

ORIGINAL ARTICLE

Cognitive complaints and cognitive impairment following BEP chemotherapy in patients with testicular cancer

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Abstract

Introduction. There is growing concern that some cytotoxic regimens for cancer affect cognitive functioning. This study examined the prevalence of cognitive complaints and deficits in testicular cancer (TC) patients treated with the worldwide standard BEP (bleomycin, etoposide and cisplatin) chemotherapy. **Materials and methods.** Seventy TC patients treated with BEP chemotherapy after surgery (S+CT) were examined with interviews and neuropsychological tests. These patients were compared with 57 TC patients treated with radiotherapy after surgery (S+RT) and with 55 TC patients that received surgery only (S). Patients were examined a median of 3 years after completion of treatment. **Results.** Thirty two percent of the S+CT patients reported cognitive complaints compared with 32% of the S+RT patients and 27% of the S patients ($p=0.85$). No differences in mean cognitive test performance were observed between the groups. On individual impairment scores, more S+CT patients showed cognitive dysfunction compared with S patients, but not compared with S+RT patients (S+CT versus S [$p=0.038$, OR=4.6, CI=1.1–19.7], S+CT versus S+RT [$p=0.70$, OR=0.8, CI=0.3–2.4] and S+RT versus S [$p=0.070$, OR=3.7, CI=0.8–15.7]). Cognitive complaints were not related to cognitive test performance, but to emotional distress and fatigue. **Discussion.** Cognitive complaints are common among TC patients, independent of treatment modality. These complaints are related to emotional distress and fatigue and not to formal cognitive deficits. The finding of a small group of TC patients treated with chemotherapy exhibiting cognitive deficits should be confirmed in a prospective study before we can decide on its cause and relevance.

In recent years, interest in cognitive problems after chemotherapy in patients with cancer has been expanding. Several studies have indicated the occurrence of cognitive impairment in a number of patients treated with chemotherapy, based on data of predominantly breast cancer patients and lymphoma patients [1–11]. Studies on the cognitive sequelae of cytotoxic regimens other than those applied in the treatment for breast cancer or lymphoma disease are sparse and in the case of cytotoxic therapy given for testicular cancer (TC) even absent.

Testicular cancer is the most prevalent form of cancer in young men and its cytotoxic treatment is a success story in terms of survival. In the context of growing evidence for cognitive dysfunction after other cytotoxic treatments, investigation into the cognitive sequel following this BEP (bleomycin, etoposide and cisplatin) chemotherapy is relevant [12]; the BEP regimen is a world-wide standard treatment given to a young group of cancer patients, and should allow patients to regain a socially and professionally acceptable lifestyle after treatment. Many of the TC patients return to employment

and other activities for which integrity of cognitive functions is a prerequisite.

In general, TC patients treated with chemotherapy indicate levels of emotional distress and health-related quality of life similar to those of TC patients receiving other treatments. But compared to the general male population, TC patients as a whole do show a higher level of anxiety symptoms and fatigue, independent of treatment modality or intensity [13–18]. In a study by Fossa et al. on health related quality of life in testicular cancer patients treated with BEP chemotherapy [19], it was noticed that approximately 20% of patients also reported worsening of cognitive functioning on the EORTC quality of life questionnaire, two years after chemotherapy. It is not known, however, whether these cognitive complaints are exclusively linked to patients treated with chemotherapy, or that TC patients receiving other treatment strategies experience cognitive problems as well. It is also not known whether these self-reported cognitive complaints mirror cognitive difficulties as assessed with objective standardized neuropsychological tests or reflect emotional distress or fatigue — an observation which is frequently made in this kind of research and which has important implications in terms of potential rehabilitation of patients [12].

The aim of the current study is therefore to examine both cognitive complaints and neuropsychological performance of TC patients following BEP chemotherapy, in comparison with TC patients treated with radiotherapy and TC patients treated with surgery only.

Materials and methods

Patients

The study population consisted of three groups of patients with TC (either seminomatoma or nonseminomatoma) 1. TC patients who received chemotherapy after surgery (the S+CT group), 2. TC patients who received radiotherapy after surgery (S+RT group) and 3. TC patients who received surgery only (the S group). For all patients the surgical treatment consisted of unilateral orchiectomy. In case surgery was followed by radiotherapy, para-aortic and ipsilateral iliac lymphnodes were treated. The dose ranged from 20 to 30 Gray (Gy). In case surgery was followed by chemotherapy, 4 courses of BEP chemotherapy were given (bleomycin 30 mg on days 2, 8 and 15; etoposide 100 mg/m² on days 1 through 5; cisplatin 20 mg/m² on days 1 through 5).

All patients were recruited from the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in the periods between January 1994 and May 2003.

Patients had to fulfill the following inclusion criteria to be eligible for the neuropsychological study: 1) no recurrence of TC, 2) no history of neurological/psychiatric signs or symptoms that might lead to deviant neuropsychologic test results, 3) no use of medication that might lead to deviant neuropsychologic test results, 4) no alcohol and/or drug addiction and 5), basic proficiency in the Dutch language. Only patients who were off treatment for at least 6 months were enrolled in the neuropsychological study.

Informed consent was obtained from all patients according to institutional guidelines. The study was approved by the Netherlands Cancer Institute's protocol review committee and the committee for medical ethics of the Netherlands Cancer Institute.

Methods

The neuropsychological status of all patients was assessed with a standard battery of neuropsychological tests. In addition, patients were interviewed concerning cognitive problems, health-related quality of life, anxiety and depression, and fatigue.

Cognitive problems in daily life, health-related quality of life, depression, anxiety and fatigue

All patients were asked whether they experienced cognitive problems in the domains of memory, attention, thinking, and language [7,8] and were asked to indicate on a 5-point scale (1 = never, 2 = occasionally, 3 = regularly, 4 = often, or 5 = always) how often the problems in each of these domains occurred in their daily life. The patients were also instructed to indicate the extent to which they were bothered by the complaints (1 = not, 2 = slightly, 3 = moderately, 4 = quite a bit, or 5 = extremely). Health-related quality of life of patients was assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire [20]. Anxiety and depression was assessed with the Hopkins Symptom Checklist-25 (HSCL-25) [21]. Based on a cut-off score [22], an indication of the percentage of patients in each group defined as a potential pathological case was also obtained. In addition, the multi-dimensional fatigue inventory (MFI-20) was included in the study [23].

Neuropsychological tests

The cognitive functioning of the patients was evaluated using a fixed battery approach. The choice of the neuropsychological tests was based upon reliability, validity and availability of (Dutch) norms. The cognitive functions that were assessed during the test session are routinely evaluated in

neuropsychological examinations. The battery consisted of ten tests [24 test indices], covering the domains of focused/sustained attention, working/verbal/visual memory, processing speed, mental flexibility, and verbal/motor functioning [11]. The Dutch Adult Reading test was used as a measure for pre-morbid verbal intelligence [24]. This test was included in the study because meaningful interpretation of current cognitive functioning requires, among others, accurate assessment of pre-morbid intelligence. The adult reading test provides such an estimate of prior verbal intelligence based on the assumption that word reading ability is relatively independent of brain dysfunction.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) WINDOWS 12.0 was used for the statistical analyses. Each neuropsychological test score was converted into a standard score (z-score) by using the mean test scores and the standard deviations of the S-group as a reference. The data from the questionnaires (EORTC QLQ-C30, HSCL-25 and MFI-20) were converted to scores according to standard scoring rules. With regard to the occurrence of cognitive problems as assessed with the interview, only a score of 3 or more was considered as a complaint about the cognitive functioning in the domain concerned. With regard to the extent by which a patient was bothered by a complaint, also only of score of 3 or more was considered as being bothered by the occurrence of a complaint.

Between-group differences in sociodemographic characteristics were analyzed by Chi-squared tests for contingency tables and univariate analysis of variance (ANOVA). Differences in mean questionnaire scores between the groups were determined by univariate ANOVA. The percentage of patients identified by the HSCL as possible psychiatric cases was tested for differences by use of a χ^2 test. Between group differences in the percentages of patients reporting cognitive complaints and the percentages reporting being bothered by such complaints, were tested with χ^2 tests. The between-group differences in raw neuropsychological test scores were tested by univariate ANOVA. Because comparisons of group means only may obscure cognitive impairment evaluation at the level of the individual patients, an individual approach was also used for the determination of neuropsychological impairment [7,8]. In concordance with our previous neuropsychological studies in breast cancer patients, this was done as follows: a patient who scored two standard deviations below the mean of the surgery only group on a test was considered as impaired on that test. An

overall impairment score was calculated for each individual patient by counting all tests on which the patient was impaired. The fifth percentile of the overall impairment scores of the patients in the surgery only group was used as a cut-off score to distinguish between disturbed and unaffected cognitive functioning; the application of this algorithm to the data indicated that a participant was classified as cognitively impaired when he had deviant test scores on at least 3 of the 24 test indices. Following this criterion (i.e. 2 SDs below the mean of the surgery only group on at least 3 tests) each participant was classified as cognitively intact or impaired.

Relations between neuropsychological test performance and subjective measures of cognitive functioning, anxiety/depression, and cancer specific symptoms were analyzed by using Spearman rank order correlations or logistic regression models.

Logistic regression analysis was used to determine the risk of being classified as impaired in neuropsychological functioning. The independent variable consisted of type of therapy. Odds ratios were calculated with adjustment for age and IQ. "Time since treatment", "anxiety and depression", and "fatigue" were included as possible confounding factors to assess their effect on the risk of cognitive impairment. For all analyses, a p-value less than 0.05 was required for significance.

Results

Patient accrual

In total 205 patients with TC met the inclusion criteria to participate in the neuropsychological study. Of these patients, 77 received chemotherapy after surgery, 63 were treated with radiotherapy after surgery and 65 patients received surgery only. In total 23 patients (11.2%) declined to participate; 7 patients (9.1%) that were treated with chemotherapy after surgery, 6 patients (9.5%) who received radiotherapy after surgery and 10 patients (15.4%) who received surgery only. Most patients refused to participate for practical reasons. The final study sample therefore consisted of 182 patients; 70 patients who received chemotherapy after surgery (the S+CT group), 57 who received radiotherapy after surgery (the S+RT group) and 55 who received surgery only (the S group).

Sociodemographic and clinical characteristics

Table I gives the sociodemographic and clinical characteristics of the study sample. There were no significant differences between the three groups for level of education and for premorbid IQ, as measured with the Dutch Adult Reading test. An equal

Table I. Sociodemographic and clinical characteristics of the 3 study groups.

	S+CT*(n=70)	S+RT*(n=57)	S*(n=55)	p-value
Mean age, y (SD) ^a	32.1 (7.6)	38.9 (8.4)	34.4 (9.5)	0.00
Level of education, % ^b				
Low	20%	19%	13%	0.82
Middle	33%	30%	36%	
High	47%	51%	51%	
Mean time since last therapy, y (SD)	3.1 (1.4)	3.2 (1.5)	3.0 (1.8)	0.79
Premorbid IQ ^c (Dutch reading test) ^d	95.6 (12.9)	96.3 (12.2)	93.4 (13.4)	0.45

*S+CT = surgery followed by BEP chemotherapy; S+RT = surgery followed by radiotherapy, S = surgery only. See "Methods" section for definition of the BEP chemotherapy regimen.

^aSD = standard deviation.

^bLow = primary school; middle = secondary school; and high = university and graduate school; and % is percentage of patients in treatment group.

^cThe Dutch Adult Reading provides a measure of pretreatment verbal intelligence.

high percentage of patients were employed in the groups (95%, results not shown). The time since completion of therapy was on average 3 years. The patients in the S+RT group were significantly older compared with those in the S+CT group and those in the S group (S+CT vs S+RT $p=0.00$, S+CT vs S $p=0.32$, S+RT vs S $p=0.02$). As a consequence, all further analyses were adjusted for age.

Self-reported cognitive problems

Table II shows the results of the cognitive interview. A high percentage of TC patients reported at least regularly occurrence of cognitive problems, in both the S+CT group (32%) as well as in the S+RT group (32%), and in the S-group (27%). In each treatment group, on average 50% of the patients with cognitive complaints indicated that they were seriously bothered by these complaints. The majority of TC patients treated with chemotherapy (S+CT group) stated that their cognitive problems were

connected with the cancer treatment (77%); they either indicated that these problems had started after treatment or that the problems worsened following treatment. Some patients also reported that they had become aware of the cognitive problems only after resumption of their work. Of the patients treated with radiotherapy after surgery (S+RT group), 67% related the occurrence of cognitive problems specifically to their cancer treatment, compared to 60% in the surgery only (S) group.

Health-related quality of life, anxiety, depression and fatigue

Table III shows the results the quality of life questionnaire, the anxiety and depression scale and the multi-dimensional fatigue index. No significant differences were found between the three groups on any of the outcome measures, with the exception of the global quality of life scale of the EORTC QLQ-C30. On this scale, the S+RT group reported lower scores

Table II. Cognitive complaints in daily life for the 3 study groups.

	S+CT*(n=70)	S+RT*(n=7)	S*(n=55)	p-value
Occurrence of cognitive complaints ^a	32.4 (22)	31.6 (18)	27.3 (15)	0.85
● Since treatment	31.8 (7)	22.2 (4)	6.7 (1)	
● Since illness	13.6 (3)	16.7 (3)	20.0 (3)	
● Become worse since treatment	13.6 (3)	16.7 (3)	26.6 (4)	
● Noticed since start working again	18.2 (4)	11.1 (2)	6.7 (1)	
● Since some years (not specified)	4.5 (1)	5.6 (1)	13.3 (2)	
● Was always like this	9.1 (2)	22.2 (4)	26.7 (4)	
● No idea	9.1 (2)	5.6 (1)	—	
Bothered by cognitive complaints ^b	50.0 (11)	44.4 (8)	53.3 (8)	0.87

*S+CT = surgery followed by BEP chemotherapy; S+RT = surgery followed by radiotherapy, S = surgery only. See "Methods" section for definition of the BEP chemotherapy regimen.

^aResults are shown as the percentage of patients who reported having cognitive problems in at least one of the domains of memory, concentration, thinking, language.

^bResults are shown as the percentage of patients with complaints who reported being bothered by this complaint in at least one of the domains of memory, concentration, thinking and language.

Table III. EORTC QLQ-C30 quality of life, HSCL-25 anxiety and depression, MVI fatigue.

	S = CT*(n = 70) Mean (SD) ^a	S + RT*(n = 57) Mean (SD)	S*(n = 55) Mean (SD)	p-value ^g
EORTC CQC-C30 Function scales^b				
Physical	96.1 (8.2)	96.6 (7.0)	97.1 (7.3)	0.619
Role	93.6 (15.6)	88.3 (20.2)	91.1 (18.7)	0.336
Cognitive	87.9 (13.6)	90.1 (15.1)	85.5 (25.5)	0.376
Emotional	94.3 (12.3)	89.2 (18.8)	93.3 (15.2)	0.287
Social	88.3 (13.0)	83.2 (19.1)	81.5 (22.1)	0.095
Global quality of life	85.8 (12.1)	79.8 (15.5)	81.1 (14.5)	0.028 ^h
Symptom scales and/or items^b				
Fatigue	19.8 (17.1)	23.8 (20.8)	22.4 (17.4)	0.282
Nausea and vomiting	0.9 (4.8)	2.3 (7.3)	3.6 (7.6)	0.101
Pain	5.9 (12.4)	8.2 (17.8)	7.6 (15.3)	0.932
Dyspnea	4.8 (14.2)	5.8 (12.8)	5.5 (12.4)	0.990
Sleep disturbance	12.9 (20.7)	11.7 (23.1)	17.0 (22.1)	0.467
Appetite loss	1.4 (6.8)	4.1 (12.7)	6.1 (18.2)	0.065
Constipation	1.4 (6.8)	1.7 (9.8)	2.4 (8.7)	0.645
Diarrhea	4.3 (12.6)	5.3 (12.3)	8.5 (18.4)	0.250
Financial impact	3.8 (12.1)	8.2 (18.1)	5.5 (19.0)	0.239
HSCL-25^c				
Total score	7.3 (6.5)	9.1 (11.5)	9.4 (10.3)	0.331
Anxiety	7.2 (6.5)	9.1 (10.6)	9.3 (11.1)	0.271
Depression	7.3 (7.6)	9.0 (13.2)	9.4 (10.7)	0.447
Possible pathologic case ^d	11.4 (8)	10.5 (6)	16.4 (9)	0.602
MFI-20^e				
General fatigue	8.4 (4.1)	8.9 (4.7)	9.1 (4.4)	0.478
Physical fatigue	7.0 (3.1)	7.9 (4.0)	7.3 (3.8)	0.443
Reduced activities	7.5 (2.9)	8.1 (3.5)	7.9 (3.1)	0.504
Reduced motivation	6.6 (2.9)	6.9 (2.7)	6.8 (3.2)	0.816
Mental fatigue	9.4 (4.1)	8.4 (3.9)	9.3 (4.1)	0.707

*S + CT = surgery followed by BEP chemotherapy; S + RT = surgery followed by radiotherapy, S = surgery only. See "Methods" section for definition of the BEP chemotherapy regimen. ^a SD = standard deviation.

^bEORTC = European Organization for Research and Treatment of Cancer; EORTC QLQ-C30 is a health-related quality of life questionnaire (see "Methods" section for more details). Scores on function scales range from 0 to 100, with a higher score meaning better functioning; scores on symptom scales and/or items range from 0 to 100, with a higher score meaning more bothered by complaint.

^cHSCL = Hopkins Symptom Checklist: scores range from 0 to 100, a higher score indicates more complaints.

^dDefinition of possible pathological case (mean score ≥ 1.55).

^eMFI = Multi-dimensional fatigue index; scores range from 0 to 100, a higher score indicates more complaints.

^gTwo-sided p-values, corrected for age.

^hPost hoc comparison: mean raw score of S + RT group lower than mean raw score of S + CT group and S group (two-sided $p < 0.05$).

compared to the S + CT group and the S group, indicating a lower level of functioning ($p = 0.028$).

Neuropsychological tests

There were no differences on any of the individual tests between the mean scores of the S group and the published norms of healthy individuals. No significant differences were found between the three patient groups in mean raw scores on any of the 24 test indices (results not shown). As group mean values may obscure cognitive impairment evaluation at the level of the individual, we determined for each patient whether this patient could be classified as cognitively impaired: 14.3% of the patients in the S + CT group were classified as impaired in cognitive functioning, compared with 17.5% in the S + RT

group and 5.5% in the S group. Binomial testing showed that the percentages of patients in the S + CT group and in the S + RT group that were classified as cognitive impaired were significantly different compared to percentage of the patients in the S group classified as cognitively impaired ($p = 0.001$ and $p = 0.000$ respectively). After controlling for age and IQ by use of a logistic regression model, the percentage of patients classified as impaired in the S + CT group remained significantly different from the S group (S + CT versus S [$p = 0.038$, OR = 4.6, CI = 1.1–19.7] and S + RT versus S [$p = 0.070$, OR = 3.7, CI = 0.8–15.7]). Time since treatment, anxiety and depression, and fatigue had no significant contribution to the risk of being classified as impaired. The results are shown in Table IV.

Table IV. Risk of cognitive impairment.

Treatment Group*	Comparison Group	odds ratio ^a	95% confidence interval	P ^b
S+CT	S	4.6	1.1–19.7	0.038
S+CT	S+RT	0.8	0.3–2.4	0.701
S+RT	S	3.7	0.8–15.7	0.070

*S+CT = surgery followed by BEP chemotherapy; S+RT = surgery followed by radiotherapy, S = surgery only. See “Methods” section for definition of the BEP chemotherapy regimen.

^aAdjusted for age and IQ.

^bTwo-sided p-value.

Relation between cognitive test performance and self-reported complaints

The correlation between cognitive complaints as reported in the cognitive interview and cognitive impairment found on neuropsychological testing was investigated. For all groups, there appeared to be no correlation between the overall cognitive impairment score and the occurrence of cognitive problems reported at the interview or the extent to which patients were bothered by the occurrence. Also no correlation was found between the overall cognitive impairment score and the scores on the cognitive functioning scale of the EORTC QLQ-C30. The self-reported occurrence of cognitive problems as expressed in the interview were related to the anxiety and depression scales of the HSCL and fatigue of the EORTC as well as of the total score of the MFI ($\rho = 0.40$, $\rho = 0.50$, $\rho = 0.36$ and $\rho = 0.52$, respectively).

Specifically, the identification as a “possible psychiatric case” by the HSCL-25 appeared to be a strong predictor of both the occurrence of cognitive complaints as well as the extent to which a patient is bothered by these complaints ($p = 0.000$, OR = 9.0, CI = 3.3–24.5 and $p = 0.000$, OR = 10.2, CI = 3.9–26.6, respectively), and not for the overall impairment scores.

In general, time since treatment was not of influence on the relationship between the different self-reported problems, nor on the relation between different self-reported problems and neuropsychological test results.

Discussion

There is growing evidence for cognitive dysfunction after several cytotoxic treatments. The world-wide standard BEP regimen given to patients with testicular cancer has never been thoroughly examined with regard to its potential sequel for patients’ cognitive functioning. In the current study, we report how patients describe their cognitive functioning and how patients perform on formal cognitive tests. We also report how factors such as emotional distress

and fatigue can influence these outcomes. TC patients who received BEP chemotherapy were compared to TC patients who received radiotherapy after surgery and to TC patients who received surgery only. The results of our study indicated that approximately 30% of TC patients treated with BEP chemotherapy expressed cognitive problems. In TC patients treated with surgery followed by radiotherapy and in TC patients treated with surgery only, a similar prevalence of self-reported cognitive problems was found. Roughly half of the patients with cognitive complaints indicate that they were substantially bothered by these complaints in daily life. The majority of the patients stated that the cognitive problems either started or worsened following treatment.

Our neuropsychological test data indicated that in mean cognitive performance, there were no differences between any of the three groups. Based on the individual impairment scores, a small difference was observed in the percentages of patients being classified as cognitively impaired between the groups, with a higher percentage of cognitively impaired patients in the BEP group compared to the surgery only group, but not compared to the radiotherapy group.

The subjective cognitive complaints did not correlate to objective cognitive testing, but were instead related to distress and fatigue. Especially a score on the anxiety and depression scale indicative of a potential psychiatric case was predictive of the occurrence of subjective cognitive complaints. A number of other studies has also related cognitive complaints to psychological distress instead of formal test performance [1,3,7,8,12] this finding has important implications for clinical practice in terms of screening and potential rehabilitation of patients.

Summarizing, no difference was found between any of the three groups on self-reported cognitive complaints, whereas neuropsychological testing showed impaired cognitive functioning in patients treated with BEP chemotherapy compared to patients who underwent surgery only, but not to patients receiving radiotherapy after surgery. With regard to the possible effects of BEP chemotherapy on cognitive functioning, our findings are

inconclusive, and further research is warranted. This research should incorporate a prospective design to allow for the investigation of changes in cognitive functioning. This is important because the cognitive performance of a patient can deteriorate from pre-treatment levels of functioning within normal limits, i.e. without showing apparent cognitive deficits. With regard to the origins of the self-reported cognitive complaints, our findings seem to point to a psychological factor, rather than to a specific treatment-induced physiological effect.

For the patients with complaints about their cognitive functioning, we therefore believe that the administration of an interview with an accent on mood disturbances and fatigue is to be recommended. It is known from other studies that elevated levels of anxiety are not uncommon in TC cancer patients, irrespective of treatment modality and up to many years after completion of treatment [16]. Providing patients with information relating experienced cognitive problems to emotional distress is in our opinion the most practical intervention to start out with. Subsequent treatment could consist of interventions that address a patient's specific stressors and promote effective coping strategies.

The current study confirms previous data of self-reported cognitive problems in TC patients treated with BEP chemotherapy, but shows that these complaints are not unique for this treatment modality. The finding of a small group of TC patients treated with BEP chemotherapy exhibiting objectively assessed cognitive deficits should be confirmed in a study of prospective nature before we can decide on its cause and clinical relevance.

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References

- Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol* 2002;20:485-93.
- Brezden CB, Phillips KA, Abdoell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2000;18:2695-701.
- Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol* 2004;26:955-69.
- Fan HG, Houede-Tchen N, Yi QL, Chemerynsky I, Downie FP, Sabate K, et al. Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. *J Clin Oncol* 2005;23:8025-32.
- Jenkins V, Shilling V, Deutsch G, Bloomfield D, Morris R, Allan S, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer* 2006.
- Kreukels BP, Schagen SB, Ridderinkhof KR, Boogerd W, Hamburger HL, van Dam FS. Electrophysiological correlates of information processing in breast-cancer patients treated with adjuvant chemotherapy. *Breast Cancer Res Treat* 2005;94:53-61.
- Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after post-operative adjuvant chemotherapy for breast carcinoma. *Cancer* 1999;85:640-50.
- van Dam FS, Schagen SB, Muller MJ, Boogerd W, vd Wall E, Droogleever Fortuyn ME, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy. *J Natl Cancer Inst* 1998;90:210-8.
- Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: Results of a prospective, randomized, longitudinal trial. *Cancer* 2004;100:2292-9.
- Harder H, Van Gool AR, Cornelissen JJ, Duivenvoorden HJ, Eijkenboom WM, Barge RM, et al. Assessment of pre-treatment cognitive performance in adult bone marrow or haematopoietic stem cell transplantation patients: A comparative study. *Eur J Cancer* 2005;41:1007-16.
- Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, van Dam FSAM. Change in cognitive function after chemotherapy: A prospective longitudinal study in breast cancer patients. *J Natl Cancer Inst* 2006;98.
- Tannock IF, Ahles TA, Ganz PA, van Dam FS. Cognitive impairment associated with chemotherapy for cancer: Report of a workshop. *J Clin Oncol* 2004;22:2233-9.
- Fleer J, Hoekstra HJ, Sleijfer DT, Hoekstra-Weebers JE. Quality of life of survivors of testicular germ cell cancer: A review of the literature. *Support Care Cancer* 2004;12:476-86.
- Miyake H, Muramaki M, Eto H, Kamidono S, Hara I. Health-related quality of life in patients with testicular cancer: A comparative analysis according to therapeutic modalities. *Oncol Rep* 2004;12:867-70.
- Joly F, Heron JF, Kalusinski L, Bottet P, Brune D, Allouache N, et al. Quality of life in long-term survivors of testicular cancer: A population-based case-control study. *J Clin Oncol* 2002;20:73-80.
- Dahl AA, Haaland CF, Mykletun A, Bremnes R, Dahl O, Klepp O, et al. Study of anxiety disorder and depression in long-term survivors of testicular cancer. *J Clin Oncol* 2005;23:2389-95.
- Mykletun A, Dahl AA, Haaland CF, Bremnes R, Dahl O, Klepp O, et al. Side effects and cancer-related stress determine quality of life in long-term survivors of testicular cancer. *J Clin Oncol* 2005;23:3061-8.
- Fleer J, Hoekstra HJ, Sleijfer DT, Tuinman MA, Klip EC, Hoekstra-Weebers JE. Quality of life of testicular cancer survivors and the relationship with sociodemographics, cancer-related variables, and life events. *Support Care Cancer* 2006;14:251-9.
- Fossa SD, de Wit R, Roberts JT, Wilkinson PM, de Mulder PH, Mead GM, et al. Quality of life in good prognosis patients with metastatic germ cell cancer: A prospective study of the European Organization for Research and Treatment of Cancer Genitourinary Group/Medical

- Research Council Testicular Cancer Study Group (30941/TE20). *J Clin Oncol* 2003;21:1107–18.
- [20] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
- [21] Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behav Sci* 1974;19:1–15.
- [22] Sandanger I, Moum T, Ingebrigtsen G, Sorensen T, Dalgard OS, Bruusgaard D. The meaning and significance of case-ness: The Hopkins Symptom Checklist-25 and the Composite International Diagnostic Interview. II. *Soc Psychiatry Psychiatr Epidemiol* 1999;34:53–9.
- [23] Smets EM, Garssen B, Bonke B, de Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39:315–25.
- [24] Schmand B, Bakker D, Saan R, Louman J. The Dutch Reading Test for Adults: A measure of premorbid intelligence level. *Tijdschr Gerontol Geriatr* 1991;22:15–9.