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Cognitive dysfunction and subjective complaints of cancer patients: a cross-sectional study in a cancer rehabilitation centre

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Abstract

Although the neurotoxicity of many anticancer therapies is well documented, the impact of cancer treatment on cognitive functioning has been studied less frequently. The present study examines deficits in cognitive functioning and their correlation with medical data as well as with psychosocial variables. A standardised neuropsychological test battery and several questionnaires were administered to a random sample of 119 patients. 24% of our patients fulfilled our criterion for cognitive impairment. There were no significant associations between the results of the neuropsychological testing and the current affective status or self-reports of attentional deficits in daily life. Cognitive impairment occurs in a clinically relevant percentage of cancer patients and cannot be explained exclusively due to depression or anxiety. Since subjective and objective cognitive impairment data showed little correlation, neuropsychological evaluation should not only be based on subjectively-reported complaints, but also on objective measurements.

Keywords: Cancer; Psycho-oncology; Neurotoxicity; Oncological rehabilitation; Neuropsychological diagnostics; Quality of life

1. Introduction

While research in oncology has led to significant improvements in therapeutic strategies, there is an increasing interest in patients' quality of life, which has become a central evaluation criterion in clinical studies [1,2]. Cognitive functioning is closely connected with the central dimensions of quality of life, such as personal autonomy and social functioning [3].

The neurotoxicity of many commonly used oncological therapies is well documented [4], but is mostly defined by symptoms of the peripheral nervous system, such as polyneuropathy, or by severe central nervous system (CNS) disorders like encephalopathy. Cognitive symptoms which are associated with such severe dysfunctions as delirium or dementia are mostly easily identified and do not need formal neuropsychological assessment.

Only a few studies have employed differentiated neuropsychological test procedures for the assessment of mild cognitive impairments. Studies have mostly focused on a wide spectrum of cognitive domains, such as attention, memory, problem-solving, and psychomotoric performance [3], reflecting the lack of a consistent pathophysiological model for the possible effects of the disease itself or the oncological treatment on the CNS.

In addition, the prevalence of neuropsychological impairments in tumour patients is still unclear. Folstein and colleagues [5] identified cognitive deficits in 14–29% in different oncological samples; data by Andrykowski and colleagues [6] and Meyers and colleagues [7] suggest even higher prevalence rates.

Neuropsychological deficits after high-dose chemotherapy have been investigated in patients undergoing bone marrow transplantation (BMT) or peripheral blood stem cell therapy (PBSCT). Meyers and colleagues [8] found mnestic problems in 19% of their patients, even 8 months after the BMT. Deficits were

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not associated with the patients' current emotional status and the intake of psychoactive drugs. Neuropsychological examination prior to BMT revealed cognitive impairments in 11% of patients. Similar results were reported by Andrykowski and colleagues [6] in a study on candidates for allogenic BMT. Patients with a history of CNS disease, intrathecal methotrexate administration, high-dose cytosine arabinoside (ara-C)-administration or prophylactic cranial irradiation seemed to be at a higher risk for cognitive deficits.

Ahles and colleagues [9] showed an increasing deterioration in neuropsychological parameters during the course of BMT, while patients' emotional status improved over the same time period. Several studies [10,11] showed that cognitive deficits may either be stable or deteriorate over time after treatment.

Neuropsychological deficits after conventional chemotherapy (i.e. no high dosage; extrathecal) have been investigated in a small number of studies on breast cancer patients. Studies focusing on other diagnostic and treatment groups [6,8,12,13] do not report any data on sex-related differences regarding neuropsychological status after oncological therapy. Wieneke and Dienst [14] found neuropsychological deficits in 75% of women with breast cancer after adjuvant chemotherapy, which could be detected especially in the non-verbal domains, which are not immediately obvious in an explorative interview. Based on a controlled design, Schagen and colleagues [15] found a significantly higher rate of cognitive deficits in patients after adjuvant chemotherapy than in women having received only surgery and local radiation therapy (28% versus 12%). Similar to a study published in 2000 by Brezden and colleagues [16], deficits were still identifiable more than 6 months posttreatment.

Van Dam and colleagues [17] also identified neuropsychological deficits after adjuvant chemotherapy for breast carcinoma. In particular, patients having received high-dose chemotherapy and PBSCT showed an increased risk for impairments of the memory and attentional functions.

Cull and colleagues [12] found in a sample of adult lymphoma patients after treatment that self-perception of the patients regarding their current level of cognitive functioning did not correlate with data from a formal neuropsychological assessment of concentration and memory. Complaints about cognitive problems were strongly correlated with higher levels of anxiety and depression, and also fatigue. As the authors pointed out, the interdependence between 'mental fatigue', emotional disturbances and neuropsychological deficits is still unclear.

The present study was designed to investigate the prevalence of neuropsychological deficits of cancer patients in a rehabilitation unit, focusing on the relationship between patients' subjective complaints about neuropsychological impairments and the results of a formal neuropsychological testing. These data should help to identify the need for diagnostic assessment strategies and to implement cognitive training programmes in oncological rehabilitation.

2. Patients and methods

The study was conducted at the rehabilitation unit of the Tumor Biology Center, Freiburg, Germany. Most patients (~70%) were admitted immediately after the end of acute care within a time frame of a few weeks. Approximately 30% demanded a rehabilitation programme for up to 1 or 2 years. Patients took part in a 3- to 5-week rehabilitation programme including medical treatment, physiotherapy and psychosocial interventions [18]. All participants were recruited consecutively in February and March 1998. No selections were made concerning oncological diagnoses and treatment regimen. Inclusion criteria were: no history of severe psychiatric or neurological symptoms probably leading to cognitive deficits; no history of substance abuse; no current use of psychoactive medication; sufficient command of the German language.

All patients who gave their informed consent to participate in the study were given a comprehensive neuropsychological test battery, which took approximately 45 min to complete. The test battery was sensitive to mild cognitive impairments and focused on attentional functions, speed of information processing, cognitive flexibility and memory. All test scores were adjusted for age and gender according to reference data provided by the test authors or by Lezak [19]. In addition to formal neuropsychological testing, all participants completed questionnaires regarding subjective complaints about cognitive functioning and current emotional status.

Information on medical aspects (diagnosis, tumour status, treatment procedures, side diagnoses) as well as sociodemographical data (scholar education, occupational status) were taken from the documentation system of the clinic.

2.1. Measures

For neuropsychological testing we used a variety of instruments:

1. The Wechsler Memory Scale Revised (WMS-R) [20] is a commonly used clinical test to measure the central dimensions of memory. The patients were administered the sub-tests Logical Memory I and II, Digit Span Forward and Backward.
2. The Trail Making Test (TMT) [21] assesses information processing speed by requiring the subject to connect a series of digits placed in

random order on a sheet of paper in ascending order (TMT A) and cognitive flexibility by connecting a series of numbers and letters in ascending order, alternating between both (TMT B).
3. The computer-based Test Battery for Assessment of Attention (TAP) [22] measures several dimensions of attention. Three sub-tests were administered: Alertness; Divided attention; Reaction change.
4. As the Multiple-Choice-Vocabulary-Test (MWT-B) [23] focuses on knowledge accumulated over the life-span, it is commonly used to estimate premorbid functioning in patients with brain damage. The test contains 37 items, in which patients have to select one correctly written word out of lines with four neologisms.
5. The patients' self-ratings of cognitive functioning in every-day life were assessed with the 'Questionnaire for Self-perceived Deficits in Attention' (FEDA) [24]. The 27 items refer to three scales: 'Distractibility and retardation in mental processes'; 'Fatigue and retardation in activities of daily living'; 'Drive'.
6. We used the Hospital Anxiety and Depression Scale (HADS-D) [25] as a measure of anxiety and depression which provides information regarding the clinical significance of those symptoms.

2.2. Statistical methods

We used the Statistical Package for Social Sciences (SPSS; Windows 6.0 software) for statistical analyses. Differences in sociodemographic characteristics between our sample and patients of the Tumor Biology Center in general were analysed by means of the χ^2-test for contingency and the Student's t-test.

All raw scores of neuropsychological testing were transformed into z-scores. Due to the fact that group means may cover individual cognitive impairment, we calculated indices for the amount of cognitive impairment. Based on a classification of ability levels proposed by Lezak [19], single test performances lower than the 10th percentile were classified as 'deficitary'. Patients were classified as 'cognitively impaired' when their results in at least two tests of different cognitive domains (Digit span; Logical memory; Trail making test; Alertness; Divided attention; Reaction change) scored below the 10th percentile.

Analysis of the correlation between the neuropsychological test results and questionnaire data is based on Pearson's product moment correlations. Univariate (t-tests) as well as multivariate procedures (ANCOVA, Multiple Regression Analysis) were used to analyse the effects of medical and psychosocial variables on neuropsychological functioning.

3. Results

3.1. Description of the sample

Within 2 months, 119 patients (66.5% of all new admissions meeting the study criteria in this time-frame) were recruited. The mean age of the 119 subjects (80 female; 39 male) was 52.6 years (standard deviation (S.D.) = 12.3; range 20–75 years). Concerning age, gender and diagnosis, there was no selection bias in comparison with the population of all patients admitted during the first 6 months of the year.

The most common diagnosis was breast cancer (35%), followed by haematological malignancies (23%), genitourinary (15%) and gastrointestinal (15%) tumours. Tumours of the CNS were found in 2 subjects. Lung cancer was diagnosed in 1 patient. Various rare tumours (e.g. sarcoma) are summarised in a group 'Others' (9%) (Table 1).

Time since initial diagnosis varied from several weeks to 19 years. At the time of testing, 58% of patients were in complete remission or showed no evidence of disease, 18% were in partial remission, and in 2% metastases had been found. In 23% of patients, no information about the present tumour status was available.

The different combinations of treatments are shown in Table 2. Approximately two-thirds of the patients underwent a combination therapy reflecting the common clinical practice. The average time since last treatment was 4.6 months (S.D. = 8.6; range 0–60 months).

3.2. Results of neuropsychological assessment

The sample mean scores in all neuropsychological tests are in the unimpaired range. According to the classification of ability levels proposed by Lezak [19], patients' mean scores in divided attention are low average; immediate and delayed recall of logical verbal information are high average. Patients' z-scores, SDs and percentiles are presented in Table 3. The estimated premorbid IQ (MWT-B) scored between 92 and 143 with a mean of 119 (S.D. = 13.6), suggesting the mean premorbid intelligence level of our sample to be at least normal.

Based on the defined criteria for neuropsychological impairment, 29 patients (24%) showed test performances below the 10th percentile in at least two different domains of cognitive functioning. Thus, despite the mean scores for the entire group, almost one-quarter of the study sample suffered from considerable deficits in cognition. 72 patients (61%) displayed deficits in at least one test. A survey of the distribution of cognitive deficits is given in Fig. 1.

In general, our subjects showed far more deficitary results in tests of attentional functioning than in memory tasks. The computer-based tests 'Reaction change'

and 'Divided attention' were particularly responsible for most of the deficitary results, while there was only one person who showed deficits in the 'logical memory' tasks.

With respect to sex differences, we compared the percentages of patients being classified as 'cognitively impaired' according to our criterion and found nearly equivalent ratios (26.3% in the female subgroup versus 20.5% in the male subgroup; Fisher's exact test $P = 0.650$ (two-sided)).

3.3. Results of patients' self-reports measured by questionnaires

Table 4 shows the results of the questionnaires. Using the criterion of scores under the 10th percentile, 38.7% of patients complained about fatigue and retardation in practical tasks (FEDA 2). 21.8% of patients reported considerable difficulties during mental tasks which required attention (FEDA 1). A reduced drive was mentioned by 18.5% of patients (FEDA 3).

Concerning current emotional status, Table 4 shows that the mean scores of anxiety for the entire sample lay within the average norm range, whereas the mean score of depression was above average, indicating that our patients experienced a higher degree of depression.

According to the standard scores of the HADS [25], we took raw scores between 8 and 11 as cut-off scores for a possible affective disturbance and raw scores $\geqslant 11$ for psychiatric mood disorders. Approximately one-third of the patients showed signs of possible depression; approximately 40% may suffer from an anxiety disorder. Since 45 patients displayed at least signs of an

Table 1
Diagnoses

	N (%)
Diagnosis	
Breast cancer	42 (35)
Haematological malignancies	27 (23)
Genitourinary malignancies	18 (15)
Gastrointestinal cancer	18 (15)
CNS tumours	2 (2)
Lung cancer	1 (1)
Others	11 (9)
Σ	119 (100)
Tumour status	
Complete remission	69 (58)
Partial remission	21 (18)
Metastatic disease	2 (2)
No information	27 (23)
Σ	119 (100)

CNS, central nervous system.

Table 2
Treatment regimen

Treatment combinations	*N* (%)	
Radiochemotherapy and surgery	23 (19)	
Radiotherapy and surgery	23 (19)	
Chemotherapy and surgery	22 (18)	
Surgery alone	19 (16)	
Radiochemotherapy	10 (8)	
BMT allogenic	1 (1)	
BMT autologous	9 (8)	
Radiotherapy or chemotherapy	9 (8)	
Cranial surgery and radiotherapy	2 (2)	
Hormonal therapy alone	1 (1)	
Σ	119 (100)	
Time since treatment	M (S.D.)	Range
	4.6 months (S.D. 8.6)	0–60 months

S.D., standard deviation; BMT, bone marrow transplantation; M, mean.

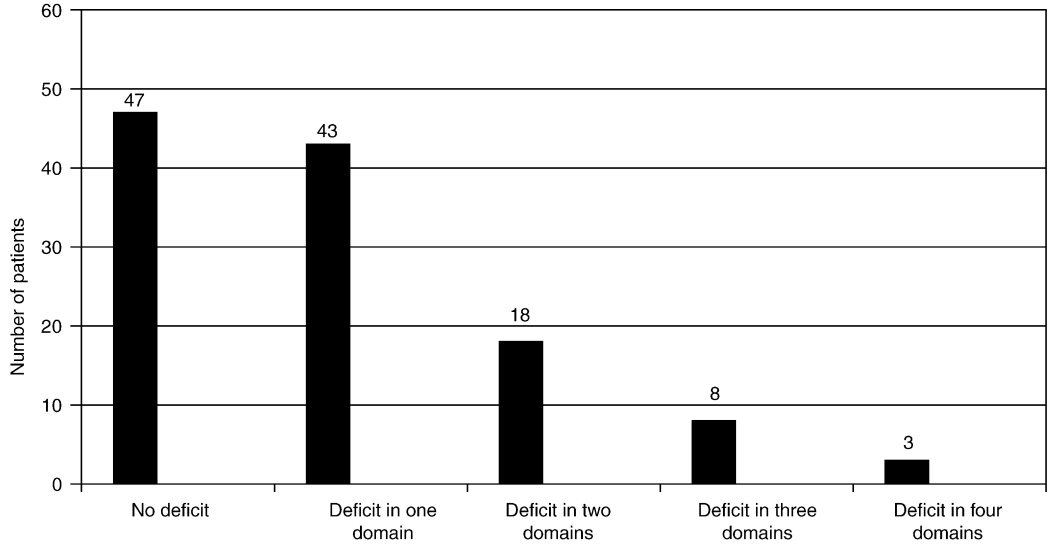

Fig. 1. Neuropsychological test performance of patients. The number of impaired test domains per patient is shown.

anxiety disorder *or* depression, 38% of the sample were affected by emotional disturbances. These results are in line with previous studies using the HADS for the assessment of emotional disturbances in samples of cancer patients [26].

3.4. Intercorrelations between current affective status and self-perceived cognitive deficits

Table 5 shows the correlations between the *z*-transformed scores of current affective status and self-perceived cognitive problems in daily life. All scales of the two instruments showed significant correlations with one another, indicating that affective disturbances are associated with complaints about problems with practical and mental activities in daily life. For all FEDA scales, correlations with depression proved to be higher than those with anxiety.

Table 3
Results of neuropsychological tests

Test procedure	Mean *z*-score	S.D.	Mean percent rank	*N*
Divided attention	−0.60	0.29	27.4	117
Change of reaction	−0.53	0.49	29.8	114
Digit span forward	−0.21	0.93	41.7	117
Tonic alertness	−0.11	1.05	45.7	119
Phasic alertness	−0.06	1.07	47.6	119
Alertness index	0.07	1.34	52.8	119
Digit span backward	0.12	0.96	54.7	116
Trail making test B	0.46	1.01	67.7	118
Trail making test A	0.58	1.08	71.9	119
Logical memory II	0.80	0.85	78.8	117
Logical memory I	0.91	0.87	81.8	118

Table 4
Mean *z*-scores and standard deviations of questionnaire data

Instrument	Mean *z*-score	S.D.	*N*
FEDA			
Distractibility and retardation in mental processes	0.13	1.24	109
Fatigue and retardation in activities of daily living	−0.39	1.86	109
Drive	0.24	1.42	109
HADS			
Anxiety	−0.01	1.18	113
Depression	0.77	1.22	113

FEDA, 'Questionnaire for Self-perceived Deficits in Attention'; HADS, 'Hospital Anxiety and Depression Scale'.

3.5. Affective status and neuropsychological functioning

Concerning the established diagnostic criteria for affective disorders, especially depression, cognitive aspects like attention deficits are mentioned as relevant symptoms. We analysed the connections between affective symptoms and neuropsychological performance and found only a small number of mostly moderate correlations (Table 6). Anxiety seemed to have a more negative impact on cognitive performance than depressive symptoms, especially on mnestic functioning which, in general, showed only a small number of deficits in our sample. So, for the most relevant dimensions of cognitive deficits in our sample, i.e. attentional processes, affective problems seemed to have only a small influence.

3.6. Subjective complaints and neuropsychological test results

One of our main aims was to investigate the relationship between self-estimated and objectively-tested cognitive functioning. Correlation analyses revealed only a few significant scores on lower level indicating weak associations between the results of the neuropsychological test data and patients' self perceptions, as assessed by the FEDA (Table 7). Only the 'Trail Making Test B' and the tasks of the WMS-R correlated with subjectively-perceived disturbances of attention.

Since patients' self-reports are significantly related to emotional aspects (as shown in Table 5), additional partial correlations were computed. Using anxiety and depression as control variables, no significant correlations between the patients' subjective estimation of attentional deficits in everyday life and formal neuropsychological test results could be found.

Table 5
Correlations between scales of questionnaires

Scales	Distractability/ retardation mental tasks	Fatigue/retardation activities daily living	Drive	HADS-D	HADS-A
Distractability/retardation					
Mental tasks	–	0.47***	0.55***	−0.49***	−0.42***
Fatigue/retardation		–			
Activities daily living			0.54***	−0.48***	−0.41***
Drive			–	−0.40***	−0.33***
HADS-D				–	0.53***
HADS-A					–

*$P<0.05$, **$P<0.01$, ***$P<0.001$.

Table 6
Correlations between current affective status and neuropsychological functioning

Neuropsychological tests	HADS anxiety	HADS depression
Tonic alertness	−0.14	−0.09
Phasic alertness	−0.07	−0.04
Alertness index	0.14	−0.17*
Divided attention	−0.05	−0.03
Reaction change	−0.15	−0.06
Trail making test A	−0.07	−0.16
Trail making test B	−0.21*	−0.20*
Logical memory 1	−0.21*	−0.15
Logical memory 2	−0.23*	−0.14
Digit span forward	−0.26**	−0.16
Digit span backward	−0.11	−0.12

*$P<0.05$, **$P<0.01$, ***$P<0.001$.

Table 7
Correlations between objectively-measured and subjectively-perceived functioning

Domain	Test	FEDA 1	FEDA 2	FEDA 3
Attention (TAP)				
	Tonic alertness	−0.07	−.03	0.06
	Phasic alertness	−0.01	0.01	0.04
	Alertness index	−0.17	−.02	−0.05
	Divided attention	0.01	0.13	−0.02
	Change of reaction	−0.07	0.00	0.10
Cognitive Speed/flexibility				
	Trail making A	0.06	0.13	0.14
	Trail making B	0.09	0.22**	0.22*
Memory (WMS)				
	Logical memory I	0.24*	0.07	0.19*
	Logical memory II	0.15	0.12	0.17
	Digit span forward	0.11	0.18*	0.23*
	Digit span backward	0.11	0.20*	0.11

WMS, Wechsler Memory Scale; TAP, Test Battery for Assessment of Attention.
*$P<0.05$**, $P<0.01$, ***$P<0.001$.

4. Discussion

One aim of the present study was to investigate the prevalence of cognitive deficits in patients of a cancer rehabilitation unit in order to identify the need for specific neuropsychological interventions. As suggested by the results of former studies, we focused especially on correlations between objective neuropsychological test data, affective status and subjective complaints about deficits in daily life.

We found a relatively high percentage of patients showing neuropsychological deficits. Though mean scores for most of the neuropsychological tests were within the normal range for the entire study sample, approximately a quarter of our study sample fulfilled the criterion for cognitive impairment. These rates are in line with Folstein's [5] and Cull's [12] data on the prevalence of cognitive deficits in tumour patients.

As we controlled the level of estimated premorbid intelligence and took additional neurological or psychiatric disorders as exclusion criteria, our data indicate the clinical relevance of treatment-induced cognitive deficits in oncological rehabilitation. The results give evidence for the hypotheses that these deficits are mostly subtle and need differentiated formal assessment to be detected.

In contrast to some studies, which showed deficits especially in mnestic functioning [6,8], the results of our sample in tests of mnestic aspects lie within the range of age-adjusted norm data. We found remarkably low results in attentional functions, a result that confirms other studies [14,15,17].

Studies in paediatric oncology give support to the hypothesis that deficits in specific attentional processes are responsible for other deficits (e.g. in mnestic functioning) [27] and that a differentiated diagnostic of several dimensions of attention can be relevant in the planning of rehabilitative interventions [28]. Further studies are necessary to show whether these results are applicable to adult cancer patients.

Due to its cross-sectional design and the heterogeneous sample, our study was not able to analyse the direct effects of different treatment strategies on cognitive functioning. Studies with more homogenous groups regarding diagnosis, tumour status and treatment regimen are needed in order to obtain more information about the specific medical risk factors for cognitive sequelae among tumour patients. This is also true for the evaluation of the impact of other factors, such as age or gender.

In line with the results of other studies [12,15,17], we found no significant correlations between patients' subjective estimations of neuropsychological functioning in everyday life and the results of our neuropsychological test battery. Our data showed significant correlations between patients' self-evaluation of cognitive capacity and their current affective status. We found only weak correlations between their current affective status and objectively-measured cognitive functioning, and here especially between anxiety and mnestic functions, which, in general, showed only small deficits in our study sample.

Weak correlations between subjective and objective measures of cognitive capacity cannot simply be attributed to a distorted self-perception by the patients. It should be taken into consideration that a person's subjective appraisal of cognitive deficits is primarily based on an intra-individual comparison between the time before tumour diagnosis and the current status. In contrast, formal neuropsychological testing compares the results of a person with norm data, the aggregated scores of a 'suitable' reference group.

Furthermore, Schuri and colleagues [29] point out that the effect of a depressive mood on cognitive performance is much more important in everyday-life tasks

than in a highly structured test situation. Whenever possible, the combination of subjective self-evaluations with objective neuropsychological test data and the assessment of the patients' current affective status should be 'the method of choice' in clinical practice.

To conclude, there is a need for a comprehensive test battery, suitable for diagnostic screening in clinical practice. Our data, in line with others, suggests that a differentiated assessment of attentional functioning could be the focus of such a diagnostic strategy. Another scope for further development should be the assessment of intervention-oriented diagnostic tools, providing information for the clinical neuropsychologist for individually-tailored rehabilitation strategies.

Our results confirm that cognitive deficits in tumour patients are a relevant topic of study in clinical oncology. Although not a central concern for most patients, this topic should be taken into consideration, e.g. in the process of informed consent for treatment regimens. It has clear implications with regard to the future quality of life of patients.

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