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Testicular-cancer survivors experience compromised language following chemotherapy: Findings in a Swedish population-based study 3–26 years after treatment

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Abstract

Background. Studies suggest an increased risk for compromised cognitive function among cancer survivors. It is unclear to what extent chemotherapy is the cause and how the dysfunction, when present, affects everyday life. The objective was to study self-reported behaviours that may depend on cognitive function, among testicular-cancer survivors who received various cycles of cisplatin-based chemotherapy by comparing them with those who did not. *Material and methods.* We identified 1173 eligible men diagnosed with non-seminomatous testicular cancer treated according to the national cancer-care programs SWENOTECA I–IV between 1981 and 2004. During an 18-month qualitative phase we constructed a study-specific questionnaire including questions about specific activities and behaviour in everyday life. *Results.* We obtained information from 960 of 1173 (82%) testicular-cancer survivors diagnosed on average 11 years previously. The prevalence of "saying similar but incorrect words" at least once a week was 5% among those having received no chemotherapy versus 16% among those having received five or more cycles, giving a prevalence ratio ("relative risk", RR) of 3.3 with a 95% confidence interval of 1.5 to 7.1. The corresponding figure for "saying words in the wrong order" was 3.1 (1.7–5.8), for "difficulties understanding what other people mean" 3.1 (1.3–7.7), for "saying words other than planned" 2.2 (1.1–4.5) and for "difficulties completing sentences" 2.0 (1.0–3.6). The relative risks for those with a low level of education ranged between 4.9 (1.6–14.9) and 15.3 (1.9–120.5). *Conclusion.* Testicular-cancer survivors in Sweden who have received five or more cycles of cisplatin-based chemotherapy experience an increased incidence of long-term compromised language; the effect is primarily seen among men with a low level of education.

The dramatic increase in the survival of patients with testicular cancer is a great success in modern oncology. Due to efficient cisplatin-based chemotherapy the cure rate has increased to more than 90% [1]. The success has produced a substantial number of young male cancer survivors. We know that peripheral neurological symptoms are common among those treated with chemotherapy, even years after treatment [2]. Our knowledge is, however, sparse about the potential cognitive side effects in this population.

A long-term study of Swedish twins showed that cancer survivors tend to exhibit compromised cognitive function [3]. Results from breast cancer populations indicate that chemotherapy, especially in high doses [4], is associated with impaired cognitive function. Available data primarily concern follow-up durations shorter than five years, and survivors have often received concomitant hormonal treatment [5–8]. Testicular-cancer survivors, not exposed to hormonal manipulations, are likely to

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provide better opportunities for examining potential cognitive long-term effects, and their influence on everyday life, as a consequence of chemotherapy.

An expert panel agreed in a workshop that we need to learn more about possible long-term effects of chemotherapy in everyday activities related to cognitive demands, adding to the information already gained from studies based on neuropsychological testing [6]. In the present study we focused on specific activities and behaviour in everyday life that may depend on cognitive function. Using this questionnaire we conducted a follow-up of Swedish men treated for non-seminomatous testicular cancer in the preceding three to 26 years. The analyses are based on a comparison between men having received various cycles of cisplatin-based chemotherapy and those not treated with chemotherapy.

Method

Study population

In Sweden, the handling of adult men diagnosed with non-seminomatous testicular cancer is guided by the Swedish-Norwegian cancer-care program 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 18 and 75 years old and had a residential address in the Swedish population-based register (Figure 1). These men were treated according to four different SWENOTECA protocols (Figure 2). The SWENOTECA database is regularly matched with the Swedish cancer register and has a close to 100% coverage of the studied population. We excluded 49 patients leaving 1173 eligible men for the analyses (Figure 1). The study was approved by the research ethics committee at The Sahlgrenska Academy in Gothenburg.

Construction of the questionnaire

During an initial 18-month qualitative phase we constructed a study-specific questionnaire according to procedures developed at the Division of Clinical
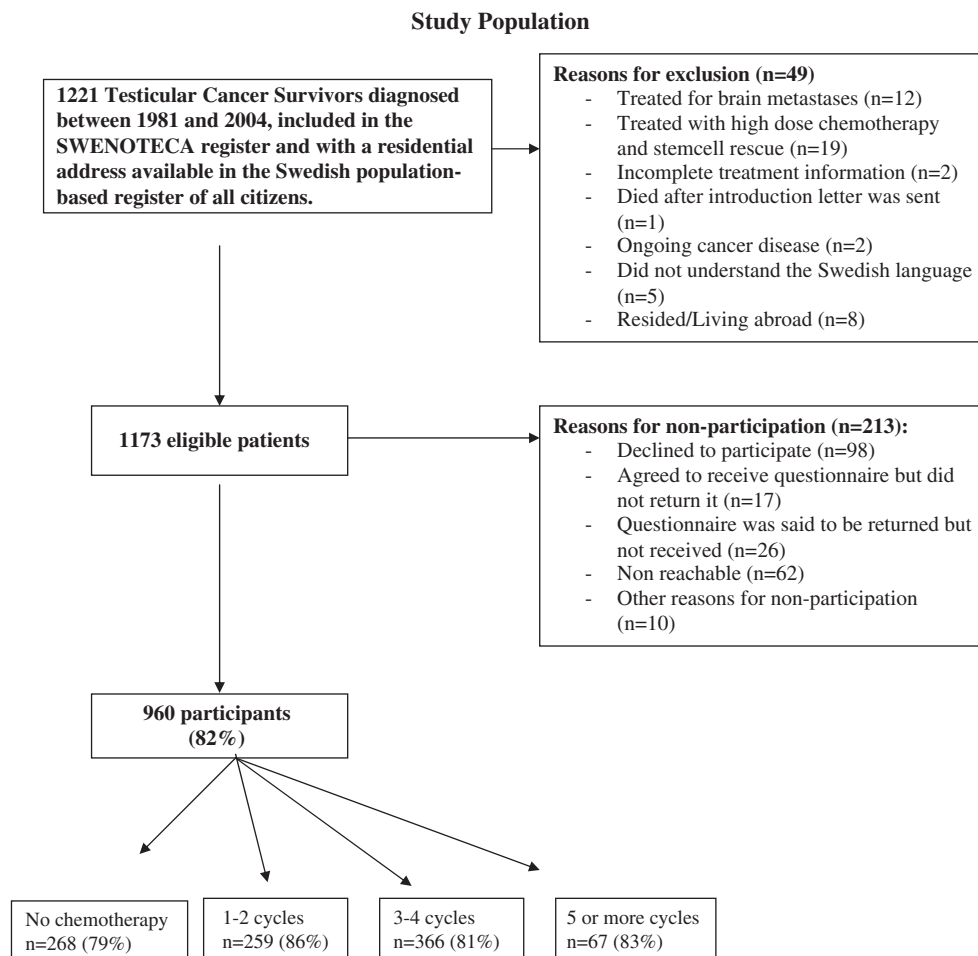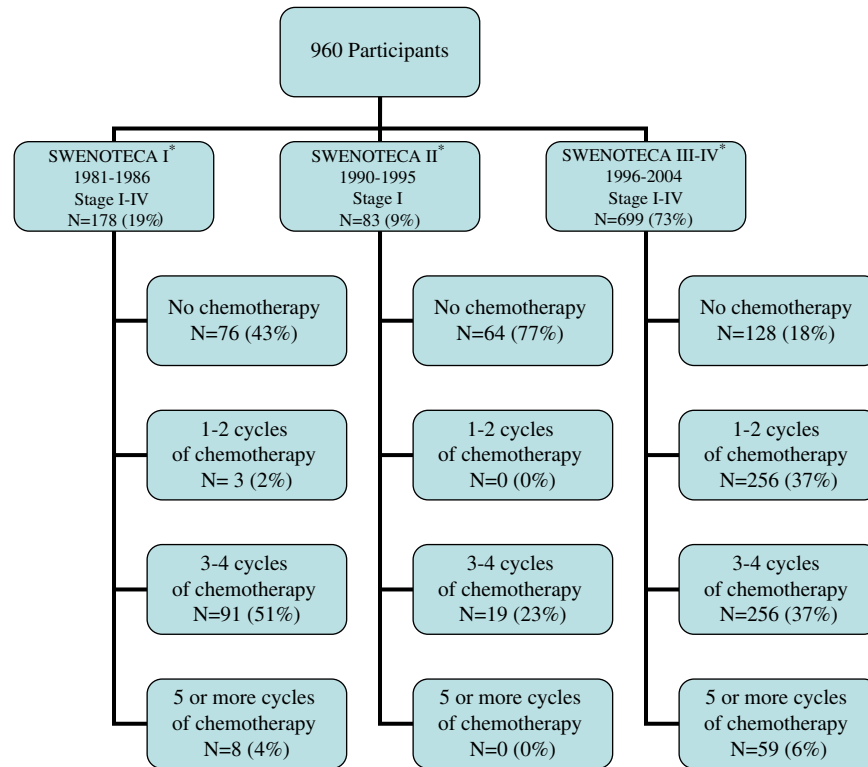
Study Population

Figure 1. Flow chart study population.

Chemotherapeutic regimens used in SWENOTECA I–IV
All regimens have a cycle length of 21 days.

BEP-if
Cisplatin 20 mg/m^2 days 1–5
Etoposide 75 mg/m^2 days 1–5
Bleomycin 30 000 IE fix dose days 1, 5, 15
Ifosfamide 1200 mg/m^2 days 1–5
Mesna 240 mg/m^{2}x3 days 1–5

CVB
Cisplatin 20 mg/m^2 days 1–5
Vinblastine 0.15 mg/kg body weight days 1–2
Bleomycin 30 000 IE fix dose days 1, 5, 15

PEI
Cisplatin 20 mg/m^2 days 1–5
Etoposide 100 mg/m^2 days 1–5
Ifosfamide 1200 mg/m^2 days 1–5
Mesna 240 mg/m^{2}x3 days 1–5

BEP
Cisplatin 20 mg/m^2 days 1–5
Etoposide 100 mg/m^2 days 1–5
Bleomycin 30 000 IE fix dose days 1, 5 , 15

Figure 2. Study population according to SWENOTECA I–IV protocols.

Cancer Epidemiology [9–12]. To familiarise ourselves with problems that patients with *diagnosed* cognitive impairment face in everyday life, we interviewed patients (n = 13) at the Memory Clinic of Sahlgrenska University Hospital and some of their relatives (n = 7). Subsequently we interviewed 20 cancer survivors who had received cisplatin-based chemotherapy three to eight years earlier.

Using an open interview format, the first author (JS) asked for detailed examples of behaviour in various everyday activities at work, in leisure time and when performing household activities. A broad range of problems were reported, for example difficulties finding the right words, being dependent on notes to aid in remembering and feelings of lack of energy. At this stage we asked in more detail about these kinds of problems without any references to affected cognitive domains, nor did we regard it as

relevant to relate experienced difficulties to treatment (chemotherapy or non-chemotherapy) in this phase. The recorded interviews were transcribed to identify distinct and concrete behaviour elements such as "word dropping" or "looking for things". These elements were then categorised into themes such as "communicating" and "forgetfulness". When phrasing questions for the questionnaire we deliberately tried to use the wordings given by the survivors as exactly as possible, without compromising the conceptual entity.

Response scales were developed to match each conceptual theme as carefully as possible. For questions about frequency such as "Have your words come out in the wrong order, in the last 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 questions such as "Have you had difficulties concentrating during conversations with others, in the last month?" we used 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. Questions considered difficult to quantify were phrased in the following manner, "Some people have difficulties learning new phone numbers. How does that apply to you?" They were to be answered on the scale: "Do not agree at all", "Agree to some extent", "Agree to a large extent" and "Agree completely". All questions were restricted to experiences during the preceding month without any reference to before or after cancer treatment.

From a total of about 800 questions retrieved from the pilot interviews we gradually reduced the number to about 300. We prioritised questions with a clear conceptual entity and those enabling the use of a person-incidence scale. To ensure that the questions and response alternatives were accurately comprehended, the first author (JS) accompanied 20 testicular-cancer survivors while they answered the questionnaire. In addition to the study-specific questionnaire, we also included questions about demographics, well-being, neurological symptoms, sexual activity, and the HADS – Hospital Anxiety and Depression Scale [13]. A pilot study of 36 testicular-cancer survivors indicated what a likely participation rate would be and whether or not the men would leave certain questions unanswered. After receiving 33 of the 36 questionnaires we proceeded to the main study [14,15]. The final questionnaire included 295 questions sorted into 19 sections according to common themes.

Methods of data collection

Data collection proceeded during nine months from January 17, 2007 until October 18, 2007. We initially sent an introductory letter to all eligible men explaining the objectives of the study. Three to four days later telephone-calls were made to all of those whose phone numbers we found. Those who agreed to participate we mailed the questionnaire. About 10 days later they received a combined thank-you and reminder card. Fourteen days 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.

Before analysing data, an expert panel [authors 1, 6, 7, 8] categorised the study-specific questions into broader cognitive domains best reflecting the main cognitive function engaged in the behaviour asked for in each question. This categorisation was first made independently by each expert followed by a group discussion until consensus was reached. We identified 59 questions mainly reflecting one specific cognitive domain; six were judged to reflect attention, 26 memory, five visual-spatial ability, seven language, two speed and 13 executive function. These 59 questions within six domains were taken to analyses in the present report.

In addition to the 59 questions about everyday life behaviour we also analysed the answers to six broader questions regarding affected well-being if having difficulties with attention, memory, visual-spatial ability, language, speed or executive function. These questions were stated in the following manner, "If you have difficulties with memory, do you experience that it has affected your well-being during the past month?". We defined those answering "Yes, little", "Yes, moderately" or "Yes, much" as experiences of compromised cognition, contrary to those answering "No, this does not apply to me as I have no memory problems" or simply "No", who were defined as not having self-assessed cognitive dysfunction.

Statistics

Results are presented as relative risks, with a 95% confidence interval (95% CI), calculated as the percentage with a specific outcome (e.g. having said words in the wrong order at least once a week, the last month), among those who received one to two, three to four, and five or more cycles of chemotherapy divided by the percentage of men, with the same specific outcome, not treated with chemotherapy. Answers were dichotomised using cut-off values according to the tradition at our division of Clinical Cancer Epidemiology, reassuring that these values were reasonable according to both the nature of the question and the frequency of having an outcome in the no-chemotherapy group.

Variables potentially affecting reported experiences (potential confounders) were systematically examined, including scores on the HADS depression and anxiety scales, fatigue, retirement status, sexual lust, hearing, tumour stage and whether the patient reported retroperitoneal lymph-node dissection. The potential confounding effects was for some variables examined through restriction, i.e. when examining depression as a confounder, we calculated the relative risk for the subgroup of non-depressed participants. In the adjustment of the relative risk for variables that may reflect confounding factors, our second strategy for examining potential confounding, we utilised the GENMOD procedure with binomial distribution and log link (SAS version 9.2), i.e. logistic regression. Possible effect modifiers were

Table I. Characteristics of men treated for testicular cancer during 1981 to 2004.

Characteristics	All men No. (%)	No chemotherapy No. (%)	1–2 cycles No. (%)	3–4 cycles No. (%)	5 or more cycles No. (%)
Total eligible	1173	339	304	449	81
Total answering the questionnaire	960 (82)	268 (79)	259 (85)	366 (82)	67 (83)
Study age					
Mean	41	44	38	41.5	40
Median	39	43	36	40	38
Interquartile range	33–48	36–51	32–42	33–49	33–47
Range	20–74	20–72	22–68	21–74	22–64
Age at diagnosis					
Mean	30	30	31	30	31
Median	29	28	30	28	28
Interquartile range	24–35	24–34	25–35	24–34	24–38
Range	16–64	16–59	16–61	16–64	17–50
Years since diagnosis					
Mean	11	14	7	12	9.5
Median	9	14	7	9	9
Interquartile range	6–14	8–22	5–9	6–17	5–11
Range	3–26	3–26	3–24	3–26	3–26
Tumor stage at diagnosis					
I	602 (63)	262 (98)	253 (98)	84 (23)	3 (4)
II	215 (22)	3 (1)	5 (2)	176 (48)	31 (46)
III	16 (2)	0 (0)	0 (0)	12 (3)	4 (6)
IV	86 (9)	0 (0)	0 (0)	58 (16)	28 (42)
Mk+	41 (4)	3 (1)	1 (0)	36 (10)	1 (1)
Mean dose of each drug for those treated					
Cisplatin mg/m^2; Mean dose (Number treated/N)			133 (258/259)	365 (365/366)	594 (67/67)
Etoposide mg/m^2; Mean dose (Number treated/N)			612 (200/259)	1837 (273/366)	2536 (66/67)
Bleomycin IE; Mean dose (Number treated/N)			119 (258/259)	288 (365/366)	299 (67/67)
Vinblastine mg/kg; Mean dose (Number treated/N)			16 (62/259)	36 (93/366)	42 (8/67)
Ifosfamide mg/m^2; Mean dose (Number treated/N)			6000 (1/259)	10909 (11/366)	15444 (54/67)
Retroperitoneal lymph node dissection (self-reported)	440 (46)	113 (43)	23 (9)	239 (66)	54 (81)
Radiotherapy (self-reported)	26 (3)	6 (2)	4 (2)	8 (2)	7 (10)
Testosterone supplement (self-reported)	96 (10)	11 (4)	38 (15)	33 (9)	14 (22)
Marital status					
Married/Cohabit	708 (73)	200 (75)	179 (69)	275 (75)	45 (67)
Live-apart	70 (7)	25 (9)	22 (8)	17 (5)	5 (7)
Single	176 (18)	39 (15)	52 (20)	64 (17)	17 (25)
Not stated	20 (2)	4 (1)	6 (2)	10 (3)	0 (0)
Level of education					
Compulsory or elementary school	119 (12)	43 (16)	18 (7)	42 (11)	14 (21)
Secondary school	546 (56)	136 (51)	154 (59)	208 (57)	38 (57)
University	306 (31)	88 (33)	86 (33)	115 (31)	15 (22)
Not stated	3 (0)	1 (0)	1 (0)	1 (0)	0 (0)
Current employment status (more than one is possible)					
Employed	849 (87)	225 (84)	227 (88)	327 (89)	57 (85)
Unemployed	36 (4)	11 (4)	8 (3)	13 (4)	4 (6)
Student	34 (3)	11 (4)	15 (6)	6 (2)	2 (3)
At home with children	10 (1)	3 (1)	2 (1)	4 (1)	1 (1)
On sick leave (long-/short-/part-time)	30 (3)	8 (3)	4 (2)	11 (3)	6 (9)

(Continued)

Table I. *(Continued)*.

Characteristics	All men No. (%)	No chemotherapy No. (%)	1–2 cycles No. (%)	3–4 cycles No. (%)	5 or more cycles No. (%)
Early retirees/Retired due to illness	39 (4)	9 (3)	9 (4)	12 (4)	9 (13)
Retired due to age	20 (2)	7 (3)	4 (2)	9 (2)	0 (0)
Not stated	7 (1)	4 (1)	1 (0)	2 (1)	0 (0)
Living; residential region					
Rural	175 (18)	58 (22)	50 (19)	53 (14)	12 (18)
Village/town	519 (53)	132 (49)	130 (50)	205 (56)	41 (61)
Large city (> 500 000 inhabitants)	277 (28)	77 (29)	78 (30)	107 (29)	14 (21)
Not stated	3 (0)	1 (0)	1 (0)	1 (0)	0 (0)
Swedish citizen					
Yes, born in Sweden	914 (94)	253 (94)	247 (95)	340 (93)	61 (91)
Yes, born outside Sweden	39 (4)	10 (4)	5 (2)	20 (5)	3 (4)
No	19 (2)	4 (1)	7 (3)	5 (1)	3 (4)
Not stated	2 (0)	1 (0)	0 (0)	1 (0)	0 (0)
HADS-Depression subscale					
Mean	2.7	2.6	2.7	2.6	2.9
Median	2.0	1.0	2.0	1.0	2.0
Cut off 8+	81 (8)	22 (8)	25 (10)	29 (8)	4 (6)
HADS-Anxiety subscale					
Mean	4.3	3.9	4.5	4.1	4.8
Median	3.0	3.0	4.0	3.0	4.0
Cut off 8+	167 (17)	37 (14)	48 (19)	64 (17)	15 (22)
Fatigue					
Often feeling tired Agree rather well/totally	259 (27)	60 (23)	78 (30)	101 (28)	20 (30)
Felt tired during daytime At least half of the days	327 (34)	82 (31)	101 (39)	118 (33)	26 (39)
Sexual desire					
Sexual desire at least once a week	828 (86)	233 (87)	234 (91)	304 (84)	57 (85)
Hearing					
Noise in the ears (beeping, murmuring and/or shrieking)	267 (28)	57 (21)	64 (25)	117 (32)	29 (44)

examined by comparing relative risks in subgroups of, for example, different educational levels. To test for the presence of effect modification, homogeneity between strata was calculated with the Cochran-Mantel-Haenszel statistic, using the CMH option in the FREQ procedure (SAS version 9.2).

Results

Among the 1173 eligible testicular-cancer survivors, 960 (82%) answered the questionnaire. Participation rates were not statistically significantly different by number of cycles of chemotherapy (Figure 1). Non-participating men and participating men had similar age at diagnosis, age at follow-up and years since diagnosis (data not shown). Demographic data are shown in Table I. For each specific question, a few men did not respond which explains the different denominators in the tables.

For answers to 51 of the 59 questions the confidence intervals overlapped 1.0 when we compared survivors who received five or more cycles of che-motherapy with those who received no chemotherapy. For eight questions the confidence interval did not overlap 1.0. Five of the eight were language questions, constituting five of the seven language questions in the questionnaire, with p-values ranging from 0.0002 to 0.0266 (Table II, Figure 3). The other three were the following memory questions: "felt uncertain about what others have said or not said", RR 2.6 (1.1–6.2, p = 0.0135), "experienced problems with memory", RR 2.5 (1.3–4.5, p = 0.0010) and "having problems learning phone numbers by heart", RR 1.6 (1.0–2.7, p = 0.0338).

When adjusting for time since diagnosis the relative risks decreased at most by 0.4, for level of education the relative risks increased or were unaffected, for anxiety the relative risks decreased at most by 0.3 (Table II). Among other possible confounding variables examined (see Statistics) we did not find any indication of confounding (results not shown).

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

Table II. Relative risk (prevalence ratio) and adjusted relative risks for experienced compromised language*.

Type of language difficulty	Definition of outcome category No./Total No. (%)	Relative Risk (95% CI) & p-values	Relative Risk Adjusted for time since diagnosis (SWENOTECA III-IV)	Relative Risk Adjusted for level of education	Relative Risk Adjusted for anxiety
Saying similar but wrong words	Occurring at least once a week				
No chemotherapy	13/267 (4.8%)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–2 cycles	14/259 (5.3%)	1.1 (0.5–2.3)	1.1 (0.4–2.7)	1.2 (0.6–2.6)	1.0 (0.5–2.1)
3–4 cycles	18/366 (4.9%)	1.0 (0.5–2.0)	1.4 (0.6–3.5)	1.1 (0.5–2.2)	0.9 (0.5–1.8)
5 or more cycles	11/67 (16.4%)	3.3 (1.5–7.2)	3.5 (1.3–9.2)	3.6 (1.7–7.8)	3.0 (1.4–6.3)
		p-value 0.0011			
Difficulties understanding what other people mean	Occurring at least once a week				
No chemotherapy	10/265 (3.7%)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–2 cycles	20/260 (7.6%)	2.0 (0.9–4.2)	1.7 (0.7–4.1)	2.3 (1.0–4.9)	†
3–4 cycles	12/362 (3.3%)	0.8 (0.3–2.0)	0.9 (0.4–2.5)	1.0 (0.4–2.3)	†
5 or more cycles	8/66 (12.1%)	3.2 (1.3–7.8)	2.9 (1.1–8.1)	3.4 (1.4–8.5)	†
		p-value 0.0079			
Words coming out in the wrong order	Occurring at least once a week				
No chemotherapy	19/267 (7.1%)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–2 cycles	24/259 (9.2%)	1.3 (0.7–2.3)	1.0 (0.5–1.9)	1.4 (0.8–2.5)	1.0 (0.6–1.7)
3–4 cycles	28/363 (7.7%)	1.0 (0.6–1.8)	1.1 (0.6–2.2)	1.1 (0.6–2.0)	1.2 (0.7–2.1)
5 or more cycles	15/66 (22.7%)	3.1 (1.7–5.9)	3.0 (1.5–6.0)	3.3 (1.8–6.3)	2.6 (1.4–4.7)
		p-value 0.0002			
Saying words other than planned	Occurring at least once a week				
No chemotherapy	19/267 (7.1%)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–2 cycles	14/260 (5.3%)	0.7 (0.3–1.4)	0.6 (0.3–1.4)	0.8 (0.4–1.5)	0.7 (0.4–1.3)
3–4 cycles	30/366 (8.1%)	1.1 (0.6–2.0)	1.3 (0.6–2.6)	1.1 (0.7–2.0)	1.0 (0.6–1.8)
5 or more cycles	11/67 (16.4%)	2.3 (1.1–4.6)	2.1 (0.9–4.8)	2.3 (1.1–4.5)	2.1 (1.0–3.9)
		p-value 0.0183			
Difficulties completing sentences	Occurring at least once a week				
No chemotherapy	26/266 (9.7%)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–2 cycles	26/254 (10.2%)	1.0 (0.6–1.7)	0.9 (0.5–1.6)	1.0 (0.6–1.8)	1.0 (0.6–1.6)
3–4 cycles	46/362 (12.7%)	1.3 (0.8–2.0)	1.3 (0.7–2.2)	1.3 (0.8–2.0)	1.2 (0.8–1.9)
5 or more cycles	13/66 (19.6%)	2.0 (1.0–3.7)	1.6 (0.8–3.3)	2.0 (1.1–3.6)	1.8 (1.0–3.2)
		p-value 0.0266			

*Relative risks are based on comparing those who received 1–2 cycles, 3–4 cycles versus 5 or more cycles with those who received no chemotherapy.
†Estimation was not possible due to small numbers.

**Experienced compromised language, frequency above cut-off,
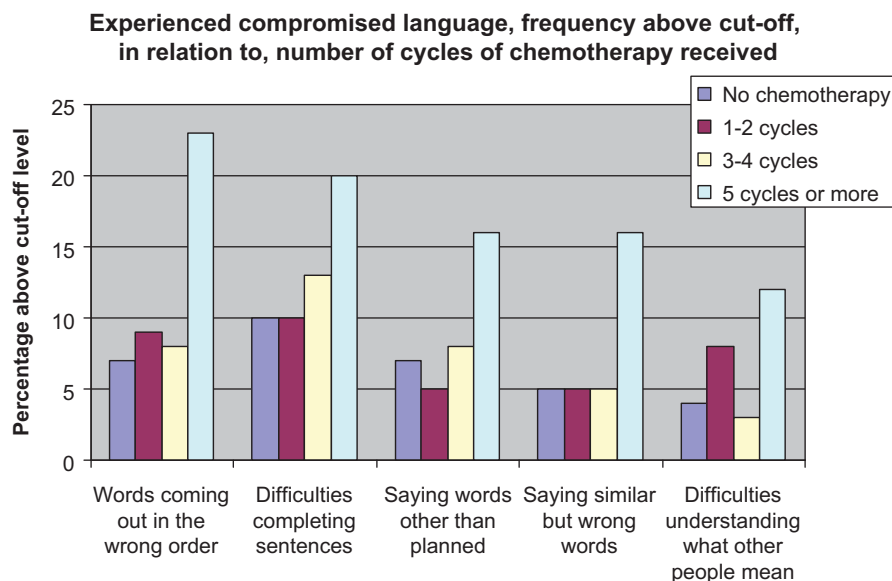in relation to, number of cycles of chemotherapy received**

Figure 3. Experienced compromised language.

(Compulsory and Elementary school), somewhat less among those with medium level of education (High school) and least among those most highly educated (University/College). Thus, level of education modified the effects from five or more cycles of chemotherapy with p-values ranging from 0.0001 to 0.0229 for the different language questions (Table III). Among those who received no chemotherapy we found no association between compromised language and educational level. We did not find any association between age at diagnosis and level of education (results not shown).

To separate a possible effect of different treatment strategies from a possible effect of time since diagnosis we restricted our analyses to those patients included in the SWENOTECA III-IV protocols, who had received similar treatment regiments (Figure 2). When stratifying into two groups referring to time since diagnosis, and comparing those who received five or more cycles with those who received no chemotherapy, we found that the point estimate of the relative risk was greater in four of five language questions among those treated 8–11 years before follow-up than among those treated more recently. For example, the relative risk of "saying similar but wrong words" at least once a week was 4.9 (1.0–25.5) for those treated between 1996–1999 and 2.8 (0.9–9.1) for those treated between 2000–2004 (p = 0.0076).

Additionally, we 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 (Table IV, 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 to either depression or anxiety scores (results not shown).

Discussion

We found a greater incidence of experienced long-term compromised language among those who had received five or more cycles of cisplatin-based chemotherapy compared with those not treated with chemotherapy. The extent of this effect was related to education.

In three prior studies concerning testicular-cancer patients and cognition none included patients treated with more than four cycles of chemotherapy [16–18]. On average three years after treatment, Schagen and co-workers found that cognitive problems in the domains of memory, attention, thinking and language were experienced by 22 (32%) of 70 testicular-cancer survivors who had received four cycles of chemotherapy, 18 (32%) of 57 who had received radiotherapy to abdominal lymph nodes and 15 (27%) of 55 testicular-cancer survivors who had received neither chemotherapy nor radiotherapy [18]. Results for specific cognitive domains were not reported. In a European study with information from 286 of 666 testicular-cancer survivors treated with three or four cycles of chemotherapy, Fosså and colleagues found that 24% reported better and 19% worse cognition two years after treatment, compared with their pretreatment level [16]. These results were based on answers given to two questions about

Table III. Relative risks (prevalence ratio) for experienced compromised language stratified for level of education[*].

Definition of outcome category Type of language difficulty	No./Total No. (%) Relative Risk (reference)	No./Total No. (%) Relative Risk	Chi-sq; P-value[†]
Saying similar but wrong words	No chemotherapy	5 or more cycles	
All men	13/269 (4.8%)	11/67 (16.4%)	
	RR 1.0	RR 3.3 (1.5–7.2)	
Compulsory and Elementary school	1/43 (2.3%)	5/14 (35.7%)	
	RR 1.0	RR 15.3 (1.9–120.5)	
High School	5/135 (3.7%)	6/38 (15.7%)	11.1176; 0.0009
	RR 1.0	RR 4.2 (1.3–13.2)	
University or College	6/88 (6.8%)	0/15 (0.0%)	
	RR 1.0	RR –	
Difficulties understanding what other people mean	No chemotherapy	5 or more cycles	
All men	10/265 (3.7%)	8/66 (12.1%)	
	RR 1.0	RR 3.2 (1.3–7.8)	
Compulsory and Elementary school	1/42 (2.3%)	3/14 (21.4%)	
	RR 1.0	RR 9.0 (1.0–79.6)	
High School	6/134 (4.4%)	4/37 (10.8%)	7.1755; 0.0074
	RR 1.0	RR 2.4 (0.7–8.1)	
University or College	2/86 (2.2%)	1/15 (6.6%)	
	RR 1.0	RR 2.8 (0.2–29.6)	
Words coming out in the wrong order	No chemotherapy	5 or more cycles	
All men	19/267 (7.1%)	15/66 (22.7%)	
	RR 1.0	RR 3.1 (1.7–5.9)	
Compulsory and Elementary school	3/43 (6.9%)	6/13 (46.1%)	
	RR 1.0	RR 6.6 (1.9–22.8)	
High School	7/135 (5.1%)	6/38 (15.7%)	15.1038; 0.0001
	RR 1.0	RR 3.0 (1.0–8.5)	
University or College	8/86 (9.3%)	3/15 (20.0%)	
	RR 1.0	RR 2.1 (0.6–7.1)	
Saying words other than planned	No chemotherapy	5 or more cycles	
All men	19/267 (7.1%)	11/67 (16.4%)	
	RR 1.0	RR 2.3 (1.1–4.6)	
Compulsory and Elementary school	2/43 (4.6%)	5/14 (35.7%)	
	RR 1.0	RR 7.6 (1.6–35.2)	
High School	10/135 (7.4%)	5/38 (13.1%)	5.1747; 0.0229
	RR 1.0	RR 1.7 (0.6–4.8)	
University or College	7/88 (7.9%)	1/15 (6.6%)	
	RR 1.0	RR 0.8 (0.1–6.3)	
Difficulties completing sentences	No chemotherapy	5 or more cycles	
All men	26/266 (9.7%)	13/66 (19.6%)	
	RR 1.0	RR 2.0 (1.0–3.7)	
Compulsory and Elementary school	4/43 (9.3%)	6/13 (46.1%)	
	RR 1.0	RR 4.9 (1.6–14.9)	
High School	11/134 (8.2%)	6/38 (15.7%)	4.8102; 0.0283
	RR 1.0	RR 1.9 (0.7–4.8)	
University or College	11/86 (12.7%)	1/15 (6.6%)	
	RR 1.0	RR 0.5 (0.0–3.7)	

[*]Relative risks are based on comparing those who received 5 or more cycles with those who received no chemotherapy.
[†]Cochran-Mantel-Haenszel test for homogeneity between strata.

memory and concentration from the quality of life instrument QLQ C-30 [19].

The particular difficulties reported by men in our study who received five or more cycles of chemotherapy included a higher frequency of saying words other than planned, similar but wrong words and producing words in the wrong order, difficulties completing sentences and difficulties in comprehension. Downie et al. found similar types of language difficulties among 16 of 21 (78%) breast cancer patients in interviews two to six weeks after they received three to six cycles of chemotherapy [20]. Evidence for compromised language function after treatment with chemotherapy was also presented in a meta-analysis performed by Stewart et al. [21]. When combining results from nine individual studies on breast-cancer survivors the greatest effect sizes were observed in data from neuropsychological tests of language performance.

In our study, level of education modified the effects from five or more cycles of chemotherapy. The relationship between higher education and

Table IV. Relative risks (prevalence ratio) for affected well-being if having difficulties with…*

Difficulties with…	No./Total No. (%) Relative Risk No chemotherapy	No./Total No. (%) Relative Risk 1–2 cycles	No./Total No. (%) Relative Risk 3–4 cycles	No./Total No. (%) Relative Risk 5 or more cycles
Language	46/267 (17.2%)	47/258 (18.2%)	75/365 (20.5%)	24/67 (35.8%)
"Finding words or other language difficulties"	RR 1.0	RR 1.0 (0.7–1.5)	RR 1.1 (0.8–1.6)	RR 2.0 (1.3–3.1)
Speed	43/267 (16.1%)	55/258 (21.3%)	72/365 (19.7%)	19/67 (28.3%)
"Slow thinking"	RR 1.0	RR 1.3 (0.9–1.8)	RR 1.2 (0.8–1.7)	RR 1.7 (1.1–2.8)
Memory	51/267 (19.1%)	60/259 (23.1%)	86/365 (23.5%)	23/67 (34.3%)
"Memory"	RR 1.0	RR 1.2 (0.8–1.6)	RR 1.2 (0.9–1.6)	RR 1.7 (1.1–2.7)
Concentration	67/267 (25%)	77/258 (29.8%)	101/365 (27.6%)	27/67 (40.2%)
"Concentration"	RR 1.0	RR 1.1 (0.8–1.5)	RR 1.1 (0.8–1.4)	RR 1.6 (1.1–2.2)
Visual–spatial function	12/267 (4.4%)	15/257 (5.8%)	20/365 (5.4%)	4/67 (5.9%)
"Orientation"	RR 1.0	RR 1.2 (0.6–2.7)	RR 1.2 (0.6–2.4)	RR 1.3 (0.4–3.9)
Executive function	71/266 (26.6%)	83/257 (32.2%)	90/365 (24.6%)	23/67 (34.3%)
"Activating"	RR 1.0	RR 1.2 (0.9–1.5)	RR 0.9 (0.7–1.2)	RR 1.2 (0.8–1.8)

*Relative risks are based on comparing those who received 1–2 cycles, 3–4 cycles versus 5 or more cycles with those who received no chemotherapy.

better cognitive function is a rather well-established fact [22,23]. Valenzuela et al. found that 10 of 13 studies of the association between level of education and longitudinal cognitive decline provided evidence that those with higher level of education were more resistant to age-related changes than those with a lower education [22]. White et al. documented that those with the lowest level of education are most affected by cognitive impairment, those with mid-level education moderately affected and those with a college education not at all affected [23]. In Alzheimer's disease patients, cognitive tests and positron emission tomography (PET) imaging studies have shown that individuals with a higher education withstand the disease better than those with a lower education [24,25].

We did not find any clear effects across cognitive domains for the effects of chemotherapy. As most of us are forced to use language in numerous situations in everyday life, questions about language may be a more sensitive indicator of difficulties compared to other cognitive abilities. Noteworthy, the answers given to the questions regarding affected well-being if cognitive dysfunction is at stake suggest a broader effect than indicated by the answers to the questions about behaviour (Table IV). We found a statistically significantly higher percentage amongst those who received five or more cycles, compared to those who had not received chemotherapy that reported affected well-being due to difficulties with language, memory, concentration as well as slow thinking.
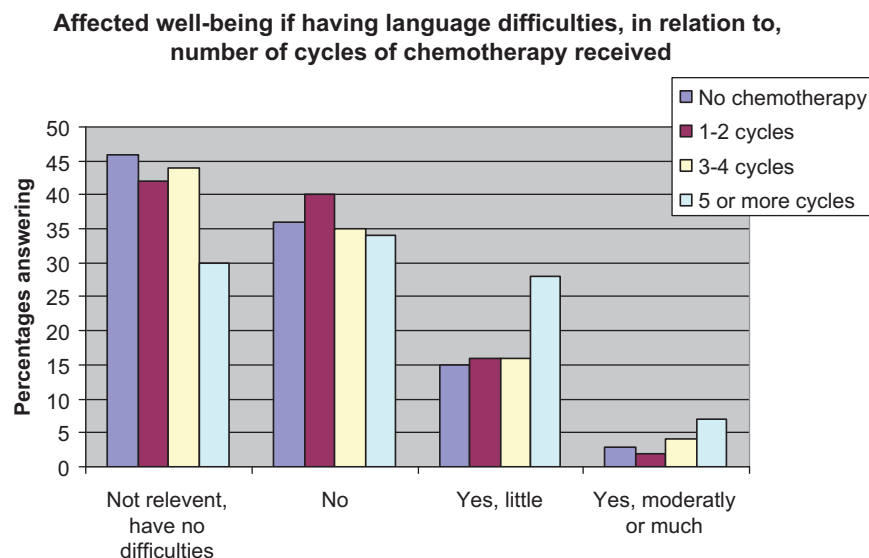
Affected well-being if having language difficulties, in relation to, number of cycles of chemotherapy received

Figure 4. Affected well-being if language having language difficulties. Answers in response to the following question: "If you have difficulties with finding words or other language difficulties, do you experience that it has affected your well-being during the past month?"
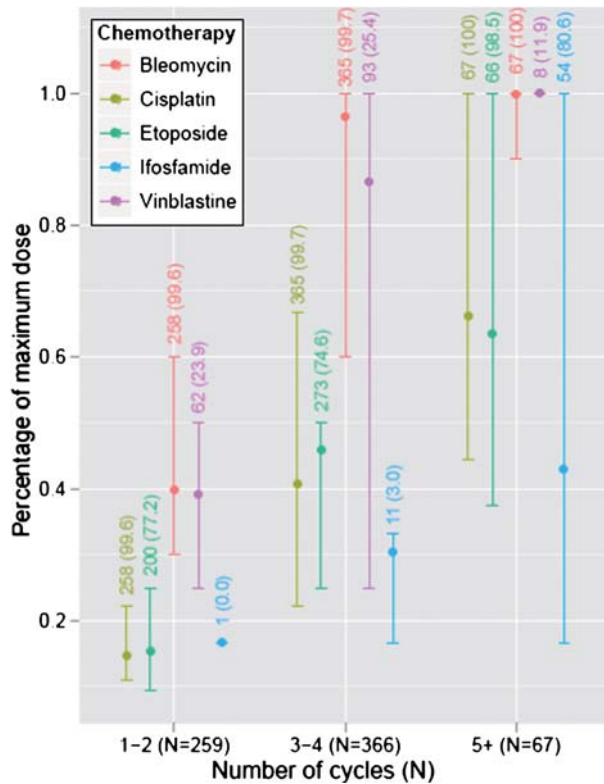
Figure 5. Minimum, maximum and mean dose, for those who received each drug respectively, standardised by dividing with the highest dose obtained. The bottom and upper part of the line stands for the minimum and maximum whereas the circle stands for the medium dose received. The numbers refer to the number and the percentage of survivors in each treatment group who have received each drug, respectively.

Men who received five or more cycles of chemotherapy received higher doses of cisplatin and etoposide (see 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. We know platinum persists for decades in various tissues of the body after treatment [26]. If it also persists in the brain it might, in common with other heavy metals, produce brain damage [27]. A high percentage of those who received five or more cycles of chemotherapy were treated with ifosfamide, which very few of those who received less than five cycles received were (Table I). "Ifosfamide encephalopathy" is an acute state occurring in up to 30% of those who receive ifosfamide [28]. Confusion and delirium are common acute symptoms, suggesting that ifosfamide passes the blood brain-barrier and has immediate effects [29,30]. These well-documented short-term effects provide reason to suspect that ifosfamide may have long-term cognitive effects, e.g. affecting language function.

One can postulate that a mechanism of chemotherapy causing experienced compromised language

is due to chemotherapy-induced lower serum levels of testosterone [31,32], or by causing more general fatigue, which in turn influences language function. Our question about "sexual desire" provided no evidence for differential effects between groups receiving varying cycles of chemotherapy. However, such a general question is neither sensitive nor specific enough compared with serum levels of testosterone [33]. Moreover, long-term fatigue after chemotherapy needs to be measured more accurately than we did in our study. We cannot exclude chemotherapy cause fatigue in testicular-cancer survivors from our data.

One may believe that our results of compromised language can be accounted for by the fact that those who received five or more cycles, compared to those who received fewer cycles, were in more advanced stages of the disease. However, we found no evidence in support of this otherwise likely objection. Self-reported language difficulties among those who received five or more cycles was not related to tumour burden, retroperitoneal lymph node dissection or compromised hearing. We excluded survivors who had brain metastases.

We employed epidemiological methods as adapted to this field by the hierarchical step-model for study design and data interpretation [12]. For practical reasons we restricted the study to Swedish men. To study experiences of everyday life, two different approaches can be distinguished. We can either ask direct questions about specific behaviour (e.g. "Do you say similar but incorrect words?") or we can ask about general self-assessed function (e.g. "How is your language function?"). For the latter type of questions, researchers have documented responses may be confounded with emotional distress [34,35]. In accordance with what has been asked for [6], and what seems more related to objective measures [35–37], we chose the former approach and deliberately focused on specific activities and behaviour in everyday life. The high participation rate reduces the likelihood of selection-induced problems. Our extensive preparatory process and the use of anonymous, self-administered questionnaires mimic the technique of blinding and prevent interviewer-related bias. Our use of a study-specific questionnaire, might be considered as a weakness since it do not allow comparisons of our results with studies based on previously developed scales and questionnaires. We cannot exclude the possibility that the association between cisplatin-based chemotherapy and cognition is different in non-participants. The extent to which these results may be generalised to other populations than Swedish men may vary by genetic and cultural differences.

Detailed investigations of potential effects of chemotherapy across cognitive domains are as

important in future studies as examining whether chemotherapy specifically affects language. For those men who seek help after experiencing cognitive problems following chemotherapy, communication about their experience of language function may well prove to be rewarding. Furthermore, experiences from language rehabilitation obtained from stroke and brain-injury patients [38,39], may be applicable also to cancer survivors treated with chemotherapy.

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