

# Towards a retained health in testicular–cancer patients

- long–term cognitive function,  
missing a testicle and  
psychological needs

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UNIVERSITY OF GOTHENBURG

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Ring the bells that still can ring

Forget your perfect offering

There is a crack in everything

That's how the light gets in

**Leonard Cohen**

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# ABSTRACT

**Background:** Many breast-cancer survivors experience chemotherapy-induced cognitive decline. Our knowledge about potential cognitive side-effects among testicular-cancer survivors is, however, sparse. We also lack information concerning these men's psychological health and needs, at diagnosis as well as over time.

**Aim:**

The main aim of this thesis was to investigate whether chemotherapy leads to long-term decreased self-reported cognitive function among testicular-cancer patients or not. We also wanted to get a deeper understanding of the psychological needs in this population.

**Methods:**

We identified 1173 eligible men diagnosed with non-seminomatous testicular cancer treated according to the bi-national cancer-care programs SWENOTECA I-IV between 1981 and 2004. During an 18-month qualitative phase we constructed a study-specific questionnaire built on information gained from interviews with cancer survivors. In these interviews, problems emerged concerning the survivors' cognitive function, their feelings of loss concerning the testicle or testicles that had been removed, and also the men's statements that they would have appreciated more psychological care during both diagnosis and treatment. Following these interviews, we continued by making a quantitative study where all these issues were taken up, however, with a focus on cognitive function.

**Results:**

In 2007 we obtained information from 960 of 1173 (82%) testicular-cancer survivors diagnosed on average 11 years previously. We found that a higher percentage of the survivors who received five or more cycles of chemotherapy, compared with those who received no chemotherapy, reported language difficulties in five of the seven language questions included in the questionnaire, with p-values ranging from 0.0002 to 0.0266. Two thirds of Swedish testicular-cancer survivors report they experienced a crisis due to their diagnosis. A similar percentage of the men report that they wish they had received information about common stress and crisis reactions and had been offered counseling. Furthermore, we found that 32 percent of the testicular-cancer survivors miss or previously missed their removed testicle(s) and that 26 percent have or previously had feelings of uneasiness or shame about their body because of the removed testicle(s). Among the 794 men who answered "No" to the single-item question "Are you depressed?", 790 (99.5%) were not considered as depressed according to HADS-D 11+.

**Conclusions:**

We found that Swedish testicular-cancer survivors who received five or more cycles of cisplatin-based chemotherapy experience an increased incidence of compromised language. Furthermore we found that some men miss their testicle or testicles and that many testicular-cancer patients have psychological needs that are not satisfactorily met by the health-care professionals.

**Implications:**

We believe all testicular-cancer patients should receive information about possible cognitive side-effects after treatment with chemotherapy as well as common psychological reactions when being diagnosed with cancer. By increasing preparedness and normalizing symptoms and reactions we might decrease long-term morbidity in this group of men.

Keywords: testicular-cancer patients, testicular-cancer survivors, chemotherapy, cognitive function, compromised language, single-item question, depression, feelings of loss, feelings of shame, psychological needs, crises.

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# SAMMANFATTNING

**Bakgrund:** Testikelcancer är den vanligaste tumörformen bland män i åldrarna 20-40 år. Sedan cisplatinbaserad kemoterapi introducerades i slutet av 1970-talet botas nu mer än 90 procent av de som drabbas,<sup>1</sup> vilket gett oss ett ökat antal testikelcanceröverlevare med eventuella långtidssymtom. Vi vet sedan tidigare att behandling med kemoterapi kan leda till neurologiska biverkningar, som exempelvis försämrad hörsel och vita fingrar (Raynauds fenomen).<sup>2</sup> Vid studiens utformande visste vi däremot inte om testikelcanceröverlevare, i likhet med bröstcanceröverlevare,<sup>3,4</sup> upplevde kognitiva långtidssymtom. Det saknades också kunskap om dessa mäns psykiska hälsa och behov av psykologiskt omhändertagande.

**Syfte:** Vårt huvudsyfte var att undersöka huruvida behandling med kemoterapi leder till kognitiv nedsättning. Vi ville också få en djupare förståelse för testikelcancerpatienters psykiska hälsa och psykologiska behov både vid diagnos och över tid.

**Metod:** Vi identifierade 1173 män som diagnostiserats med icke-seminomatös testikelcancer och som behandlats enligt de svensk-norska vårdprogrammen SWENOTECA I-IV mellan 1981 och 2004. Under en 18-månaders lång kvalitativ fas utarbetade vi ett studiespecifikt frågeformulär som bygger på information vi fått i intervjuer med testikelcanceröverlevare. Frågeformuläret innehöll frågor om beteende som refererar till alla kognitiva domäner (språk, minne, koncentration, visuo-spatial förmåga, exekutiv förmåga, hastighet). Vi inkluderade också frågor om psykologiska reaktioner och behov vid diagnos och behandling.

**Resultat:** Databasinsamlingen genomfördes under 2007. Av de 1173 män som kontaktades besvarade 960 (82 procent) testikelcanceröverlevare vår enkät. De var i genomsnitt 40 år och hade i genomsnitt diagnostiserats elva år tidigare.

I jämförelse med dem som inte behandlats med någon kemoterapi rapporterade två till tre gånger fler av de som behandlats med fem eller fler cykler av kemoterapi, att de hade språksvårigheter som "Säga andra ord än planerat", "Säga ord i fel ordning", "Säga liknande men fel ord", "Orden kommer i fel ordning" och "Svårt att avsluta meningar" minst en gång i veckan.

Vi fann att 32 procent av testikelcanceröverlevarna saknar eller har saknat sin/sina borttagna testikel/testiklar och att 26 procent kände eller tidigare hade känt obehag eller skämts för sin kropp med anledning av sin/sina borttagna testikel/testiklar. En tredjedel av männen hade blivit erbjudna att få en testikelprotes i samband med operation av den/de sjuka testikeln/testiklarna.

Två tredjedelar av testikelcanceröverlevarna rapporterar att de upplevde någon form av psykologisk kris i samband med att de fått sin cancerdiagnos. En liknande procentandel angav att de önskar att de blivit erbjudna information om vanliga stress- och krisreaktioner samt någon form av samtalskontakt.

På den enskilda frågan “Är du deprimerad?” svarade 55 män (6 procent) “Ja”, 118 (12 procent) “Jag vet inte” och 794 (82 procent) “Nej”. Med utgångspunkt från HADS-D 11+ som den gyllene standarden svarade 88 procent av de deprimerade “Ja” eller “Jag vet inte” och 84 procent av de ej deprimerade “Nej” på denna fråga. Nästan ingen (99,5 procent) av dem som svarade “Nej” var deprimerade enligt HADS-D 11+.

**Slutsatser:** Vi fann att svenska testikelcanceröverlevare som har behandlats med fem eller fler cykler av kemoterapi har en ökad risk för självrapporterade språksvårigheter. Vi fann också att det inte är ovanligt att sakna den bortopererade testikeln eller att känna obehag eller skam för sin kropp på grund av den bortopererade testikeln. Två tredjedelar av männen upplevde någon form av kris i samband med diagnos. Flertalet önskar att de fått information om vanliga stress- och krisreaktioner samt blivit erbjudna någon form av samtalskontakt. Nästan ingen av de män som svarat nej på frågan “Är du deprimerad?” uppfyllde kriterierna för en klinisk depression enligt HADS-D 11+. Den höga andelen “Jag vet inte”-svar tyder på att det behövs mer än ett entydigt ja- eller nej-svar när frågan ställs.

**Nytta:** Information om eventuella kognitiva effekter samt vanliga krisreaktioner vid diagnos gör patienten förberedd inför eventuell nedsatt funktion samt befriar honom från självanklagelser. Att introducera frågan “Är du deprimerad?” kan minska antalet oupptäckta depressioner och därmed på sikt minska långtidsmorbidityten hos testikelcanceröverlevare.



# LIST OF PAPERS

This thesis is based on the following studies:

1. Skoogh J, Steineck G, Stierner U, Cavallin-Ståhl E, Wilderäng U, Wallin A, Gatz M, Johansson B on behalf of SWENOTECA. Testicular-Cancer Survivors Experience Compromised Language following Chemotherapy: Findings in a Swedish Population-based Study 3 - 26 years after Treatment. *Acta Oncol.* 2012 Feb; 51(2):185-197. Epub 2011 Aug 18.
2. Skoogh J, Steineck G, Johansson B, Wilderäng U, Stierner U on behalf of SWENOTECA. Psychological crises among testicular-cancer survivors – results from a population-based long-term follow-up. Submitted Manuscript
3. Skoogh J, Steineck G, Cavallin-Ståhl E, Wilderäng U, Håkansson U, Johansson B, Stierner U on behalf of SWENOTECA. Feelings of loss and uneasiness or shame after removal of a testicle by orchiectomy: a population-based long-term follow-up of testicular cancer survivors. *Int J Androl.* 2011 Apr; 34(2):183-92.
4. Skoogh J, Ylitalo N, Larsson-Omérov P, Hauksdottir A, Nyberg U, Wilderäng U, Johansson B, Gatz M, Steineck G on behalf of the Swedish-Norwegian Testicular Cancer Group. “A no means no”- measuring depression using a single-item question versus Hospital Anxiety and Depression Scale (HADS-D). *Ann Oncol.* 2010 Sep; 21(9):1905-9. Epub 2010 Mar 15.

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# 1 INTRODUCTION

If the goal of research is to retrieve new knowledge, then the goal for the individual researcher might be said to be to learn more, or maybe of even greater importance, to understand better. During my time as a doctoral student, I have identified two partly related elements of the “reaching-a-higher-level-of-understanding” process that I believe you experience when working with more complex phenomena that are difficult to understand immediately. One element of the process works by putting the researcher in an ever narrower spiral-shaped forward movement leading ever closer to the core of the knowledge being sought, and with the level of understanding steadily rising. But there is also a process where you more or less suddenly find yourself either closer to or further away from some kind of feeling of complete understanding. For just a moment, everything seems self-evident, and the entire solution to the problem seems obvious, but this sense of clarity quickly fades. For me, one of the essential lessons I have learned during my time as a doctoral student is to increasingly dare to simply accept these processes, knowing that understanding not only takes time but also has its ups and downs. If I as a researcher insist that I must understand everything without delay, then I may not get anywhere. Instead, I must be able to set the questions aside and engage in a process where “understanding” and “not understanding” go hand in hand.

That the patient has correct information and understanding about possible physical and psychological side-effects of a disease and its treatment is of the utmost importance in any disease. Several studies<sup>5,6</sup> have clarified that patient information may have positive effects on both short- and long-term psychological health among cancer patients. Still, it seems as if this important work is often overlooked. In interviews with testicular-cancer survivors that took place in the beginning of this project it occurred to me that several of these men distinguished their experience with physical care, which they were satisfied with, from their psychological care, which they were dissatisfied with. Amongst other things, they did not feel they were sufficiently informed regarding the cognitive side-effects or psychological reactions some of them experienced after diagnosis and treatment.

I hope my thesis can be a contribution to the important work in improving health care for testicular-cancer patients so we can move towards a retained health for these men.

## 2 BACKGROUND

### 2.1 Testicular cancer

Testicular cancer only constitutes one percent of all of the types of cancer experienced by males. Nevertheless, it is the most common type of tumour in men between the age of 20 and 40. Each year approximately 300 men are diagnosed with this form of cancer in Sweden.<sup>7</sup> Since cisplatin-based chemotherapy was introduced at the end of the 1970s, there has been a dramatic increase in survival, from around 10 percent before that to the present rate above 90 percent.<sup>1</sup>

There are two kinds of testicular cancer, seminoma and non-seminoma. Seminoma displays a lower tendency to spread than does non-seminoma and most patients are in stage I at the time of diagnosis. Patients with non-seminoma have a more aggressive form of cancer, which means that the tumour will grow more rapidly and has a greater tendency to spread beyond the testicle. This research project deals only with patients who have non-seminoma.

The most common symptom of testicular cancer is that one testicle is enlarged and feels swollen. Approximately one half of the patients experience pain or tenderness in the testicle. For some, the first symptom is back pain and sometimes an ischia-like pain. This symptom can indicate that the cancer has spread to the lymph nodes along the backbone.

Testicular cancer is separated into stages on the basis of the degree of spreading. In stage I the cancer is confined to the testicle. Stage Mk+ means elevated tumour markers in serum without visible tumour on computer tomography. In stage II the cancer has spread to abdominal lymph nodes. In stage III there are lymph node metastases above the diaphragm. Stage IV is defined by the presence of hematogenous metastases, most often in the lungs, but sometimes also in the liver, the skeleton, and the brain. The diseased testicle is always surgically removed. This intervention is called orchiectomy. In the case of metastases, the patient is treated with chemotherapy.

At the beginning of the 1980s, a Swedish-Norwegian program for the treatment of patients with non-seminoma was started and given the name SWENOTECA I. All treatment was registered in a database from where we could extract the Swedish data. Patients in stage I with a high risk of recurrence receive adjuvant (preventive) chemotherapy, however with fewer

courses of treatment than those who already have developed metastases. The basis for the treatment is a combination of cisplatin, vinblastin or etoposide and bleomycin. In the case of insufficient effect, treatment with the addition of ifosfamide has been given, and a smaller group has even received high-dose treatment with stem cell rescue. For patients in stage II-IV if remaining tumour visible on computer tomography after chemotherapy surgery has been performed to examine if there are viable tumour left. In that case additional adjuvant chemotherapy has been given.<sup>1</sup>

After chemotherapy most of the men are sterile, but sperm production returns in most cases. Since a subset of patients (about 10 to 15 percent)<sup>8</sup> remain sterile, all patients are offered the chance to preserve sperm prior to the beginning of treatment in order to be able to make use in the future of in vitro fertilization.

Boys having a testicle remaining in the abdomen or groin instead of descending to scrotum have an increased risk of developing testicular cancer even if the position is surgically corrected. Other risk factors are infertility and chromosomal abnormalities. Researchers have postulated that factors early in the fetal uterine life, for example hormonal imbalance, may interfere with the maturation of testicular cells and lead to testicular cancer.

## **2.2 Neurological and sexual side-effects after treatment with chemotherapy**

Well-known side-effects resulting from treatment with cisplatin-based chemotherapy are symptoms of paresthesia (abnormal skin sensations such as tingling, tickling, itching or burning) and Raynaud phenomenon (white/numb fingers/toes). It is also quite common for patients to experience tinnitus and long-term hearing loss.<sup>2</sup>

When following up 1402 testicular-cancer survivors over a mean time of 11 years after diagnosis, Brydoy et al.<sup>9</sup> found that a significantly higher proportion of those treated with one to four or five or more cycles of chemotherapy, in comparison with those only treated with orchiectomy, reported being “quite a bit” or “very much” troubled by Raynaud phenomenon (12%, 35%, 61%), paresthesia (10%, 28%, 40%) or tinnitus (12%, 19%, 28%).

Regarding sexual side-effects, the use of different measurements makes results difficult to compare. Besides fertility issues, a reduction in or

complete loss of orgasm and decreased sexual desire have been reported.<sup>10,11</sup> Surgical treatment with retroperitoneal lymph node dissection often affects ejaculation since this function is directly related to innervation. Men who have undergone retroperitoneal lymph node dissection alone or a secondary resection after chemotherapy have a higher incidence of problems than those who have not.<sup>10-12</sup> In a meta-analysis Jonker-Pool and colleagues<sup>10</sup> summarized 36 studies (28 retrospective and 7 prospective), concerning 2786 cases of testicular cancer. They found ejaculatory dysfunction to be the most frequently reported sexual problem (mean 44 percent in retrospective studies and 51 percent in prospective studies) and strongly connected with surgical techniques concerning retroperitoneal lymph node dissection. There are also results that suggest body image might be affected with a significant proportion of men feeling less attractive after than before diagnosis and treatment.<sup>12,13</sup>

It is also well known that chemotherapy has a major effect on the hormonal, vascular and nervous systems and may cause reduction of sexual activity, sexual lust, orgasmic dysfunction, ejaculation problems and erectile dysfunction.<sup>14,15</sup> However, these effects are often transient<sup>16</sup> and have not seemed to be related to a cumulative effect.<sup>16-18</sup> Other factors associated with sexual problems are increased age, lack of partner, higher overall anxiety and lower testosterone level.<sup>17,19</sup>

## **2.3 Cognitive function after treatment with chemotherapy**

Cognitive function is a collective term for intellectual resources and usually is separated into the following six cognitive domains: language, memory, concentration, visual-spatial ability that constitutes the ability to understand spatial relationships, executive function that determines how we plan and deal with different situations, and mental speed.

Some of the earliest findings of chemotherapy-induced cognitive decline were reported in 1980<sup>20,21</sup> by researchers who had found that mild cognitive impairment was relatively common and independent of affective disorders. In 1998, van Dam published an article that, by using disease-specific comparison groups, with greater certainty could confirm that chemotherapy did cause cognitive decline. Compared with breast-cancer survivors who had not received any adjuvant treatment a statistically significantly higher proportion of those treated with even standard-dose as well as high-dose

chemotherapy were classified as cognitively impaired based on results of cognitive tests.<sup>22</sup>

Over the years there has been a growing interest in the postulated cognitive effects of chemotherapy. The number of published articles on this topic has increased from 10 between the years 1990-1994 to 128 between the years 2000-2004.<sup>23</sup> The overall results of these studies indicate that treatment with higher doses of chemotherapy leads to decreased cognitive function<sup>4,24</sup> and that this decrease continues over time for some individuals.<sup>25</sup> It is not completely certain which cognitive functions are affected, but concentration, memory, and quickness of reaction are among the cognitive domains that are most frequently cited as being affected.<sup>24</sup> It is consistently observed that a greater percentage of cancer survivors report decreased function than what can be confirmed by neuropsychological test performance.<sup>26</sup> Considering methodological differences such as the definition of “case-control” and “cognitive impairment”, it is difficult to compare results from different studies. When analysing data from breast-cancer survivors, using seven different criteria from the literature, Shilling et al.<sup>27</sup> found that the odds ratio ranged from 1.21 to 3.68 in comparisons of those treated with chemotherapy with controls.

The etiology is still not clear but is likely to be multifactorial. Possible mechanisms for chemotherapy-induced cognitive dysfunction include direct neurotoxic effects (damaged neurons or surrounding cells), oxidative damage, and immune dysregulation.<sup>28</sup> Researchers have also wondered if genetic differences can explain the finding that certain individuals experience more difficulties than others.<sup>29</sup> One smaller study has found a relationship between the e4 allele, a gene that is associated with dementia, and diminished cognitive function after treatment with chemotherapy.<sup>30</sup>

There are reservations concerning the data published to date. Most studies have been made on breast-cancer survivors who, in addition to chemotherapy, have been treated with hormones. As hormones probably also affect cognitive function,<sup>31,32</sup> it is difficult to draw firm conclusions about the possible effects of chemotherapy. Small studies with short follow-up times make it difficult to clear out the effect of dose-response, moreover if decreased function persists with time.<sup>24</sup> Those studies that have investigated cognitive function after treatment with chemotherapy have primarily employed neuropsychological tests in order to measure cognitive function. During the past several years, however, the ecological validity of these tests (the extent to which the test measures the extent of difficulties experienced on a daily basis) have been increasingly questioned, and researchers have



asked for instruments which to a greater degree measure the difficulties that people with cognitive impairment experience on a daily basis.<sup>33,34</sup>

Apart from our own study we have found results from four other studies concerning cognitive function after treatment with chemotherapy among testicular-cancer survivors. One study concerned self-reported cognitive function,<sup>35</sup> another employed neuropsychological tests<sup>36</sup> while two studies included data from both sources.<sup>37-39</sup>

Following up 286 of 666 testicular-cancer survivors two years after treatment with three or four cycles of chemotherapy, Fosså et al. found that 24 percent reported better and 19 percent worse cognition two years after treatment, compared with their pretreatment level.<sup>35</sup> These results were based on answers given to two questions about memory and concentration from the quality of life instrument QLQ C-30.<sup>40</sup>

In a population of 72 testicular-cancer survivors, and after a mean time interval of four years after diagnosis, Pedersen et al. observed no difference in neuropsychological test performance comparing those treated with three to four cycles of chemotherapy (n=36) with those treated with radiotherapy (n=36) or orchiectomy alone.<sup>36</sup>

Comparing 182 testicular-cancer survivors on average three years after treatment, Schagen and co-workers<sup>37</sup> found no difference when comparing neuropsychological test performance among those treated with four cycles of chemotherapy with those only treated surgically. Neither did they find any group differences regarding self-assessed cognitive functioning. However, they did not publish results for separate domains.

When following up 122 testicular-cancer survivors one year after baseline, Skaali et al. found that a statistically significantly higher proportion of those treated with one or more cycles of chemotherapy, compared with those only treated with orchiectomy, assessed their memory and/or concentration function as “not so good” or “poor”. Moreover a higher percentage of these men reported having cognitive problems affecting daily functioning.<sup>39</sup> These results were not confirmed in neuropsychological test performance where no statistically significant differences were found between treatment groups.<sup>38</sup>

## 2.4 Psychological health and psychological needs

There is a lack of information regarding both the short- and long-term psychological consequences of being diagnosed and treated for testicular cancer. At the time of diagnosis and treatment results are mostly based on information from small interview studies, making results hard to evaluate. Results from long-term, large-scale follow-up questionnaire studies are, on the other hand, mostly based on questions not especially designed for testicular-cancer survivors.

According to results based on answers to questions included in quality-of-life questionnaires, testicular-cancer survivors have been found to have a general life satisfaction similar to that of the normal population.<sup>41-43</sup> However, as data based on narratives and answers to more specific questions indicate, the psychological health of at least a subgroup of survivors may be impaired<sup>44-48</sup> these questions may be too general, not asking about the more specific psychological problems some testicular-cancer patients and survivors struggle with.

In addition to the fact that receiving a potentially deadly disease might trigger existential thoughts, we also know that many men diagnosed with testicular cancer are preoccupied by thoughts related to sexual functioning and fertility.<sup>45,49</sup> Interview studies also suggest some men process deep-seated fears related to masculinity, feeling vulnerable and having a sense of loss of power and control.<sup>49</sup> Possibly these feelings of fear persist. In a cross-sectional questionnaire study Skaali et al. found that as many as one third of the 1336 participating testicular-cancer survivors had “Been afraid of relapse of your disease” “Quite a bit” or “Very much” during the preceding week as long as 11 years (mean value) after diagnosis.<sup>46</sup>

When comparing quality-of-life reports from cancer survivors with a normal population, it is important to remember that similar results at the group level might hide important differences that prospective studies with subgroup analyses might reveal. We know that some people who experience a trauma, such as being diagnosed with a severe disease, go through what is called a “response shift”, a change in the meaning of one's self-evaluation of quality of life as a result of: change in the respondent's internal standards of measurement, change in the respondent's values or redefinition of life quality.<sup>50,51</sup> This implies some cancer survivors might estimate a higher quality of life than before treatment even though they may be experiencing side effects of treatment. This shift is believed to be the result of traumatic

events, such as a “near-death experience”, that may lead the individual to see what is really important in life and, as a result, to display less worry about “small things.” Studies indicate that this crisis must reach a certain level to cause the “response shift” to take place, but must not be too far above this level.<sup>52</sup> It is not impossible that testicular cancer, with a good prognosis for survival, for most patients is an event that just reaches this threshold level, but for a minority of individuals, who already are vulnerable, proves to be the proverbial “drop in the bucket that causes it to overflow”. The findings of Fleer et al. might support this hypothesis. When 354 testicular-cancer survivors were asked “Do you think that the experience with testicular cancer affects your current quality of life?” a mean of 10 years after diagnosis, a minority (11.2 percent) reported it had a negative or very negative impact, while the majority (52.6 percent) reported it had both a negative and a positive impact.<sup>53</sup>

We found three studies examining cancer-related stress among testicular-cancer patients<sup>38,54,55</sup> that used the “Impact of Event Scale”,<sup>56</sup> gaining similar results, finding that approximately 30 percent of recently diagnosed testicular-cancer patients were distressed. When Fleer et al.,<sup>57</sup> examined 354 testicular-cancer survivors with the same scale after a mean of 10 years after diagnosis, they found that 13 percent of all men experienced cancer-related stress. For prediction of those who will suffer most psychologically when diagnosed with testicular cancer, cancer-related variables seem to have an insignificant role.<sup>58</sup> Instead, personal and social characteristics of personality (neuroticism),<sup>59</sup> being single,<sup>57</sup> low education,<sup>57</sup> unemployment,<sup>57</sup> besides experience of side-effects<sup>42</sup> seem to be predictive factors.

According to an abridged version of the Eysenck Personality Inventory included in a questionnaire, Grov et al.<sup>59</sup> found that 12 percent of 1428 answering testicular-cancer survivors (participation rate: 78 percent) were identified with high neuroticism (e.g., nervous, worrying personality). Compared to those with a low neuroticism, a statistically significantly higher proportion of those with a high neuroticism reported psychological as well as physical symptoms of morbidity in 20 of 22 examined variables.

When comparing mental health based on scores on the subscale mental health of the RAND-36 among testicular-cancer survivors an average of 10 years after diagnosis based on relationship status, Tuinman et al. found that men who were single during diagnosis had the lowest degree of mental health whether they had established a relationship later on or not.<sup>60</sup> These results are confirmed in many other studies that suggest single men and newly married couples have more problems than those living in a more steady relationship at

diagnosis.<sup>57,61</sup> One reason single men are more vulnerable than those in a relationship might be that they to a higher degree have no one whom they can confide in. Helgasson et al.,<sup>62</sup> examining 661 men diagnosed with prostate cancer (participation rate: 76 percent), found that as many as 67 percent of those living alone had no one to confide in. These men were less content with their life and had a poorer psychological and overall well-being.

We have sparse information about preferred support among testicular-cancer survivors. However, Jonker-Pool et al.<sup>63</sup> found that more than half of testicular-cancer survivors reported a lack of information and support concerning sexuality both at diagnosis and follow-up. Those who reported sexual dysfunction expressed the highest need for information and support.

Having counselled testicular-cancer patients for many years, Rieker suggests that sexual function, concerns about fertility and quality of relationships should be assessed at the time of diagnosis and treatment planning.<sup>49</sup> Rieker also emphasizes the importance of proceeding from an understanding of the individual man's previous and present life. For example the relevance of altered/decreased sexual function might differ among men depending on sexual drive and relationship status. Furthermore, men with previous emotional problems might experience extreme distress at diagnosis and therefore need counselling at once.

We only found one published study concerning psychological interventions among testicular-cancer patients. When comparing scores on the Hospital Anxiety and Depression Scale (HADS) in groups of 73 newly diagnosed men who were randomly assigned to either six hours of adjuvant psychological therapy or a control condition, Moynihan et al. did not find any treatment effects.<sup>64</sup>

### 3 AIMS

The objective was to study psychological health among testicular-cancer survivors, focusing cognitive function after treatment with chemotherapy.

Specific aims of this thesis were:

1. To study whether treatment with chemotherapy leads to long-term decreased self-reported cognitive function among testicular-cancer patients or not by comparing answers to questions about behaviours among testicular-cancer survivors who received various cycles of cisplatin-based chemotherapy with those only treated with orchiectomy.
2. To study psychological reactions and needs among testicular-cancer patients by asking testicular-cancer survivors to retrospectively answer questions about experienced crises, crises and stress information given and counseling offered within the period of diagnosis and treatment.
3. To study the prevalence of feelings of loss and uneasiness or shame among testicular-cancer survivors who have had one or two testicles removed by orchiectomy in relation to those having been offered a testicular prosthesis.
4. To compare the sensitivity, specificity, positive predictive value and negative predictive value when measuring depression with a single question versus using the depression subscale, including seven questions, of the Hospital Anxiety and Depression Scale (HADS).

## 4 MATERIALS AND METHODS

### 4.1 Study population

The study population in this thesis comprises men diagnosed with non-seminomatous testicular cancer. In Sweden, the handling of these men is guided by the Swedish-Norwegian cancer-care programs by SWENOTECA. Since 1981, with a break between 1987 and 1989, assigned clinicians have prospectively reported clinical data to the SWENOTECA database. In this database we identified 1221 living men diagnosed between January 1981 and December 2004 who on 15 January 2007 were between age 18 and 75 and had a residential address in the Swedish population-based register of all citizens. These men were treated according to four different SWENOTECA protocols (figure 1). The SWENOTECA database is regularly matched with the Swedish cancer registry and has a close to 100 percent coverage of the studied population. In Paper 2 and 4 we excluded 29 patients for various reasons: treated for brain metastases (n=12), incomplete treatment information (n=2), died after introduction letter was sent (n=1), ongoing cancer disease (n=2), did not understand the Swedish language (n=5) and resided/lived abroad (n=7), leaving 1192 eligible men. In Paper 1 and 3 we additionally excluded 19 men treated with high-dose chemotherapy and stem cell rescue, leaving 1173 eligible men.

### 4.2 Construction of the questionnaire

During an 18-month phase we constructed a study-specific questionnaire according to procedures developed at the Division of Clinical Cancer Epidemiology<sup>65-68</sup> integrating qualitative and quantitative methods as in the following steps:

1. Interviews with patients with diagnosed cognitive impairment
2. Interviews with cancer patients who have been treated with chemotherapy
3. Assignment of the content of the interviews to categories
4. Construction of questions based on the information from interviews following previously established experience of the Division of Clinical Cancer Epidemiology
5. Face validation (the questions are tested on the intended population)

6. Pilot study (questionnaire to a small number of individuals)
7. Questionnaire to the entire population

Steps 2 through 4 overlapped to some extent when some categorization of the content of the interviews as well as the formulation of questions were begun before all interviews had been completed

## 4.2.1 Interviews

To familiarize ourselves with the problems that patients with *diagnosed* cognitive impairment face in everyday life, I initially performed open interviews with patients (n=13) at the Memory Clinic of Sahlgrenska University Hospital and their relatives (n=7). Subsequently I interviewed 20 cancer survivors, recruited by clinicians working at the Department of Oncology at Sahlgrenska University Hospital, who had received chemotherapy three to eight years earlier. These 20 cancer survivors consisted of ten women who had been treated for breast cancer, two men who had been treated for lymphoma, two men treated for bladder cancer and six men treated for testicular cancer. During the final part of this process we decided our main study should focus on non-seminomatous testicular-cancer survivors.

Using an open interview format, I asked for detailed examples of behaviour in various everyday activities at work, in leisure time and when performing household activities. I asked about functioning in everyday life (for example remembering meetings, when communicating, performing several activities simultaneously) without reference to domains of cognitive function. Besides achieving an enhanced understanding of the cognitive difficulties experienced, our main goal was to identify how these difficulties are manifested through behaviour in everyday life.

Our open interviews were semi-structured and were carried out with the point of departure being “grounded theory”, a method developed by Glaser and Strauss in the 1960s.<sup>69</sup> The method is based on the principle that the theory to be developed is to be based on the data collected. Another distinguishing feature is that the analysis and collection of data go hand in hand by seeing to it that the analysis of the first body of data (read interviews) is to affect the continuation of data collection (each interview leads to new ideas for questions). The method is first and foremost inductive in that it gives rise to specific hypotheses, but it is also deductive in as much as the hypotheses that are developed to some extent can be tested. This combination of deductive and inductive efforts has been called “abductive efforts” by Alvesson and

Sköldberg.<sup>70</sup> At the beginning of the interview there is often some kind of prior understanding of the subject area, often based on clinical experience and/or previous research. These hypotheses are tested through the interviews (deduction), but most important is the generation of new knowledge (induction) in order to be able to refine and expand the number of hypotheses.

In interviewing, we focused on present functioning, but the men also told us about their experiences and feelings related to their cancer disease and treatment. For example, we learned that some men had feelings of loss and shame after having lost a testicle due to orchiectomy. Further, we noted that not all men had been offered a prosthesis. Several of the men distinguished their experience with physical care, which they were satisfied with, from their psychological care, which they were dissatisfied with. This background information led us to formulate and add some additional items to our questionnaire, otherwise primarily focusing on behaviour in everyday life.

## **4.2.2 Categorization**

A secretary transcribed the recorded interviews. In order to obtain a deeper understanding of each subject's personal situation, I read each interview at least three times. The meaning-bearing units were categorized with respect to content. For example, the meaning-bearing unit "looking for things" was sorted into a single category: "forgetfulness". Furthermore, various kinds of problems in speech were placed into the single category "communicating", which also formed a theme and a title for one of the chapters in the questionnaire. As the main purpose of the interviews in our study was to identify experiences of everyday life, that is behaviours indicative of cognitive dysfunction that could be transformed into concrete questions to be used for a study-specific questionnaire, we concentrated our efforts on sorting interview data, rather than creating themes.

## **4.2.3 Construction and choice of questions and response scales**

When phrasing questions for the questionnaire we tried to use the wordings given by the survivors as exactly as possible, without compromising the conceptual entity. A recurring concern was: "What are the conceptual entities that can be identified?" If an informant complained about difficulties with speech, did he provide examples of the specific type of difficulty he experienced? If, for example, he was more specific and said that he often "dropped words", did we know what he meant by that? Did he mean that he simply forgot to say a word or that he had difficulty in completing sentences?



And if someone said that he had said the wrong word, what was the exact nature of that mistake? The task of transforming the behaviour identified in the interviews into questions that could be part of our questionnaire consisted in part of trying to identify the conceptual entity the informant was referring to and in part to consider whether the question could be understood by others. Expressions such as “difficulties with speech” were transformed to concrete examples of different types of difficulties with speech. Examples given by informants such as “saying something wrong” were transformed to more precise conceptual definitions such as, for example, “to say the words in the wrong order”. The choice of the formulation of questions and response alternatives was also based on experience and results from previous questionnaires developed at the Division of Clinical Cancer Epidemiology.

We developed response scales trying to match each concept as carefully as possible. For questions about frequency such as “Have your words come out in the wrong order, in the past month?” we used a person-incidence scale with the verbal categories “No”, “Yes, less than once a week”, “Yes, at least once a week”, “Yes, at least three times a week” and “Yes, at least once a day”. For another type of question with frequency responses such as “Have you had difficulties concentrating during conversations with others, in the past month?” we found a person-prevalence scale: “No”, “Yes, on some occasions”, “Yes, less than half of the time”, “Yes, more than half of the time” and “Yes, all of the time” to be more appropriate. All questions were restricted to experiences during the preceding month without any reference to before or after cancer treatment.

Starting with about 800 questions originating from the interviews we gradually reduced the number of questions to about 300 by excluding questions that resembled one another. As the questions were based on interviews from different populations, we decided to give priority to questions concerning the difficulties that testicular-cancer survivors had described. Since we planned to also use the questionnaire for a group of patients from the Memory Clinic who had memory-related problems, personnel from the clinic took part in choosing which questions should be retained, taking into consideration their relevance to this particular population. Furthermore we prioritized questions with a clear conceptual entity and those that could be answered by giving a category on a person-incidence scale.

#### 4.2.4 Validation of the questionnaire

At this stage, to ensure that all questions and answer alternatives were both relevant and fully understood, I accompanied 20 men, who had been treated for testicular cancer between three and nine years earlier, while they filled out the questionnaire. In addition to questions derived from the interviews, the questionnaire contained questions about well-being, neurological symptoms, sexual activity, demographics and the Hospital Anxiety and Depression Scale (HADS).<sup>71</sup> The informants were encouraged to spontaneously express both questions they had as well as personal reflections that might arise as they were filling in the questionnaire.

The primary goal at this stage was to determine if there was something essential that we had missed (validation of content). The interviews were indirectly evaluated in this way. If we had not carried out a sufficient number of interviews we should during this stage, given that we are sufficiently attentive, be given additional examples of changes in behaviour that can be caused by cognitive dysfunction (which we did not). Face-to-face validation also gave us the chance to see if some questions or alternative answers were unclear or differently understood by different individuals (validation of interpretation). The men were encouraged to “think aloud” and express questions they had that had arisen during the interviews. In order to ensure that neither the subjective opinion of the interviewer (JS) nor the comparable opinions of others in the research group would alone guide the choice of question formulation and alternative answers, we saw to it that the opinions of the 20 testicular-cancer survivors were given priority in choosing between similar questions and similar alternative answers (validation of choice). During this stage, the total number of questions was reduced to 292.

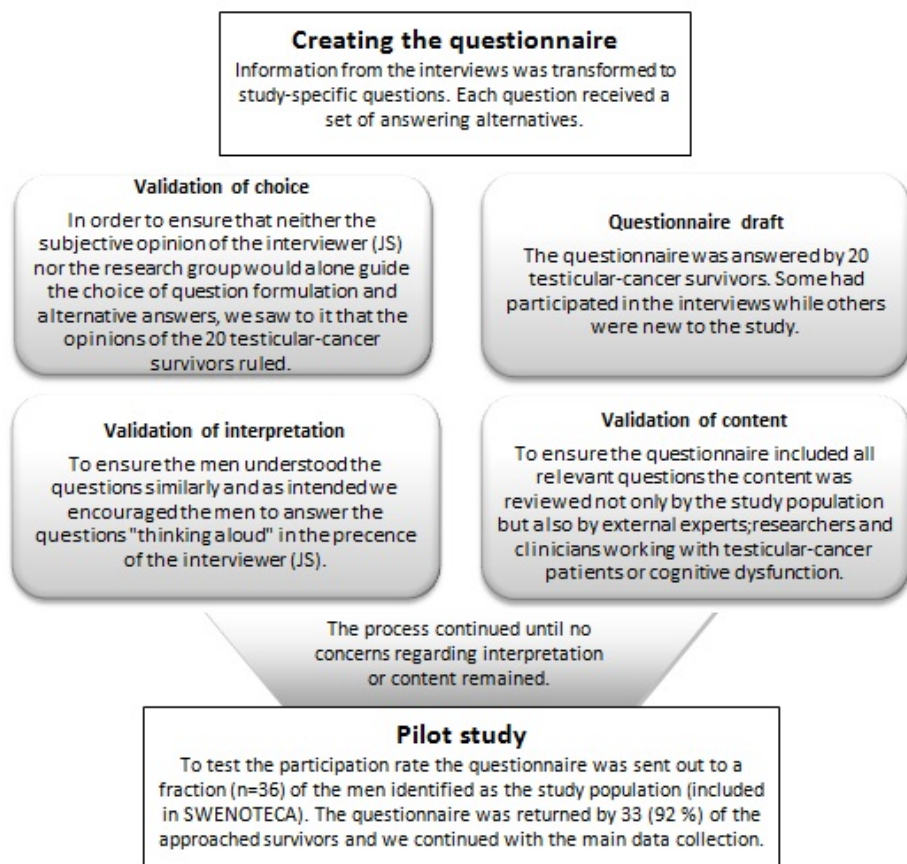


Figure 1. Overview of the steps in the validation process of the questionnaire

#### 4.2.5 Pilot study

To test our data collection methods and see whether or not the men would leave certain questions unanswered we performed a pilot study of 36 testicular-cancer survivors that indicated what a likely participation rate would be. After receiving 33 of 36 questionnaires we proceeded to the main study, including three additional questions about treatment procedures. The final questionnaire included 295 questions sorted into 19 sections according to common themes.

**Section: Title (Number of questions)**

1. Questions about your treatment (12)
2. Well-being (25)
3. Conversation (34)
4. Read, Write, Watch TV and Listen to music (16)
5. Travel and Orientation (8)
6. Buy, Cook and Eat food (19)
7. Cleaning and other Household activities (25)
8. Economy and Purchases (7)
9. Work, Leisure and Energy (27)
10. Learning and Forgetting (15)
11. Thinking and Planning (8)
12. Balance and Body function (18)
13. Body Image and Sexuality (8)
14. Experienced difficulties (13)
15. Disease and Treatment (21)
16. General information (17)
17. Health (20)
18. Well-being the last week (14)
19. Questions about the investigation (6)

Each questionnaire had a code, making it possible to match answers to SWENOTECA treatment protocols.

### **4.3 Methods of data collection**

Data collection proceeded during nine months from January 17, 2007 until October 18, 2007. A patient-contact database was developed in the Epidata software program to keep track of included participants and time-points for sending and receiving the questionnaire. We initially sent an introductory letter, explaining the objectives of the study, to all eligible men. Three to four days later we made telephone calls to all of those whose phone number we found. To those who agreed to participate we mailed the questionnaire, and ten days later they received a combined thank-you and reminder card. Two weeks later an interviewer called those who had not returned the questionnaire giving the informants the possibility to ask questions or decline further participation. Reminder phone-calls followed for those who agreed.

## 4.4 Classification of the questions derived from the interviews

Before analysing data, an expert panel (Margareth Gatz, Boo Johansson, Sindre Rolstad, Johanna Skoogh and Anders Wallin) categorized the study-specific questions into broader cognitive domains best reflecting the main cognitive function engaged in the behaviour asked for in each question. This categorization was first made independently by each expert followed by a group discussion until consensus was reached. We distinguished questions of differing levels of specificity, where the more specific questions were considered to refer to a specific cognitive domain and the less specific questions to more than one cognitive domain or that they possibly also measured, for example, depression. We identified 59 questions mainly reflecting one specific cognitive domain; 6 were judged to reflect attention, 26 memory, 5 visual-spatial ability, 7 language, 2 speed and 13 executive function. These 59 questions within six domains were taken to analyses in the present report (See Appendix).

During the preparatory interviews we deliberately did not focus on which cognitive domain a certain difficulty or difficulties might be connected with. As a result, we did not strive to extract an equal number of examples for each cognitive domain. Instead, the unequal numbers of questions for the various cognitive domains reflect the amount of problems actually experienced.

## 4.5 Data entry

Assistants entered the answers from the collected questionnaires in the EpiData software program, which was pre-programmed to identify possible false entries in the form of inappropriate values, such as an effort at minimising bias. All doubtful answers, such as double-marked or written notes on the side, were decided upon me and in some cases referred to the principal investigator. These decisions were registered to enable later references as well as to ensure consistency of data-entries by different assistants, and over time. Answers to open-ended questions and all written comments were copied, identified by question and questionnaire number, to be referred to or analysed.

### 4.5.1 Statistical analyses

All statistical analyses were performed with SAS version 9.2 (see manuscript I-IV for details of statistically analyses of each study).

## 5 RESULTS

### 5.1 Participation rate and overall characteristics

Among the 1192 eligible testicular-cancer survivors, 974 (82 percent) answered the questionnaire (Paper 2 and 4). Reasons for non-participation (n=218) were “Declined to participate” (n=103), “Agreed to receive questionnaire but did not return it” (n=17), “Questionnaire was said to be returned but not received” (n=26), “Not reachable” (n=62) and “Other reasons for non-participation” (n=10). In paper 1 and 3, where 19 patients treated with high-dose chemotherapy also were excluded, 960 of 1173 (82 percent) eligible testicular-cancer survivors responded. Participation rates were not significantly different by treatment regimen. The mean age was 30 years at diagnosis and 41 years at follow-up. A majority were living with a partner (73 percent), were employed (87 percent) and born in Sweden (94 percent). The mean age of non-participants did not differ from the mean age of all men at diagnosis, study age or years since diagnosis (data not shown). For each specific question, a few men did not respond, which explains the different denominators in the tables. For further details of the population’s characteristics, see Table 1 in Paper 1–4.

### 5.2 Paper 1

To study if treatment with chemotherapy leads to self-reported compromised cognitive function we compared answers to 59 questions about behaviour among those treated with one to two, three to four or five or more cycles of chemotherapy with those treated only surgically. We found that a two to three times higher percentage of the survivors who received five or more cycles of chemotherapy, compared with those who received no chemotherapy, reported language difficulties in five of the seven analysed language questions, with p-values ranging from 0.0002 to 0.0266.

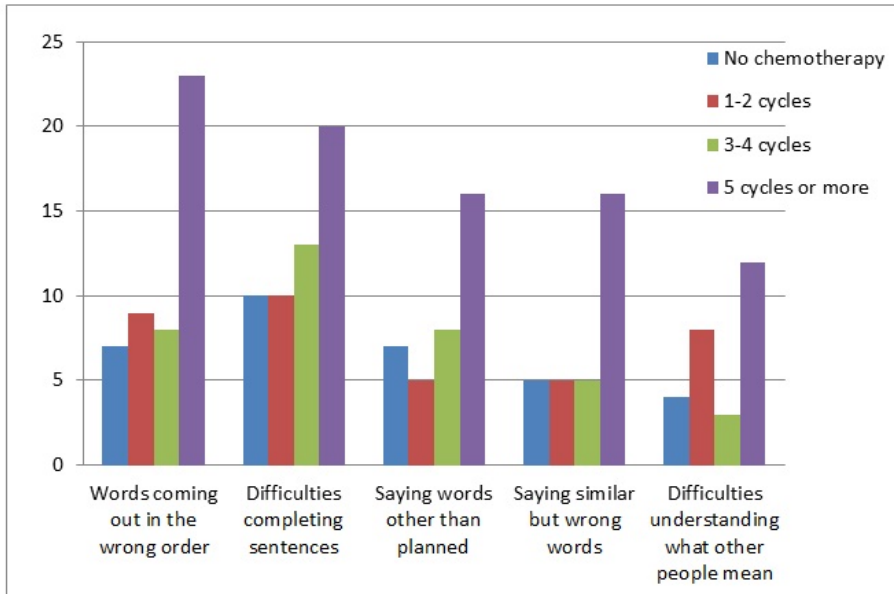


Figure 2. Experienced compromised language

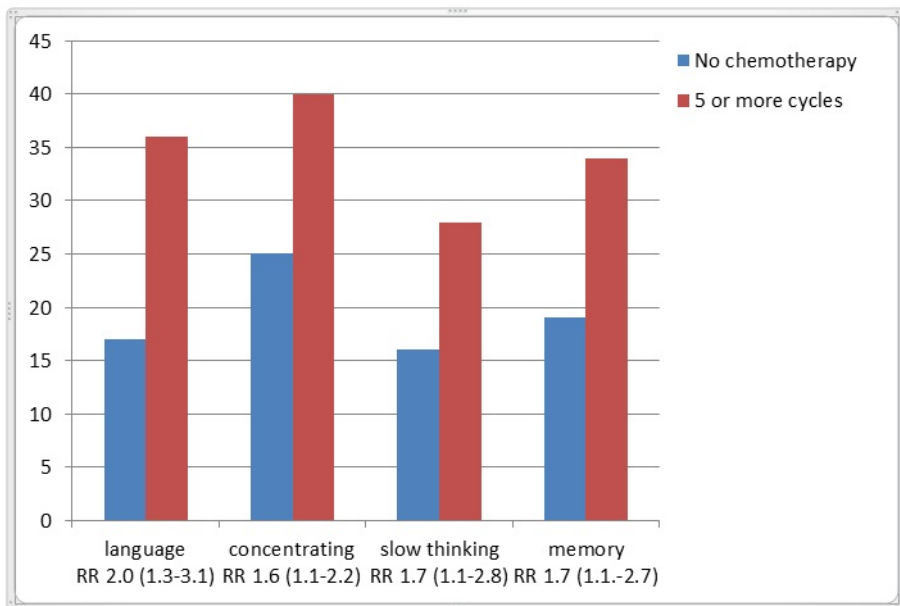
Of those treated with five or more cycles of chemotherapy 26 of 67 (39 percent) reported that they had at least one of the five language difficulties. The largest proportion reported “words coming out in the wrong order” (23 percent), thereafter “difficulties completing sentences” (20 percent), “saying similar but wrong words” (16 percent), “saying words other than planned” (16 percent) and “difficulties understanding what other people mean” (12 percent). The different language questions did not seem to largely overlap. Nine of the men (35 percent) had one of the five language difficulties, seven (27 percent) had two, five had three (19 percent), one (4 percent) had four and four men (15 percent) had all five.

When adjusting for years since diagnosis the relative risks decreased the most by 0.4 (Paper 1, Table 2), for level of education the relative risks increased or were unaffected (Paper 1, Table 2) and decreased the most by 0.3 for anxiety (Paper 1, Table 2). Among other possible confounding variables examined, such as depression, fatigue, retirement status, sexual desire, hearing, tumour stage and retroperitoneal lymph node dissection, we did not find any indications of confounding.

When examining possible effect modifiers we found the incidence of compromised language to be greatest among those with lower education level

(Compulsory and Elementary school), somewhat less among those with medium level of education (High school) and least among those with the highest formal level of education (University/College) (Paper 1, Table 3).

We also analysed the answers given to the six questions regarding affected well-being if having difficulties with language, speed, memory, concentration, visual-spatial function and executive function (Paper 1, Table 4, Figure 4). A greater percentage of those who received five or more cycles of chemotherapy, compared to those who received no chemotherapy, reported “affected well-being if having difficulties with...” language, memory, concentration and slower thinking speed, with relative risks ranging from 1.6 to 2.0. These outcomes were not related either to depression or to anxiety scores (results not shown).



*Figure 3. Affected well-being of having little, moderate or much difficulties with “Language”, “Concentration”, “Slow thinking” versus “Memory”. Relative risks are based on comparing those who received 5 or more cycles of chemotherapy with those who received none.*



## 5.3 Paper 2

The purpose of this study was to investigate how common it is for testicular-cancer patients to experience a psychological crisis due to their cancer diagnosis. Furthermore, we wanted to estimate the need for counselling and information about crisis symptoms in this group of men.

Two thirds (63 percent) of the men reported that they had experienced a crisis due to their cancer diagnosis, to some extent (36 percent), to a large part (12 percent) or completely (14 percent). For most men (76 percent) the crisis was worst at the time of diagnosis and treatment (Paper 2, Table 2). We did not find that the percentage of men who experienced a crisis was statistically significantly related to tumour stage, age at diagnosis, time since diagnosis, civil status, or education (Paper 2, Table 3).

Of those *not* informed about stress and crisis reactions, 353 (69 percent) wished that they had been (Table 5), and of those *not* offered counselling 251 (62 percent) wished that they had been (Table 6). The percentage who wished they had been informed or offered counselling did not significantly differ from the rest depending on civil status, age at diagnosis or tumour stage (Paper 2, Table 5 & 6).

## 5.4 Paper 3

In this study we wanted to investigate how common “feelings of loss” and “feelings of uneasiness or shame” are among testicular-cancer survivors who have had one or two testicles removed by orchiectomy.

We found that 313 (33 percent) of those 960 men who had one or two testicles removed by orchiectomy answered either that they missed their removed testicle(s) now (16 percent) or had missed it/them previously (16 percent). We also found that 250 (26 percent) of all responding men had (13 percent) or previously had had (13 percent) feelings of uneasiness or shame about their body because of the removed testicle(s) (Paper 3, Table 5). Feelings of loss and uneasiness or shame were more common among younger men (20–34 years old) compared with older men (44–74 years old) and more common among singles compared to non-singles (Paper 3, Results).

Of the 960 men who underwent orchiectomy, 337 (35 percent) diagnosed between 1981 and 2004 were offered a prosthesis (Paper 3, Table 2). It was more common among men who had never been offered a prosthesis to report that they had feelings of loss (RR 2.0, 95% CI 1.3–3.0) and uneasiness or

shame (RR 2.0, 95% CI 1.3–3.2) compared with those who had been offered, but rejected a prosthesis (Paper 3, Table 4, 5)

## 5.5 Paper 4

The aim of this study was to examine the use of a single-item question, when screening for depression, by comparing it with the depression subscale of the Hospital Depression and Anxiety Scale (HADS-D) containing seven items.

Of the 974 men answering our questionnaire, 971 (99.7 percent) answered both the HADS-D and our single-item question about depression. According to HADS-D, the prevalence of depression was 8 percent with the cut-off score  $\geq 8$  (8+), and 3 percent with the cut-off score  $\geq 11$  (11+). When HADS-D was compared to our single-item question “Are you depressed?”, the cut-off value of 11+ gave a better balance of prediction (sensitivity 0.88, specificity 0.84) than the cut-off value of 8+ (sensitivity 0.73, specificity 0.87).

Fifty-nine men (6 percent) answered “Yes” to the question “Are you depressed?” while 118 (12 percent) answered “I don’t know” and 794 (82 percent) answered “No”. Among the 794 men who answered “No” to the question “Are you depressed?”, 790 (99.5 percent) were not considered as depressed according to HADS-D 11+. Of those answering “Yes”, 34 percent (20/59) were identified as depressed according to the same cut-off. The sensitivity of “Yes” compared with HADS-D 11+ was 61 percent, increasing to 88 percent when “Yes” and “I don’t know” were combined.

*Table 1. Sensitivity, specificity, positive predictive value, and negative predictive value comparing HADS-Depression to the single-item depression question depending on if “I don’t know” is counted as a “Yes” or a “No” response.*

“Answer to “Are you depressed?”	No.	Sens	Spec	Pos. pred value	Neg. pred value	False neg. No.	False pos. No.
“Yes” versus “No”+ “I don’t know”	971	0.61	0.96	0.34	0.99	13	39
“Yes” + “I don’t know” versus “No”	971	0.88	0.84	0.16	0.995	4	148

## 6 DISCUSSION

### 6.1 METHODOLOGICAL CONSIDERATIONS

#### 6.1.1 Validity

For a measurement to be valid, we need to know that it measures what it is intended to measure. When it comes to a disease this is usually decided by rates of sensitivity and specificity, thus, how many of those who are ill can be captured by a “Yes” answer and how many of those that are unaffected can be captured by a “No” answer. Depending on field, available measurements and seriousness of disease different rates of sensitivity and specificity are judged as “good enough”. To be able to trust results regarding outcomes such as if “A (exposure) leads to B (outcome)” we do not only need valid measurements but we also need to ensure quality across the entire research process, from choosing the population to analysing the results, to minimize errors (bias).

Within our research group, we have utilised epidemiological methods, as applied by the hierarchical step-model for causation of bias,<sup>72</sup> with the aim of minimising systematic errors and understanding the research process. According to the model each new phase of the study introduces a novel and special source of error: confounding, misrepresentation, misclassification and analytic adjustment (Figure below). Most examples are given from our first study, which was the main focus for the initiation of the present research and where the exposure and outcome are clearly defined.

#### **Moving from perfect to targeted person–time**

For the perfect study we would need to start with at least two study populations that are similar in all respects concerning outcome occurrence. After having introduced the exposure (A) we could measure the outcome (B) without having to worry about any kind of bias introduced. However, as we cannot clone one population into two, “the perfect study” is not attainable in real life and we must instead try to do what is second best or, at least, “good enough”. Targeted person-time is the population and time that would be possible to study in reality (in our case, all men included in SWENOTECA). The period studied is, for our outcome in study 1, the month preceding completion of the questionnaire.

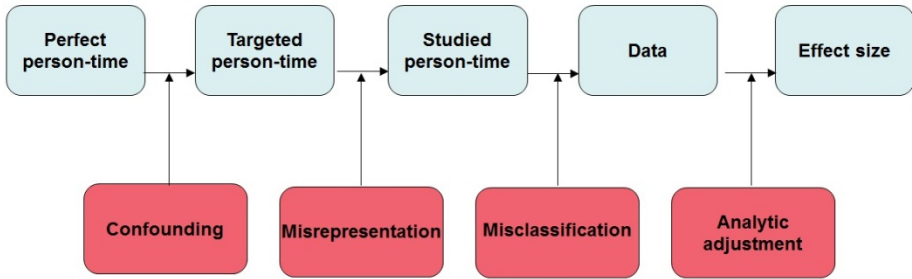


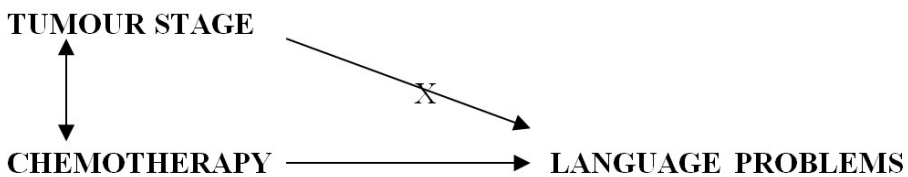
Figure 4. The hierarchical step-model for causation of bias.

## 6.1.2 Step 1: Confounding

### Confounding

Confounding occurs when your results are explained by a factor other than exposure; the factor is associated with the exposure and is an independent risk factor for the outcome. It is very important to consider possible confounding factors at the very beginning of the project to be sure that you can gather information on as many possible confounders as possible. To be able to control for confounding is central for an epidemiologic study.<sup>73</sup>

In our first paper there was a question raised about whether there might be something else rather than chemotherapy that explains why a higher percentage of those treated with five or more cycles of chemotherapy experience compromised language than those who received no chemotherapy. Those raising the questions argued that those treated with five or more cycles of chemotherapy may be a special group of patients with a more advanced disease and that this in itself explains why a higher percentage of these patients report compromised language. However, in this case there must be a factor associated with the exposure (chemotherapy) that is an *independent* risk factor for the outcome (in this case; language difficulties). For example, tumour stage is associated with chemotherapy, yes, but do we have any reason to believe that the size and spreading of the tumour itself (apart from brain metastases which are excluded) can cause language problems? Probably not.



Being an independent risk factor also implies that the factor cannot be part of a causal link. Once again there is an example from our first paper in which we found that a higher proportion of those treated with five or more cycles of chemotherapy not only experienced more language problems but also reported symptoms of anxiety. By adjusting our results for anxiety we found that anxiety, if it were a confounding factor, did not explain, but rather only partly modified our results. There is, however, a possibility that we have wrongly adjusted for anxiety not realising that this factor in fact is part of a causal link: chemotherapy causing language problems causing anxiety. If so, anxiety is not a confounding factor and should rightly not be adjusted for. Another example could be fatigue. We did not find that a statistically significantly higher proportion of those treated with five or more cycles of chemotherapy reported symptoms of fatigue, but if we had, could we be sure that high doses of chemotherapy caused fatigue that caused language difficulties:

**CHEMOTHERAPY —→ FATIGUE —→ LANGUAGE PROBLEMS**

or could it just as well be the high doses of chemotherapy that caused language difficulties that caused fatigue?

**CHEMOTHERAPY —→ LANGUAGE PROBLEMS —→ FATIGUE**

In the former case, fatigue is a confounding factor while in the second case it is part of a causal link.

In order to investigate possible causal relationships, we can often make use of the existing literature, which may be able to tell us which factors have previously been shown to be related or not. As concerns newer areas of research, it may be difficult to find evidence and one must frequently be satisfied with following a process of reasoning that leads to thoughts about what factors might reasonably be related and in that case in what way. In real life many factors are not “either-or” but instead they might explain our results partly as a result of working independently of one another and/or partly being part of causal links. In our case, we have for safety’s sake adjusted for anxiety, but we cannot exclude the possibility that this factor can be part of the link of causality, and therefore is not a confounding variable.

### **6.1.3 Step 3: Misrepresentation**

If the relation between the exposure and outcome is different among non-participants and participants this will affect the validity of our results. With a high participation rate, losing as little information as possible, we minimise the effect of such a bias.

You may not always know who your non-responders are, in that case making a high response rate even more important. In our case, having access to SWENOTECA's data base, including personal data of all men generating our targeted person-time, we know that non-responders do not significantly differ regarding age at diagnosis, age at follow-up, years since diagnosis and number of cycles of chemotherapy received. For the first factors mentioned, non-response would probably not affect our effect measure as we found no significant relation between any of them and having language difficulties. However, with a higher percentage of non-responders among those treated with five or more cycles of chemotherapy it is possible that our effect measure would be affected.

### **6.1.4 Step 4: Misclassification**

The usefulness of a measurement instrument or diagnostic test is determined on the basis of the percentage of people having poor health or good health who are correctly recognized as being ill (sensitivity) or healthy (specificity). In order to be able to determine the sensitivity and specificity of a test/measurement instrument it must be possible to compare it with another test/measurement instrument that has already been proven to be of good quality. This test/measurement value, represents the "gold standard". If a diagnostic test has a sensitivity of 0.90 and a specificity of 0.80 this means that this test correctly identifies 90 percent of the "ill" and 80 percent of the "healthy". Where the boundary lies for a measurement/diagnostic test to be judged as "good enough" varies between different disciplines and depends on what it is that is to be measured. In this thesis you will find an example of how a diagnostic test (in this case a question) is compared with another (in this case a scale including seven questions) in Paper 4 where the single-item question with a relatively high sensitivity and specificity (0.88 and 0.84) was found to be reasonably valid.

When measuring behaviour in everyday life as done in Paper 1 we do not know to what extent the men's answers represent actual behaviour in everyday life that might exist both to a larger or smaller extent than reported. Most certainly some men are better than others at making a correct judgment. Moreover some men may have filled in our questionnaire very carefully

while other men might have answered each question more or less randomly. However, if any of these measurement errors are to be of importance for our relative risks (the size of the relationship) they must be unevenly distributed between treatment groups, something for which we found no indication. Most important, a possible decreased sensitivity (under-reporting) does not affect our relative risks (the size of the relationship) if the dropout rate is not different between treatment groups.<sup>73</sup>

## **6.1.5 Step 4: Analytical adjustment**

We adjust the effect-measures, most often the relative risk, in an effort to eliminate the errors in the previous steps, primarily confounding, but sometimes also misrepresentation and misclassification. The variables we have adjusted for in the statistical models primarily reflect the occurrence of a confounding factor. We have performed a thorough data cleaning to ensure that we do not introduce errors in this step.

## **6.1.6 Precision**

Assuming random errors to occur, we give confidence intervals around effect measures such as relative risks. We also test for statistical significance as an indication that a difference in outcome occurrence between two groups did not happen by chance. In this thesis, we have considered an effect measure to indicate a statistically significant difference when its 95 percent confidence interval does not cover 1.0. Moreover, a p-value below 0.05 in a statistical test has been considered to indicate statistical significance.

# 7 FINDINGS AND INTERPRETATIONS

## 7.1 Paper 1

We did not find that testicular-cancer survivor treated with four or less cycles of cisplatin-based chemotherapy had any symptoms of compromised cognitive function. However, since data from breast-cancer patients indicate that chemotherapy-induced cognitive dysfunction decreases with time<sup>74</sup> it is possible we would also have found a greater incidence of compromised cognitive function among those treated with fewer than five cycles of chemotherapy if we had had a shorter follow-up time.

When chemotherapy-induced cognitive dysfunction has been found it is not so often language, but mostly memory, concentration or speed that are found to be affected.<sup>24</sup> If we hypothesize that different chemotherapeutic agents affect different cognitive domains, one reason that language findings are rare might be that most studies have been performed within the breast-cancer population who partly are treated with drugs different from those used on testicular-cancer patients. Another reason language findings are rare might be that the cognitive tests, which most results rely on, are not always equally balanced. While most cognitive batteries include several memory tests, language function is not always measured accurately. Thus, our language findings might be quite unique because language has not been measured sufficiently in any other studies.

Answers to our more global questions about self-assessed cognitive dysfunction indicate that not only language but also memory, concentration and speed might be affected by chemotherapy. It is possible that these questions, by being linked to well-being, compromise the identification of other kinds of difficulties with language, memory, concentration and slow thinking more than our specific questions about behaviour do. Another possible explanation why answers to our more global questions indicate a broader effect might be that a higher degree of consciousness is required to be able to quantify one's behaviour than just state that one has a difficulty that affects one's behaviour. In this case there could be an unknown number of men answering "No" to having specific problems like "Saying words in the wrong order" simply because they are unable to assess how frequently they experience this specific language problem.

In our study, the level of education modifies the effect on self-reported compromised language resulting from five or more cycles of chemotherapy.



The association between education and cognitive function is a rather well established fact.<sup>75-78</sup> One reason that highly educated people seem to withstand the effects of aging better than less well educated might be that they have a larger “cognitive reserve”.<sup>76</sup> Stern, who coined this concept, explains cognitive reserve as a combination of genetic and environmental components protecting the individual from cognitive decline through higher resilience against aging and brain damage. One hypothesis is that the cognitive reserve works through compensation and recovery.<sup>76</sup> Possibly someone with a higher level of education easier finds new strategies and by using them learns to compensate for the damage. It is also possible that those with a higher level of education find themselves in a more active and intellectually stimulating environment that results in their being better equipped thanks to this training and being able to more quickly stimulate the neural network to recover after being damaged.

High education + chemotherapy → no or small brain damage

Low education + chemotherapy → larger brain damage

High education + chemotherapy → brain damage → good recovery

Low education + chemotherapy → brain damage → worse recovery

*Figure 5. Possible genetic and environmental casual explanations why education modifies the effect of our language findings*

As those troubled by testicular cancer are of an age where decisions about education are made, you might question the causal link. Did we find that a higher percentage of those with a lower level of education had chemotherapy-induced compromised language because they were more strongly affected or recovered less well, or is it that those affected worst by chemotherapy-induced compromised language function made other educational choices? We did not find any association between age at diagnosis and years of education which we, however, should have found in this case.

Men who received five or more cycles of chemotherapy received higher doses of cisplatin and etoposide (Paper 1, Figure 5). It is possible that the cut-off between four and five cycles is a critical threshold at which the cumulative dose of cisplatin or etoposide affects language. A high percentage of those who received five or more cycles of chemotherapy were treated with ifosfamide, which was only used for a small percentage of those who received less than five cycles (Paper 1, Table 1). “Ifosfamide

encephalopathy” is an acute state occurring in up to 30 percent of those who receive ifosfamide.<sup>79</sup> Confusion and delirium are common acute symptoms,<sup>80</sup> suggesting that ifosfamide may pass the blood-brain barrier affecting cognitive function (e.g., language) even on a long-term basis.

It is consistently observed that the percentage of cancer survivors reporting impaired cognitive function is greater than what can be confirmed in neuropsychological test performance.<sup>26</sup> This may result because many patients report impairment that has actually not occurred, but it might also result because the test that is used has low ecological validity (does not measure behaviour in everyday life) and/or is not sensitive enough to recognize the subtle forms of impairment that chemotherapy-induced cognitive dysfunction often seems to be associated with.<sup>29</sup> When interpreting results from answers to questions that are concerned with measurement of cognitive function it is important to distinguish questions about self-reported behaviour (e.g., “Do you say a similar but incorrect word?”) and questions about self-assessed function (e.g., “How is your language function?”). For the latter type of questions, researchers have documented that answers may be confounded by emotional distress.<sup>26,81</sup>

Detailed investigations of potential effects of chemotherapy across cognitive domains are as important in future studies as examining whether chemotherapy specifically affects language. Cognitive rehabilitation shown to be effective for other groups of cognitively impaired<sup>82</sup> may also be applicable to cancer survivors who experience chemotherapy-induced cognitive dysfunction.

## 7.2 Paper 2

The great number of testicular-cancer survivors (66 percent) that retrospectively reported that they experienced a crisis in connection with their illness suggests that a substantial proportion of men experienced this as a traumatic event. Compared to the men with a less serious disease we did not find that a higher number of the men with a more serious disease experienced a crisis (table 3). This result supports data from other studies that suggest it is not cancer-related variables that decide who will suffer most psychologically when diagnosed with testicular-cancer<sup>58</sup> but factors such as personality (neuroticism),<sup>59</sup> being single,<sup>57</sup> low education,<sup>57</sup> and unemployment.<sup>57</sup>

Of all men one third reported that they were offered professional counselling at some time during their illness. Even though this number, as well as the number informed about crises and stress reactions, has increased fivefold

(Paper 2, Table 4), comparing those diagnosed between 2000 and 2004 with those diagnosed during the 1980s there is still in the period 2000–2004 a great discrepancy between the number who wish they had been informed or offered professional counselling and the number who actually were informed/offered counselling (Paper 2, Table 4–6).

About two thirds of the men wish they had received information about crisis and stress reactions (Paper 2, Table 5). A similar percentage of the men wish they had been offered professional counselling (Paper 2, Table 6). We have no specific information about what the men might have wanted to talk about. One theme might be processing the psychological trauma experienced. Besides the fact that being afflicted by a potentially deadly disease might trigger existential thoughts we also know that many men diagnosed with testicular cancer are preoccupied by thoughts related to sexual functioning and fertility.<sup>45,49</sup>

### 7.3 Paper 3

We found that feelings of loss and shame due to having had one or two testicles removed by orchiectomy not only arise at the time of surgery, but also persist thereafter for a substantial percentage of Swedish testicular-cancer survivors. These feelings were more common among younger and single men compared with older and non-single men. We found no relationship between feelings of loss or uneasiness and shame and having or not having a prosthesis. However, a higher percentage of those who never had been offered a prosthesis reported these feelings than did those who had been offered, but rejected a prosthesis.

Feelings of shame are a quite common theme in interview studies with testicular-cancer patients.<sup>83,84</sup> However, we found no data regarding feelings of loss after having had a testicle removed by orchiectomy. One reason might be that feelings of loss are more indirect and not merely felt with regard to the testicle. As the testicles, at least for a percentage of men, are regarded as an important part of masculinity<sup>49,83</sup> feelings of loss might be related to having lost part of one's self-image.

Comparing the minority of men in our study having a prosthesis (n=29) with those who did not, we did not find any difference in the percentage having feelings of loss or uneasiness and shame. However, compared with the men who rejected an offered prosthesis, we found that a higher percentage of those who had not been offered a prosthesis had long-lasting feelings of loss and uneasiness or shame. High preparedness of a forthcoming psychological

trauma can decrease the risk of psychological morbidity afterwards.<sup>85,86</sup> It is possible that simply asking “Would you like to have a prosthesis?” starts psychological processes that increase preparedness for what will come, and this in turn decreases the likelihood for experiencing long-lasting feelings of loss and uneasiness or shame.

## 7.4 Paper 4

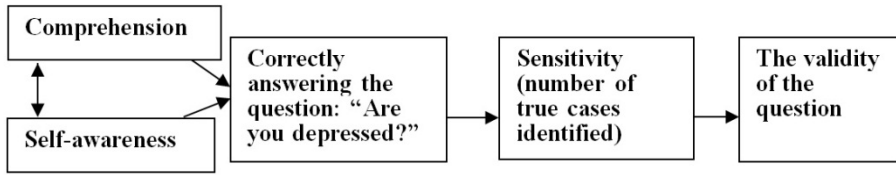
We found that almost none of those responding “No” to the written question “Are you depressed?” were depressed according to HADS-D 11+. The fact that a substantial percentage of the men answered “I don’t know” when asked if they were depressed indicates that more than a simple yes-or-no alternative is needed when asking about depression.

It is possible that those answering “I do not know” have difficulties assessing their own state of mind. It is also possible that a certain percentage is unsure of how to perceive the concept of depression. Thus, it is reasonable to believe that giving a valid answer to the question “Are you depressed?” relies both on self-awareness and comprehension, factors that besides being very likely to be highly related when it comes to answering a question about depression, probably vary between different populations.

Depending on how much a society focuses on the individual’s psychological well-being the concept of depression might be more or less well-known, affecting the ability of the individual to correctly assess his or her state of mind. Within the same society it is also possible to think of populations that compared to each other understand the concept of depression more or less well and are better or worse at assessing their own state of mind. For example, compared with the normal population, it is not impossible that a higher proportion of the individuals in a psychiatric population (being diagnosed by a psychiatrist, having undergone psychoeducation) understand the concept as well to a higher extent are able to judge if their state of mind would be categorized as depressed or not. However, if the perception of reality is affected this relation might instead be opposite.

The reasoning above implies that the question “Are you depressed?” will identify a varying percentage of true cases (sensitivity) within different populations. Thus, in a population where the understanding of the concept depression is high, you can expect that a higher proportion of the individuals correctly assesses whether they are depressed or not, compared to a population where the understanding of the concept depression is low. As the

usefulness of a question depends on how many cases that are identified, validity and sensitivity are directly related.



*Figure 6. The relation between comprehension, self-awareness, sensitivity and validity.*

In theory neither sensitivity nor specificity is affected by prevalence. This implies that if our question is judged on the basis of the respective proportions of ill and healthy patients that the answers to this question capture, then this measurement instrument (our question), with its relatively high sensitivity and specificity, may be classified as usable independent of the occurrence of depression. If our question's usefulness is judged instead on the percentages of true "Yes" answers, and/or on the percentage of true "No" answers no answers (the positive and negative predictive value), which stands in a direct relation to the occurrence of illness, then the usefulness of the question can depend on the percentage of depressed respondents. With increasing prevalence, the positive predictive value increases at the same time that the negative predictive value decreases.

For example, when the prevalence of depression according to HADS-D  $\geq 11$  rises from 3 to 28 percent the negative predictive value decreases to 0.95 while the positive predictive value increases to 0.70. This means that our conclusion that a no is a no is relatively stable and that our question can be used to sort out non-depressed individuals also in populations with a relatively high percentage of depressed individuals.

However, it is not until the prevalence is above 80 percent, given that sensitivity and specificity are constant, before the positive predictive value is high enough ( $\geq 0.90$ ) to consider a "Yes" answers to be true with a relatively high reliability. Thus, to avoid unnecessary treatment, additional diagnostics are necessary if not almost all in the population are to be classified as highly depressed.

## 8 CONCLUSION

This thesis shows that being diagnosed with and treated for testicular cancer has a long-term impact for a greater proportion of testicular-cancer patients than, perhaps, has previously been acknowledged.

In conclusion we found that:

Swedish testicular-cancer survivors who receive five or more cycles of cisplatin-based chemotherapy have an increased incidence of self-reported compromised language compared to those who received no chemotherapy. Furthermore, this group of men reported experiencing affected well-being due to an even broader range of cognitive difficulties (e.g. language, memory, concentration and slow thinking).

Two thirds of Swedish testicular-cancer survivors report that they experienced a crisis due to their diagnosis. The same proportion wishes they had been informed about stress and crisis reactions and had been offered counselling.

Feelings of loss and uneasiness or shame are not uncommon even many years after having lost a testicle. Of all testicular-cancer survivors 32 percent reported that they miss or previously missed their removed testicle(s) and 26 percent that they have or previously had feelings of uneasiness or shame about their body because of the removed testicle(s). Only one third of the men reported that they were offered a prosthesis at orchiectomy

A single screening question “Are you depressed?”, gives a sensitivity and specificity of 88 and 84 percent when validated against the commonly used HADS-D scale (Almost none, i.e. 99.5 percent, of those responding “No” to the question “Are you depressed?” met criteria for depression according to HADS-D 11+). The fact that as many as 12 percent answered “I don’t know” indicates that more detailed information is needed than an answer to a simple yes-or-no question to identify potential cases.

## 9 FUTURE PERSPECTIVES

To gain an improved understanding about the effect of different chemotherapeutic agents on cognitive function we need more large-scale follow-up studies. If some agents are shown to be more harmful than others, as we hypothesize (Paper 1), it might be possible to avoid these without decreasing the total beneficial effects of chemotherapy.

Though we still lack knowledge regarding which patients are definitely affected and why these are affected, we believe it is important that all testicular-cancer patients are informed that some survivors, especially those treated with high doses of chemotherapy, *experience* cognitive side-effects. Furthermore, they should be informed that the cause for effects on the individual patient might as well be the psychological crisis itself. It is important that patients are prepared that they, independent of reason, might go through a period when their intellectual capacity will be reduced, but that in time it will return for most of them. The interviews performed during our initial qualitative phase suggest that this information, which few cancer patients receive today, can relieve much of the burden placed on the individual who otherwise often accuses himself for his reduced function.

In Paper 4 we validated our single question: “Are you depressed?” against the depression subscale of HADS. A further step could be to validate both of these measurements against “the gold standard”; a psychiatrist who, relying on the criteria from DSM-IV, decides if a person should be diagnosed as being depressed or not. It would also be interesting to explore if our single-item question is more or less sensitive in another population, hypothesizing that this is possible as comprehension and self-awareness vary. By performing interviews in different populations we might get an enhanced understanding of how the concept of depression is understood and which factors that decide if you answer “No”, “Yes” or “I don’t know”.

Encouragingly enough, our findings in Paper 3, which showed that only one third of the men had been offered a prosthesis, have already lead to an implication in the health-care and it is now enrolled in SWENOTECA’s cancer-care program that all men diagnosed with testicular-cancer should be offered a prosthesis at the time of orchiectomy. Findings from Paper 2 reveal that a majority of testicular-cancer patients experienced a psychological crisis due to their diagnosis. Furthermore, we found that they lacked psychological support, i.e. information about common stress and crisis reactions and counseling. Thus, a further implication of our results is that the health-care

system might be modified to better meet the testicular-cancer patients' psychological needs.

One way to provide the men with information about common stress and crisis reactions when being diagnosed with cancer might be through constructing an information brochure especially directed towards testicular-cancer patients. What exact information such a brochure should include would need to be evaluated before the brochure could be put into use, for example by using the methods for constructing a questionnaire used within our research group.

In addition to information on the usual stress- and crisis reactions following the diagnosis of cancer, the brochure could contain information on the thoughts and questions that are common when a man is diagnosed with testicular cancer. We know that such information is important in order to help the patient normalise thoughts and feelings that he may have difficulty in talking about or that he has difficulty putting in concrete form. With an information brochure for support, it may also become much easier for health-care personnel to initiate a conversation about issues that many people find delicate to talk about. The brochure could also preferably contain recommended reading and internet links leading to information on where one might turn if one wishes to have further talks to, for example a counselor or a psychologist.

However, before proceeding with any intervention it might be wise to investigate if testicular-cancer patients have a higher wish/need for some other kind of psychological support than we asked about. This might, for example, be done by constructing and collecting questionnaires and/or by performing (group) interviews. It is also possible to ask professionals working with these patients what kind of psychological support they think is needed. However, as neither professionals nor patients might be familiar with all the kinds of psychological support that have been developed (for example psycho-education, supportive therapy (individual or group), cognitive-behavioural training (individual or group), and expressive writing) and/or what is proved effective it is also important to investigate/review the literature.

In the end we must set "What support do the (testicular-cancer) patients want?" against "What support do others (professionals, research) consider helpful for these patients?" This must also be evaluated against "What support is already given today?", "How is that working or how is it appreciated?" and "What resources are available (money, personnel)?"



Compared with women, men are more likely to hesitate asking for psychological help<sup>87</sup> and it might therefore be important that health-care providers initiate the contact, not expecting the man to ask for help himself. Possibly, men are also more sensitive towards how the help is introduced and how it is named. In focus-group discussions with men in Scotland about “help-seeking”, and “its relation and implications for the practice of masculinity”, O’Brien et al.<sup>88</sup> found that few men expressed present or former feelings of feeling “down” or “depressed”, instead they spoke about being “stressed”.

In conclusion, an important future research priority is to learn more about what kind of psychological support testicular-cancer patients may benefit from at the time of diagnosis, during therapy and directly afterwards and to design and investigate the effectiveness of such interventions. Earlier studies indicate that the majority of the men diagnosed with testicular cancer have sufficient resources of their own to be able to manage the crisis. Possibly these patients not only *do not* have any need for any support, but maybe such support would not be at all helpful for them. Data from previous studies indicate that resources should first and foremost be focused on those who already have a low psychological health and on those with an elevated risk for developing psychological morbidity. In addition to disseminating existing knowledge of known vulnerability factors, we need to develop the tools needed to more efficiently identify the men in need of help and psychological support.

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