints in TCPs.

6.2.2. Paper II (The distress paper)

In this study we found that 24% (95 CI 17%-31%) of the TCPs had clinically significant distress by our definitions at baseline, shortly after receiving the cancer diagnosis. This prevalence is in line with the findings in two small-scale studies on post-diagnosis emotional distress in TCPs (Trask *et al.* 2003; Tuinman *et al.* 2007). The majority of recently diagnosed TCPs seem to adapt relatively quickly to the situation, probably since a good prognosis is to be expected. However, we must consider a possible selection bias in our study sample, since some of the most distressed patients may have declined to participate in the study. Also, patients with very advanced disease when diagnosed were excluded from study participation due to medical reasons.

Surprisingly, and contrary to our second hypothesis, none of the cancer-related variables were significantly associated with the levels of emotional distress. Based on

studies from other cancer groups (Gurevich *et al.* 2002), we hypothesized that patients with metastatic disease would be more concerned than those with non-metastatic disease, but this expectation was not confirmed. Explanations for this finding may be the good prognosis expected even in metastatic disease, or that patients had not perceived the stage of their disease at the baseline evaluation of our study. Since we found that high level of neuroticism, current smoking and high alcohol-use were significantly associated with an increased distress-level, personality and lifestyle seemed more relevant for the level of distress than the cancer-related variables. This finding confirms the results from a study of long-term TC survivors (Fleer *et al.* 2006), which reported that patient-related variables rather than cancer-related variables were associated with levels of cancer related distress.

Our study indicates that some patients may be vulnerable to increased levels of distress shortly after the TC-diagnosis without regard to the stage of disease, and such vulnerability warrants clinical attention. Future prospective studies could explore the relation between level of post-diagnosis distress and long-term emotional functioning in TCPs.

As to the main focus of this study, we found that the scores on four of the 18 neuropsychological test measures were significantly associated with at least one of the three distress scores at baseline, thus partly confirming our third hypothesis. These four test-scores represent cognitive domains of working memory/attention/concentration, speed of information processing, and executive functions. Interestingly, these cognitive domains partly overlap with the cognitive domains possibly affected after treatment for breast cancer (Vardy *et al.* 2008). Reduced attention due to current emotional distress may partly explain a reduced cognitive performance, as visualized in Figure 1 (Section 1.2.1)

However, with multiple testing using 0.05 as the significance level, some of the significant associations between the distress- and the test-scores found in this study may be due to chance alone. Importantly, the majority of the neuropsychological test measures used in our study (14 out of 18 measures) were <u>not</u> significantly associated with current distress-levels. We therefore conclude that the neuropsychological test battery was relatively resistant to any *confounding* effect of distress, and that neuropsychological testing of TCPs may be undertaken shortly after the diagnosis with valid results.

6.2.3. Paper III (The neuropsychological paper)

In this prospective study of neuropsychological functioning in TCPs, we found no statistically significant group differences regarding decline in neuropsychological test

performance from baseline to a median of one-year follow-up. This was shown both in the group analyses as well as in the individual ones. Hence, the hypothesis that TCPs with multiple chemotherapy cycles more often would show decline in test performance compared with those treated with no or only one cycle was not confirmed.

We performed analyses using two different proportional cut-off levels on both the *basic* and the *total* test-battery. All these analyses gave the same result of no significant group differences concerning proportions of TCPs with decline of test performances. We therefore conclude that today's standard chemotherapy for TC does not seem to have a negative impact on neuropsychological functioning in the patients at one-year follow-up. This result confirms the cross-sectional findings by Pedersen et al (Pedersen *et al.* 2009).

Our study had some limitations. The study sample was relatively small, with the control group consisting of 31 patients only. Hence, our results need confirming in larger prospective studies before definite conclusions can be made. Further, positive results on test performance may have appeared if testing were done closer to the termination of chemotherapy, since chemotherapy possibly may have *transient* negative effects on cognitive function. However, long-term functioning is considered to be more important for the patients than any transient short-term dysfunction.

When using the 10% cut-off on the data from the total test battery, 42 of our TCPs showed individual decline in neuropsychological test performance (with a non-significant difference in proportions across the treatment groups). This should, however, not be interpreted as if one-third of the sample actually declined in neuropsychological functioning, but is most probably related to a liberal definition of decline and to the natural variation in neuropsychological test performance in general. When we applied the 15% cutoff, only 17 TCPs (14% of the sample) were classified with individual decline. Lastly, with our definition of *overall decline* (which takes into account the relation between declined and improved test scores), 18 TCPs (15%) were classified as showing decline.

Counter intuitively, significantly more TCPs in both chemotherapy-groups compared to the no-chemotherapy group had individual *improvement* on test performance from baseline to follow-up. However, we hardly believe that chemotherapy has a positive effect on cognitive function. Several explanations might be given for this finding. Some of the TCPs assigned for chemotherapy may have experienced relatively high levels of emotional distress at baseline due to metastatic disease, and the increased distress-level could have affected their neuropsychological test performance in a negative way (ref paper II). At follow-up, these patients were probably less distressed, and they, therefore, performed better

on the tests. Another explanation could be that some TCPs treated with chemotherapy were highly motivated to perform at their very best at the follow-up evaluation, due to fear of "chemo brain". Anyhow, the improvement effect is probably not of large clinical importance, since we did not detect any significant group differences on the test raw-scores neither at baseline (except one score), at follow-up, or for the change-scores.

As to our second study aim, we wanted to explore if any patient-related or disease-related variables were significantly associated with a decline in neuropsychological test performance from baseline to follow-up. In particular, we hypothesized that chemotherapy could be a risk factor for such decline, but this hypothesis was not confirmed. None of the demographic, cancer-related or emotional distress / fatigue variables (except increase of ototoxic symptoms) showed significantly association with a decline in test performance. This is in line with results from breast cancer patients (Jenkins *et al.* 2006). We had no 'a priori' hypothesis of an association between ototoxic symptoms and decline in neuropsychological performance, and this association may possibly be significant by chance due to multiple testing.

In future prospective neuropsychological studies in TCPs, assessment of cognitive function at 5 or 10 year follow-up intervals might also be valuable, since adverse effect of cancer treatment may have a long latency before they become clinically apparent (Fossa *et al.* 2009). A working hypothesis of our research group is that chemotherapy may induce premature aging of the different organs. Hence, it could be of interest to explore age-related cognitive decline in long-term TC survivors treated with or without chemotherapy. However, age was not a significant predictor of decline in neuropsychological test performance in our sample of TCPs.

A problem with neuropsychological testing in general is that the testing does not measure the *effort* needed to solve the tasks. Such effort, however, can be assessed in part by functional neuro-imaging of the brain. In a small functional MRI-study by Ferguson and colleagues, a pair of monozygotic twins (two females aged 60, one had completed chemotherapy for breast cancer 22 months earlier) performed a working memory task during brain imaging. The sisters performed almost identical on the memory task, however more brain activation was noted during task performance in the twin who had received chemotherapy compared to other twin, indicating that a larger effort was needed to solve the task (Ferguson *et al.* 2007b). Functional neuro-imaging could possibly have added valuable information in our study of TCPs; however such assessment was too comprehensive in our research setting.

6.2.4. Paper IV (The self-report paper)

In this study, prospectively exploring cognitive complaints in the TCPs included in the Oslo-study, we hypothesized that a higher proportion of TCPs in the MULTIPLE-CHEMO group would report an increase of cognitive complaints from baseline to follow-up compared to the NO-CHEMO and the ONE-CHEMO groups. This hypothesis was only partially confirmed, as significantly more patients in *both* chemotherapy groups had an increase of cognitive complaints compared to the NO-CHEMO group, and since no significant difference appeared between the two chemotherapy groups. This result is in contrast to the neuropsychological findings in paper III, and indicates that chemotherapy may have a negative impact on self-reported cognitive complaints, in line with findings among breast cancer patients (Shilling and Jenkins, 2007). That patients treated with chemotherapy to some extent had been primed about this eventual side-effect when entering the study, implying expectation bias as an alternative explanation of the findings.

Our second hypothesis was confirmed, as we found that an increase of self-reported cognitive complaints from baseline to follow-up was significantly associated with follow-up scores of increased emotional distress and fatigue, but not with a decline in neuropsychological test performance. These results confirm findings from other studies (Hermelink *et al.* 2010; Schagen *et al.* 2008), and they indicate that cognitive complaints in TCPs may represent emotional rather than neurocognitive response. Chronic fatigue is common in TCPs (Orre *et al.* 2008), and the symptoms of mental fatigue and cognitive complaints seem to be highly correlated (Cull *et al.* 1996; Hermelink *et al.* 2010).

The discrepancy observed between "subjective" and "objective" decline in cognitive function could be explained in several ways. Low ecological validity of neuropsychological tests and the standardized test situation imply that cognitive performance in stressful situations of daily life, requiring good multitasking capacity, were not adequately evaluated by our test battery. Further, the validity of self-reported cognitive complaints was threatened by expectation or memory bias. Interestingly, studies on elderly in the general population have demonstrated a significant association between self-reported cognitive complaints and neuroimaging findings in the absence of reduced neuropsychological test performance (Haley *et al.* 2009; Saykin *et al.* 2006). Cognitive complaints may, in some cases, represent subtle cognitive reduction not (yet) identified by neuropsychological testing.

Cognitive complaints in TCPs seem to have a multi-factorial etiology, in which emotional distress, fatigue, hormonal factors (Fossa *et al.* 2009; Nord *et al.* 2003) and treatment modalities might play a role. The majority of the TCPs included in our study,

however, had no cognitive complaints at one-year follow-up, indicating that cognitive complaints are not very prevalent in TCPs. However, for the minority of patients experiencing such cognitive problems, adequate clinical assessment of eventual precipitating or maintaining factors such as current emotional distress, fatigue or hypogonadism should be evaluated. Adequate interventions should eventually be undertaken in order to alleviate such symptoms.

7. CONCLUSIONS

7.1. Summary of results related to the study aims

7.1.1. Paper I (The 1990-ies study)

Aim 1: Among TCPs treated with chemotherapy during the 1990'ies, there was a significantly increase in prevalence of cognitive complaints from baseline to 3 month follow-up. At 12 month follow-up these rates had returned to baseline levels. For TCPs treated with radiotherapy no significant changes over time in prevalence of cognitive complaints were observed. In multivariate analyses with adjustments for self-reported QoL function and symptoms, *treatment modality* [chemotherapy vs. radiotherapy (reference)] was not significantly associated with the presence of cognitive complaints neither at any time point. In these analyses, current fatigue, insomnia, reduced emotional function and reduced social function were significantly associated with cognitive complaints at several time points.

Aim 2: In bivariate analyses, several pre-treatment QoL function / symptom scores were significantly associated with concentration problems at 12 months, however in multivariate analyses none of these associations remained statistically significant.

7.1.2. Paper II (The distress paper)

Aim 1: About one-fourth (24%) of the included TCPs in the Oslo-study had clinical significant cancer-related distress at the baseline evaluation, shortly after their TC-diagnosis.

Aim 2: Cancer-related distress at baseline was significantly associated with patient-related variables such as high level of neuroticism, smoking and high alcohol-use, but not with the stage of TC.

Aim 3 (Main study aim): The majority of the neuropsychological test-scores (14 out of 18 test measures) at baseline were not significantly associated with current distress scale scores at that time point.

7.1.3. Paper III (The neuropsychological paper)

Aim 1: No significant group differences between the NO-CHEMO, the ONE-CHEMO, and the MULTIPLE-CHEMO groups in proportions of TCPs with a *decline* in neuropsychological test performance from baseline to one-year follow-up were observed.

Aim 2: Decline in neuropsychological test performance from baseline to follow-up was not associated with treatment with chemotherapy or with any of the other patient or cancer-related variables, except for an increase of subjective ototoxic symptoms (tinnitus and reduced hearing).

7.1.4. Paper IV (The self-report study)

Aim 1: Significantly higher proportions of TCPs in the ONE-CHEMO and the MULTIPLE-CHEMO groups had an *increase* of subjective cognitive complaints from baseline to one-year follow-up compared to the NO-CHEMO group.

Aim 2: Increase of cognitive complaints from baseline to follow-up in the Oslo-study was significantly associated with symptoms of emotional distress and fatigue at follow-up and treatment with chemotherapy, but not with a decline in neuropsychological test performance.

In both paper I and IV cognitive complaints were found significantly associated with levels of emotional distress and fatigue, and both papers displayed bivariate associations between chemotherapy and post-treatment cognitive complaints. However in paper I, the association between chemotherapy and cognitive complaints did not remain significant after adjustment in multivariate analysis.

7.2. Conclusions and clinical implications of the study results

- About one-fourth of TCPs experience high levels of emotional distress shortly after their diagnosis of TC, and their level of such distress is not necessarily associated with the stage of the disease at diagnosis. Some TCPs may be vulnerable to emotional distress after a TC-diagnosis, and this should be kept in mind by clinicians.
- Neuropsychological testing can be performed in a valid way in TCPs shortly after their diagnosis, although some test measures (of attention and working memory) may be negatively influenced by high levels of emotional distress in some individuals.
- Current standard treatment with chemotherapy for TC does not seem to have a negative impact on neuropsychological functioning in patients at one-year follow-up. There is a risk of type II statistical error due to our sample sizes, and this result should be investigated further in future prospective studies with larger samples than ours.
- The association between cognitive complaints and chemotherapy in TCPs seem uncertain and may be explained by confounding variables such as emotional distress and

fatigue. There is a certain risk of expectation bias in current studies of cognitive complaints after chemotherapy.

- Cognitive complaints in TCPs probably have a multi-factorial etiology and seem to be related to current emotional distress and fatigue rather than to objectively reduced neurocognitive functioning. Clinical interventions for reducing emotional distress and fatigue may eventually help reducing self-experienced cognitive complaints in TCPs.
- The low correlation between cognitive complaints and neuropsychological test parameters in TCPs seem to document that both these issues should be included in studies of cancer-related cognitive function.

8. FUTURE CONSIDERATIONS AND RESEARCH QUESTIONS

- Prospective studies with large samples of TCPs assessing cognitive complaints by validated cognitive questionnaires and with the inclusion of a standardized neuropsychological test battery are needed to further elaborate the association between cisplatin-based chemotherapy and cognitive function in TCPs.
- In such studies the recruitment of TCPs should be offered special consideration, since the Oslo-study probably missed the patients with the best and the worst coping with their recent diagnosis of TC.
- In future prospective studies, one should consider long-term follow-up evaluation at 5 and 10 years post-treatment, since any adverse effects of chemotherapy may have long latency before they become clinically apparent.
- Future studies of cognitive function in cancer patients including functional neuro-imaging of the brain can possibly add valuable information to the field, and may also be relevant in TCPs.
- Since a small proportion of TCPs develop hypogonadism, and since cognitive function possibly may be affected by hormone levels, cognitive complaints and neuropsychological functioning in relation to testosterone level in TCPs could be explored in future studies.
- There is a continuous search for the minimal though effective dose of chemotherapy in TCPs. In randomized controlled treatment studies, instruments covering cognitive complaints and brief neuropsychological testing should be included, since eventual reduced cognitive function may have serious consequences for these mostly young patients.

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APPENDIX A: Order of assessments in evaluations of the Oslo-study

Baseline and follow-up evaluations (90-120 min, all performed by Tone Skaali)

1) Information about the evaluation, informal talking
2) Semi-structured interview
3) Neuropsychological testing
4) Collection of questionnaires filled in by the patients before the evaluation
5) Patient evaluation of study participation

APPENDIX B: Semi-structured interviews in the Oslo-study

Baseline interview

Demography

Date of birth

Place of living

Civil status

Fathered children

Completed years of education ☐ *≤ 9* ☐ *10-12* ☐ *13-15* ☐ *≥16*

Current occupation ☐ *working* ☐ *student* ☐ *not working*

Health and lifestyle

Somatic health problems during childhood, adolescence, adulthood?

Mental health problems during adulthood?

Sleeping problems?

Smoking / alcohol / drugs?

Severe health problems last year before the diagnosis of TC?

Current medications?

Cognitive complaints

In general, how is your concentration?

Very good *Good* *Not so good* *Poor*

In general, how is your memory function?

Very good *Good* *Not so good* *Poor*

Have you experienced any long-term cognitive problems before the TC-diagnosis? If yes, when did these problems start and what were they like?

Please indicate with a number on a *scale from 0 to 10* if any cognitive problems affect your habitual daily functioning (before the diagnosis of TC) (0: no affection, 10: major impact on daily functioning).

This study (to be answered at the end of the evaluation)

How has participation in this study been for you?

To be rated by the interviewer after the evaluation

Perceived satisfaction by the patient concerning information about TC at the local hospital

Satisfied *Not satisfied*

Patient generally well informed about TC

Yes *No*

Follow-up interview

Demography

Change in civil status or fathered children since the baseline evaluation?

Completed more years of education since the baseline evaluation?

Current occupation ☐ *working* ☐ *student* ☐ *not working*

Health and lifestyle after TC

Somatic health problems after TC?

Mental health problems after TC?

Current sleeping problems?

Change in smoking / alcohol / drugs behavior after TC?

Current medications?

Self-reported cognitive complaints after TC

How is your concentration?

Very good Good Not so good Poor

How is your memory function?

Very good Good Not so good Poor

Have you experienced any concentration or memory problems after the TC-diagnosis?

If yes, when did you experience such problems, how where they, and are they still present?

Please indicate with a number on a *scale from 0 to 10* if any cognitive problems affect your current daily functioning (0: no affection, 10: major impact on daily functioning).

This study (to be answered at the end of the evaluation)

How has participating in this study been for you?

APPENDIX C - Description of neuropsychological methods and test-measures in the Oslo-study

Cognitive domain	Neuropsychological test	Cognitive function assessed	Sub-test measure
Learning / memory	Hopkins Verbal Learning Test-Revised	Verbal learning Verbal memory	*Learning /acquisition* (total words) *Delayed recall* (percent retained)
	Paired Associates Learning *(CANTAB)*	Visual learning /memory	*Total errors 6 shapes*
Attention/ concentration/ working memory	Spatial Working Memory *(CANTAB)*	Visuo-spatial working memory Strategy	*Between errors* (total errors) *Strategy* (efficiency)
	Choice Reaction Time *(CANTAB)*	Speed of choice response	*Mean latency* (time)
Motor function	Grooved Pegboard	Visual-motor coordination and speed	*Dominant hand* (time) *Non-dominant hand* (time)
Speed of information processing	Trail Making Test A	Psychomotor speed	*TMT-A* (time)
	Color-Word Interference Test part 1+2	Psychomotor speed – naming Psychomotor speed – reading	*CW-1* (time) *CW-2* (time)
Executive functions	Color-Word Interference Test part 3+4	Response inhibition Response inhibition and shifting	*CW-3* (time) *CW-4* (time)
	Trail Making Test B	Set-shifting	*TMT-B* (time)
	Word fluency (FAS) Test	Controlled oral association ability	*Total words*
	*Stockings of Cambridge *(CANTAB)*	Spatial planning /motor control	*Mean initial thinking time* *Problems solved in minimum moves*
	*Intra-Extra Dimensional Set Shift (*CANTAB*)	Rule acquisition /set-shifting	*Total errors (adjusted for completed stages)*

CANTAB: computer test
* supplementary test

APPENDIX D - Questionnaires used in the Oslo-study

Questionnaires	**Baseline evaluation**	**Follow-up evaluation**	**Used in paper**
Impact of Event Scale (IES)	x	x	II, III, IV
Hospital Anxiety and Depression Scale (HADS)	x	x	II
Fatigue Questionnaire (FQ)	x	x	III, IV
Positive and Negative Affect Schedule (PANAS), state version	x	x	II
Scale for Chemotherapy-Induced Neurotoxicity (SCIN)	x	x	III, IV
Short Eysenck Personality Questionnaire, Neuroticism scale	x	-	II, III, IV
CAGE questionnaire (alcohol problems)	x	-	II, III, IV

I

A prospective study of cognitive complaints in testicular cancer patients treated in the pre "chemo brain" era

Tone Skaali, MD[1], Sophie D. Fosså, MD, PhD[1], Alv A. Dahl, MD, PhD[1]

[1] National Resource Center for Late Effects, Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, and University of Oslo, Oslo, Norway

Running head: A prospective study of cognitive complaints in testicular cancer patients

Corresponding author:
Tone Skaali, MD,
Oslo University Hospital,
The Norwegian Radium Hospital,
P.O. Box 4953, Nydalen,
N-0424 Oslo, Norway
Phone +47-22934000 Fax +47-22934553
E-mail: Tone.Skaali@oslo-universitetssykehus.no

ABSTRACT

***Background*:**

Cognitive complaints are frequent among cancer patients, and both oncologists and patients have become concerned if systemic chemotherapy may have cognitive side-effects ("chemo brain"). After this concern became public there is a risk of expectation bias in future studies of cognitive complaints. Therefore, we prospectively explored cognitive complaints in testicular cancer patients (TCPs) treated with chemotherapy or radiotherapy during the 1990-ies, before today's increased awareness of this possible side-effect.

Materials and methods:

The EORTC QLQ-C30 and a testicular cancer module were completed before treatment (baseline), at 3-months, and at 12-months by 276 chemotherapy and 71 radiotherapy patients enrolled in three EORTC-studies. Cognitive complaints were studied as concentration problems, memory problems and cognitive function (CF) problems based on the QLQ-C30 ratings. Other QLQ-C30 functions and symptoms represented adjustment variables.

Results:

The chemotherapy group showed a significant increase in prevalence of concentration problems and CF problems from pre-treatment to 3-months. At 12-months these rates were back at baseline levels. The radiotherapy patients showed no significant change over time in prevalence of cognitive complaints. Significant differences between the two treatment groups were observed only at 3-months and concerned concentration problems and CF problems. In multivariate analyses, treatment modalities did not show significant associations with any of the cognitive complaint measures at any time-point, while current fatigue showed significant associations at all time points. Among pre-treatment variables,

reduced emotional function (i.e. anxiety and depression) and fatigue were significantly associated with cognitive complaints at 12-months in bivariate analyses.

Conclusions:

In this study from the era before the risk of "chemo brain" was known to the public, we found that the increased rate of cognitive complaints shortly after chemotherapy was back at baseline level at 12-month follow-up. In multivariate analyses chemotherapy versus radiotherapy was not significantly associated with cognitive complaints at any time point.

Keywords:

Cognitive complaints, Testicular cancer patients, Prospective study, Chemotherapy, Expectation bias

INTRODUCTION

Since the 1990-ies oncologists and cancer patients have been concerned that systemic chemotherapy may have a negative effect on cognitive function [1], a phenomenon popularly called "chemo brain" [2,3]. According to the Mayo Clinic: "Chemo brain is a common term used by cancer survivors to describe thinking and memory problems that can occur after cancer treatment. Chemo brain can also be called chemo fog, cognitive changes or cognitive dysfunction." (ref. http://www.mayoclinic.com/health/chemo-brain, retrieved August 26, 2010). "Chemo brain" is by now a well-established adverse effect after chemotherapy for cancer with 30%-80% of the patients reporting cognitive complaints (problems with concentration or memory) [4-6]. Both major oncology clinics and cancer societies in the Western world mention chemo brain or cognitive complaints in their reviews of adverse effects after cancer treatment.

Since the term chemo brain and the potential risk of such an adverse effect have been introduced to the oncological communities, many new cancer patients will be acquainted with the symptoms through various sources of information. For example, recent Googling of "chemo brain" gave 290.000 hits (http://www.google.no/search, retrieved August 26, 2010). The spread of knowledge about chemo brain leads to a considerable risk for information and expectation biases in new studies, since today's patients asked about cognitive complaints may be primed for them. Consequently, they may report falsely high levels of cognitive complaints in relation to chemotherapy. Schagen et al [7] recently documented such biases in a sample of breast cancer patients who randomly got information about 'cognitive problems' versus 'neutral' information. The primed patients showed significantly higher levels of cognitive complaints. In their study of cognitive complaints in breast cancer patients, Shilling & Jenkins [5] stated: "Self-report (of cognitive complaints)

may be high, simply because we asked patients to take part in a study investigating the potential effects of treatment on their memory."

Based on this knowledge, particular interest should be paid to studies of cognitive complaints in historical samples of cancer patients, from time periods when chemo brain was unknown to the public. Cognitive complaints can be clinically assessed by the oncologists by asking about memory and concentration problems in the clinical examination. These functions can also be explored by patient-completed questionnaires like the European Organization of Research and Treatment of Cancer cancer-specific quality of life (QoL) instrument (EORTC QLQ-C30) [8], which defines cognitive function based one question concerning memory and another on concentration problems during the past week.

The present study is based on the QLQ-C30 datasets from testicular cancer patients (TCPs) enrolled in three studies performed by the EORTC group during the 1990-ies, and treated with either chemotherapy or radiotherapy. With prospective data on cognitive complaints in TCPs treated before the "chemo brain" era, this study had the following aims: 1) To study the prevalence of self-reported cognitive complaints and its changes from before treatment (baseline) to 3 and 12-month follow-up among TCPs treated with either chemotherapy or radiotherapy, and to identify variables associated with such cognitive complaints; and 2) To identify self-reported QoL dimensions before treatment that were predictive for cognitive complaints at 12-month follow-up.

MATERIALS AND METHODS

Patients

The patients in this study were identified from the electronic records of three randomized treatment-studies on orchidectomized TCPs organized by the EORTC / MRC (Figure 1). Our *chemotherapy group* consisted of TCPs with metastatic non-seminoma or seminoma

included in trial 30941/ TE20 [9,10] (study start 1995) which evaluated treatment with four different schedules of bleomycin, etoposide and cisplatin (BEP) chemotherapy (3 or 4 cycles given over 5 or 3 days). Our *radiotherapy group* consisted of irradiated non-metastatic seminoma patients included in trial 30942 /TE18 [11] (study start 1995) and trial 30982 /TE19 [12] (study start 1996). The TE18 study compared the effects of 20 Gy versus 30 Gy abdominal radiotherapy, while the TE19 study evaluated radiotherapy (20 or 30 Gy) versus a single-dose of carboplatin chemotherapy. From the TE18/TE19 studies we only had access to the data on the Norwegian patients (n=126).

According to the protocols, the QLQ-C30 and a TC-module [10,13] should be completed before treatment (baseline), and then again approximately 3 months and 12 months later. In the TE20 study the 3 months assessment was done shortly after the end of chemotherapy. The time-windows for valid questionnaire responses in our study were: *TE20*: baseline: +/-30 days from randomization, 3 months: 9-20 weeks after baseline, and 12 months: 9-18 months after baseline. For *TE18/TE19*: baseline: 0-28 days before treatment start, 3 months: 9-18 weeks after baseline, and 12 months: 9-15 months after baseline.

We only included TCPs who were tumor-free at 12 months, had delivered questionnaires within the defined time windows, had filled in both cognitive items of the QLQ-C30 before treatment and at 3 and 12 months follow-up, and who were in the age range from 15 to 59 years at baseline. The final sample thereby consisted of 347 TCPs with valid cognitive data (Figure 1), 276 treated with chemotherapy (CHEM group) and 71 with radiotherapy (RAD group).

Cognitive complaints (outcome measures)

Cognitive complaints were assessed by responses to the two cognitive questions of the QLQ-C30 [8]: “Have you had difficulty in concentrating on things, like reading a

newspaper or watching television?" (item #20) and "Have you had difficulty remembering things?" (item #25). There were four response-alternatives: "not at all" (1), "a little" (2), "quite a bit" (3) and "very much" (4), and the time frame were the past week.

We defined threes separate outcome measures: the scores of item #20 (concentration), the scores of item #25 (memory) and the *cognitive function* (CF) scores defined according to the QLQ-C30 [8] as a combination of the memory and concentration scores and transformed by the formula: CF-score = (1 – [(mean score of items #20 and #25 – 1)/3]*100). This transformation gives seven steps on a scale from 0 (worst) to 100 (best), with intervals of 16.67 points.

Cognitive complaints in this study were defined by the scores on either memory, concentration or CF. A representative sample of Norwegian men aged 20 to 59 years had mean CF scores between 86.5 and 91.6 according to 10 year age groups [14]. On this background cognitive complaints were defined by three outcomes as follows: concentration and memory problems absent ("not at all") or present ("a little"/"quite a bit"/"very much"), and CF problems absent (score 100) or present (score ≤83.33).

Independent variables

EORTC Quality-of-Life Questionnaire (QLQ-C30)

In addition to CF, the QLQ-C30 [8] assessed *physical function*, *emotional function* (EF), *social function* (SF) and *role function* (RF), as well as *global QoL*, and nine symptom scales including *fatigue, pain* and *insomnia.* By established algorithms the QLQ-C30 items were transformed to function scales with scores from 0 (worst) to 100 (best), and fatigue, pain and insomnia from 0 (no symptoms) to 100 (worst symptoms) [8]. For our regression analyses we selected the functions and symptoms which from a clinician's point of view were most likely to be associated with cognitive complaints: EF, RF, SF, fatigue, and

insomnia. Pain was excluded due to high correlation with fatigue before treatment. Since we expected the diagnosis of testicular cancer to affect these functions and also considering the mean scores in the population sample [14], we defined the cut-off for good function at a score of ≥75 and <75 for reduced function. By the same way of reasoning, the symptoms of fatigue and insomnia were defined as absent by scores ≤16.67 and present as scores >16.67.

TC-module questionnaire

From the TC-module [10,13] we used the items covering peripheral neuropathy, Raynaud's phenomenon and reduced hearing/tinnitus, for simplicity summarized as neurotoxic symptoms, and linearly transformed to a summary score from 0 (no symptoms) to 100 (worst symptoms) [8,10]. Since neurotoxic symptoms also exists in the general population [15], we dichotomized the transformed score into symptom absent (score≤16.67) or present (score >16.67).

Age at baseline was also registered.

Statistical analyses

Data were analyzed by the SPSS program for PC version 16.0 (SPSS Inc, Chicago IL), using standard descriptive measures. The distribution of scores on the three outcome measures concentration, memory and CF at baseline, 3 and 12 months are presented. The selected functions and symptoms of the QLQ-C30 and of the TC-module as well as age and cancer-related variables were considered as independent variables. Changes over time in the proportions of patients with cognitive complaints were analyzed with 2x2 contingency tables and Fisher's exact test.

At each time-point, bivariate and multivariate logistic regression analyses examined the association between cognitive complaints (dependent variable) and independent variables (treatment group [RAD group as reference] and the self-reported QoL

function/symptoms). The strength of the associations was expressed as odds ratios (ORs) with 95% confidence intervals (95%CI). Age was not entered as independent variable in the multivariate analyses since it did not show significant bivariate associations with the outcome variables at any time point.

With bivariate and multivariate logistic regression analyses we then explored if any of the pre-treatment independent variables were predictors of cognitive complaints at 12 months. All tests were two-sided, and p-values<0.01 were considered to be statistical significant due to multiple testing.

Ethics

The TE18, TE19 and TE20 trials were approved by the local research ethical committees of each participating center. All patients provided written informed consent.

RESULTS

Attrition analysis

Attrition analyses showed no significant differences in age or in proportions of patients with concentration or memory problems before treatment between the examined sample of 347 TCPs fulfilling the selection criteria and the 404 TCPs with valid baseline data but excluded due to missing data at 3 or 12 months (Figure 1). However, a larger proportion of the excluded patients had non-seminoma compared to the included patients (70% vs. 61%, p=0.005).

Characteristics of the CHEM and RAD groups

Among the 347 included TCPs, the mean age of patients at baseline was significantly lower in the CHEM group (33.0 years ±8.8) compared to the RAD group (38.2 years ±8.0). The

distribution of the four different BEP-regimens in the CHEM group was as follows: 3 cycles over 5 days: 23%, 3 cycles over 3 days: 27%, 4 cycles over 5 days: 21% and 4 cycles over 3 days: 29%.

At baseline, in the CHEM group 23% had concentration problems, 23% had memory problems, and 37% had CF-problems. The corresponding proportions in the RAD group were 21%, 20% and 27%. No statistically significant inter-group differences in the distributions of the scores for concentration, memory and CF were observed at any of the time points (Table 1).

In the total sample 23% had concentration problems, 23% had memory problems, and 35% had CF-problems before treatment. At 12 month follow-up the corresponding proportions were 15%, 28% and 33%.

At 3 month follow-up, the CHEM group had significantly higher proportions with reduced function on EF, RF and SF compared to the RAD group (Table 2). At that time-point, fatigue and neurotoxic symptoms were also significantly more prevalent in the CHEM group than in the RAD group. Except for neurotoxic symptoms at 12 months, none of these functions or symptoms showed significant inter-group difference before treatment or at 12 month follow-up.

Changes in cognitive complaints over time and intergroup differences

The changes over time and the inter-group differences in the dichotomized cognitive complaints are depicted in Figures 2A-2C which also includes legends concerning statistical significance.

Significantly more patients in the CHEM group had *concentrations problems* at 3 months compared to baseline and 12 months. The proportion of patients with concentration problems at 3 months was also significantly higher in the CHEM than in the RAD group. In

contrast, the proportions with concentration problems at baseline and 12 month follow-up did not significantly differ between the CHEM and the RAD group (Figure 2A).

As for *memory problems* no significant changes over time were found for any of the treatment groups and no significant inter-group differences were observed at any time point. (Figure 2B).

The proportion with *CF-problems* in the CHEM group at 3 months was significantly higher compared to the proportions at baseline and 12 months. At 3 months, the CHEM group also had significant higher proportion of patients with CF-problems than the RAD group. No significant inter-group differences concerning proportions of patients with CF-problems at baseline and 12 month follow-up were observed (Figure 2C).

Associations between independent variables and cognitive complaints at each time-point

Bivariate analyses

At 3 month follow-up, belonging to the CHEM rather than the RAD group was significantly associated with concentration problems and CF-problems in bivariate analyses, while this was not the case before treatment or at 12 month follow-up (Table 3).

Multivariate analyses

In multivariate analyses no significant associations were observed between *treatment type* and cognitive complaints at any time point (Table 3).

However, *concentration problems* before treatment were significantly associated with reduced EF and fatigue. These associations held up at 3 month follow-up, but in addition reduced SF and insomnia also showed significant associations with concentration problems. At 12 month follow-up, none of the independent variables were significantly associated with concentration problems.

As for *memory problems*, no independent variables showed significant associations before treatment. At 3 months insomnia and at 12 months reduced SF and fatigue were significantly associated with memory problems.

Fatigue was significantly associated with *CF-problems* at all time points. In addition reduced SF and insomnia were significantly associated with such problems at 3 and 12 month follow-up.

Focusing on the *independent variables,* fatigue was significantly associated with cognitive complaints in 6 out of 9 analyses (Table 3). Correspondingly, insomnia and reduced SF were associated in 4, and reduced EF in 3 analyses. Reduced RF and neurotoxic symptoms showed no significant association with cognitive complaints at any time points.

Baseline predictors of cognitive complaints at 12 month follow-up

In bivariate analyses reduced EF and SF, fatigue and neurotoxic symptoms before treatment were significant predictors of concentration problems at 12 month follow-up (Table 4). For memory problems no significant predictors before treatment were observed, and for CF-problems only reduced EF was significant in bivariate analyses.

In multivariate logistic regression analyses no significant associations were observed between the independent variables before treatment and concentration problems, memory problems or CF-problems at 12 month follow-up (Table 4).

DISCUSSION

Based on our definitions between 23% and 35% of the TCPs reported cognitive complaints (defined by the presence of memory, concentration or CF-problems) before treatment, and 15% to 35% had such complaints at 12 months follow-up. The proportions of patients with either one of the three cognitive complaints did not differ significantly between baseline and

12 months, and no significant differences between the CHEM and RAD groups were observed at these two time points. In contrast, at 3 month follow-up, the proportion of patients in the CHEM group with concentration problems and CF-problems were significantly higher than both before and after. In bivariate analyses, the CHEM group had a doubled risk for concentration and CF problems at 3-months (OR 2.6 and 2.1 respectively) compared to the RAD group. However, in multivariate analyses these associations were not significant. Current fatigue was significantly associated with one or more of the cognitive complaints in multivariate analyses at all three time points. In bivariate analyses we identified some significant self-reported QoL predictors before treatment for concentration problems at 12 months, while that hardly was the case for memory problems and CF-problems. However, in multivariate analyses none of these baseline variables remained statistically significant predictors.

Kohli et al [4] described the course of self-reported cognitive complaints (trouble with concentration or memory) from before treatment to 6 months after in a mixed cancer sample of 595 patients (34% men). A peak prevalence of cognitive complaints was found shortly after termination of chemotherapy. For patients treated with radiotherapy no significant change over time in prevalence of cognitive complaints was observed. These results are in agreement with ours. However, Kohli et al observed overall higher prevalence rates than ours, which may be due to the different methods of assessment or to different groups of cancer patients.

At 12-months, one-third of our TCPs had CF-problems, and this proportion was similar to the findings by Schagen et al [6] in TCPs at an average of 3 years after treatment. However, we assessed CF-problems by a questionnaire (the QLQ-C30) while Schagen et al assessed cognitive complaints by an interview.

Our prevalence rates of cognitive complaints at 12 month follow-up in TCPs are lower than the rate found in breast cancer patients interviewed by Shilling et al one year after treatment [5] since approximately 60% of their patients had memory complaints and 40 % had concentration complaints at follow-up. Härtl et al [16] prospectively examined breast cancer patients with QLQ-C30 before start of adjuvant treatment (mixed group of radiotherapy, chemotherapy and/or endocrine therapy) and then at every six months for two years. Most of the QLQ C-30 function scores improved over time, but the mean CF scores in these patients remained stable around a score of 79 points from baseline and during the whole observation period. The comparable mean CF scores in our TCPs were at all times better (range 84-92 points, data not shown) than those found by Härtl et al. In sum, TCPs seem to report less CF-problems than breast cancer patients 12 months post-treatment.

We found that the prevalence of concentration problems and CF-problems was significantly higher at 3 month follow-up in the CHEM versus RAD group compared to before treatment, while the comparable prevalence was similar in both groups at 12 month follow-up and had almost reached the baseline levels. This result indicates that the increase in cognitive complaints is limited to the time period shortly after the end of chemotherapy, and is not a long-term feature. Our results are in some contrast to the findings of the original publication from the EORTC group [10] reporting that 19% of the patients had a worsening of CF-scores from baseline to 2-years follow-up. However, their selection of patients and the study design differed considerably from the current study.

As to the “chemo brain” debate, our probably most important clinical result is the non-significant difference between the CHEM and RAD groups in proportions of patients with existing cognitive complaints at 12-months. Hence, chemotherapy does not seem to exert a long-term negative effect on subjectively experienced cognitive function in TCPs. However, due to previous findings of a low correlation between subjectively and objectively

assessed cognitive function [6;17], prospective studies with objective cognitive measurements are needed to further explore any possible relation between chemotherapy and cognitive function in TCPs.

In multivariate analyses, the treatment modality of our TCPs was not associated with cognitive complaints at any of the 3 time points. Significant pre-treatment predictors for cognitive complaints at 12-months mainly concerned concentration problems and included pre-treatment reduced EF and SF as well as fatigue and neurotoxic symptoms. Among these variables, reduced EF (i.e. anxiety and depression) and fatigue are established [6,17-19], while reduced SF and neurotoxic symptoms represent new findings. The two latter variables could be operating independently, and considering the known peripheral neurotoxic effect of cisplatin in TCPs [20-22] the association with neurotoxic symptoms is an interesting finding which warrants further evaluation in subsequent studies. However, reduced SF and slight neurotoxic symptoms as defined in our study may also reflect a more general personality factor like increased neuroticism [23].

The strength of our study is that we, by our design and selection of patients, could prospectively study the prevalence of cognitive complaints in the *same* 347 TCPs through the whole observation period. Our results are valid for today's patients as the treatment modalities investigated in these EORTC-trials are still in use. Even though self-reported cognitive complaints may not be a sufficient measure to capture "objective" cognitive adverse effect of chemotherapy, knowledge about prevalence and associated factors of self-reported cognitive complaints are important for intervention strategies towards cognitive problems in TCPs. Further, the choice of our patient sample from the 1990-ies minimizes the risk of expectation bias possibly valid in current studies of cognitive complaints after chemotherapy [7,24]. Our TCPs were treated 10-15 years ago, before "chemo brain" was publicly known, and our unbiased results may add some valuable information to the field.

Our study also has several limitations. Firstly, responses to the two cognitive items of the QLQ-C30 represent a very rough measurement of self-experienced cognitive function. Further, by defining the presence of cognitive complaints as a transformed CF-score <100 we might have over-estimated the prevalence of existing cognitive complaints. On the other hand, a main focus was on the differences between the CHEM and the RAD groups which we consider less dependent on our cut-off definitions. Also more important than the prevalence rates are probably the *course* of these rates over time. We find it reassuring that the 12-months prevalence of cognitive complaints almost had returned to baseline levels in both treatment groups.

We have not included the extent of metastases as an independent variable, but all patients in the CHEMO group belonged to the "good prognosis groups" as defined by the International Germ Cell Cancer Collaborative Group [25]. We lacked demographic variables such as level of basic education that has shown a significant association with cognitive function [26]. Our RAD group consisted only of Norwegian patients, while CHEM group also included patients from other European countries mainly from England. Lastly, our sample of 347 TCPs represents only 46% of the patients with valid cognitive data at baseline. However, since cognitive function in the QLQ-C30 is assessed by two questions only, we regarded that imputation was contraindicated in this study.

CONCLUSIONS

For TCPs treated with today's standard chemotherapy during the 1990-ies, the prevalence of self-reported cognitive complaints increased significantly shortly after treatment, and then returned almost to the pre-treatment levels at 12 month follow-up. In multivariate analyses considering important QoL domains such as emotional and social function, fatigue

and insomnia, treatment modality was not significantly associated with cognitive complaints at any time point.

Regardless of their etiology, cognitive complaints in TCSs may have considerable consequences for the QoL and functioning in education and work life. In order to reduce distress related to cognitive complaints, the evaluation and treatment of emotional distress and fatigue seem particularly relevant.

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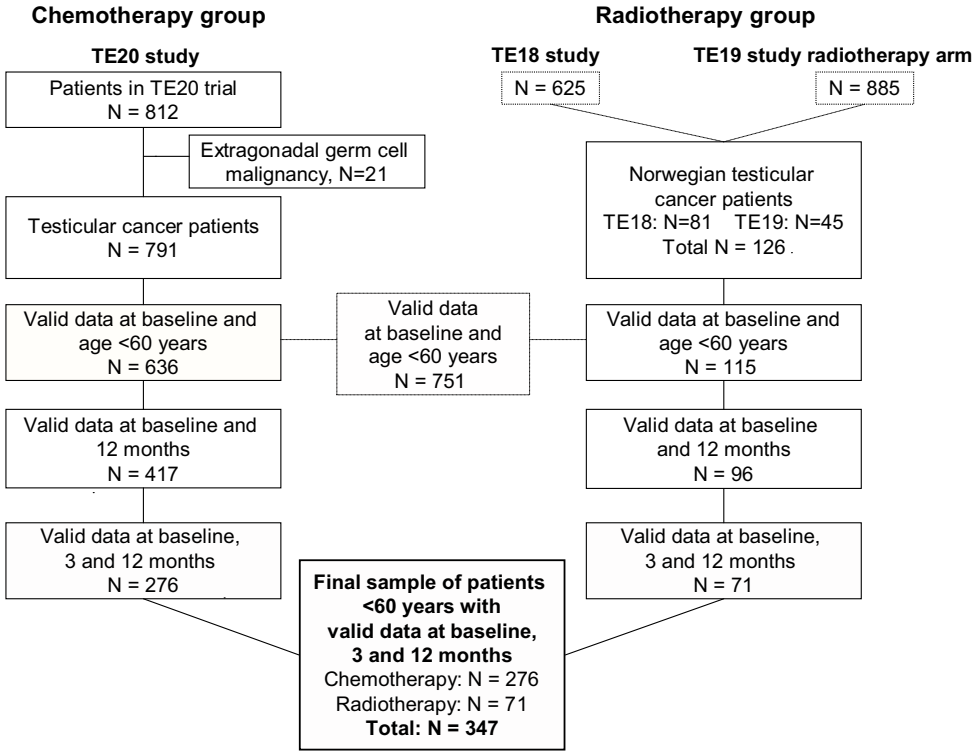
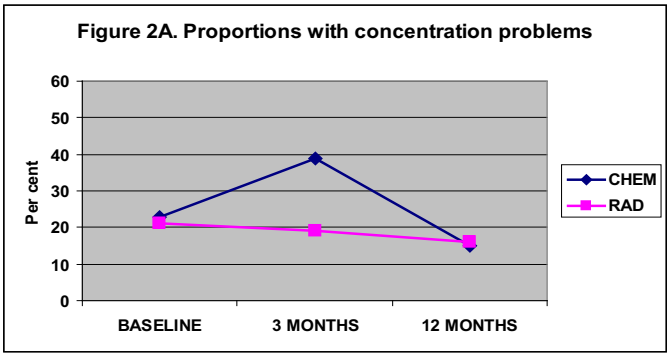
Conflicts of interest: None of the authors have any conflicts of interest.

Figure 1. Patients in the study



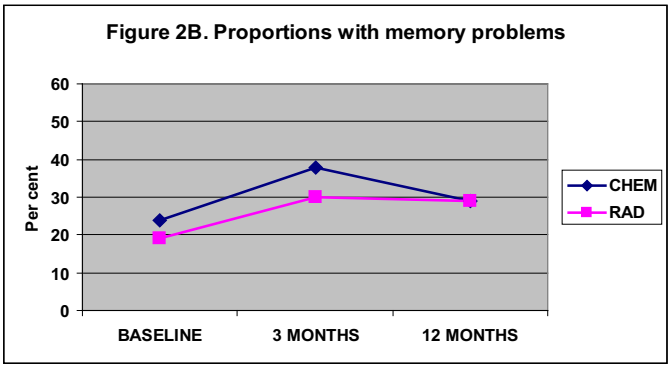
Valid data: Patients who delivered questionnaire in defined time-window and had filled in both cognitive items (#20 and #25) of the EORTC QLQ-C30



2A. Statistical significance legend:

At 3 months the proportion with concentration problems in the CHEM group was significantly higher than in the RAD group.

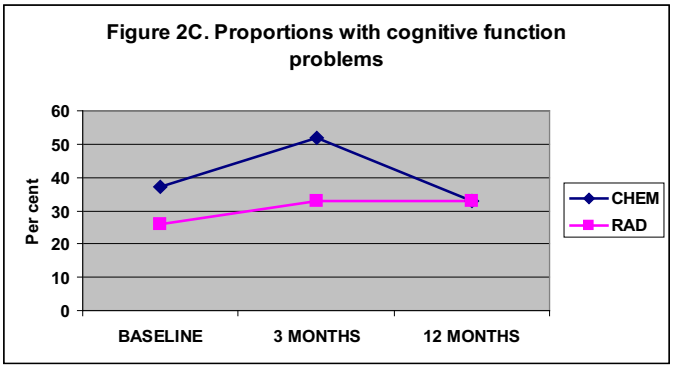
The proportion of the CHEM group with concentration problems at 3 months was significantly higher than at baseline and 12 months.



2B. Statistical significance legend:

At 3 months the proportion with memory problems in the CHEM and RAD groups did not differ significantly.

The proportion of the CHEM group with concentration problems at 3 months did not significantly differ from baseline or 12 months.



2C. Statistical significance legend:

At 3 months the proportion with cognitive function problems was significantly higher in the CHEM compared to the RAD group.

The proportion of the CHEM group with cognitive function problems was significantly higher at 3 months than at baseline and 12 months.

Table 1. Distributions of scores on the outcome measures (cognitive complaints) in the chemotherapy group (CHEM, n=276) and in radiotherapy group (RAD, n=71) at the tree time points.

	Before treatment		3 months		12 months	
Outcome measures	**CHEM**	**RAD**	**CHEM**	**RAD**	**CHEM**	**RAD**
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*
Concentration problems						
Not at all	*213 (77)*	*56 (79)*	*169 (61)*	*57 (80)*	*234 (85)*	*60 (85)*
A little	52 (19)	11 (16)	85 (31)	12 (17)	32 (12)	10 (14)
Quite a bit	7 (3)	4 (5)	16 (6)	2 (3)	10 (3)	1 (1)
Very much	4 (1)	0 (0)	6 (2)	0 (0)	0 (0)	0 (0)
Memory problems						
Not at all	*211 (76)*	*57 (80)*	*170 (62)*	*49 (69)*	*197 (71)*	*50 (70)*
A little	52 (19)	12 (17)	81 (29)	18 (25)	65 (24)	17 (24)
Quite a bit	7 (3)	2 (3)	21 (8)	4 (6)	13 (5)	3 (4)
Very much	4 (1)	0 (0)	4 (1)	0 (0)	1 (0)	1 (2)
Cognitive function						
100.00 (best)	*174 (63)*	*52 (73)*	*132 (48)*	*47 (66)*	*184 (67)*	*48 (67)*
83.33	62 (23)	7 (10)	66 (24)	12 (17)	58 (21)	14 (20)
66.67	30 (11)	8 (11)	49 (18)	8 (11)	20 (7)	5 (7)
50.00	5 (2)	4 (6)	16 (6)	2 (3)	9 (3)	2 (3)
33.33	3 (1)	0 (0)	8 (3)	2 (3)	4 (2)	2 (3)
16.67	1 (0)	0 (0)	4 (1)	0 (0)	1 (0)	0 (0)
0.00 (worst)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 2. Self-reported quality of life functions and symptoms before treatment and at 3 and 12 months in the chemotherapy group (CHEM, n=276) and the radiotherapy group (RAD, n=71)

Independent variables	Before treatment		3 months		12 months	
	CHEM	**RAD**	**CHEM**	**RAD**	**CHEM**	**RAD**
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*
EORTC QLQ-C30 functions						
Reduced emotional function	114 (41)	24 (34)	**103 (37)***	**12 (12)**	53 (19)	10 (14)
Reduced role function	95 (34)	26 (37)	**178 (65)**	**15 (21)**	50 (18)	8 (11)
Reduced social function	91 (33)	30 (42)	**144 (52)**	**15 (21)**	39 (14)	13 (18)
EORTC QLQ-C30 symptoms						
Presence of fatigue	128 (46)	39 (55)	**217 (79)**	**37 (52)**	101 (37)	33 (47)
Presence of insomnia	125 (45)	26 (36)	103 (37)	17 (24)	83 (30)	23 (32)
TC module symptoms						
Neurotoxic symptoms	14 (5)	4 (6)	**115 (42)**	**9 (13)**	**63 (22)**	**6 (9)**

*Statistical significant differences ($p<0.01$) on an item between the CHEM and the RAD group at that time point in **bold fonts**

Table 3. Bivariate and multivariate regression analyses with relevant independent variables at the three time points and concentration problems, memory problems and cognitive function (CF) problems as dependent variables

Independent variables	Before treatment			3 months			12 months		
	Concentration	***Memory***	***CF***	***Concentration***	***Memory***	***CF***	***Concentration***	***Memory***	***CF***
Crude association	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*O (95% CI)*	*OR (95% CI)*
CHEM (RAD = reference)	1.1 (0.6–2.1)	1.3 (0.7-2.4)	1.6 (0.9-2.9)	**2.6 (1.4-4.9)***	1.4 (0.8-2.4)	**2.1 (1.2-3.7)**	1.0 (0.5-2.0)	1.0 (0.5-1.7)	1.0 (0.6-1.8)
Adjusted associations									
CHEM/RAD	1.2 (0.6-5.5)	1.3 (0.7-2.7)	1.8 (0.9-3.5)	1.3 (0.6-2.8)	0.8 (0.4-1.6)	1.1 (0.6-2.2)	1.1 (0.5-2.7)	1.1 (0.5-2.1)	1.2 (0.6-2.3)
Reduced function[a] *:*									
Emotional	**4.4 (2.3-8.3)**	2.0 (1.1-3.6)	**3.9 (2.3-6.8)**	**2.3 (1.3-4.0)**	1.5 (0.9-2.6)	1.5 (0.9-2.7)	1.9 (0.8-4.3)	0.7 (0.3-1.6)	0.8 (0.4-1.8)
Role	0.5 (0.2-1.1)	1.2 (0.6-2.3)	0.9 (0.5-1.7)	0.9 (0.5-1.6)	1.5 (0.9-2.5)	1.0 (0.6-1.8)	2.0 (0.8-4.8)	1.1 (0.5-2.4)	1.3 (0.6-2.7)
Social	2.2 (1.1-4.2)	1.0 (0.5-1.9)	1.2 (0.6-2.2)	**2.6 (1.5-4.7)**	2.0 (1.2-3.5)	**2.8 (1.6-4.8)**	2.5 (1.1-5.8)	**4.0 (1.9-8.4)**	**3.9 (1.8-8.3)**
Symptoms present[b]									
Fatigue	**3.2 (1.6-6.5)**	2.2 (1.1-4.2)	**3.0 (1.7-5.4)**	**4.3 (1.8-10.3)**	1.7 (0.9-3.3)	**2.4 (1.3-4.7)**	2.8 (1.2-6.6)	**3.4 (1.8-6.3)**	**3.0 (1.6-5.4)**
Insomnia	1.3 (0.7-2.5)	1.6 (0.9-3.0)	1.5 (0.9-2.6)	**2.7 (1.5-4.7)**	**2.4 (1.4-4.1)**	**4.1 (2.3-7.2)**	2.8 (1.3-6.2)	1.9 (1.0-3.5)	**2.2 (1.2-4.0)**
Neurotoxicity	1.7 (0.6-4.9)	2.2 (0.8-6.2)	1.3 (0.4-3.9)	1.1 (0.3-3.2)	1.0 (0.3-2.9)	0.8 (0.3-2.6)	0.7 (0.3-1.7)	1.9 (1.0-3.7)	1.7 (0.9-3.2)

* Statistical significant association ($p<0.01$) in **bold fonts**

[a] Dichotomized into good function (score ≥75 = reference) or reduced function (score <75)

[b] Symptom absent (score ≤16.67 = reference) or present (score >16.67)

Table 4. Bivariate and multivariate regression analyses with relevant independent variables before treatment and concentration problems, memory problems and cognitive function (CF) problems at 12 month follow-up as dependent variables

Independent variables	Concentration problem		Memory problem		CF-problem	
	Bivariate	***Multivariate***	***Bivariate***	***Multivariate***	***Bivariate***	***Multivariate***
	OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*	*OR (95% CI)*
CHEM (RAD = reference)	1.0 (0.5-2.0)	1.2 (0.5-2.5)	1.0 (0.5-1.7)	1.0 (0.6-1.9)	1.0 (0.6-1.8)	1.1 (0.6-2.1)
Reduced function[a] *:*						
Emotional	**2.7 (1.5-4.9)***	1.7 (0.9-3.4)	1.6 (1.0-2.6)	1.3 (0.8-2.2)	**1.8 (1.2-2.9)**	1.4 (0.8-2.3)
Role	2.0 (1.1-3.6)	0.9 (0.4-2.0)	1.5 (0.9-2.3)	1.1 (0.6-2.0)	1.3 (0.9-2.2)	0.9 (0.5-1.6)
Social	**2.2 (1.2-4.0)**	1.5 (0.7-3.0)	1.1 (0.7-1.8)	0.7 (0.4-1.3)	1.4 (0.9-2.2)	1.0 (0.6-1.8)
Presence of symptoms[b]						
Fatigue	**2.4 (1.3-4.4)**	2.0 (0.9-4.1)	1.7 (1.1-2.8)	1.7 (1.0-3.0)	1.7 (1.1-2.7)	1.6 (1.0-2.8)
Insomnia	1.6 (0.9-3.0)	1.0 (0.5-1.9)	1.7 (1.1-2.7)	1.3 (0.7-2.1)	1.7 (1.1-2.6)	1.2 (0.7-2.0)
Neurotoxic symptoms	**3.9 (1.4-10.5)**	2.3 (0.8-6.6)	2.0 (0.8-5.2)	1.4 (0.5-3.8)	2.6 (1.0-6.7)	1.8 (0.6-4.8)

* Statistical significant association ($p<0.01$) in **bold fonts**

[a] Dichotomized into good function (score ≥75 = reference) or reduced function (score <75)

[b] Symptom absent (score ≤16.67 = reference) or present (score >16.67)

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II

III

Original article

A prospective study of neuropsychological functioning in testicular cancer patients

T. Skaali[1], S. D. Fosså[1], S. Andersson[2], M. Cvancarova[1], C.W. Langberg[3], G. Lehne[4], A. A. Dahl[1]

[1] National Resource Center for Late Effects, Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, and The University of Oslo, Oslo, Norway

[2] Department of Neuropsychiatry and Psychosomatic Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway

[3] Department of Oncology, Oslo University Hospital, Ullevål Hospital, Oslo, Norway

[4] Department of Oncology, Oslo University Hospital, The Norwegian Radiumhospital, Oslo, Norway

Corresponding author:

Tone Skaali, MD

National Resource Center for Late Effects,

Department of Oncology, Oslo University Hospital,

The Norwegian Radium Hospital,

Postboks 4953 Nydalen,

N-0424 Oslo, Norway

Fax: +47 22934553 Phone: +47 22934000

E-mail: Tone.Skaali@oslo-universitetssykehus.no

SUMMARY

BACKGROUND: Whether systemic chemotherapy has a negative effect on cognitive function in patients, concern oncologists. In testicular cancer patients (TCPs) treated with cisplatin-based chemotherapy, only few cross-sectional studies have addressed this concern. We prospectively studied neuropsychological functioning in TCPs.

PATIENTS AND METHODS: In a consecutive sampling, 122 TCPs were examined at baseline (after orchidectomy, before any additional treatment) and then at follow-up a median of 12 months after end of treatment. The examinations included a neuropsychological test battery, interview on background variables, and questionnaires on mental distress, fatigue and neurotoxic symptoms. Changes in neuropsychological functioning from baseline to follow-up were compared between three treatments groups: no chemotherapy (N=31), one cycle of chemotherapy (N=38), and two or more cycles of chemotherapy (N=53). Variables associated with a decline in neuropsychological test performance from baseline to follow-up were explored.

RESULTS: No statistically significant differences in proportions of TCPs with a decline in neuropsychological test performance were observed between the three treatment groups. Decline in neuropsychological test performance was not associated with demographic variables, distress, fatigue, or with chemotherapy.

CONCLUSION: No negative effect of systemic chemotherapy on neuropsychological test performance in TCPs at one-year follow-up was found in this study.

Key words: chemotherapy, cognitive function, neuropsychological functioning, neurotoxicity, prospective study, testicular cancer patients

INTRODUCTION

Eventual negative effects of systemic chemotherapy on cognitive function (CF) in cancer patients have been investigated during the last decades [1,2]. Most studies concern breast cancer patients [2-8] and have shown divergent results regarding the association between systemic chemotherapy and reduced neuropsychological test performance. However, subtle post-treatment neuropsychological reduction has been observed in a small subgroup of breast cancer patients, possibly related to chemotherapy and/or hormonal factors [1,2].

More prospective neuropsychological studies of CF after different regimens of chemotherapy have been requested [1,9]. Neuropsychological function in testicular cancer patients (TCPs) several years after cisplatin-based chemotherapy has so far been examined in two cross-sectional studies [10,11]. Schagen et al. [10] found that significantly more TCPs treated with chemotherapy showed reduced neuropsychological test performance compared with those with no treatment after orchidectomy. No significant difference in proportions with reduced test performance was observed between TCPs treated with chemotherapy or with radiotherapy. In contrast, Pedersen et al. [11] observed no difference in neuropsychological test performance between TCPs treated with chemotherapy or not.

We conducted a prospective study of neuropsychological functioning in a consecutive Norwegian sample of TCPs. Evaluation of CF was done after orchidectomy prior to any additional treatment (baseline) and then at one year after end of treatment (follow-up). The aims of the study were: 1) To compare *changes* from baseline to follow-up of neuropsychological test performance in TCPs exposed to three different treatment modalities: no chemotherapy, one cycle of chemotherapy, and multiple cycles of chemotherapy; 2) To study *variables* associated with a decline in neuropsychological test performance from baseline to follow-up.

PATIENTS AND METHODS

Patients and treatment

Newly orchidectomized TCPs aged 18 to 60 years evaluated at two university hospital (the Norwegian Radium Hospital and Ullevål Hospital) between 2006 and 2008 were invited to participate in this prospective study. Exclusion criteria were: 1) Severe mental disorders like psychoses or substance dependence disorders; 2) Degenerative brain disease or previous severe brain trauma; 3) Brain metastases or severe somatic dysfunction; or 4) Lacking proficiency of Norwegian language.

Information about *histology*, *stage* of testicular cancer (TC) [12], *risk-adapted treatment* and *follow-up time* (months from end of treatment to follow-up evaluation) was obtained from the medical records.

Data collection

At both time points TCPs had neuropsychological testing, questionnaires and a semi-structured interview on background and self-reported CF (separate paper). The evaluations took 90-120 minutes and were performed by the first author. The baseline evaluation was done prior to any additional treatment, and the follow-up evaluation was scheduled to a regular out-patient visit approximately 12 months after end of chemotherapy or start of surveillance (or radiotherapy).

Neuropsychological test battery Verbal learning and memory, motor function, psychomotor speed and executive functions were assessed with traditional neuropsychological tests [13-16].Visual learning and memory, attention and working memory were assessed with computer tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) [17-19]. The *basic* test battery consisted of 8 tests yielding 15 sub-test measures (Table 1).

At baseline if time allowed and the patients were motivated, the *basic* test battery was supplemented with two more CANTAB-tests of executive function [18,19], which yielded additional three sub-test measures. Hence, the *total* test battery included 18 measures: 15 basic and three supplementary ones (Table 1). The same tests were given both at baseline and follow-up. To minimize practice effects from repeated testing, alternate test versions were used if available and employed on the two learning/memory-tests and one of the executive tests.

Intellectual functioning was estimated at baseline by the Norwegian version of the National Adult Reading Test (NART) [20,21], where a lower score indicates better intellectual functioning (range 0-50).

The psychological response to the trauma of getting TC was assessed with the *Impact of Event Scale* (IES) [22] which covered *intrusion* [7 items; Cronbach's α=0.90(baseline)/0.86 (follow-up)] and *avoidance* (8 items, α=0.78/0.85) within the past week. Each item was rated from 0 (not at all) to 5 (often), with higher scores denoting more distress. An IES-total score of >26 was the cut-off for clinically significant distress [23], and changes in dichotomized IES-total score from baseline to follow-up was noted.

The *Fatigue Questionnaire* [24] provided scores for physical and mental fatigue items that are summed up as total fatigue with Cronbach's α=0.82(baseline)/0.88(follow-up). Each of the 11 items was rated from 0 (less) to 3 (much more), so total fatigue ranged from 0 (low) to 33 (high). Increase of total fatigue was defined if total score was ≥ 3 points higher at follow-up compared to baseline (≈10% change on scale).

Scale for Chemotherapy-Induced Neurotoxicity [25] assessed symptoms of *peripheral neuropathy*, *Raynaud's phenomenon* and *ototoxicity* on 4-point scales from 1 (no symptoms) to 4 (much symptoms). Item-scores were dichotomized into *symptoms* (score 3

or 4) vs. *no symptoms* (score 1 or 2). *Increase of neurotoxic symptoms* was defined as a change from *no symptoms* to *symptoms* from baseline to follow-up.

Neuroticism is a basic personality trait covering the tendency to be nervous and was rated at baseline with 6 items of an 18-items version of the *Eysenck Personality Questionnaire* [26,27]. The sum-scores ranged from 0 (low) to 6 (high), and Cronbach's α was 0.54.

Alcohol use at baseline was assessed with a 4-items version the of the *CAGE questionnaire* [28], with sum-scores ranging from 0 (low) to 4 (high). A sum-score of ≥2 defined a possibly hazardous alcohol use.

Other variables: The level of *education* was dichotomized into ≤12 years and >12 years of completed basic education. *Paired relation* consisted of those being married or cohabiting. *Employment status* was categorized as working, being full-time student, or not working (long-term sickness leave, disability pension or unemployed). *Mental problems before TC* were defined as requiring help from medical professionals or the use of psychotropic medication at least once.

Data management and statistics

General

Data were analyzed with the SPSS PC version 16.0 (SPSS Inc, Chicago IL), using standard descriptive measures, parametric and non-parametric tests as appropriate. Pearson's chi-square and Fisher's exact tests were used to compare categorical variables between groups. Cronbach's coefficient α described internal consistency. Bivariate correlations were examined with Pearson's coefficient r. Due to the explorative nature of this study, the significance level was not corrected for multiple testing, and p-values<0.05 indicated statistical significance. All tests were two-sided.

Neuropsychological test scores

Raw-scores on the neuropsychological tests at baseline and follow-up were compared across treatment groups with the Kruskall-Wallis test. Changes in raw-scores (follow-up score subtracted from baseline score) were compared with analyses of covariance (ANCOVAs) with *age at baseline* and *follow-up time* as covariates.

In addition to analyses on the group level, we performed analyses of changes in the individual patients [9] using a standardized regression-based model (SRB) [29,30], which allowed adjustment of the neuropsychological test findings for relevant covariates. The SRB-model utilizes the baseline and follow-up scores of the control group (no chemotherapy group in our study) to derive regression equations that predict an individual's follow-up score on a test-measure based on his baseline-score and selected covariates. Due to limited group sizes, only age and estimated intelligence (NART-score) were used as covariates. Some neuropsychological test-scores were logarithmic or square-root transformed to achieve a better model fit.

Applying SRB, a predicted follow-up score on each test-measure for each individual was obtained. An individual *z-score of change* was then obtained *for each test-measure* by subtracting the person's actual follow-up score from the predicted score and dividing the difference by the standard error of estimate (derived from the control group). The obtained z-score represented the standardized magnitude and direction of the difference between the expected and the actual follow-up score. A z-score outside ±1.64 was defined as a *reliable decline or improvement from baseline to follow-up* on the reported test-measure.

Cognitive domain z-scores of change were computed by averaging the z-scores of change for all test-measures of a given cognitive domain in each individual (see Table 1 for

test-measures in each cognitive domain). These *domain z-scores of change* were compared across treatment group using analyses of variance (ANOVAs).

Definition of individual change

There are no established cut-off values in the literature concerning the proportion of declined or improved test-measures needed in order to define a relevant individual *change* in neuropsychological performance over time. Studies inclusive like those by Jenkins et al. [6] and Stewart et al. [7] have defined decline/improvement when reliable change appeared on *two* or more test-measures. However, since the number of measures varied from 14 to 23 in these studies, that definition imply variable proportions (15% and 8%, respectively) of the number of test-measures.

We defined that individual *decline* had occurred with reliable decline on ≥10 % of our test-measures, and individual *improvement* correspondingly. We also assessed individual changes using 15% as a cut-off to examine the consequences of our chosen proportion. Finally, we explored the relationship between the proportion of test-measures with decline and improvement for each individual. If the proportion of test-measures with decline was ≥10% larger than the proportion with improvement, the individual was defined as showing *overall decline* in neuropsychological test performance.

The *proportions* of patients with individual *decline*, *improvement* and *overall decline* with the various definitions described above were compared across the treatment groups. All analyses were performed both on the *total* test battery (18 test-measures), and on the *basic* test battery (15 test-measures).

Ethics

The study was approved by the Ethical Committee of the Southern Health Region of Norway and the National Data Inspectorate. All patients delivered a written informed consent.

RESULTS

Patients

Among 202 eligible TCPs, 129 (64%) were recruited at baseline. Non-inclusion was due to administrative reasons or declination by the patients. Attrition analyses showed no significant differences between included and non-included patients concerning age or stage of TC at diagnosis.

At follow-up examination (median 12 months, range 8-23 months after end of chemotherapy/start of surveillance), 122 disease-free TCPs (95% follow-up rate) were re-evaluated. Seven patients were lost to follow-up: three patients denied re-evaluation, one had moved abroad and three were excluded due to development of mental disorders or somatic diseases. The sizes of the treatment groups at follow-up were: NO-CHEMO group (N=31) (including one patient with radiotherapy only); ONE-CHEMO group (N=38) and MULTIPLE-CHEMO group (N=53), with 33 patients having 3 or 4 cycles with bleomycin, etoposide and cisplatin (BEP, Table 2). Among 122 TCPs, 89 (73%) were tested with supplementary neuropsychological tests.

Age at baseline was significantly higher in the ONE-CHEMO group compared to the NO-CHEMO and the MULTIPLE-CHEMO group (Table 2). No statistically significant group differences were found for follow-up time, NART-score, level of education or other demographic variables (Table 2).

The two chemotherapy groups had significantly higher total-fatigue score than the NO-CHEMO group both at baseline and follow-up. Presence of neurotoxic symptoms did not differ significantly across treatment groups at baseline, while at follow-up a larger proportion of the MULTIPLE-CHEMO group had Raynaud-like symptoms compared to the other groups (Table 2).

Changes in neuropsychological test performance

Group analyses

There were no significant group differences on raw-scores at baseline or follow-up on any of the 18 test-measures (Table 3), except that the NO-CHEMO group had significantly fewer errors on the Spatial Working Memory test at baseline compared with the two other groups. Further, no significant group differences were found for *change* in raw-scores (adjusted for age and follow-up time) of any of the 18 test-measures (Table 3).

Individual analyses

In the control (NO-CHEMO) group, the correlation coefficients between baseline and follow-up test scores used for deriving the SRB-models ranged between r=0.48 and r=0.90 (Table 4). The proportions of patients that exhibited reliable *decline* on any of the 18 test-measures ranged from 0% to 23%, whereas the proportions of patients that exhibited reliable *improvement* ranged from 0% to 39% (Table 4). The proportions of TCPs in all treatment groups (inclusive the subgroup with 3 or 4 BEP) showing reliable decline/improvement on each of the test-measures are listed in Table 4.

No significant group differences in *cognitive domain z-scores of change* were found for any of the five cognitive domains studied (data not shown).

No statistically significant group differences were observed in proportions with individual *decline* on ≥10% of the test-measures or *overall decline* (Table 5). However, significantly larger proportions in the ONE and the MULTIPLE-groups showed *improvement* on ≥10% of the tests compared to the NO-CHEMO group. Employing the 15% cut-off did not significantly change these results, except no significant difference was found between the NO- and the ONE-CHEMO groups concerning proportions with improvement (Table 5). When the above analyses were performed on the dataset from the *basic* test battery only (15 measures), no substantial different results were observed.

Sub-analyses showed no significant differences between the group of TCPs with 3-4 BEP and the NO-CHEMO group in proportions with individual *decline* and *overall decline*, while the 3-4 BEP group had significantly larger proportions with individual *improvement* than the NO-CHEMO group (Table 5).

Variables associated with a decline in neuropsychological test performance

A significantly larger proportion of the 42 TCPs that exhibited decline on ≥10% of the neuropsychological test-measures reported worsening of tinnitus/hearing loss compared with those without such decline, while no such association was found for peripheral neuropathic or Raynaud-like symptoms (Table 6). None of the demographic variables (age, education or NART-score) or cancer-related variables (given chemotherapy, metastatic disease or follow-up time) were significantly associated with a decline in neuropsychological test performance, neither were scores (or change-scores) of mental distress or fatigue (Table 6).

DISCUSSION

In this prospective study, we found no statistically significant difference across treatment groups in proportions of TCPs with a decline in neuropsychological test performance from baseline to median one-year follow-up after end of treatment. Decline in neuropsychological test performance was not significantly associated with chemotherapy. Hence, we did not find any evidence that BEP-chemotherapy has a detrimental effect on neuropsychological functioning one year after treatment.

Cisplatin has a known peripheral neurotoxic effect [25,31], and it has also been detected in the central nervous system (CNS) after systemic administration [32]. Therefore our result of no significant association between multiple chemotherapy cycles and decline in neuropsychological test performance seems reassuring for the patients. Our results are in concordance with the cross-sectional findings by Pedersen et al. [11]. However, presuming any transitory effect of cisplatin on the CNS, our results could have been different if cognitive testing had been performed closer to the end of treatment. Long-term functioning is, though, of larger clinical importance for the patients than short-term. Further, our group sizes were relatively small, so we could have missed small statistically significant group differences concerning decline of performance due to type II errors. However, such differences regularly have little clinical significance. Counter-intuitively, we did find that the two chemotherapy groups had significant larger proportions with *improvement*; but we hardly believe that chemotherapy has a positive effect on cognitive function. As shown in table 3, there were no significant group differences for raw-scores of tests neither at baseline (except one), at follow-up, or for change-scores between baseline and follow-up.

Research on CF after breast cancer has observed reduced functioning on several cognitive domains including attention, memory and processing speed [2]. This contrasts

with our findings **since** we did not identify any specific cognitive domain affected by chemotherapy in TCPs.

None of the chosen demographic or cancer-related variables, except from increase in self-reported ototoxic symptoms, were significantly associated with a decline in neuropsychological test performance. Ototoxic symptoms (tinnitus / hearing loss) are well-known neurotoxic effects of cisplatin-based chemotherapy [31], but most probably this is a spurious finding due to multiple testing that eventually should be explored in future studies. It would also be of clinical importance to further elaborate if a decline in neuropsychological test performance corresponded to the patients' own report of change in CF.

Current level of mental distress may interfere with neuropsychological test performance [33]. Hence, a change in distress-level from baseline to follow-up could possibly imply changes in neuropsychological performance between the two time points [30]. In spite of this, we chose not to include distress-score as a covariate in the SRB-models due to relatively small group sizes implying allowance for few covariates. The relation between a change in distress-score and decline in neuropsychological test performance was explored separately, and no significant association was found.

A small subset of TCPs may have reduced testosterone level [34], and testosterone deficiency is associated with reduced cognitive function in older men [35]. Hence, the possible impact of testosterone level on neuropsychological functioning in TCPs warrants investigation in future studies.

Our study has several strengths. We included a consecutive sample of TCPs and evaluated CF prospectively. TCPs without any chemotherapy constituted a suitable control group, and the drop-out rate from baseline to follow-up was low. The prospective design

enabled us to apply recommended statistical methods for assessing individual changes in neuropsychological test performance [9,30].

There are some limitations, however. After initiation we realized that the *total* test-battery was too comprehensive for some patients. We therefore defined a *basic* test-battery and made two relatively time-consuming tests of executive function supplementary. We also had some missing data on some of the other tests. Altogether this complicated the analyses; however by defining individual decline and improvement with proportions instead of with absolute number of test-measures, this problem was mostly overcome. Since a portion of patients of the MULTIPLE-CHEMO group received only two cycles of chemotherapy or had additional chemotherapy (14 had 2 x BEP, three had no bleomycin, and three additional chemotherapy to BEP), we performed a sub-analysis comparing proportions with a decline in test performance between the group with 3 or 4 BEP and the NO-CHEMO group. No significant difference emerged. Lastly, the SRB method is based on the assumption that the control group is representative. However, the size of our control group was limited which may have influenced our results.

CONCLUSIONS

Results from this prospective study indicate that systemic chemotherapy does not have a negative effect on neuropsychological test performance in TCPs one year after end of treatment. These findings should be replicated in larger studies before a final conclusion can be made. However, our results seem reassuring for TCPs awaiting cisplatin-based chemotherapy.

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Disclosure

None of the authors have any conflicts of interest.

Table 1. Description of neuropsychological methods and test-measures

Cognitive domain	Neuropsychological test	Cognitive function assessed	Sub-test measure
Learning / memory	Hopkins Verbal Learning Test-Revised (HVLT-R) [13]	Verbal learning Verbal memory	*Learning /acquisition* (total words) *Delayed recall* (percent retained)
	Paired Associates Learning (PAL)[a] [19]	Visual learning /memory	*Total errors 6 shapes*
Attention / concentration / working memory	Spatial Working Memory (SWM)[a] [19]	Visuo-spatial working memory Strategy	*Between errors* (total errors) *Strategy* (efficiency)
	Choice Reaction Time (CRT)[a] [19]	Speed of choice response	*Mean latency* (time)
Motor function	Grooved Pegboard (GP) [14]	Visual-motor coordination and speed	*Dominant hand* (time) *Non-dominant hand* (time)
Psychomotor speed	Trail Making Test (TMT)A [14]	Psychomotor speed	*TMT-A* (time)
	Color-Word Interference Test (CW) 1+2 [15]	Psychomotor speed - naming Psychomotor speed - reading	*CW-1* (time) *CW-2* (time)
Executive function	Color-Word Interference Test (CW) 3+4 [15]	Response inhibition Response inhibition and shifting	*CW-3* (time) *CW-4* (time)
	Trail Making Test (TMT)B [14]	Set-shifting	*TMT-B* (time)
	Word fluency (FAS) [16]	Controlled oral association ability	*Total words*
	Stockings of Cambridge (SOC)[a,b] [19]	Spatial planning /motor control	*Mean initial thinking time* *Problems solved in minimum moves*
	Intra-Extra Dimensional Set Shift (IED)[a,b] [19]	Rule acquisition /set-shifting	*Total errors (adjusted for completed stages)*

[a] computerized test
[b] supplementary executive test

Table 2. Characteristics of the sample (and of each treatment group for selected variables or if statistically significant group differences)

	TOTAL *N=122*	**NO-CHEMO** *N=31*	**ONE-CHEMO** *N=38*	**MULTIPLE-CHEMO** *N=53*
Age at baseline (years), median [range]*	32.5 [19-60]	**32 [21-60]**	**35 [23-52]**	**30 [19-60]**
Follow-up time (months[a]), median [range]	12 [8-23]	12 [10-21]	12 [9-23]	12 [8-20]
NART-score, mean (SD) [range]	17.9 (8.0) [3-37]	17.6 (7.6) [5-36]	18.2 (7.2) [4-33]	17.9 (8.8) [3-37]
	N (%)		*N (%)*	
*Histology**				
Seminoma / Non-seminoma (or mix sem/non-sem)	62 (51) / 60 (49)	**20 (65) / 11 (35)**	**32 (84) / 6 (16)**	**10 (19) / 43 (81)**
*TC-stage according to treatment**				
Stage I / Stage II-IV[b]	88 (72) / 34 (28)	**30 (97) / 1 (3)**	**38 (100) / 0**	**20 (38) / 33 (62)**
Treatment modalities				
Surveillance / Radiotherapy only	30 (25) / 1 (1)	30 (97) / 1 (3)	- / -	- / -
Chemotherapies				
Carboplatin x 1	34 (28)	-	34 (90)	-
Bleomycin, Etoposide and Cisplatin (BEP) x 1	4 (3)	-	4 (10)	-
Etoposide and Cisplatin (EP) x 2	3 (2)	-	-	3 (6)
BEP x 2	14 (12)	-	-	14 (26)
BEP x 3	27 (22)	-	-	27 (51)
BEP x 4	6 (5)	-	-	6 (11)
BEP x 4 + additional chemotherapy	3 (2)	-	-	3 (6)
Retroperitoneal lymph node dissection	24 (20)	0	0	24 (45)
Neurotoxic symptoms (SCIN)				
Peripheral neuropathy, baseline / follow-up[c,d]	5 (4) / 18 (15)	1 (3) / 3 (10)	3 (8) / 6 (16)	1 (2) / 9 (17)
Raynaud-like symptoms, baseline / **follow-up**[c,d]*	11 (9) / 31 (25)	4 (13) / **1 (3)**	3 (8) / **5 (13)**	4 (8) / **25 (48)**
Tinnitus or hearing loss, baseline / follow-up[c,d]	11 (9) / 23 (19)	2 (7) / 2 (7)	6 (16) / 10 (26)	3 (6) / 11 (21)

	Mean (SD)	*Mean (SD)*		
Fatigue Questionnaire total score **Baseline* / Follow-up***[d]	13.7 (3.7) / 13.4 (4.7)	**12.2 (3.5) / 11.4 (3.5)**	**14.8 (4.2) / 14.0 (4.2)**	**13.8 (3.1) / 14.3 (5.3)**
Impact of Event Scale (IES) total score Baseline / Follow-up[d]	17.8 (12.2) / 14.0 (10.8)			
Neuroticism score (Baseline)	1.6 (1.5)			
	N (%)			
Education level Baseline / Follow-up				
≤12 years	63 (52) / 60 (49)			
>12 years	59 (48) / 62 (51)			
Paired relation Baseline / Follow-up	77 (63) / 86 (71)			
Employment status Baseline / Follow-up				
In work	106 (87) / 101 (83)			
Student	9 (7) / 10 (8)			
Not working	7 (6) / 11 (9))			
Mental problems before TC	30 (25)			
Possibly hazardous alcohol-use (Baseline)	27 (22)			
IES total score >26 Baseline / Follow-up[d]	26 (21) / 19 (16)			

* statistically significant difference ($p<0.05$) across treatment groups; values marked in **bold** fonts
[a] months from end of chemotherapy/start of surveillance (or radiotherapy) to the follow-up evaluation
[b] includes one patient with advanced extra-gonadal germ cell tumor
[c] N=30 in NO-CHEMO group
[d] N=52 in MULTIPLE-CHEMO group

Table 3. Raw-scores of the neuropsychological test-measures at baseline and follow-up

		Baseline				Follow-up				Change[a]
Test measure	**N[b]**	**NO CHEMO**	**ONE CHEMO**	**MULTIPLE CHEMO**	***p-value*[c]**	**NO CHEMO**	**ONE CHEMO**	**MULTIPLE CHEMO**	***p-value*[c]**	***p-value*[d]**
HVLT-R Total words[e]	117	29.3 (3.5)	29.3 (3.8)	28.2 (3.9)	*0.24*	27.6 (2.8)	28.0 (4.2)	27.4 (3.2)	*0.67*	0.54
HVLT-R Delayed recall (%)[e]	115	94.1 (13.1)	93.2 (11.8)	91.9 (10.7)	*0.53*	93.7 (10.0)	94.6 (11.4)	96.0 (10.8)	*0.65*	0.35
PAL Errors 6 shapes	120	3.8 (8.3)	2.6 (3.1)	4.2 (5.6)	*0.23*	3.8 (3.2)	5.2 (6.4)	5.3 (4.9)	*0.42*	0.26
SWM Between errors	121	8.0 (9.1)	14.1 (13.1)	13.9 (12.6)	***0.04***	8.7 (9.3)	10.2 (10.9)	11.3 (12.8)	*0.80*	0.22
SWM Strategy	121	27.4 (6.0)	28.4 (5.7)	27.9 (5.5)	*0.71*	26.6 (6.5)	26.2 (5.7)	26.6 (5.9)	*0.93*	0.52
CRT Mean latency (ms)	121	296.2 (35.0)	305.9 (48.2)	297.0 (34.3)	*0.86*	293.8 (39.1)	293.3 (33.3)	294.5 (39.9)	*0.99*	0.27
GP Dominant (s)	111	66.6 (8.2)	68.2 (8.6)	71.5 (11.6)	*0.15*	67.2 (10.0)	65.8 (9.7)	69.9 (10.5)	*0.12*	0.21
GP Non-dominant (s)	111	77.0 (11.1)	70.9 (11.3)	77.2 (12.6)	*0.06*	73.9 (10.8)	68.7 (9.1)	74.7 (15.2)	*0.10*	0.85
TMT-A (s)	114	24.2 (6.7)	26.4 (7.0)	26.7 (8.9)	*0.34*	22.2 (5.8)	25.5 (9.8)	24.9 (6.6)	*0.16*	0.77
CW-1 (s)	114	29.1 (3.9)	28.8 (4.6)	30.3 (5.7)	*0.68*	29.2 (4.0)	28.7 (3.9)	29.6 (5.4)	*0.89*	0.43
CW-2 (s)	114	21.4 (3.0)	21.5 (2.8)	21.8 (4.5)	*0.94*	21.9 (3.3)	21.9 (2.7)	21.8 (4.4)	*0.60*	0.37
CW-3 (s)	114	52.2 (13.3)	52.3 (12.1)	53.4 (11.9)	*0.79*	50.3 (10.6)	50.3 (10.3)	50.0 (10.7)	*0.99*	0.48
CW-4 (s)	113	57.9 (12.9)	59.6 (11.1)	60.9 (17.2)	*0.74*	53.1 (13.0)	58.0 (11.3)	58.0 (14.3)	*0.35*	0.49
TMT-B (s)	112	56.6 (16.0)	62.9 (19.9)	67.9 (27.1)	*0.13*	54.3 (16.7)	63.5 (22.0)	60.5 (17.9)	*0.14*	0.11
FAS Total words[e]	112	38.9 (9.9)	44.3 (11.3)	39.8 (9.1)	*0.11*	42.3 (11.0)	46.7 (10.4)	41.8 (10.6)	*0.15*	0.69
SOC Initial thinking time (ms)	83	16448 (14097)	13784 (6615)	15501 (9849)	*0.78*	16881 (9684)	11124 (6212)	12424 (6976)	*0.08*	0.40
SOC Probl. in min. moves[e]	83	10.9 (1.1)	10.7 (1.1)	10.4 (1.3)	*0.33*	10.9 (1.1)	10.8 (1.3)	10.6 (1.2)	*0.57*	0.79
IED Total errors	80	15.5 (12.4)	13.6 (10.5)	20.2 (15.1)	*0.13*	21.7 (20.6)	17.8 (16.9)	18.9 (17.2)	*0.77*	0.17

[a] Follow-up score subtracted from baseline score
[b] Number of patients with baseline and follow-up scores on each test-measure
[c] Kruskall-Wallis test between 3 groups
[d] ANCOVA between 3 groups with *age* and *follow-up time* as covariates
[e] *Higher* score represents better performance (for the other measures a *lower* score represents better performance)

Table 4. Number* and proportions (%) of patients with reliable decline and improvement on each neuropsychological test-measure

		Declined (N /total **%**)				**Improved** (N /total **%**)			
Test-measure	r[a]	**NO-CHEMO**	**ONE-CHEMO**	**MULTIPLE-CHEMO**	**3 or 4 BEP**	**NO-CHEMO**	**ONE-CHEMO**	**MULTIPLE-CHEMO**	**3 or 4 BEP**
HVLT-R Total words	.61	2 / 30 **7**	6 / 36 **17**	1 / 51 **2**	1 / 31 **3**	0 / 30 **0**	7 / 36 **19**	7 / 51 **14**	7 / 31 **23**
HVLT-R Delayed recall	.48	2 / 30 **7**	5 / 35 **14**	4 / 50 **8**	3 / 31 **10**	0 / 30 **0**	3 / 35 **9**	10 /50 **20**	4 / 31 **13**
PAL Errors 6 shapes[b]	.51	0 / 31 **0**	3 / 36 **8**	3 / 53 **6**	3 / 33 **9**	2 / 31 **7**	2 / 36 **6**	3 / 53 **6**	1 / 33 **3**
SWM Between errors[c]	.60	0 / 31 **0**	2 / 37 **5**	4 / 53 **8**	3 / 33 **9**	1 / 31 **3**	8 / 37 **22**	5 / 53 **9**	3 / 33 **9**
SWM Strategy	.79	2 / 31 **7**	2 / 38 **5**	2 / 53 **4**	2 / 33 **6**	2 / 31 **7**	5 / 38 **13**	5 / 53 **9**	4 / 33 **12**
CRT Mean latency	.80	2 / 31 **7**	3 / 37 **8**	3 / 53 **6**	2 / 33 **6**	0 / 31 **0**	6 / 37 **16**	5 / 53 **9**	3 / 33 **9**
GP Dominant	.65	2 / 29 **7**	1 / 33 **3**	2 / 49 **4**	0 / 30 **0**	0 / 29 **0**	1 / 33 **3**	5 / 49 **10**	4 / 30 **13**
GP Non-dominant	.72	1 / 29 **3**	0 / 33 **0**	7 / 49 **14**	6 / 30 **20**	2 / 29 **7**	5 / 33 **15**	8 / 49 **16**	6 / 30 **20**
TMT A	.66	2 / 30 **7**	8 / 35 **23**	5 / 49 **10**	1 / 29 **3**	1 / 30 **3**	0 / 35 **0**	1 / 49 **2**	1 / 29 **3**
CW-1	.77	2 / 29 **7**	1 / 35 **3**	2 / 50 **4**	0 / 30 **0**	1 / 29 **3**	1 / 35 **3**	5 / 50 **10**	3 / 30 **10**
CW-2	.90	1 / 29 **3**	7 / 35 **20**	3 / 50 **6**	1 / 30 **3**	1 / 29 **3**	5 / 35 **14**	9 / 50 **18**	4 / 30 **13**
CW-3	.89	2 / 29 **7**	2 / 35 **6**	5 / 50 **10**	4 / 30 **13**	1 / 29 **3**	1 / 35 **3**	1 / 50 **2**	1 / 30 **3**
CW-4	.72	1 / 29 **3**	4 / 35 **11**	5 / 49 **10**	5 / 29 **17**	1 / 29 **3**	0 / 35 **0**	1 / 49 **2**	0 / 29 **0**
TMT B	.72	1 / 30 **3**	5 / 35 **14**	4 / 47 **9**	3 / 28 **11**	3 / 30 **10**	1 / 35 **3**	4 / 47 **9**	1 / 28 **4**
FAS Total words	.70	1 / 29 **3**	1 / 34 **3**	4 / 49 **8**	2 / 29 **7**	1 / 29 **3**	4 / 34 **12**	1 / 49 **2**	1 / 29 **3**
SOC Initial thinking time[b]	.63	0 / 21 **0**	1 / 24 **4**	3 / 38 **8**	1 / 23 **4**	1 / 21 **5**	5 / 24 **21**	12 /38 **32**	9 / 23 **39**
SOC Problems in min. moves	.58	0 / 21 **0**	2 / 24 **8**	3 / 38 **8**	1 / 23 **4**	1 / 21 **5**	3 / 24 **13**	4 / 38 **11**	3 / 23 **13**
IED Total errors[b]	.55	1 / 20 **5**	2 / 22 **9**	4 / 38 **11**	2 / 23 **9**	1 / 20 **5**	2 / 22 **9**	10 /38 **26**	7 / 23 **30**

*Maximum N in each treatment group: NO-CHEMO: N = 31, ONE-CHEMO: N = 38, MULTIPLE-CHEMO: N = 53 (3 or 4 BEP: N = 33)

[a] Pearson's correlation coefficient between baseline and follow-up score in NO-CHEMO (control) group

[b] log-transformed score

[c] square-root transformed score

Table 5. Proportions of TCPs in treatment groups with individual decline, improvement and overall decline

		NO-CHEMO N (%)	**ONE-CHEMO** N (%)	**MULTIPLE-CHEMO** N (%)	*p-value*[a]	NO vs. ONE *p-value*[b]	NO vs. MULTI *p-value*[b]	ONE vs. MULTI *p-value*[b]	**3 or 4 BEP** N (%)	NO vs. 3 or 4 BEP *p-value*[b]
***Total* test battery (18 measures)**	***Decline* ≥10%** of test-measures	7 (23)	15 (40)	20 (38)	0.27	0.20	0.23	1.00	13 (39)	0.18
	***Decline* ≥15%** of tests-measures	4 (13)	7 (18)	6 (11)	0.62	0.74	1.00	0.38	4 (12)	1.00
	***Improvement* ≥10%** of tests-measures	3 (10)	16 (42)	30 (57)	<0.001	0.003	<0.001	0.21	18 (55)	<0.001
	***Improvement* ≥15%** of tests-measures	1 (3)	5 (13)	18 (34)	0.001	0.21	0.001	0.03	13 (39)	0.001
	Overall decline	4 (13)	6 (16)	8 (15)	0.94	1.00	1.00	1.00	5 (15)	1.00
***Basic* test battery (15 measures)**	***Decline* ≥10%** of test-measures	7 (23)	14 (37)	16 (30)	0.44	0.29	0.61	0.65	11 (33)	0.41
	***Decline* ≥15%** of test-measures	4 (13)	7 (18)	6 (11)	0.62	0.74	1.00	0.38	4 (12)	1.00
	***Improvement* ≥10%** of test-measures	3 (10)	15 (40)	21 (40)	0.009	0.006	0.005	1.00	13 (39)	0.009
	***Improvement* ≥15%** of test-measures	1 (3)	4 (11)	12 (23)	0.04	0.37	0.03	0.17	11 (33)	0.003
	Overall decline	5 (16)	5 (13)	10 (19)	0.77	0.75	1.00	0.57	8 (24)	0.54

[a] Pearsons chi-square test
[b] Fisher's exact test

Table 6. **Description of TCPs with a decline from baseline to follow-up on ≥10% of the neuropsychological test-measures**

Independent variables	***p-value****	**Decline (N=42) vs. not (N=80)**
Age at baseline (median years)	0.11	34 vs. 31.5
NART (mean score)	0.56	17.3 vs. 18.2
High level of education (baseline)	0.70	45% vs. 50%
Metastatic disease (TC stage II-IV)	0.65	24% vs. 20%
Any chemotherapy (≥1 cycle)	0.13	83% vs. 70%
Follow-up time (median months)	0.85	12 vs. 12
Neuroticism (mean score)	0.49	1.5 vs. 1.7
Possibly hazardous alcohol use at baseline	0.25	29% vs. 19%
Mental problems before TC	0.66	21% vs. 26%
Impact of Event Scale (IES) (mean total-score)		
Baseline	0.97	17.6 vs. 18.0
Follow-up	0.32	14.8 vs. 13.6
Change in dichotomized IES total-score	0.64	
Most distress at baseline		14% vs. 9%
No change in distress-level		81% vs. 86%
Most distress at follow-up		5% vs. 5%
Fatigue Questionnaire (mean total-score)		
Baseline	0.55	13.5 vs. 13.8
Follow-up	0.47	14.0 vs. 13.1
Worsening of total fatigue-score	0.53	31% vs. 25%
Worsening of neurotoxic symptoms		
Peripheral neuropathy	0.57	17% vs. 12%
Raynaud-like symptoms	1.00	21% vs. 21%
Tinnitus or hearing loss	**0.03**	**21% vs. 6%**

* T-test and Mann Whitney Wilcoxon test used for *continuous* independent variables with normal and skewed distributions respectively, and Pearson chi-square or Fisher's exact tests used for *categorical* independent variables

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IV

Self-reported cognitive problems in testicular cancer patients: Relation to neuropsychological performance, fatigue and mental distress

T. Skaali M.D.[1], **S. D. Fosså** M.D. PhD[1], **S. Andersson** PhD[2], **M. Cvancarova** M.Sc[1], **C. W. Langberg** M.D. PhD[3], **G. Lehne** M.D. PhD[4], **A. A. Dahl** M.D. PhD[1]

[1] National Resource Center for Late Effects, Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, and The University of Oslo, Oslo, Norway

[2] Department of Neuropsychiatry and Psychosomatic Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway

[3] Department of Oncology, Oslo University Hospital, Ullevål Hospital, Oslo, Norway

[4] Department of Oncology, Oslo University Hospital, The Norwegian Radiumhospital, Oslo, Norway

Running head: Prospective study of self-reported cognitive problems in testicular cancer patients

Corresponding author:
Tone Skaali, MD
National Resource Center for Late Effects,
Department of Oncology,
Oslo University Hospital,
The Norwegian Radium Hospital,
Box 4953, Nydalen
N-0424 Oslo, Norway
Fax: +47 22934553 Phone: +47 22934000
E-mail: Tone.Skaali@oslo-universitetssykehus.no

ABSTRACT

OBJECTIVE: There is a concern about negative cognitive effects of systemic chemotherapy. We prospectively explored self-reported cognitive problems in testicular cancer patients (TCPs) treated with and without chemotherapy.

METHODS: One hundred and twenty-two TCPs were interviewed about self-reported cognitive problems shortly after orchidectomy but before any additional treatment (baseline), and then at a median of one year after end of treatment (follow-up). Symptoms of mental distress, fatigue and peripheral neurotoxicity were assessed by questionnaires, and patients also underwent neuropsychological testing. Self-reported cognitive problems were compared between three treatments groups: no chemotherapy, one cycle of chemotherapy, and multiple cycles of chemotherapy. Variables associated with an increase of self-reported cognitive problems from baseline to follow-up were explored.

RESULTS: Significantly larger proportions of TCPs in the two chemotherapy groups had an increase of self-reported cognitive problems from baseline to follow-up compared to the no-chemotherapy group. Increase of self-reported cognitive problems was significantly associated with mental distress, fatigue, lower level of education and Raynaud-like symptoms, but not with a decline in neuropsychological test-performance.

CONCLUSION: In TCPs**,** an increase of self-reported cognitive problems from baseline to one-year follow-up was associated with chemotherapy treatment, fatigue and mental distress, but not with a decline in neuropsychological test-performance.

Keywords: adverse effects, chemotherapy, prospective study, self-reported cognitive problems, testicular cancer patients

INTRODUCTION

Cognitive problems are frequently reported by cancer patients [1-3]. This has led to an increasing scientific focus on cognitive function (CF) after cancer treatment. There is a concern that systemic chemotherapy may have a negative effect on CF in cancer patients, but this association is still not well documented [4-6]. Most studies in this field have explored CF in breast cancer patients, and the prevalence of self-reported cognitive problems is high in this group of cancer patients [7,8]. However, a low concordance between self-reported cognitive problems and objectively assessed neuropsychological functioning has been observed repeatedly [6,9-11]. Self-reported cognitive problems, but not reduced neuropsychological test performance, have been found significantly associated with emotional distress and fatigue [6,10,12]. Regardless of etiology, cognitive problems may have negative consequences for patients' daily functioning and well-being. More systematic knowledge of self-reported CF in several groups of cancer patients of both sexes are needed [2,13].

Two studies have investigated self-reported CF in testicular cancer patients (TCPs). Fosså et al. [14] prospectively studied CF as a dimension of quality of life in 666 TCPs treated with cisplatin-based chemotherapy. They found that 19% of the patients reported worsening of CF two years after chemotherapy compared to the pre-treatment level; however, a comparison with patients not treated with chemotherapy was not available. In a cross-sectional study of 182 TCPs assessed at a median of 3 years after end of treatment, Schagen et al. [15] observed that approximately one-third of the TCPs in all treatment groups (chemotherapy, radiotherapy and surveillance) reported some cognitive problems. As for breast cancer patients, self-reported cognitive problems were associated with emotional distress and fatigue, but not with reduced neuropsychological test performance.

As part of a Norwegian study of CF in TCPs, we prospectively explored self-reported cognitive problems in patients treated with and without chemotherapy. Evaluations were performed after orchidectomy (surgery) but prior to any additional treatment (*baseline*), and at one year after end of treatment (*follow-up*). To our knowledge, this is the first prospective study of self-reported CF in TCPs, and the aims of the study were: 1) to compare proportions of TCPs with an *increase of self-reported cognitive problems from baseline to one-year follow-up* among patients treated with different treatment modalities (no chemotherapy, one cycle of chemotherapy or multiple cycles of chemotherapy); and 2) To study *variables* associated with an increase of self-reported cognitive problems from baseline to one-year follow-up.

METHODS

Patients and procedures

Between August 2006 and September 2008, recently orchidectomized TCPs aged 18-60 were invited to participate in the present prospective study. Exclusion criteria were: 1) Severe mental disorders like psychoses or substance dependence disorders; 2) Degenerative brain disease or previous severe brain trauma; 3) Brain metastases or severe somatic dysfunction, or 4) Lacking proficiency of Norwegian language.

Evaluations consisted of a semi-structured interview on self-reported CF and background variables, some questionnaires and a neuropsychological assessment (complete neuropsychological results presented in a separate paper accepted for publication in Annals of Oncology). The baseline evaluation was done prior to start of any additional treatment, and the follow-up evaluation was scheduled approximately 12 months after end of chemotherapy or start of surveillance/radiotherapy. All evaluations were performed by the

first author. Information about *stage* of testicular cancer (TC) [16] and *treatment* was obtained from the medical records.

Among 202 eligible TCPs, 129 (64%) were recruited at baseline. Attrition analyses showed no significant differences between included and non-included patients in age or stage of TC. From 129 patients examined at baseline, 122 disease-free TCPs (95% follow-up rate) were re-evaluated at follow-up at a median of 12 months (range 8-23 months) after end of chemotherapy/start of surveillance (or radiotherapy). Seven patients were lost to follow-up: three denied re-evaluation, one had moved abroad and three had developed severe mental disorders or somatic disease.

Among the 122 TCPs re-evaluated at follow-up, 31 TCPs had received no chemotherapy (inclusive one patient with radiotherapy only; *NO-CHEMO group*), 38 TCPs had received one cycle with chemotherapy (*ONE-CHEMO group*), and 53 TCPs had received two or more cycles with chemotherapy (*MULTIPLE-CHEMO group*). The chemotherapy regimens consisted of one treatment with carboplatin or of cycle(s) with bleomycin, etoposide and cisplatin (BEP-chemotherapy).

Data collection

Self-reported cognitive problems

In semi-structured interviews at baseline and follow-up, the TCPs were asked to describe their general *concentration* and *memory* function with the response alternatives very good, good, not so good, or poor. The responses to both concentration and memory function were then dichotomized into *no problems* (very good/good) and *problems* (not so good/poor). A change of category in the dichotomized function-scores from baseline to follow-up was noted. If a patient changed category from *no problems* to *problems* in either the

dichotomized concentration and/or the memory score, he was defined as reporting an *increase of self-reported cognitive problems* from baseline to follow-up.

At baseline, the patients were additionally asked if they had experienced any long-term (>3 months) cognitive problems before their TC-diagnosis, eventually when these problems started, and finally to indicate on an 11-point Likert scale if these cognitive problems affected habitual daily functioning before the TC-diagnosis (0: no affection, 10: major impact on daily functioning). At follow-up, the patients were asked if they had noticed any cognitive problems after the TC-diagnosis, and eventually to rate them on the same 11-point scale described above. Responses on the 11-point scales were dichotomized using the median value (which was 0 both at baseline and follow-up) as a cut-off into *no cognitive problems affecting daily functioning* (rating 0) and *at least some cognitive problems affecting daily functioning* (rating 1-10). An *increase of cognitive problems affecting daily functioning* was defined when a patient changed category from *no* to *at least some cognitive problems affecting daily functioning* from baseline to follow-up.

Background variables from interviews

The level of *education* was dichotomized into ≤12 years and >12 years of completed basic education. *Paired relation* was defined as being married or cohabiting. *Employment status* was categorized as working, being full-time student, or not working. *Mental problems before TC* were defined as requiring help from medical professionals or the use of psychotropic medication at least once.

Questionnaires

The *Impact of Event Scale* (IES) assessed the psychological response to the trauma of getting TC [17;18]. The IES measures symptoms of *intrusion* (7 items) and *avoidance* (8

items) during the past week, and each item is scored from 0 (not at all) to 5 (often) with higher scores denoting more distress. We used *IES total score* >26 as cut-off score for clinical significant distress [19]. A change in dichotomized distress status from baseline to follow-up was noted.

The *Fatigue Questionnaire* assessed total fatigue symptoms with 7 items on physical fatigue and 4 items on mental fatigue [20]. Items are rated from 0 to 3 with the *total fatigue score* ranging from to 0 (low) to 33 (high). Worsening of fatigue symptoms was defined if follow-up score of total fatigue was at least 3 points higher than the baseline score (≈10% change on scale).

Scale for Chemotherapy-Induced Neurotoxicity (SCIN) assessed symptoms of peripheral neuropathy (paresthesias in hands or feet), Raynaud's phenomenon (white fingers or cold feet), and ototoxic symptoms (tinnitus or hearing loss) [21]. Items are rated on 4-point scales ranging from 1 (no symptoms) to 4 (much symptoms), and the scores were dichotomized into *symptoms* (score 3 or 4) vs. *no symptoms* (score 1 or 2). Worsening of neurotoxic symptoms was defined as a change in category from *no symptoms* to *symptoms* from baseline to follow-up.

Neuroticism, a basic personality trait covering the tendency to be nervous, was rated at baseline by 6 items of an 18-items version of the *Eysenck Personality Questionnaire* (EPQ-18) [22,23]. Sum-scores range from 0 (low) to 6 (high).

Alcohol use at baseline was assessed with a 4-items version the of the *CAGE questionnaire* [24,25], with sum-scores ranging from 0 (low) to 4 (high). A sum-score of ≥2 defined a possibly hazardous alcohol use.

Neuropsychological assessment

A neuropsychological test battery assessing the main cognitive domains was used, and is described in the neuropsychological paper (ref). Through a standardized regression model (SRB) [26], individual *decline in neuropsychological test performance* was defined when a patient exhibited decline on at least 10% of the neuropsychological test-measures from baseline to the follow-up evaluation.

An estimate of *intellectual functioning* was measured at baseline by the Norwegian version of the National Adult Reading Test (NART) [27,28]. Scores range from 0 to 50 and lower scores represent better functioning.

Data management and statistics

Data were analyzed with the SPSS program for PC version 16.0 (SPSS Inc, Chicago IL), using standard descriptive measures, parametric and non-parametric tests as appropriate. Pearson's chi-square and Fisher's exact tests were used to compare categorical variables across groups. P-values<0.05 were considered as statistically significant, and all tests were two-sided.

Ethics

The study was approved by the Ethical Committee of the Southern Health Region of Norway and the National Data Inspectorate. All patients delivered written informed consent.

RESULTS

Patients

As expected, significantly larger proportion of TCPs in the MULTIPLE-CHEMO group had metastatic disease compared to the NO-CHEMO and the ONE-CHEMO groups (Table 1).

Age at baseline was significantly higher in the ONE-CHEMO group compared to the two other groups. The two chemotherapy groups had significantly higher total-fatigue score than the NO-CHEMO group both at baseline and at follow-up. At follow-up, a larger proportion in the MULTIPLE-CHEMO group reported Raynaud-like symptoms compared to the two other groups. No significant group differences were found for other demographic variables, follow-up time, decline in neuropsychological test performance, alcohol-use, mental problems before the TC-diagnosis, neuroticism or level of mental distress (IES total score) (Table 1).

Self-reported cognitive problems

Twenty-five TCPs (20%) had an *increase of self-reported cognitive problems* from baseline to follow-up. There was a significant (p=0.02) difference across the treatment groups in proportions of TCPs with an increase of self-reported cognitive problems: larger proportions in the ONE-CHEMO group (29%) and the MULTIPLE-CHEMO group (25%) had an increase of problems compared to the NO-CHEMO group (3%, Table 2). However, no significant difference appeared between the ONE- and the MULTIPLE-CHEMO group (p=0.64).

Thirteen patients (11%) had an *increase of cognitive problems affecting daily functioning* from baseline to follow-up. No statistically significant group difference was observed for this variable (p=0.08, Table 2).

Variables associated with an increase of self-reported cognitive problems

Among the 25 TCPs with an increase of self-reported cognitive problems, a significantly larger proportion had received chemotherapy (96% vs.69%), had worsening of fatigue score (50% vs.22%) and of Raynaud-like symptoms (42% vs.16%), had lower education level

(68% vs.44%) and had mental problems before TC (48% vs.19%) compared with those without an increase of self-reported cognitive problems (Table 3). Further, the TCPs with an increase of cognitive problems had significantly higher follow-up scores of mental distress (median score 15.5 vs.10) and fatigue (median score 16 vs.11) compared with those with no increase of cognitive problems (Table 3).

No statistically significant association was found between an increase of self-reported cognitive problems and a decline in neuropsychological test performance from baseline to follow-up (p=0.82, Table 3). Eight patients were classified with both an increase of self-reported cognitive problems and a decline in neuropsychological test performance (Table 4). Among these eight patients, three had received one cycle of carboplatin and five had received 3 cycles of BEP-chemotherapy.

DISCUSSION

In this prospective study we found that significantly larger proportions of TCPs treated with one or more cycles of chemotherapy had an increase of self-reported cognitive problems from baseline to one-year follow-up compared with patients who did not receive chemotherapy. Increase of self-reported cognitive problems from baseline to follow-up was significantly associated with higher levels of mental distress and fatigue, lower level of education and worsening of Raynaud-like symptoms, but not with a decline in neuropsychological test performance.

We observed that TCPs treated with chemotherapy were more likely to report an increase of cognitive problems compared with those not treated with chemotherapy. A plausible explanation for this finding is that chemotherapy may have a toxic effect on CF in some TCPs. However, no significant association between an increase of self-reported cognitive problems and a decline in neuropsychological test performance appeared in our

sample (and no significant group difference in proportions of TCPs with a decline in neuropsychological test performance was observed). Hence, the decline in self-reported CF was not mirrored by a decline in neuropsychological performance. Despite the non-significant association between "subjective" and "objective" CF-decline in this study, eight of our TCPs had both an increase of self-reported cognitive problems and a decline in neuropsychological test performance. Five out of these patients had received 3 cycles of BEP-chemotherapy. Larger studies are needed in order to identify if there are any subgroups of TCPs that may be susceptible for negative cognitive effects of cisplatin-based chemotherapy.

Another explanation for the observed group difference could be that some patients gave biased report about CF after being "primed" about negative cognitive effects of chemotherapy when entering the study. In a study of breast cancer patients, Schagen et al. [29] observed that patients who had pre-existing knowledge about a possible risk of reduced CF after chemotherapy reported significantly more cognitive problems compared with patients who did not have such pre-existing knowledge.

As reported in several studies [12,15], we found that an increase of self-reported cognitive problems in the TCPs was associated with increased levels of mental distress and fatigue symptoms, but not with a decline in neuropsychological test performance. Self-reported cognitive problems in TCPs may possibly reflect emotional status rather than actual neurocognitive functioning. Numerous studies of cancer patients have demonstrated a high concordance between self-reported cognitive problems and emotional distress/fatigue as well as a low concordance between "subjective" and "objective" CF. It is debated if self-reported cognitive problems and reduced neuropsychological functioning largely represent different constructs in cancer patients [12], and our results might support such a notion.

After TC, 11% of the patients in our sample reported an increase of cognitive problems that had at least some impact on their daily functioning. To date, no single causal factor of such cognitive problems in TCPs has been identified. The etiology is probably multi-factorial, and mental distress, fatigue, side-effects of treatment and other factors like hormonal changes [30] could play a role. However, self-reported cognitive problems in TCPs warrant clinical attention since such problems may indicate current mental distress or fatigue with a need for intervention.

A strength of our study is that we could prospectively explore individual change in self-reported cognitive problems from baseline to one-year follow-up in TCPs treated with chemotherapy and not. Also, the follow-up rate was high. However, some limitations of our study should be mentioned. Self-reported CF was assessed with semi-structured interviews rather than with a validated questionnaire. Because of this, comparisons of the prevalence of cognitive problems with other samples of cancer patients should be done with caution. Dichotomizing the responses on CF from the interviews reduced the variability in the data, and this may have influenced the results. As the same person conducted both the interviews and the neuropsychological testing there was a risk of interpretation bias.

CONCLUSIONS

In this prospective study of TCPs, increase of self-reported cognitive problems from baseline to a median of one-year follow-up was significantly associated with chemotherapy treatment and symptoms of mental distress and fatigue, but not with a decline in neuropsychological test performance. Self-reported cognitive problems in TCPs probably have a multi-factorial etiology, and current emotional distress and fatigue seem to be important factors.

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Table 1. Characteristics of the sample (and for each treatment group if statistically different group changes)

Variables	TOTAL N=122	NO-CHEMO group (N=31)	ONE-CHEMO group (N=38)	MULTIPLE-CHEMO group (N=53)
Age at baseline (years), median [range]*	32.5 [19-60]	**32 [21-60]**	**35 [23-52]**	**30 [19-60]**
Metastatic disease (TC stage II-IV[a]), N (%) *	34 (28)	**1 (3)**	**0**	**33 (62)**
Neurotoxic symtoms (SCIN), N (%)				
Peripheral neuropathy, baseline / follow-up[b,c]	5 (4) / 18 (15)	1 (3) / 3 (10)	3 (8) / 6 (16)	1 (2) / 9 (17)
Raynaud-like symptoms, baseline / **follow-up**[b,c]*	11 (9) / 31 (25)	4 (13) / **1 (3)**	3 (8) / **5 (13)**	4 (8) / **25 (48)**
Tinnitus or hearing loss, baseline / follow-up[b,c]	11 (9) / 23 (19)	2 (7) / 2 (7)	6 (16) / 10 (26)	3 (6) / 11 (21)
Fatigue Questionnaire, total score, **Baseline*** / **Follow-up***[c], mean (SD)	13.7 (3.7) / 13.4 (4.7)	**12.2 (3.5)** / **11.4 (3.5)**	**14.8 (4.2)** / **14.0 (4.2)**	**13.8 (3.1)** / **14.3 (5.3)**
Follow-up time (months[d]), median [range]	12 [8-23]			
Paired relation, Baseline / Follow-up, N (%)	77 (63) / 86 (71)			
In work or student, Baseline / Follow-up, N (%)	115 (94) / 111 (91)			
High education level (>12 years), Baseline / Follow-up, N (%)	59 (48) / 62 (51)			
NART score, mean (SD) [range], Mean (SD)	17.9 (8.0) [3-37]			
Possibly hazardous alcohol-use (Baseline), N (%)	27 (22)			
Mental problems before TC, N (%)	30 (25)			
Neuroticism (Baseline), Mean (SD)	1.6 (1.5)			
Impact of Event Scale, total score, Baseline / Follow-up[c] , Mean (SD)	17.8 (12.2) / 14.0 (10.8)			
Decline in neuropsychological test performance from baseline to follow-up, N (%)	42 (34)			

* statistically significant difference ($p<0.05$) across treatment groups; values marked in **bold** fonts
[a] includes one patient with advanced extra-gonadal germ cell tumor
[b] N=30 in NO-CHEMO group
[c] N=52 in MULTIPLE-CHEMO group
[d] months from end of chemotherapy/start of surveillance (or radiotherapy) to the follow-up evaluation

Table 2. Self-reported cognitive problems (dichotomized responses from interviews)

		N (%)				
		TOTAL N=122	**NO-CHEMO N=31**	**ONE-CHEMO N=38**	**MULTIPLE-CHEMO N=53**	***p-value****
Concentration problems	Baseline	8 (7)	1 (3)	4 (11)	3 (6)	0.45
	Follow-up	16 (13)	1 (3)	8 (21)	7 (13)	0.09
Change:	More problems	12 (10)	1 (3)	6 (16)	5 (9)	
Concentration problems	Stable	106 (87)	29 (94)	30 (79)	47 (89)	
	Less problems	4 (3)	1 (3)	2 (5)	1 (2)	
Memory problems	Baseline	13 (11)	4 (13)	4 (11)	5 (9)	0.88
	Follow-up	25 (20)	2 (7)	10 (26)	13 (25)	0.08
Change:	More problems	17 (14)	0 (0)	7 (18)	10 (19)	
Memory problems	Stable	100 (82)	29 (94)	30 (79)	41 (77)	
	Less problems	5 (4)	2 (6)	1 (3)	2 (4)	
***Increase* of self-reported cognitive (concentration and/or memory) problems from baseline to follow-up**		**25 (20)**	**1 (3)**	**11 (29)**	**13 (25)**	**0.02**
At least some cognitive problems	Before TC	20 (16)	4 (13)	8 (21)	8 (15)	0.62
affecting daily functioning	At follow-up	29 (24)	3 (10)	11 (29)	15 (29)	0.10
***Increase* of cognitive problems affecting daily functioning**		**13 (11)**	**0 (0)**	**5 (13)**	**8 (15)**	**0.08**

* Pearson's chi-square test

Table 3. Description of TCPs with an increase of self-reported cognitive problem from baseline to follow-up

	Increase of self-reported cognitive problems (N=25) vs. not (N=97)	***p-value****
Metastatic disease (TC stage II-IV)	24% vs. 21%	0.79
Follow-up time (median months)	13 vs. 12	0.13
Chemotherapy (≥1 cycle)	**96% vs. 69%**	**0.004**
Age at baseline (median years)	31 vs. 33	0.59
Paired relation (at follow-up)	68% vs. 71%	0.81
High level of education (at follow-up)	**32% vs. 56%**	**0.04**
NART (mean score)	20.6 vs. 17.2	0.06
Mental problems before TC	**48% vs. 19%**	**0.004**
Possibly hazardous alcohol use (baseline)	20% vs. 23%	1.00
Neuroticism (mean score)	1.8 vs. 1.6	0.56
Impact of Event Scale (IES) mean total-score		
Baseline	20.6 vs. 17.1	0.21
Follow-up	**18.5 vs. 12.9**	**0.03**
Change in dichotomized IES-score:		0.67
Most distress at baseline	8% vs. 11%	
No change in distress level	84% vs. 85%	
Most distress at follow-up	8% vs. 4%	
Fatigue Questionnaire mean total-score		
Baseline	14.7 vs. 13.4	0.12
Follow-up	**17.2 vs. 12.5**	**<0.001**
Worsening of total fatigue score	**50% vs. 22%**	**0.009**
Worsening of neurotoxic symptoms		
Peripheral neuropathy	21% vs. 12%	0.31
Raynaud-like symptoms	**42% vs. 16%**	**0.01**
Tinnitus or hearing loss	17% vs. 10%	0.48
Decline in neuropsychological test performance from baseline to follow-up	32% vs. 35%	0.82

* T-test and Mann Whitney test used for continuous independent variables with normal and skewed distribution respectively, and Pearson's chi-square or Fisher's exact test used for categorical independent variables; statistically significant differences ($p<0.05$) marked in **bold** fonts

Table 4. Cross-tabulation between increase / no increase of self-reported cognitive problems and decline / no decline in neuropsychological test performance from baseline to follow-up

N (% of total sample)	Increase of self-reported cognitive problems	*No* increase of self-reported cognitive problems	Total
Decline in neuropsychological test performance	**8 (6)**	**34 (28)**	42 (34)
No decline in neuropsychological test performance	**17 (14)**	**63 (52)**	80 (66)
Total	25 (20)	97 (80)	**122 (100)**

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