**The distress thermometer predicts subjective, but not objective, cognitive complaints six months after treatment initiation in cancer patients**

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**Objectives**

Research has indicated that cancer-related cognitive impairments (CRCI) may be influenced by psychosocial factors such as distress, worry and fatigue. Therefore, we aimed to validate the distress thermometer (DT) as a screening tool to detect CRCI six months post treatment initiation in a group of general cancer patients.

**Methods**

Patients (≥18 years, n=125) with a histologically confirmed diagnosis of a solid cancer or haematological malignancy, scheduled for a curative treatment, were evaluated at baseline (T0) and six months post-treatment initiation (T1) for CRCI by a neuropsychological assessment including patient-reported outcome measures (PROMs). Assessed cognitive domains included premorbid intelligence, attention, processing speed, flexibility, verbal and visual episodic memory and verbal fluency. PROMs entailed distress (DT, cut-off ≥4, range 0-10), anxiety and depression, fatigue (FACIT-fatigue scale) and subjective cognitive complaints.

**Results**

At T0, 60.4% of patients showed a DT score of ≥4, whereas 50% met this criteria at T1. According to the definition of the International Cognition and Cancer Taskforce, 25.5% and 28.3% of patients presented with a CRCI at T0 and T1, respectively. When evaluating the DT as a screening tool for CRCI at T1, data showed an inverse relationship between the DT and CRCI. ROC-curve analysis revealed an AUC <0.5. ROC-curve analyses evaluating the DT and FACIT-fatigue scale as screening tools for subjective cognitive complaints showed an AUC±SE of respectively 0.642±0.067 and 0.794±0.057.

**Conclusions**

The DT at T0 cannot be used to screen for objective CRCI at T1 but both the DT and FACIT-fatigue scale at T0 showed potential as screening tools for subjective cognitive complaints at T1.

**Background**

Chemobrain - a term coined to describe cancer-related cognitive impairment (CRCI) - is a common concern among cancer patients receiving chemotherapy (Boykoff, Moieni, & Subramanian, 2009; Wefel et al., 2004). CRCI may influence cognitive functioning such as executive functioning, processing speed, working memory and organizational skills. CRCI can have a detrimental effect on a patient’s quality of life (QoL), influencing one’s ability to use complex thinking in making treatment decisions (Ahles et al., 2002; Ketelaars et al., 2013; Lycke et al., 2014; Nelson, Nandy, & Roth, 2007; Saykin, Ahles, & McDonald, 2003). CRCI can persist throughout the whole illness trajectory and in some domains, complaints remain present long after therapy has ended (Koppelmans et al., 2012). A clear understanding of CRCI is crucial as there is a growing group of cancer survivors who have difficulties resuming their former activities (Boykoff et al., 2009). To detect CRCI, the Montreal Cognitive Assessment, Mini-Mental State Examination and Clock Draw Test are often used asides to a neuropsychological test battery. Next to these objective screening tools, subjective measures such as the Functional Assessment of Cancer Therapy-Cognitive Function and the Cognitive Symptom Checklist-Work can also be used. A combination of these objective and subjective measurements could increase diagnostic sensitivity (Isenberg-Grzeda et al., 2017).

Interestingly, CRCI may be detected before the administration of systemic chemotherapy (Lycke et al., 2016b). As a result, some authors suggested an association with psychological risk factors such as distress, worry and fatigue (Andreotti, Root, Ahles, McEwen, & Compas, 2015; Burstein, 2007; Lopez Zunini et al., 2013; Mertz et al., 2012). Distress is defined as a multifactorial unpleasant emotional experience of psychological, social and/or spiritual nature, that may interfere with the ability to cope with cancer effectively, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fear to problems that can become disabling such as depression, anxiety, panic, social isolation, and existential and spiritual crisis (National Comprehensive Cancer Network (NCCN), Version 3.2012). Studies have noted that up to 47% of newly diagnosed and recurrent cancer patients presented with a significant level of mental distress, to an extent that they can be diagnosed with a psychiatric disorder (Singer et al., 2009). The NCCN Guidelines in Distress Management recommend an early evaluation and screening of distress as it leads to poorer QoL if left untreated. Therefore, the NCCN Distress Management Panel developed the distress thermometer (DT) which uses a 11-point rating scale to identify distress caused by any kind of source, even if unrelated to cancer (Baken & Woolley, 2011; Zigmond & Snaith, 1983). A review on the clinical use of the DT stated that it could be a useful tool to initiate a dialogue between health care professionals and the patient and it is fast to administer. However, it was noted that though a lot of patients showed significant distress, more than two third of these patients refused any further support. Further, a higher implementation of the DT in clinical practice was recommended (Snowden et al., 2011).

In this paper, we present the primary and predefined clinical secondary endpoints of the CONCEPT-trial (ClinicalTrials.gov Identifier: NCT01846260). Our primary aim (1) was to examine the feasibility of the DT as a screening tool to predict CRCI six months post treatment initiation in a group of general cancer patients receiving a curative treatment. As screening for distress is already implemented in routine care, this would allow a faster identification of patients who are prone to develop CRCI. Secondary aims were to (2) analyse objective versus subjective cognitive complaints, (3) examine cognitive changes over time and (4) compare assessment results of patients with and without chemotherapy.

**Methods**

**Participants**

Patients were invited to participate in the CONCEPT-trial between May 2013 and September 2015. All patients were recruited at the Kortrijk Cancer Centre, Kortrijk, Belgium. All patients were aged 18 years or above and had a histologically confirmed diagnosis of a solid tumour (lung, gastro-intestinal, GIST, urological, breast, sarcoma or gynaecological cancer) or haematological malignancy, in an early or advanced stage. Patients were scheduled to receive a treatment (radiotherapy, chemotherapy, radiochemotherapy, radiobiotherapy, anti-hormonal, targeted therapy or a combination of the above) with curative intent. Patients receiving surgery alone were not allowed to participate. Other exclusion criteria included: a diagnosis with primary or secondary brain tumours; having a prior history of cancer during the last 5 years, with or without chemotherapy or radiotherapy; suffering from an organic brain syndrome; having an untreated or unstable major medical condition other than cancer; being alcohol or drug dependent; showing signs of mental deterioration based on the investigator’s judgement or pre-trial routine assessments; being diagnosed with dementia (DSM-IV criteria); presenting with a condition other than cancer in which fatigue is a prominent symptom (such as chronic fatigue syndrome) and having a major psychiatric or neurologic disorder that could potentially invalidate assessment. A prior or current diagnosis of a depressive or anxiety disorder was allowed since many cancer patients may suffer from this as a consequence of the cancer diagnosis. The trial was approved by the ethics committee of the General Hospital Groeninge, Kortrijk, Belgium and all patients gave written informed consent.

**Measures**

Patients were evaluated for CRCI by a neuropsychological assessment (**Table 1**) including patient-reported outcome measures (PROMs, **Table 2**) at baseline (T0) and six months post-treatment initiation (T1) (Lycke et al., 2016a). A six month time difference was chosen to rule out the learning effect of neuropsychological tests and because significant levels of distress were reported in lung and breast cancer patients after six months (Cooley et al., 2003; Gallagher et al., 2002).

An overview of the neuropsychological test battery is summarized in **Table 1**. It includes following cognitive domains: premorbid intelligence (Dutch Adult Reading Test (DART) (Bright, Jaldow, & Kopelman, 2002)), episodic memory (visual: Rey’s Complex Figure Test (CFT) delayed recall test (Osterrieth, 1944); verbal: Rey’s Auditory Verbal Learning Test (RAVLT) delayed recall test (Schmidt, 1996)), executive functions (flexibility: Trail Making Test (TMT) number-letter sequencing (Delis et al., 2007); phonetic and semantic word fluency: Controlled Oral Word Association Test (COWA) (Ruff, Light, Parker, & Levin, 1996); processing speed: TMT number sequencing (Delis et al., 2007) and WAIS-III Digit Symbol (Wechsler, 1997, 1998, 2000, 2002, 2004)) and working memory (attention: WAIS-III Digit Span (Wechsler, 1997, 1998, 2000, 2002, 2004)). An alternative form was used to minimise practice effect in case of the Rey’s Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996). All assessments were performed by either a neuropsychologist (MSc) or study trial coordinators (MSc, PhD) trained to perform these measurements.

PROMs included an assessment of distress (Distress thermometer (DT) and 39-item Problem List (Baken & Woolley, 2011)), anxiety and depression (Hospital Anxiety and Depression Scale (HADS)), fatigue (FACIT Fatigue Scale ) and subjective cognitive complaints (Cognitive Failure Questionnaire (CFQ) ) (**Table 2**).

**Statistical considerations**

Statistical analyses were conducted by use of SPSS software (version 23; IBM SPSS Statistics, Chicago, IL). Descriptive statistics were performed to present patient and tumour characteristics and neuropsychological assessment results. In accordance with the International Cognition and Cancer Task Force (ICCTF), patients were marked as having a cognitive impairment if they either presented with two or more test scores at or below -1.5 standard deviations (SDs) from the normative mean or if they presented with one test score at or below -2.0 SDs (Wefel, Vardy, Ahles, & Schagen, 2011). Published normative data, adjusted for gender, age and/or education, were used to convert raw test scores into standardized z-scores (mean = 0; SD = 1), if applicable. Data from questionnaires were converted according to standard scoring rules.

For the primary endpoint analysis, it was assumed that the neuropsychological assessment was the gold standard against which the DT was compared. Sample size calculations were based on following assumptions. A sample of 21 from the positive group and 63 from the negative group would achieve 81% power to detect a difference of 0.20 between the area under the roc curve (AUC) under the null hypothesis of 0.50 and an AUC under the alternative hypothesis of 0.70 using a two-sided z-test at a significance level of 5%.

Secondary endpoint analyses were performed and included paired-sample T-tests to detect differences between neuropsychological test scores at T0 and T1 for all patients together and for the chemotherapy and non-chemotherapy groups separately. Univariate analysis of variance, adjusted for age and IQ, were selected to compare results at T1 between the chemotherapy and non-chemotherapy group. Binary logistic regression analysis was performed in order to find predictive factors of CRCI. Regression analysis included 13 covariates: age, gender, premorbid IQ, distress level, fatigue level, cognitive complaints, days since diagnosis, days since surgery, active treatment for diabetes mellitus, active treatment for hypertension, stage (early vs. late stage), treatment (chemotherapy: yes or no) and diagnosis (breast cancer or not). Variables were included in the model if they were significant at the *p*<0.05 level.

**Results**

**Patients characteristics**

In total, 125 patients were included in the trial. Baseline patient characteristics are previously described **(Table 3)** (Lycke et al., 2016b). Of the 125 patients, 106 (84.8%) completed the second assessment. Five patients withdrew from the trial without giving a specific reason, five patients felt too ill, four patients did not want to make the extra travel to the hospital, three patients had died as a consequence of their disease or treatment and two patients declared to have no time. At T0 and T1, respectively one and five patients did not fully complete the PROMs. The mean age of the remaining 106 patients was 59.0 years (range 30.0-85.0). Patients were more likely to be female (69.8%) and presented with following types cancer: breast(48.1%), gastro-enterological(24.6%), genitourinary(11.3%), gynaecological(9.4%), haematological(5.7%) and lung(0.9%). More patients had an early stage disease (65.1%). Exactly half of patients (50.0%) received (neo)adjuvant chemotherapy with or without radiotherapy and/or hormonal treatment. Other patients characteristics and chemotherapy regimens are presented in **Table 3**.

**Primary endpoint results**

At T0, 60.4% of patients showed a DT score of ≥4, whereas 50% met this criteria at T1. According to the definition of the ICCTF, 25.5% and 28.3% of patients presented with a CRCI at T0 and T1, respectively. When evaluating the DT at T0 as a screening tool for CRCI at T1 (primary endpoint), ROC-curve analysis revealed an AUC <0.5. Binary logistic regression analysis found that less distress at T0 (B=-0.267, *p*<0.05), having a lower premorbid IQ (B=-0.066, *p*<0.05), female gender (B=1.861, *p*<0.05) and no surgery (B=-1.745, *p*<0.05) predicted CRCI at T1. Chemotherapy did not influence the risk on CRCI (B=0.186, *p*=0.666).

**CRCI vs. subjective cognitive complaints**

At both time points, only a small percentage of patients stated to have cognitive complaints based on a Cognitive Failure Questionnaire (CFQ) score of 43 or higher (14.3% at T0, 16.8% at T1). **Fig. 1.A** and **1.B** show the number of patients with a CRCI at T0 and T1 subdivided by a CFQ-score of ≥43. At baseline, the distribution of cognitive complaints was more or less equal in both groups (**Fig. 1.A**). At T1, more patients experienced subjective cognitive complaints (**Fig. 1.B**). Surprisingly, the majority of these patients were not diagnosed with a CRCI. ROC-curve analyses evaluating the DT and FACIT-fatigue scale at T0 as screening tools for subjective cognitive complaints showed an AUC±SE of respectively 0.642±0.067 and 0.794±0.057 (**Fig. 2.A** and **2.B**).

**Cognitive changes and subgroup analyses**

**Table 4**. shows mean DT scores and mean raw scores per cognitive domain at T0 and T1 for all patients and for the chemotherapy and non-chemotherapy group independently. Paired-samples T-test detected significant differences for processing speed (WAIS-III Digit Symbol) and verbal and visual episodic memory when comparing T0 and T1 in all patients. An improved performance over time was found for all domains except for verbal episodic memory.

Mean age and mean school leaving age of the chemotherapy group was calculated as 57.8 and 18.7 years, respectively, whereas the non-chemotherapy group had a mean age of 60.2 years and a mean school leaving age of 18.5 years. Mann-Whitney U test did not detect statistical significant differences between the chemotherapy and non-chemotherapy group in terms of age and school leaving age (*p*=0.459 and *p*=0.430, respectively). The chemotherapy and non-chemotherapy group both comprised primarily female individuals (58.5% and 81.1%, respectively). However, a significant difference in gender was detected between the chemotherapy and non-chemotherapy group (Χ² test: *p*<0.05). **Table 4**. shows mean distress and mean neuropsychological test results at T0 and T1 for all patients and the chemotherapy and non-chemotherapy group separately. Distress decreased over time for the chemotherapy group and slightly increased in the non-chemotherapy group (*p*<0.001 and *p*<0.01 respectively). At T1, distress was significantly lower in patients who received chemotherapy compared to patients who did not (*p*<0.01). For all patients and the chemotherapy and non-chemotherapy group, similar results in terms of cognitive changes were found: patients performed better at T1 in all domains except for verbal episodic memory. In both chemotherapy and non-chemotherapy groups, significant within group differences were found between T0 and T1 for verbal and visual episodic memory. The chemotherapy group also showed significant within group differences between T0 and T1 for attention, processing speed (WAIS-III Digit Symbol) and flexibility. Univariate analyses of variance, adjusted for age and IQ, did not reveal any significant differences between the chemotherapy and non-chemotherapy concerning the individual cognitive domains at T1 (**Table 4**).

**Conclusions**

We aimed at 1) validating the widely used DT as a screening tool to predict CRCI in a group of general cancer patients scheduled for curative treatment, 2) evaluating objective CRCI versus subjective cognitive complaints, 3) analysing cognitive changes over time and 4) comparing assessment results of patients who received chemotherapy and who did not. Our data showed that the DT at T0 failed to screen for CRCI at T1. On the contrary, baseline PROMs (T0) including the DT and FACIT-fatigue scale showed promise to screen for subjective cognitive complaints at T1. We found a lower verbal memory performance in all patients over time. Further, we did not detect differences on neuropsychological test scores at T1 between patients who received chemotherapy and who did not.

To our knowledge, this is the first study that looked into in the feasibility of the baseline DT as a screening tool to predict CRCI six months post-treatment initiation. In our sample, respectively 25.5% and 28.3% of patients presented with a CRCI at T0 and T1. We stated that we would only accept the DT as a screening tool if we would find an AUC of at least 0.70. Unexpectedly, we found a trend for an inverse relationship between the degree of distress and the risk on CRCI with an AUC<0.5. Further research is required to explain this phenomenon.

Our data indicates that IQ, gender and receiving surgery may also influence CRCI. We previously reported that IQ predicts baseline CRCI in cancer subjects (Lycke et al., 2016b). It has also been reported that IQ influences neuropsychological test scores (Diaz-Asper, Schretlen, & Pearlson, 2004). Further, female gender also increased CRCI risk. In our sample, this may be a result of including a high number of female individuals (69.8%) with the majority of those being diagnosed with breast cancer (68.9%). Gender differences have been observed previously by Lezak et al. (2012) in non-cancer subjects (Lezak, Howieson, Bigler, & Tranel, 2012). On the contrary, Visovatti et al. (2016) could not confirm these findings in a group of colorectal cancer patients (Visovatti, Reuter-Lorenz, Chang, Northouse, & Cimprich, 2016). An interesting question remains, however, why breast cancer patients seem to be more prone to develop cognitive troubles after their treatment has ended. One explanation may be that the majority of the breast cancer patients included in our trial only received radiotherapy, followed by hormonal treatment. As a result, follow up in the hospital is not required, leaving the patient alone with their concerns. This may cause a higher distress compared to patients who are followed up during their entire chemotherapy treatment. Hence, for patients receiving chemotherapy the time period between the end of treatment and T1 was shorter compared to the majority of breast cancer patients receiving only radiotherapy at the hospital (data not shown). Several other studies tried to explain the high distress in cancer patients as treatment ends. The end of treatment comprises a transition from frequent visits to the hospital and close follow up to less frequent visits to the oncologist, which may induce fear of recurrence and feeling less safe (Tross et al., 1989; Ward et al., 1992). Patients may feel unprepared to go home and to face side effects on their own (Beisecker et al., 1997). They may face contradictory feelings: relief, because treatment has been completed, but also anxiety for what the future will bring (Maher et al., 1982).

When comparing objective test scores with subjective cognitive complaints, results did not fully match. This is in line with Hutchinson et al. (2012) who stated that objective and perceived impairment could be unrelated because subjective complaints may be an indicator of distress, rather than of CRCI (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012). Interestingly, ROC-curve analysis suggested that the DT and certainly the FACIT-fatigue scale at T0 could be used to predict subjective cognitive complaints in cancer patients six months post treatment initiation (T1). Although it has been reported that distress and fatigue influences self-reported cognition (Schagen et al., 2008), we are – to our knowledge – the first to report upon the possibility of screening for subjective cognitive complaints by use of the DT and FACIT-fatigue scale. It is known that stress may induce cognitive changes (Andreotti et al., 2015). Nonetheless, these findings further highlight the importance of the early detection of psychosocial problems so that appropriate care can be implemented. A prospective trial is needed to confirm these findings.

We compared test scores at T0 and T1 of the individual cognitive domains. Most scores improved over time which could be attributed to the practice effect (Lindner et al., 2014). Verbal episodic memory (as measured by the RAVLT delayed recall test) showed decreased performance at T1. Similar results were found when comparing the chemotherapy and non-chemotherapy group. Worse RAVLT performance over time has not always been found in other studies. Deprez et al. for example found worse performance in chemotherapy patients, but increased RAVLT scores in non-chemotherapy patients and healthy controls (Deprez et al., 2012). In our trial, the RAVLT was the last test to be assessed in the test battery and was further the only test for which an alternative form was used. Therefore, we are left to speculate that lower results could be influenced by these factors.

Further, we compared patients who received and did not receive chemotherapy of all cancer types. Between group analyses did not detect any differences between test scores at T1. Although, it has been suggested that chemotherapeutic regimens may result in lower cognitive performance, researchers have not reached a consensus on the exact pathophysiology (Natori, Ogata, & Yamauchi, 2015). Further, others have previously suggested that the influence of chemotherapy in the etiology of CRCI may be smaller than initially thought (Ahles, Root, & Ryan, 2012). Our research, showing no influence of chemotherapy on CRCI, contributes to this discussion, but more research is necessary to make a final conclusion concerning this issue.

The strengths of this prospective study include multiple aspects. First, we are the first to examine the feasibility of the DT to screen for CRCI in a group of general cancer patients. Although we obtained a negative result, we found that the DT may be able to screen for subjective cognitive complaints. We also found that fatigue seems to have a high impact on patient-perceived impairment and that it may be possible to screen for subjective cognitive complaints with the FACIT-fatigue scale. These findings emphasize that it is crucial to address psychosocial issues and that it is essential to identify those at the beginning of the treatment. By using questionnaires which are already used in routine practice, such as the DT, screening for cognitive complaints could be easily implemented. Second, this trial included a variety of cancer types. Initial research on CRCI mainly focused on breast cancer patients, and in previous research, breast cancer diagnosis predicted impairments in some cognitive domains (processing speed) (Lycke et al., 2016b). Nevertheless, other cancer patients also experience cognitive disturbances. Third, we have included an equal amount of patients who did and who did not receive chemotherapy. Therefore, we were able to compare assessment results of both groups. An interesting finding was that we did not detect any differences in any of the assessed cognitive domain at T1 between the chemotherapy and non-chemotherapy group. Although imaging studies have shown that white matter integrity may be altered as a result of chemotherapy (Deprez et al., 2012; Deprez et al., 2011), our data suggest that processes other than the chemotherapeutic regimen may induce CRCI. This confirms that the term ‘chemobrain’ may have been an unfortunate choice.

The results of this trial also need to be interpreted with caution. We did not include a healthy control group. However, we were able to compare assessment results of cancer patients with and without a chemotherapeutic treatment. As a result, we were able to compare cognitive outcomes of patients who received and did not receive chemotherapy. On the other hand, when comparing the number of impaired patients to the binomial probability distribution (Ingraham & Aiken, 1996; Lycke et al., 2016b), we found significantly more impaired patients in our sample at both time points (data not shown). This suggests that other factors may also play a role in the existence of CRCI. This is supported by Kah Poh Loh et al. (2016) who suggested a multifactorial model for CRCI including psychoactive medications, comorbidities, ageing, the underlying cancer and its treatment, psychosocial, genetic and environmental risk factors (Kah Poh Loh, 2016).

Further, we did not obtain a balanced distribution of cancer types and included a high number of breast cancer patients. As initial research focuses on breast cancer patients, being able to include ‘having a breast cancer diagnosis’ as a confounding factor in the regression analyses was interesting. Especially since this variable did not predict CRCI, while research from Schmidt et al. (2016) reported that breast cancer patients had the second highest prevalence of perceived cognitive dysfunction (Schmidt et al., 2016).

In conclusion, we can state that the DT cannot be used to screen for CRCI, but that it may be used as a screening tool to predict subjective cognitive complaints six months after treatment initiation. This needs to be confirmed in a new, prospective trial. This trial further indicates that psychosocial factors have an important role in self-reported cognitive complaints and that PROMs may be used to screen for those impairments. Addressing these issues is crucial to understanding self-reported cognitive dysfunctions. Last, our findings suggest that variables other than chemotherapy may influence objective cognitive impairments in cancer patients and that more research is warranted to overtake the exact pathophysiology of CRCI.

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**Table 1. Neuropsychological assessment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cognitive domain** | **Test** | **Item** | **Outcome measure** | **Range** | **References** |
| Premorbid intelligence | Dutch Adult Reading Test (DART) | IQ estimation | IQ estimation | ≥ 0 | Bright et al., 2002 |
| *Episodic memory* | | | |  |  |
| Visual | Rey’s Complex Figure Test (CFT) | Delayed recall | Total score | 0 – 36 | Osterrieth, 1944 |
| Verbal | Rey’s Auditory Verbal Learning Test (RAVLT) | Delayed recall | Total score | 0 – 15 | Schmidt, 1996 |
| *Executive functions* | | | |  |  |
| Flexibility | Trail Making Test (TMT) | Condition 4 (number-letter sequencing) | Time needed to complete in seconds | ≥ 0 | Delis et al., 2007 |
| Semantic word fluency | Controlled Oral Word Association Test (COWA) | Animals | Number of correctly produced words in 60 seconds | ≥ 0 | Ruff et al., 1996 |
| Phonetic word fluency | Controlled Oral Word Association Test (COWA) | letter N | Number of correctly produced words in 60 seconds | ≥ 0 | Ruff et al., 1996 |
| Processing speed | Trail Making Test (TMT) | Condition 2 (number sequencing) | Time needed to complete in seconds | ≥ 0 | Delis et al., 2007 |
| WAIS-III Digit Symbol |  | Number of correct items | ≥ 0 | Wechsler, 1997, 1998, 2000, 2002, 2004 |
| *Working memory* | | | |  |  |
| Attention | WAIS-III Digit Span | Forward and backward span | Total score | 0 – 30 | Wechsler, 1997, 1998, 2000, 2002, 2004 |

WAIS: Wechsler Adult Intelligence Scale

**Table 2. Patient-reported outcome measures**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Measure** | **Indication** | **Range** | **Cut-off** | **References** |
| Distress thermometer (DT) and 39-item Problem List | Distress | 0-10 | ≥4 | Baken & Woolley, 2011 |
| Hospital Anxiety and Depression Scale (HADS) | Anxiety | 0-21 | ≥8 | Zigmond & Snaith, 1983 |
| Depression | 0-21 | ≥8 |
| FACIT Fatigue Scale | Fatigue | 0-52 | NA (lower score indicates greater fatigue) | Cella et al., 2005 |
| Cognitive Failure Questionnaire (CFQ) | Subjective cognitive complaints | 0 – 100 | ≥43 | Broadbent, 1980 |

FACIT: Functional Assessment of Chronic Illness Therapy; NA: not applicable

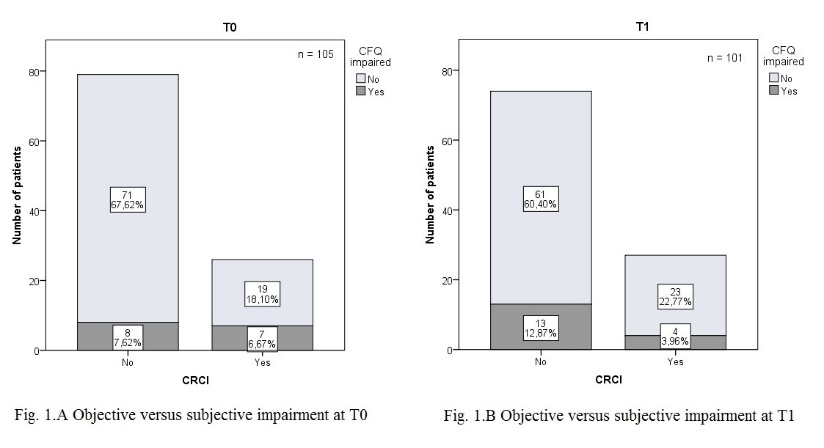
**Table 3. Demographic and clinical data (n=106)**

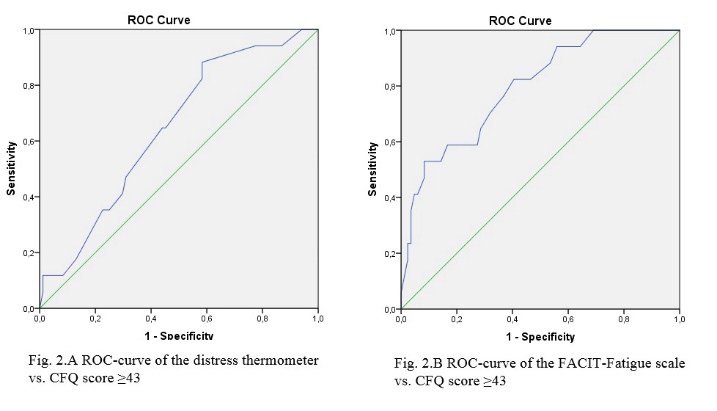
|  |  |
| --- | --- |
| **Demographics** | **n (%)** |
| Gender |  |
| Female | 74 (69.8) |
| Male | 32 (30.2) |
| Highest education |  |
| Primary education | 0 (0) |
| Lower secondary education | 25 (23.6) |
| Higher secondary education | 42 (39.6) |
| Higher education | 34 (32.1) |
| Other | 5 (4.7) |
| Clinical data |  |
| Stage |  |
| Early (I-II) | 69 (65.1) |
| Advanced (III-IV) | 37 (34.9) |
| Surgery prior to T1 | 95 (89.6%) |
| Treatment |  |
| Hormonal treatment alone | 1 (0.9) |
| Radiotherapy alone | 7 (6.6) |
| Chemotherapy alone | 29 (27.4) |
| Radiochemotherapy | 20 (18.9) |
| Radiotherapy and hormonal treatment | 45 (42.5) |
| Chemotherapy and hormonal treatment | 1 (0.9) |
| Radiochemotherapy and hormonal treatment | 3 (2.8) |
| Chemotherapy (n=53) |  |
| Folfox | 12 (22.6) |
| Cisplatin w/o other compound | 10 (18.9) |
| Carboplatinum with taxane derivate | 9 (17.0) |
| 5FU | 8 (15.1) |
| FEC w/o taxotere | 3 (5.6) |
| Cyclofosfamide with taxane derivate | 3 (5.6) |
| AC with paclitaxel | 2 (3.8) |
| ABVD | 2 (3.8) |
| Gemcitabine | 2 (3.8) |
| RCHOP21 | 2 (3.8) |

FU: fluorouracil, FEC: fluorouracil, epirubicine, cyclofosfamide , AC: adriamycine, cyclofosfamide , ABVD: doxorubicine, bleomycine, vinblastine, dacarbazine, RCHOP : rituximab ,vincristine, adriamycine, cyclofosfamide, prednisone

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 4. Mean distress and mean raw scores of all patients, patients who received chemotherapy (chemotherapy group) and patients who did not receive chemotherapy (non-chemotherapy group) at T0 and T1** | | | | | | | |
|  | **All patients** | | **Chemotherapy group** | | **Non-chemotherapy group** | | ***Chemotherapy vs non-chemotherapy\**** |
|  | **T0**  **Mean (SD)** | **T1**  **Mean (SD)** | **T0**  **Mean (SD)** | **T1**  **Mean (SD)** | **T0**  **Mean (SD)** | **T1**  **Mean (SD)** | ***p-*value between groups at T1** |
| **Distress** | 4.4 (2.4) | 3.6 (2.5) | 4.7 (2.5) | 2.9 (2.3) | 4.1 (2.2) | 4.3 (2.5) | **<0.01** |
| *p*-value within group | **<0.001** | | **<0.001** | | **<0.01** | |  |
| **Semantic word fluency** | 22.6 (6.8) | 23.0 (7.0) | 21.6 (5.6) | 22.9 (6.3) | 23.5 (7.8) | 23.1 (7.8) | 0.738 |
| *p*-value within group | 0.408 | | 0.075 | | 0.610 | |  |
| **Phonetic word fluency** | 10.4 (4.9) | 10.8 (4.8) | 10.6 (5.0) | 10.5 (4.8) | 10.3 (4.7) | 11.1 (4.8) | 0.413 |
| *p*-value within group | 0.306 | | 0.827 | | 0.069 | |  |
| **Attention** | 10.6 (3.2) | 10.9 (3.3) | 10.4 (3.3) | 11.1 (3.2) | 10.7 (3.0) | 10.8 (3.4) | 0.452 |
| *p*-value within group | 0.116 | | **<0.05** | | 0.878 | |  |
| **Processing speed: WAIS-III Digit Symbol** | 66.8 (19.5) | 68.3 (19.6) | 66.9 (18.9) | 69.4 (18.6) | 66.6 (20.2) | 67.3 (20.6) | 0.860 |
| *p*-value within group | **<0.05** | | **<0.05** | | 0.547 | |  |
| **Verbal episodic memory** | 10.9 (3.5) | 10.0 (3.7) | 10.7 (3.1) | 9.8 (3.4) | 11.2 (3.8) | 10.2 (4.0) | 0.403 |
| *p*-value within group | **<0.001** | | **<0.05** | | **<0.01** | |  |
| **Visual episodic memory** | 20.2 (4.8) | 22.5 (5.4) | 20.4 (4.7) | 22.2 (5.2) | 19.9 (4.9) | 22.9 (5.7) | 0.396 |
| *p*-value within group | **<0.001** | | **<0.01** | | **<0.001** | |  |
| **Processing speed: TMT number sequencing** | 39.8 (18.2) | 38.6 (18.9) | 38.0 (15.7) | 36.7 (17.0) | 41.6 (20.4) | 40.4 (20.6) | 0.548 |
| *p*-value within group | 0.294 | | 0.432 | | 0.492 | |  |
| **Flexibility** | 93.7 (47.7) | 87.9 (43.0) | 94.3 (45.1) | 84.3 (38.8) | 93.2 (50.5) | 91.5 (46.8) | 0.599 |
| *p*-value within group | 0.094 | | **<0.05** | | 0.777 | |  |

\*cognitive domains adjusted for age and IQ. Abbreviations: COWA: Controlled Oral Word Association, WAIS: Wechsler Adult Intelligence Scale, RAVLT: Rey’s Auditory Verbal Learning Test, CFT: Complex Figure Test, TMT: Trail Making Test



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