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Baseline cognitive functions among elderly patients with localized breast cancer

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ABSTRACT

Purpose: Cognitive deficits (CD) are reported among cancer patients receiving chemotherapy, but may also be observed before treatment. Though elderly patients are expected to be more prone to present age-related CD, poor information is available regarding the impact of cancer and chemotherapy on this population. This study assessed baseline cognitive functions (before adjuvant treatment) in elderly early stage breast cancer (EBC) patients.

Methods: Women >65 years-old with newly diagnosed EBC were included in this prospective study. Episodic memory, working memory, executive functions and information processing speed were assessed by neuropsychological tests. Questionnaires were used to assess subjective CD, anxiety, depression, fatigue, quality of life, and geriatric profile. Objective CD were defined using International Cognition and Cancer Task Force criteria. A group of elderly women without cancer coupled with published data related to healthy women were used for comparison (respectively to subjective and objective CD).

Results: Among the 123 elderly EBC patients (70±4 years) included, 41% presented objective CD, which is greater than expected in healthy population norms (binomial test $P<.0001$). Verbal episodic memory was mainly impaired (21% of patients). No correlation was observed between objective CD and cancer stage or geriatric assessment. Subjective CD only correlated with verbal episodic memory ($P=.01$).

Conclusions: This is the first large series assessing baseline cognitive functions in elderly EBC patients. More than 40% presented objective CD before any adjuvant therapy, which is a higher than what is reported among younger patients. Our results reinforce the hypothesis that age is a risk factor for CD in EBC patients.

Keywords: Cognition disorders, breast neoplasms, ageing, neuropsychology, quality of life
The registration identification number of this clinical trial is [NCT01333735](https://clinicaltrials.gov/ct2/show/study/NCT01333735).

1. Introduction

Beyond difficulties with memory, attention and concentration reported by cancer patients, it has become increasingly apparent that cytotoxic drugs given for non-central nervous system tumours might induce cognitive side-effects. This phenomenon – called “*chemobrain*” - has been particularly studied among young women treated with chemotherapy for breast cancer. According to the literature, these cognitive troubles could affect 15–50% of chemotherapy-treated patients and are usually moderate in severity [1]. Nevertheless, recent longitudinal studies revealed that about 20 to 30% of breast cancer patients have cognitive impairment before starting adjuvant treatment [2]. This indicates that beside exposure to cytotoxic drugs, other factors including postoperative dysfunctions, psychological distress related with the diagnosis, fatigue, genetic factors and also the biological adverse effects of cancer itself are involved, suggesting an impact of cancer as a whole on cognitive functions [3, 4].

The mean patients’ age in the previous studies addressing the impact of cancer on cognitive function was less than 65 years. Yet, because cancer increasingly appears among seniors, the impact of ageing on cognitive impairment is a relevant issue. Ageing by itself is known to be associated with some cognitive modifications, comorbidities and functional decline, which may all have an impact on the patients’ independence. While both ageing and cancer are expected to have an impact on cognition, biologic processes underlying cancer led to the hypothesis that age-associated declines among cancer patients would be parallel but higher to that of older adults with no cancer history, and that treatment-induced accelerated ageing would be observed only in vulnerable or frail populations [2]. Although a pretreatment cognitive evaluation is a prerequisite to define the part of cognitive chemotherapy-induced impairment, only one study, to our knowledge, addressed this issue especially among elderly breast cancer patients [5].

The aim of the present prospective study was to precisely assess cognitive functioning (objective performances and subjective complaints) among elderly EBC patients before starting adjuvant therapy, and to seek for correlations with mood, fatigue, quality of life and clinical variables.

2. Patients and methods

Participants

Newly diagnosed and consecutive elderly women with EBC were recruited from 3 French Cancer comprehensive Centers (Caen, Rouen, and Strasbourg) from January 2009 to August 2012.

Inclusion criteria were EBC and age over 65. Exclusion criteria included prior exposure to chemotherapy or radiotherapy, neurological comorbidities, known psychiatric comorbidities which might affect capacity to participate, major cognitive disorders and documented alcohol or drug abuse. Participants with a Mini-Mental State Examination (MMSE) score less than 25 out of 30 suggesting potential pathological ageing were not eligible [6-8] as well as those reporting a formal education less than 5 years (end of the primary school) due to the lack of normative data for such individuals.

Patients were assessed after surgery, but before any adjuvant treatment initiation. They were evaluated with standardized neuropsychological tests, by a graduate neuropsychologist, and through self-report questionnaires. Cognitive performances were compared to published normative data, adjusted for age and/or education. All patients gave their written informed consent to the longitudinal study which was approved by the local ethics committee.

Assessment

The neuropsychological battery included standardized neuropsychological tests assessing 4 cognitive domains: episodic memory (verbal and visual modalities), working memory, information processing speed, and executive functions (Table 1) [7, 9-13]. The subjective assessment consisted of a self-report measure of cognitive complaints (Functional Assessment of Cancer Therapy Cognitive Scale - FACT-Cog, version 3 [14, 15] – 4 subscales: *Perceived Cognitive Impairments*, *Impact on Quality of Life*, *Comments from Others*, and *Perceived Cognitive Abilities*), assessment of depression (Beck Depression Inventory – BDI [16]), anxiety (Spielberger State-Trait Anxiety Inventory – STAI [17]), fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue – FACIT-Fatigue, version 4 [18]) and quality of life (FACT-Breast - FACT-B, version 4 [19] incorporates FACT -General - FACT-G, version 4 [20]). Geriatric assessment included the Geriatric Depression Scale (GDS) [21] (4-item short form), the Instrumental Activities of Daily Living (IADL) [22], the Activities of Daily Living (ADL) [23], the Charlson comorbidity index [24], the number of medications and main previous medical history. Clinical variables were Performance Status (PS), medications with potential impact on cognition (Level 3 on the WHO analgesic ladder, anxiolytics, antidepressant treatments and hypnotics), cancer stage, time since surgery, type of surgery, HER2 positive, and hormone receptors status.

Procedure

Patients completed neuropsychological tests, geriatric scales, and some self-report questionnaires (the BDI and the STAI) in a 2 hour-session with a neuropsychologist. The other self-report questionnaires were completed by the patients at home.

Assessment criteria

According to the recommendations of the International Cognition and Cancer Task Force [25] and as described previously [26], an index for each patient's baseline overall cognitive function was operationally defined as impaired or not impaired using a 2-part criterion: if patients performed at a z-score of ≤ 1.5 standard deviation (SD) on 2 or more tests, or if they performed at a z-score of ≤ 2.0 SDs on a single test, they were classified as impaired. This 2-step approach was designed to minimize the number of potential false-positive errors resulting from multiple tests and to determine the frequency of impairment rather than low performance. By using curves based on the binomial probability distribution [27], we determined that in a battery of 8 independent tests approximately 17% of the population would perform 2 SDs below the mean on a single test, making 17% considered as the significant threshold. Like for overall cognitive function, using the classification criteria described above, a cognitive domain was considered as impaired if it included one impaired score.

As a reference of self-report cognitive complaints in the general population, a group of 71 healthy women matched on age and education to the EBC patients included (recruited through local advertisements and among associations) completed the FACT-Cog. Clinically significant symptoms of mood disorders and fatigue were operationally defined as ratings on the BDI ≥ 8 [16], STAI ≥ 56 [17] and FACIT-Fatigue < 37 [28]. Geriatric profile was established using GDS (0-4, high score = more depression), IADL (0-8, low score = no functional status problem) and ADL (0-6, high score = no functional status problem) scores; patients were considered as having a frailty profile if they had at least one alteration of these scores (GDS > 0 , IADL > 0 , ADL < 6).

Statistical Analysis

Published normative data, adjusted for age and/or education, were used to convert patients' raw neuropsychological tests scores into standardized scores (z scores; mean, 0; SD, 1). Descriptive statistics were generated for the socio-demographic and clinical variables. Comparisons were made by chi square, Student's, and Wilcoxon's tests. The correlations between cognitive complaints and objective cognitive scores and other self-report measures were assessed with Spearman's rank correlation coefficient. Given the large number of correlations performed, a p-value <0.01 was considered in order to minimize type I error. All analyses were conducted using SAS version 9.3.

3. Results

Sample characteristics

Of 221 elderly patients with EBC screened, 11 were ineligible, and 82 were not enrolled in the trial for the following reasons: lack of interest (n=17), too much burden (n=9), travel limitations (n=17), duration of the assessment (n=10), or other reason (n=29). This yielded a 61% participation rate. Moreover, 5 patients were excluded from analysis because of a score above the threshold of dementia [8]. Hence, the final sample consisted of 123 patients, whose major characteristics are presented in Table 2. The majority of elderly patients did not exhibit geriatric comorbidities, was healthy (PS 0=91%) and two thirds had a low level of education.

Neuropsychological outcomes

Using the classification criteria described above, 41% of patients (51/123, binomial test $P<.0001$) had impaired overall cognitive function which is significantly more frequent than what would be expected in the general population. Twenty nine percent (36/123) exhibited impairment on 1 test, whereas 12% (15/123) exhibited impairment on 2 or more tests. Main impairment was related to visual episodic memory and executive functions (21 and 16% of

patients, respectively - cf. Fig.1). Raw neuropsychological test scores, z-scores or standard scores are shown in Table 3.

Cognitive complaints

Healthy subjects had significantly more complaints on *Perceived Cognitive Impairments* and *Perceived Cognitive Abilities* FACT-Cog subscales than patients (Fig. 2). However, patients had more complaints than healthy subjects on the subscale *Impact on Quality of Life* of cognitive impairment ($P < .025$).

Anxiety, depression, fatigue, geriatric and quality of life scores

Anxiety, depression and severe fatigue were observed in 6%, 10% and 29% of the patients, respectively. Regarding geriatric scores, 89% and 87% of the patients had normal GDS and functional status scores. Quality of life scores are shown in Table 3.

Relation between cognitive complaints and neuropsychological scores, anxiety, depression and fatigue

As shown in Table 4, cognitive complaints were correlated with verbal episodic memory impairment (*Perceived Cognitive Impairments* subscale, $P < .01$) but overall cognitive scores were not correlated with cognitive complaints (the 4 subscales of the FACT-Cog).

However, 3 of the 4 subscales of the FACT-Cog (*Perceived Cognitive Impairments*, *Perceived Cognitive Abilities* and *Impact on Quality of Life*) were significantly correlated with the measures of depression, anxiety, and fatigue ($P < .001$; Table 4). Furthermore, the same 3 subscales were overall significantly associated to quality of life scores (FACT-B and FACT-G; Table 4).

Neuropsychological outcomes and clinical characteristics

Cognitive impairment was not significantly correlated with geriatric profile ($P=0.83$). Furthermore, there was no correlation between cognitive impairment and Charlson index, PS, medications with potential impact on cognition, cancer stage, time since surgery, type of surgery, hormonal receptor and Her2 status.

4. Discussion

This study is the first large series assessing cognitive functions in elderly EBC patients prior to adjuvant treatment. The main result is that, compared to normative data based on age and education, 41% of the patients had cognitive impairment mainly epitomized by impaired visual episodic memory before any adjuvant treatment which is significantly higher than what would be expected considering healthy population norms. To avoid confusing bias from pre-treatment status to that of chemotherapy-induced impairment, some authors proposed the term “chemobrain” to be replaced by “cancerbrain” [30, 31]. In this way, evaluation of cognitive functions before treatment appears essential to understand the impact of treatments on cognitive functions of cancer patients especially among elderly patients.

In our study, the proportion of patients exhibiting pre-treatment impairments was higher than that the one reported in studies focusing on younger breast cancer patients [45-55 years-old] ranging from 20–30% [2]. This important finding supports the hypothesis that elderly patients may be more sensitive to the impact of cancer on cognition, and would be consistent with the link between biological processes underlying cancer, ageing, neurodegeneration, and a cognitive decline as proposed by T.A. Ahles [32]. However, longitudinal studies remains necessary to investigate whether or not cancer therapies accelerate cognitive ageing [32].

In a previous pilot longitudinal study exploring baseline cognitive functioning of elderly patients with breast cancer ($n = 28$), 11% of the patients were found to have cognitive impairment before beginning chemotherapy [5]. However, 86% of the patients had an

education level superior to high school (against only 18% in our population), which may have biased the results and underestimated the impact on cognition. Thus, according to the concept of cognitive reserve suggesting that some subjects may cope better than others with brain damage, high education level could reduce the sensitivity of patients to the impact of cancer on cognition [2].

To our knowledge, the present study is unprecedented in exploring differences between elderly breast cancer patients and healthy controls with the FACT-Cog. For 2 of the 4 FACT-Cog subscales, breast cancer patients reported significantly less cognitive complaints (*Perceived Cognitive Impairments* and *Perceived Cognitive Abilities*) than healthy controls, but seemed to have more complaints on *Impact on Quality of life* subscale. One hypothesis could be that patients with breast cancer are more likely to put cognitive impairment into perspective due to the context of the disease, even though those minor difficulties may indeed have an impact on their quality of life significantly.

The present data also suggest that, in accordance with previous studies, cognitive complaint scores were correlated with anxiety, depression and fatigue scores. However, no correlation was found with overall objective cognitive scores [33], except between verbal episodic memory impairment and the *Perceived Cognitive Impairments* subscale. The latter could allow assessing this cognitive domain, especially regarding memory verbal information retrieval (accounting for one third of this subscale items). These results are consistent with those reported by Ganz and colleagues based on cognitive complaint questionnaire assessing 4 subscales specific to one cognitive domain, which suggested that subjective cognitive complaints partly reflect objective performance in domain-specific cognitive test [34].

In the present study, all patients underwent a selected geriatric assessment. Interestingly, the results showed that the presence of at least one impaired cognitive domain was not significantly correlated with geriatric fragility assessed from GDS and functional status (ADL

and IADL). However, the definition of geriatric fragility could be considered as relatively strict (at least one score of the 3 scales altered), and only a few number of patients were considered as having a geriatric frail profile, which could represent a selection bias of our sample. Furthermore, the large majority of the patients included in our study were in relatively good general health as indicated by the proportion with PS 0 (91%) or Charlson index 0 (78%), suggesting that the proportion of patients with cognitive impairments (40%) could have been underestimated. Indeed, nobody can exclude that the proportion of cancer patients with cognitive impairment prior to adjuvant treatment could be higher in a global and more heterogeneous population regarding geriatric conditions.

While the present quality of life-related data appeared to be in the same range as those reported in the overall cancer population [29], cognitive functioning in elderly patients remains an important issue to be taken into account in the decision making of adjuvant treatment.

The lack of direct comparison with a group of healthy subjects remains the main limitation of this study. Furthermore, the population of patients was clinically heterogeneous regarding some characteristics (cancer stage, hormonal receptor status, type of surgery...). Another possible selection bias could be the low number of geriatric scores in our population or the impact of patients' motivation.

In conclusion, this study is the first large series assessing baseline cognitive functions in elderly EBC patients. The main finding is that cognitive impairment prior to adjuvant therapy was more frequent than what is observed or reported in both comparative healthy elderly subjects or younger breast cancer patients; this reinforces the hypothesis that age-associated decline among cancer patients is pronounced (i.e., age is a risk factor for CD in breast cancer patients). Evaluation of cognition before treatment is essential to take into account the impact

of treatments on cognitive functions, especially among elderly cancer patients. Furthermore, cancer treatments could accelerate the ageing process in a vulnerable or frail population. In this respect, additional research including such baseline assessment is needed to understand, anticipate and manage the short- and long-term effects of cancer therapy on the cognitive function of elderly patients.

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Table 1. Neuropsychological tests grouped by main cognitive domains

Cognitive domain	Test	Outcome measure	Range
Episodic memory			
Verbal episodic memory	Grober and Buschke procedure ²⁰	4 free recalls	(4x) 0-16
Visual episodic memory	Rey Complex Figure ¹⁹	Recall score	0-36
Working memory			
	WAIS-III ²¹ : Arithmetic	Number of resolved problems	0-22
	WAIS-III: Digit-span	Correct trials, forward	0-16
	WAIS-III: Letter-number sequencing	Correct trials, backward	0-14
		Total correct trials	0-21
Information processing speed			
	TMT A ¹⁸	Time to complete and errors	≥0
Executive function			
Flexibility	TMT B ¹⁸	Time to complete and number of perseverative errors	≥0
Information generation	Verbal fluency ¹⁷ : Category (animal) and Letter P	Total score over 2 min	≥0

WAIS: Wechsler Adult Intelligence Scale, TMT: Trail Making test

Table 2. Demographic and clinical characteristics of all patients (n=123)

Demographic	
Age (years) (mean, SD, range)	70 (4.10) [65-83]
Education level (low / middle / high) (%) (mean, SD)	66 / 15 / 18 11 (2.77)
Clinical	
PS (WHO=0) (%)	91
Co-morbidities (%) Charlson index (0 / 1-2)	78 / 22
> 3 co-medications	27
Medications with potential impact on cognition* (%)	24
Cancer stage I-II (%)	87
Time since surgery (days) (median, range)	36 [19-141]
Lumpectomy / Mastectomy (%)	72 / 28
Lymph node dissection (%)	80
HER2 positive (%)	17
Hormone receptors positive (%)	88

SD: standard deviation, PS: Performance Status, WHO: World Health Organization

* Level 3 on the WHO analgesic ladder, anxiolytics, antidepressant treatments and hypnotics

Table 3. Neuropsychological test and quality of life outcomes

Cognitive scores	No.	Mean	SD	z scores or standard scores
<i>Episodic memory</i>				
FR1	123	8.84	1.94	0.17 (0.88)
FR2	123	10.61	1.94	0.28 (0.83)
FR3	123	11.66	1.87	0.21 (0.83)
DFR	122	11.95	2.30	0.17 (1.14)
Rey recall	123	15.24	6.24	-1.38 (1.27)
<i>Working memory</i>				
Arithmetic	122	10.11	4.38	8.80 (2.55)
Digit-span forward	123	7.99	2.17	
Digit-span backward	123	4.95	1.60	
Digit-span std score				8.81 (3.01)
Letter-number sequencing	123	7.62	2.44	8.75 (2.54)
<i>Information processing speed</i>				
TMT A time	123	45.71	17.50	-0.32 (0.78)
TMT A errors	123	0.17	0.46	0.27 (1.42)
<i>Executive function</i>				
Semantic fluency score	123	27.75	7.03	0.10 (0.88)
Phonemic fluency score	123	19.24	6.50	0.03 (1.03)
TMT B time	122	111.43	45.26	-0.40 (0.67)
TMT B perseverative errors	122	0.52	0.85	0.42 (1.18)
Quality of life scores				
FACIT-Fatigue	111	40.02	9.16	
FACT-B	112	23.40	6.27	
FACT-G global score	110	81.83	10.56	
PWB	110	24.54	3.31	
SWB	111	19.97	4.15	
EWB	112	19.19	3.62	
FWB	112	17.96	4.35	
FACT-Cog				
PCI	112	60.16	9.91	
QoL	106	11.63	4.06	
Oth	110	15.55	1.11	
PCA	108	19.38	4.97	

No.: number, FR: free recall, DFR: delayed free recall, TMT: Trail Making test, PWB: Physical Well-Being, SWB: Social/Family Well-Being, EWB: Emotional Well-Being, FWB: Functional Well-Being, PCI: Perceived Cognitive Impairment, QoL: Impact on Quality of Life, Oth: Comments from others, PCA: Perceived cognitive abilities

Table 4. Relations between cognitive complaints and neuropsychological, anxiety, depression, fatigue and quality of life scores

<i>Spearman correlation</i>	Cognitive complaints			
	PCI	PCA	Oth	QoL
Neuropsychological scores				
At least 1 domain impaired (<i>t test</i>)	-0.48	0.93	0.65	0.67
Verbal episodic memory impairment	-0.31*	-0.10	-0.24	-0.20
FR1	0.23	0.23	0.16	0.24
FR2	0.23	0.18	0.16	0.17
FR3	0.10	0.10	0.003	-0.02
DFR	0.19	0.04	0.17	0.24
Visual episodic memory impairment (Rey recall)	-0.05	0.009	-0.03	-0.20
Working memory impairment	<0.001	-0.07	-0.01	-0.05
Arithmetic	-0.03	0.12	0.07	0.12
Digit-span	0.09	0.12	0.10	0.10
Letter-number sequencing	0.06	0.09	0.06	0.17
Information processing speed impairment	0.04	-0.13	-0.11	0.20
TMT A time	-0.06	-0.10	0.05	0.01
TMT A errors	-0.04	-0.08	-0.10	0.21
Executive function impairment	-0.03	-0.16	0.02	-0.12
Semantic fluency score	0.05	0.18	-0.09	0.03
Phonemic fluency score	-0.06	0.06	-0.10	0.20
TMT B time	-0.06	-0.18	0.03	-0.09
TMT B perseverative errors	-0.18	-0.08	-0.17	-0.12
Demographic scores				
Age (years)	-0.06	0.02	-0.02	-0.15
Education (years)	0.05	0.13	0.23	0.20
Anxiety, depression scores				
BDI – depression	-0.38**	-0.32**	-0.20	-0.32**
STAI State - anxiety	-0.32**	-0.35**	-0.19	-0.34**
Quality of life scores				
FACIT-Fatigue	0.47**	0.44**	0.23	0.50**
FACT-B	0.26*	0.25*	0.19	0.47**
FACT-G	0.33**	0.47**	0.22	0.40**
PWB	0.25	0.34**	0.15	0.39**
SWB	0.13	0.27*	0.19	-0.02
EWB	0.32**	0.36**	0.16	0.44**
FWB	0.31**	0.39**	0.13	0.42**

FR: free recall, DFR: delayed free recall, FACT-G subscales: PWB: Physical Well-Being, SWB: Social/Family Well-Being, EWB: Emotional Well-Being, FWB: Funcional Well-Being. PCI: Perceived Cognitive Impairment, PCA: Perceived cognitive abilities, QoL: Impact on Quality of Life, Oth: Comments from others.

*p<0.01, ** p<0.001

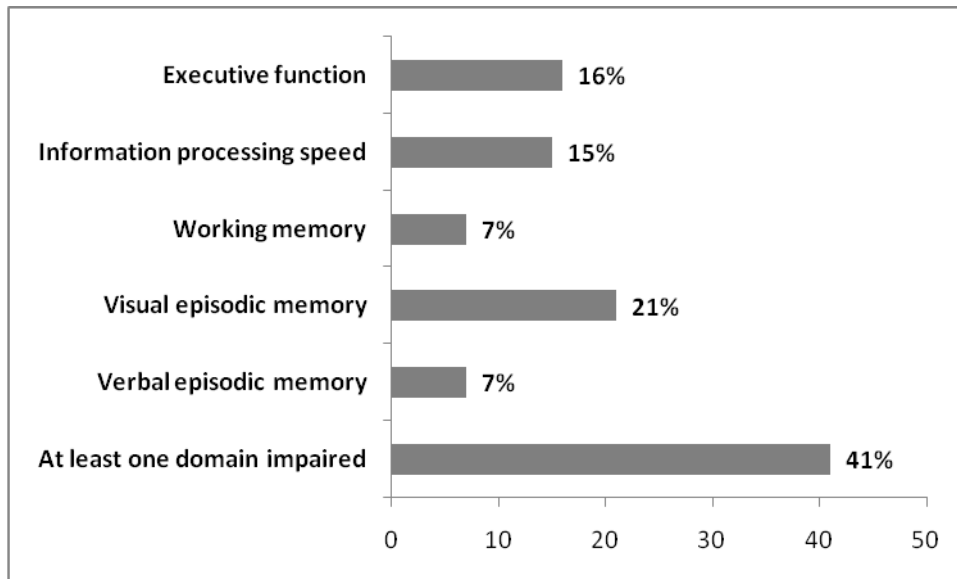
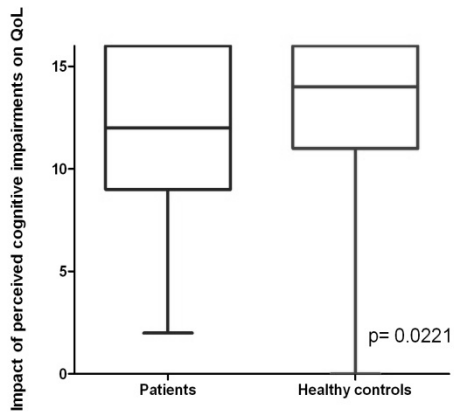
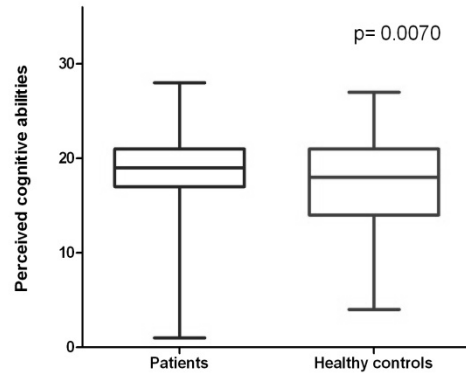
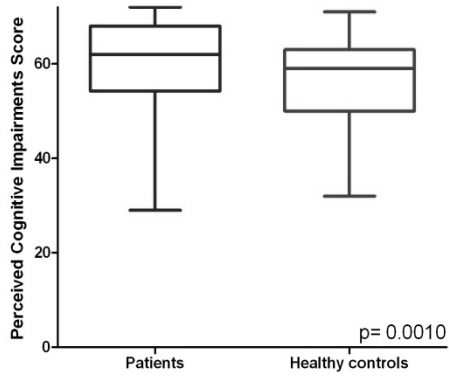


Figure 1. Distribution of patients according to impaired cognitive domain



QoL: Quality of Life

Figure 2. Median FACT-Cog scores of patients and healthy subjects.

Figure 1. Distribution of patients according to impaired cognitive domain

The percent of patients with cognitive impairment in each cognitive domain assessed and for at least one impaired cognitive domain.

Figure 2. Median FACT-Cog scores of patients and healthy subjects.

Whiskers' boxplot indicate minimum and maximum and high scores indicate low complaints. There were significant differences between patients and healthy subjects on 2 FACT-Cog subscales. The subscale *Comments from Others* was not represented because there was no difference between groups.