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Title:

**Cognitive Impairment in Testicular Cancer Survivors 2 to 7 Years after Treatment**

Running title:

Cognitive impairment in testicular cancer survivors

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## **Abstract**

*Purpose:* The aim of the present study was to determine the prevalence of cognitive impairment (CI) in a group of testicular (TC) survivors by comparing their neuropsychological test scores with normative data, and to assess their performance in specific cognitive domains.

*Methods:* Seventy-two TC survivors were evaluated 2 to 7 years post-treatment with a neuropsychological test battery that assessed multiple cognitive domains – attention and working memory, processing speed, verbal fluency, learning and memory, and executive functioning. Test scores were compared with normative data and CI status was calculated for each participant.

*Results:* In group-level analyses, survivors exhibited significantly impaired scores on a majority (9/12) of the neuropsychological outcomes ( $p < 0.01$ ). In individual-level analyses, 62.5% of the survivors were classified as having CI, significantly exceeding the expected normative frequency of 25% (binomial test:  $p < 0.001$ ). In particular, CI was observed in multiple outcomes related to verbal learning and memory (29 to 33% of participants), visual learning and memory (14-28%), processing speed (8-24%), executive functioning (17%), and attention and working memory (4-15%). No association was found between treatment modality (surgery +/- chemotherapy) and CI.

*Conclusions:* The prevalence of CI in TC survivors was unexpectedly high, with survivors performing significantly worse than expected on a majority of the neuropsychological outcomes. While the findings are preliminary in nature, they still have important implications for the diagnosis and treatment of CI in TC survivors.

**Keywords:** Testicular cancer, cognitive impairment, cognition function, quality of life, neuropsychological testing

## **Introduction**

Cognitive impairment (CI) following cancer and its treatment has been the focus of a growing number of studies over the past decade [1]. Few studies have investigated CI in the context of testicular cancer (TC) [2–6] despite the fact that TC is the most prevalent form of cancer among young men [7]. With the advent of combined bleomycin, etoposide, and cisplatin (BEP) regimens in the treatment of TC, mortality rates have decreased dramatically with a current 10-year relative survival rate of more than 95% [8]. TC patients are generally much younger than patients with other male-specific cancers, e.g. prostate cancer, and are thus expected, post-treatment, to return to normal life and work activities. Given that CI can negatively impact quality of life and daily life functioning in other cancer populations [9–11], it is important to examine such late-effects in the context of TC.

The few studies that have investigated CI in TC [2–6] have focused primarily on between-group differences of TC patients and survivors treated with and without chemotherapy. For instance, in our earlier work [3] and that of Schagen et al. [2] in which TC patients who had undergone chemotherapy were compared with those who had not, there were no significant between-group differences in mean scores on any of the applied neuropsychological tests by treatment group. With group comparisons, however, low scoring subjects may be masked by high scoring ones. Therefore, both studies also determined CI status at the individual level. CI on any given test was defined as scores of 2 standard deviations (SDs) below the mean of the non-chemotherapy group. Even at the individual level, there were no significant differences between the proportion of patients who had CI in the chemotherapy group and in the non-chemotherapy group. These results were corroborated by a prospective study by

Skaali et al. [4], who did not find any statistically significant differences across treatment groups in the proportions of TC patients with cognitive decline. In contrast, Wefel et al. [6] found that men with nonseminomatous germ cell tumors who received chemotherapy showed more frequent overall decline in cognitive functioning with a dose-response relationship over time. However, the method by which CI status has been determined, both in our previous work and in all the studies mentioned above, has been problematic for establishing a valid prevalence, because it assumed that a comparison to a pre-chemotherapy group was sufficient to characterize CI. Yet, evidence suggests that a significant proportion of TC patients may have CI even prior to adjuvant chemotherapy [5]. Indeed, by applying the International Cognition and Cancer Taskforce (ICCTF) criteria for CI [12], Wefel et al. [5] found a prevalence of 46% in recently diagnosed TC patients before adjuvant chemotherapy, significantly exceeding normative expectations. ICCTF recommends a combined stepwise approach to determine CI [12]. First, the frequency of patients with either two or more test scores at or below -1.5 SDs from the normative mean, and/or a single test score at or below -2.0 SDs from the normative mean, is determined. This frequency is then statistically compared to published probability curves of the expected impairment frequency when using several measures [13]. Currently, the prevalence of CI in TC survivors 2 to 7 years after treatment is yet to be established using ICCTF criteria.

The aims of the present study were thus: 1) to characterize CI in our previously investigated sample of TC survivors [3] using normative data and ICCTF criteria; 2) to determine whether there was any difference in the prevalence of CI between those who were treated with chemotherapy and those who were not; 3) to examine

neuropsychological test performance and prevalence of CI in various cognitive domains; and 4) to determine potential demographic and psychological predictors of CI.

## **Materials and Methods**

### Procedure

Exclusion criteria for the present study were evidence of TC within the past two years, neurological or psychiatric disease or substance abuse, and inability to read and understand Danish. A total of 244 men treated for TC within the previous 2 to 7 years and without recurrence of their cancer were identified using the registry of the Department of Oncology, Aarhus University Hospital. Of these, 13 men could not be approached due to lacking contact information or who were deceased. Letters about the study were sent to 231 eligible TC survivors. Seventy-two men (31.2%) consented to participate. This sample size allowed for the detection of a difference from a normative sample corresponding to a small effect size ( $d=0.35$ ) (one-sample t-test) with a statistical power of 0.80. Participants received a questionnaire package to be completed and returned in prepaid envelopes prior to neuropsychological testing. The regional scientific ethics committee approved the study.

### Neuropsychological and psychological assessments

All TC survivors were tested with a battery of standard neuropsychological tests. Trained research assistants administered and scored the assessments under the supervision of a registered senior specialist in clinical neuropsychology. The test results were compared with normative data. Out of 13 different neuropsychological tests administered [3], age-adjusted (+/- education-adjusted) norms were available for 9 different tests [14–16] yielding a total of 12 outcomes that assessed 6 different cognitive

domains: attention and working memory [16], processing speed [16, 17], verbal fluency [18], verbal learning and memory[19], visual learning and memory[20], and executive functioning [17] (see Table 2 for the list of tests). Education adjusted norms were available for all measures except for the Wechsler Adult Intelligence Scale – Version III (WAIS-III) subtests. Premorbid intellectual functioning was estimated with the Danish version of the National Adult Reading Test (NART) [21] and calculated by converting participants' raw scores into an IQ estimate using published regression equations [22]. The participants also completed a questionnaire package that included sociodemographic and psychological variables potentially related to cognitive functioning. Subjective stress was assessed with the Perceived Stress Scale (PSS) [23], and depressive symptoms were assessed with the Beck Depression Inventory - Second Edition (BDI-II) [24].

### Statistical Analysis

All statistical analyses were conducted with SPSS version 19.0 (SPSS, Armonk, NY: IBM Corp.). First, descriptive statistics and frequency distributions were used to characterize the participant sample based on sociodemographic, clinical, and psychological characteristics. Second, for each participant, raw scores on each neuropsychological subtest were converted to a z-score (mean of 0, SD=1) using adjusted normative means for each test measure. One-sample *t*-tests (two-tailed) were then used to test for differences between the group mean z-scores and a value of zero. Due to multiple testing, a conservative p-value of 0.01 was considered statistically significant. Third, using the recommendations of ICCTF [12], subjects with scores at or below -1.5 SDs from the normative mean on two different tests and/or scores at or below -2 SDs from the normative mean on one test were categorized as being

cognitively impaired (CI). Binomial testing was used to test whether the frequency of CI in the group of survivors was significantly higher than could be normatively expected when applying multiple tests and measures (=12). The expected frequency was determined using curves derived from comparable binomial probability distributions [13], showing that approximately 25% of a normative population could be expected to fall within the CI category when using ICCTF criteria. A Chi-square test was used to explore the possible association between treatment group (chemotherapy versus no chemotherapy [ $\pm$ CT]) and CI status ( $\pm$ CI). Finally, relevant demographic and clinical variables (age, estimated IQ, education, time since surgery), and psychological variables (depression, perceived stress) were entered in a binary logistic regression model exploring possible predictors of CI.

## **Results**

### Sample characteristics

A total of 72 histologically mixed (non-seminoma/seminoma) men successfully treated for TC within the past 2 to 7 years and without recurrence participated in the study. Thirty-six TC survivors had been treated with orchiectomy plus chemotherapy, receiving three or four cycles of bleomycin (30.000 IU intravenously on days 2, 9 and 16), etoposide (100mg/m<sup>2</sup> intravenously on days 1-5), and cisplatin (20 mg/m<sup>2</sup> intravenously on days 1-5). Another 36 survivors had been treated with orchiectomy, but without chemotherapy. In this latter group, 13 participants had received radiotherapy. Table 1 summarizes the relevant sociodemographic, clinical, and psychological characteristics of the sample.

(Insert Table 1 near here)

Compared with the mean education level of the general population [25] (12.1 years), survivors were slightly higher educated ( $t(71)=2.32$ ;  $p=0.02$ ). Mean scores for the psychological variables were 6.4 (SD=7.0) for the BDI-II and 14.6 (SD=6.6) for the PSS. The BDI-II scores were in the range of minimal depression [24] and the mean PSS score was below the average population mean for the relevant age group [26]. Furthermore, there were no statistically significant differences in these variables across treatment groups. Premorbid average intellectual functioning (IQ) for the TC group was estimated to be 103 (SD=12.56), which was marginally higher than the normative population (IQ = 100) ( $t(71)=2.04$ ;  $p=0.045$ ). Furthermore, 91.2% of all TC survivors were occupationally or educationally engaged at the time of testing.

#### Neuropsychological outcomes

Compared with normative data, the TC survivors scored significantly lower than norms ( $p<0.01$ ) on 9 out of 12 neuropsychological subtests, including WAIS-III Digit Span and Letter-Number Sequencing, Trail Making Test part A and B, Rey Auditory Verbal Learning Test (1<sup>st</sup> trial and total), and Rey Complex Figure Test (immediate and delayed recall). The group differences were all less than one standard deviation from normative means with effect sizes ranging from medium to large as indicated by the z-scores (see Table 2). An above average score was observed on the Animals category fluency test ( $p<0.001$ ). The neuropsychological test results are presented in Table 2.

(Insert Table 2 near here)

Using ICCTF criteria described above, 62.5% of survivors (45/72) were categorized as being impaired, which significantly exceeded normative expectations of 25% (Binomial test:  $p<0.001$ ). There was no significant association between treatment group ( $\pm$ CT) and

CI status ( $\chi^2(1)=1.48$ ,  $p=0.33$ ). Again, using the ICCTF two-part criteria, 9.7% of all survivors ( $n=7$ ) showed impairment on one outcome only, while 19.4% ( $n=14$ ) showed impairment on two outcomes, 13.9% ( $n=10$ ) showed impairment on three outcomes, and the remaining 19.5% ( $n=14$ ) showed impairment on 4 or more different outcomes. Domain-specific impairment frequencies, as indicated by z-scores of subtests below -1.5, was highest in the domain of verbal learning and memory (29-33%), followed by visual memory (14-28%), executive functioning (17%), and attention and working memory (4-15%), while processing speed showed a larger spread depending on the specific neuropsychological outcomes (8-24%) (see table 2).

Results of the multiple logistic regression indicated that after adjustment for demographic and clinical variables, the only statistically significant predictor of CI was estimated premorbid intellectual functioning (see Table 3). For every additional IQ point, the adjusted odds ratio was 0.87 (95% confidence interval, 0.81-0.95,  $p<0.01$ ), with higher levels of intellectual functioning being associated with lower odds of being classified as cognitively impaired.

(Insert Table 3 near here)

## **Discussion**

In the current study, we compared neuropsychological test results of 72 Danish TC survivors with normative data. In accordance with our previous results for this sample [3], we found no difference in the proportion of CI among those treated with chemotherapy and those treated without chemotherapy when using Danish normative data and ICCTF criteria for CI. However, the present results indicate that the total group of TC survivors, on average, performed significantly poorer than expected on the

majority of the neuropsychological tests. The prevalence of CI at the individual level exceeded normative expectations with almost two thirds of the TC survivors being classified as cognitively impaired (62.5%). It is important to note that given the number of applied neuropsychological tests, around 25% percent of a healthy population are expected, due to normal variability, to have test scores exceeding the applied ICCTF cut-off criteria [13]. This would likely moderate the actual prevalence of CI in the present sample. However, a remaining prevalence of approximately 38% would still remain unaccounted for, amounting to a significant proportion of the TC survivors. Furthermore, 20% of the TC survivors showed impairment on four or more (out of twelve) neuropsychological outcomes, which is substantial. CI was most pronounced in the domains of verbal learning and memory, followed by visual memory, executive functions, and attention and working memory, while processing speed showed a larger spread depending on the test applied.

Among TC survivors as a whole, the only significant predictor of CI status was estimated premorbid intellectual functioning. This finding is generally consistent with prior research with other cancer populations [27, 28]. Although Skaali et al. [4] did not find an association between estimated intellectual functioning (NART) and cognitive decline in their sample of TC patients, their calculation of cognitive decline included NART scores as a covariate, which is a likely explanation as to why no association was observed.

The present study adds to the literature by highlighting the potential negative effects of cancer and/or its treatment upon cognitive functioning in TC survivors. Studies investigating CI in TC patients and survivors are sparse, and this study provides data regarding its potential prevalence that requires further investigation. In addition,

although the focus of previous CI studies in TC survivors has mainly been on exploring possible associations between chemotherapy and CI, it has recently been shown that CI may already be evident prior to treatment [5]. Held together with the results from the study by Wefel et al. [5], our results suggest that CI may be an issue for a large proportion of individuals with TC irrespective of the use of cytotoxic regimens. Importantly, combined with previous findings [2–4], the results question the primary role of chemotherapy in CI in the context of TC. The cancer disease itself, or common premorbid factors related to both the disease and CI, may contribute to cognitive disturbances in this population.

Numerous mechanisms may explain the existence of CI in TC survivors. First, treatment-related factors, such as endocrine dysregulation following orchiectomy, may be linked with CI. Evidence suggests an association between unilateral orchiectomy and decreased Leydig-cell function in the absence of adjuvant treatment [29] and TC patients with insufficient Leydig-cell functioning have been shown to be at a significantly increased risk of hypogonadism [30], which in turn has been associated with CI [31]. Second, increased inflammation has been observed in cancer patients [32], and research indicates negative associations between cognition and elevations in the release of proinflammatory cytokines (e.g., IL-6, TNF- $\alpha$ ) [32, 33], which have also been observed in cancer populations [35]. Finally, genetic susceptibilities, such as being a carrier of the apolipoprotein E4 allele, and other genes related to reduced neural plasticity and/or repair may also play a role in cancer-related CI [36]. Overall, CI following TC treatment may be caused by a complex interplay of both treatment- and disease-related factors [36], and it is recommended that future research includes

assessments of relevant biomarkers in order to explore the role of these mechanisms in relation to CI.

Limitations exist that need to be addressed in future research. One limitation is that we did not have direct access to information about the premorbid cognitive status of the group. However, TC survivors were on average more highly educated than the average population, and their estimated premorbid intellectual functioning on the NART was within the normal range. Taken together, these results suggest that the TC survivors' premorbid cognitive functioning was likely not impaired, making the observed prevalence of CI even more remarkable. It should also be noted that in everyday health care practice, the neuropsychological evaluation of CI is typically undertaken without available premorbid data [37], and the use of normative data is usual practice (as well as the gathering of a detailed history regarding pre-illness/treatment educational status and occupational functioning). Furthermore, we chose to only include tests with available age-adjusted, and when available, education-adjusted normative data based on the Danish population, which, compared to our previous research [3] reduced the number of tests that could be included in the analyses. Despite the frequent clinical use of non-native normative data, it is generally not advisable to use such norms for characterizing CI due to the risk of confounding results [38]. Nevertheless, future research should ideally compare TC patients' longitudinal performance with that of a matched healthy control group in addition to normative data.

A second limitation may be related to recruitment bias as only one third (31.2%) of the total number of eligible survivors identified for the present study agreed to participate. It is possible that the survivors agreeing to participate experienced more cognitive problems than those who did not. However, the subjective experience of CI is rarely

associated with neuropsychological test performance [39]. Such experiences are more frequently related to emotional distress symptoms, such as depression and anxiety [40]. It should be noted here that the participating survivors in present study did not report high levels of emotional distress as evident from the mean scores on the BDI-II and PSS. Third, because we did not include assessments of fatigue and sleep quality, we were unable to explore the possible influence of these variables on CI. Finally, heterogeneity of clinical variables such as time since treatment, treatment modalities, cancer type, and stage may limit the generalizability of the results.

Taken together, the present study suggests that when compared with normative data, a considerable proportion of TC survivors may exhibit CI. Multiple domains of cognition may be affected that potentially have serious implications on a TC survivor's life. Impairments to attention and working memory can affect a person's ability to focus effectively on a task. Processing speed impairments can affect the speed and efficiency with which a person accomplishes a task. Learning and memory impairments can affect a person's ability to encode and retain information. Executive functioning impairments can affect a person's ability to plan and organize information. Hence, all of these cognitive skills are vital to a person's life functioning, both at work and at home.

Further research is needed to build upon the findings of this study in order to: i) compare neuropsychological evaluations of TC survivors to that of a matched healthy control group; ii) prospectively assess measures of brain morphology and functioning in TC patients undergoing treatment; and iii) assess potentially relevant biological markers (e.g., hormonal status, cortisol, inflammatory immune markers, genetic markers) and psychological variables (e.g., perceived stress, depression, and fatigue) in order to more accurately understand the specific mechanisms and risk factors related to CI in this

population. Such knowledge could inform the development of appropriate treatments to ameliorate CI in TC patients and survivors.

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### **Conflict of interest**

The authors declare that there is no conflict of interest. They also state that they have full control of primary data and that they agree to allow the journal to review their data if requested.

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Table 1. Sociodemographic, clinical, and psychological characteristics of testicular cancer survivors (n=72) 2 to 7 years after treatment

|   |              | Range    |
|---|--------------|----------|
| Age (years), mean (SD)                        | 40.1 (9.7)   | 24 - 70  |
| Years of education, mean (SD)                 | 13.0 (3.0)   | 7 - 18   |
| Premorbid intellectual functioning            |              |          |
| (IQ), mean (SD)                               | 103.0 (12.6) | 75 - 127 |
| Histology, n (%)                              |              |          |
| Non-seminomas                                 | 37 (51.4)    | -        |
| Seminomas                                     | 35 (48.6)    | -        |
| Disease Stage, n (%)                          |              |          |
| I   | 31 (43.1)    | -        |
| II  | 32 (44.4)    | -        |
| III   | 6 (8.3)      | -        |
| IV  | 3 (4.2)      | -        |
| Treatment, n (%)                              |              |          |
| Chemotherapy (3/4 cycles, BEP)                | 36 (50)      | -        |
| No chemotherapy                               | 36 (50)      | -        |
| Radiotherapy                                  | 13 (18.1)    | -        |
| No radiotherapy                               | 59 (81.9)    | -        |
| Time since orchiectomy (months),<br>mean (SD) | 50.2 (18.9)  | 24 - 85  |
| Perceived Stress (PSS), Mean (SD)             | 14.6 (6.6)   | 4 - 39   |
| Depressive Symptoms (BDI-II),                 |              |          |
| Mean (SD)                                     | 6.4 (7.0)    | 0 - 39   |

SD = Standard deviation; BEP = Bleomycin, Etoposide, Cisplatin; PSS = Perceived Stress Scale; BDI-II = Beck Depression Inventory - II

Table 2. Mean test scores of TC survivors (N=72) converted to z-scores and individual impairment frequency on each neuropsychological test

| Cognitive domain             | Neuropsychological test                                   | Mean z-score (SD) | <i>p</i> -value <sup>a</sup> two-tailed | Percent impaired <i>z</i> <-1.5 |
|------------------------------|---|-------------------|---|---------------------------------|
| Attention and working memory | WAIS-III <sup>b</sup> Digit Span [16]                     | -0.4 (1.0)        | 0.003                                   | 11.1                            |
|                              | WAIS-III Letter-Number Sequencing [16]                    | -0.6 (1.0)        | <0.001                                  | 15.3                            |
|                              | WAIS-III Arithmetic <sup>c</sup> [16]                     | 0.2 (1.1)         | 0.09                                    | 4.2                             |
| Processing speed             | WAIS-III Coding [16]                                      | -0.1 (1.0)        | 0.4                                     | 8.3                             |
|                              | WAIS -III Symbol Search [16]                              | -0.3 (1.1)        | 0.008                                   | 15.3                            |
|                              | Trail Making Test (TMT) part A <sup>d</sup> [17]          | -0.6 (1.4)        | <0.001                                  | 23.6                            |
| Verbal fluency               | Animals [18]  | 1.2 (1.5)         | <0.001 <sup>e</sup>                     | 2.8                             |
| Verbal learning and memory   | Rey Auditory Verbal Learning Test (RAVLT) [19], 1st trial | -0.6 (1.5)        | <0.001                                  | 29.2                            |
|                              | RAVLT total   | -0.8 (1.4)        | <0.001                                  | 33.3                            |
| Visual learning and memory   | Rey Complex Figure Test (RCFT) [20] Immediate recall      | -0.7 (1.4)        | <0.001                                  | 13.9                            |
|                              | RCFT Delayed recall                                       | -1.0 (1.3)        | <0.001                                  | 27.8                            |
| Executive function           | TMT- part B <sup>c</sup> [17]                             | -0.4 (1.4)        | 0.004                                   | 16.7                            |

<sup>a</sup>Significance level set at  $p < 0.01$

<sup>b</sup>Wechsler Adult Intelligence Scale version 3

<sup>c</sup> $n = 71$

<sup>d</sup>Reversed TMT- part A and B scores. Negative z-score indicates worse performance

<sup>e</sup>Survivors performed better than expected

Table 3. Logistic regression model of independent predictors of cognitive impairment status with odds ratios (OR) and confidence intervals (CI).

|   | B       | S.E. | OR (95% CI) |      |       |
|---|---------|------|-------------|------|-------|
|   |         |      | Lower       | OR   | Upper |
| Constant  | 16.25   | 4.94 |             |      |       |
| Age (years)                                     | 0.02    | 0.04 | 0.95        | 1.02 | 1.09  |
| Education (years)                               | -0.19   | 0.13 | 0.64        | 0.83 | 1.08  |
| Estimated intellectual functioning <sup>a</sup> | -0.14** | 0.04 | 0.81        | 0.87 | 0.95  |
| Time since surgery (months)                     | 0.01    | 0.02 | 0.97        | 1.01 | 1.06  |
| Perceived stress (PSS)                          | -0.06   | 0.09 | 0.79        | 0.94 | 1.12  |
| Depressive symptoms (BDI)                       | 0.07    | 0.08 | 0.92        | 1.07 | 1.25  |

$R^2 = 0.50$  (Nagelkerke). Model  $\chi^2(6) = 21.88, p=0.001$ .

\*\*  $p < 0.01$

<sup>a</sup>Estimated intellectual functioning (IQ) calculated from scores on the Danish version of the National Adult Reading Test.