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For the Australian and New Zealand Urogenital and Prostate Cancer Trials Group

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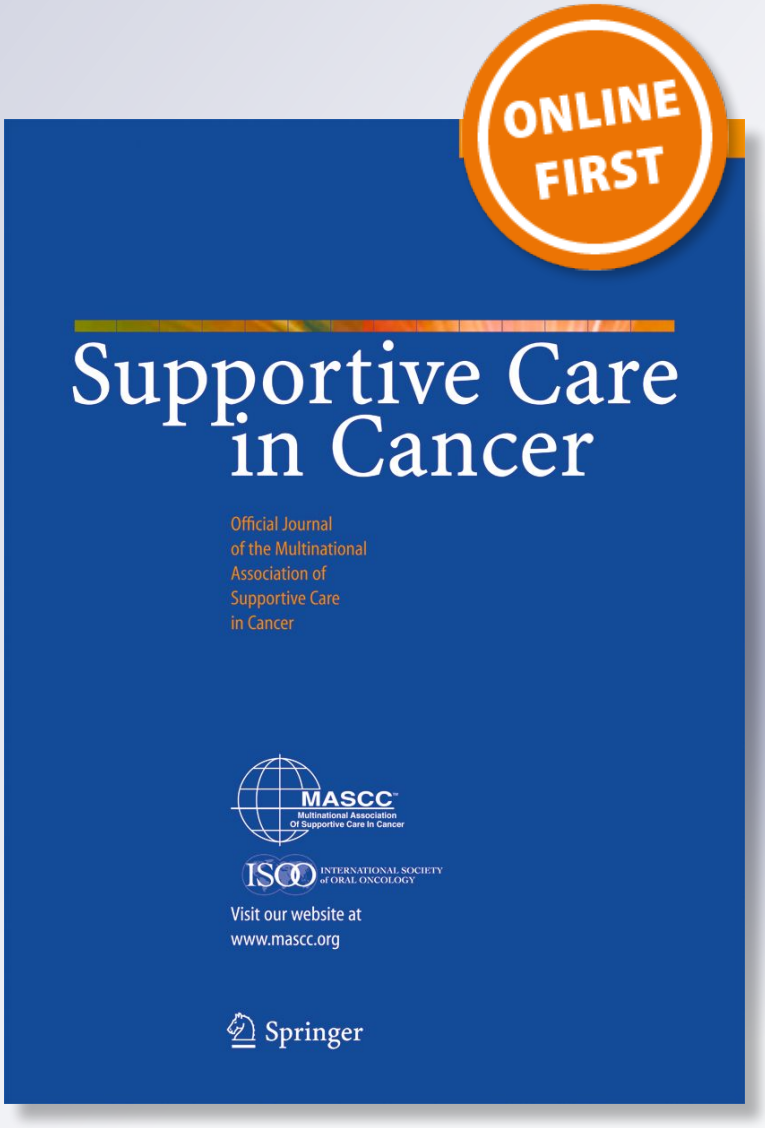

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ORIGINAL ARTICLE

The impact of chemotherapy on cognitive function: a multicentre prospective cohort study in testicular cancer

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Abstract

Purpose The causal link between chemotherapy and cognitive impairment is unclear. We studied testicular cancer patients' objective and subjective cognitive function longitudinally, comparing a surgery group with a surgery + chemotherapy group, addressing prior methodological issues using a computerized test to limit assessment issues, and controlling for confounding variables.

Methods Prospectively, of 145 patients from 16 centres with sufficient data, $n = 61$ receiving surgery + chemotherapy (etoposide and cisplatin ± bleomycin, BEP/EP; or single agent carboplatin) were compared to $n = 41$ receiving surgery alone. CogHealth assessed six objective cognitive tasks. The Cognitive Failures Questionnaire assessed self-perceived cognitive dysfunction. The Functional Assessment of Chronic Illness Therapy-Fatigue and the Hospital Anxiety and Depression Scale assessed psychological influences. Linear mixed models compared changes from baseline ($\leq$ 6 months post-surgery/pre-chemotherapy) to follow-up (12–18 months post-baseline), controlling covariates.

Results There were no significant interaction effects for five objective cognitive function tasks suggesting that changes over time were not due to group membership. However, psychomotor function (controlling for age) and physical well-being were significantly worse for the chemotherapy versus the surgery group at baseline, with groups converging by follow-up. Groups showed no differences in subjective cognitive dysfunction. The chemotherapy group showed higher anxiety, poorer functional well-being and worse fatigue compared to the surgery-only group at baseline, but not by follow-up. For both groups, emotional well-being, functional well-being and anxiety significantly improved over time.

Conclusion No substantive differences in objective or subjective cognitive dysfunction in either group persisted 12–18 months post-baseline. Patients undergoing chemotherapy for testicular cancer differ from findings in breast cancer populations.

Trial registration ClinicalTrials.gov Identifier: ACTRN12609000545268

Keywords Cognitive function · Chemotherapy · Surgery · Testicular cancer · Quality of life · Mood

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Introduction

Estimates of objective cognitive dysfunction following chemotherapy range from 13 to 70% due to differing definitions and tests used to assess this multifaceted construct [1]. Multiple methodological issues with early studies in breast cancer included uncontrolled cross-sectional designs, not accounting for possible confounding factors such as pre-existing baseline cognitive dysfunction, the impact of hormonal cycles, age or psychological factors such as depression, anxiety or fatigue that are known to influence cognitive function. Most cognitive function tests aim to assess change over time, but elements can be learned, resulting in improvements due to *practice effects*, so are inaccurate for showing changes in cognition. Based on the literature, there should also be a distinction made between objective and subjective (self-reported) cognitive dysfunction, where up to 80% of patients have reported some degree of 'chemobrain' [2–4]

Longitudinal studies were eventually performed and compared patients receiving chemotherapy with controls [5]. One meta-analysis suggested that after cancer treatment, patients evidenced cognitive dysfunction including memory impairment, processing speed and language issues. Another meta-analysis showed that age was not a confounding factor [6–8].

Findings for colorectal cancer differed from breast cancer. A 24-month longitudinal study comparing 362 patients with colorectal cancer with 72 healthy controls showed that patients with colorectal cancer had more cognitive impairment compared to healthy controls at every time-point, but there was no added effect of chemotherapy [9].

Similar discordant results are shown in patients with testicular cancer, which removes the influence of female hormone cycles and menopause, and yet has other hormonal influences at play. A neuropsychological test battery administered to testicular cancer survivors at 2 to 7 years post-treatment showed 62.5% overall cognitive impairment compared to normative data at 25% [10]. A small study of 28 patients receiving chemotherapy compared to 23 surgery-only patients showed greater cognitive impairment 14 years post-treatment for chemotherapy patients, although this did not correlate with computed tomography (CT) scan changes in the white matter of the brain [11]. A larger comparative study, which included 70 patients treated with BEP (bleomycin, etoposide and cisplatin) chemotherapy after surgery, a surgery plus radiotherapy group, and a surgery-only group, showed no differences in subjective cognitive dysfunction, although there was a small subgroup of chemotherapy patients with objective evidence of cognitive dysfunction on a battery of 10 tests [12]. The lack of concordance between objective and subjective cognitive change requires further exploration.

A longitudinal study of 65 men with testicular cancer with cognitive dysfunction designed to explore mechanisms only showed a trend towards greater cognitive impairment over 6 months in those receiving chemotherapy compared to those who did not ($p = 0.07$) but decreased cognitive dysfunction in the chemotherapy group related to prefrontal grey matter changes on magnetic resonance imaging (MRI), an increase in tumour necrosis factor alpha (TNF-α) and an interaction effect with APOE $\varepsilon 4$ genotype [13].

Other studies have shown no long-term differences in cognitive function between testicular cancer patients treated with chemotherapy and those not receiving chemotherapy. Comparing 36 testicular cancer patients receiving chemotherapy with 36 who did not, between 2- and 7-years post-treatment, there were no significant differences, with 8.3% of the chemotherapy group and 5.6% of the non-chemotherapy group ($p = 0.64$) showing objective cognitive impairment [14]. A similar result was obtained by following 122 patients for 12 months and comparing no chemotherapy with single-agent chemotherapy and two or more agents of chemotherapy. Findings indicated no impact of systemic chemotherapy on the neuropsychological testing [15]. Given the variation in methodology and findings, further studies in testicular cancer are needed.

The current prospective cohort study utilized a mixed between-within participant design to overcome previous methodological limitations. The primary endpoint of objective cognitive function was assessed at two time points (baseline, post-surgery/pre-adjuvant therapy, and follow-up, 12–18 months post-baseline) in two groups; those treated with either single-agent or multi-agent chemotherapy (surgery + chemotherapy) compared to a surgery-only group, determined by stage of disease. Secondary endpoints were subjective cognitive dysfunction and the assessment of psychological variables known to impact cognitive function, quality of life (QOL) including fatigue, and mood (anxiety and depression). Psychological variables and the other factors were assessed over time, between groups, and controlled in primary and secondary analyses. Importantly, this study utilized a reliable, computerized test of objective cognitive function, based on a familiar playing-card format, designed and validated for rapid 10-min assessment, and repeated use, to detect mild cognitive impairment over time [16]. The tool overcomes language limitations, assessment burden and practice/ceiling effects [17].

Methods

Patients

Following institutional ethics committee approvals, consecutive patients with testicular cancer aged 18 years or above spoke English and gave written consent, and were accrued across 16 oncology units in Australia and New Zealand between August 2007 and July 2012. Exclusion criteria included prior chemotherapy or patients cognitively impaired due to

psychiatric, neurological illness/dementia, head injury, substance abuse, medical illnesses or medication.

Group membership and procedures

Based upon staging and histology, some patients with testicular cancer require chemotherapy, others surgery-only (or surgery + radiotherapy, for some seminomas not treated with chemotherapy), providing naturally occurring, appropriate controls for determining if chemotherapy patients evidence significantly greater cognitive decline compared to non-chemotherapy patients. Also, compared to breast cancer, they provide a male perspective: endogenous and exogenous hormone-based similarities to hormone receptor-positive breast cancers but only few receive hormone therapy (testosterone replacement) after treatment [18]. Also, the patient populations differ in the chemotherapy that they receive, which may also impact on developing cognitive dysfunction. Patients with stages I and II testicular cancer have comparable diagnosis experiences, most undergo surgery, and on average, are younger than other 'adult' cancer patients. Thus, fewer age-related comorbidities affect cognitive function.

The patients completed a computerized battery of objective cognitive function tasks (Cog Health), usually at their treatment centre, and computer and paper-based self-report questionnaires to capture subjective endpoints and psychological variables known to influence cognitive function. Ideally after two practice tests prior to baseline, it was planned to collect seven data points starting pre-surgery up to 18 months post. Given that patients were having chemotherapy of differing duration and too few patients in each group had corresponding data at all timepoints for meaningful analysis, this report compares groups across the two largest time points by amalgamating meaningful, maximized data points: baseline ($\leq$ 6 months post-orchiectomy/pre-chemotherapy) and follow-up (12–18 months post-baseline). Additional timepoint comparisons, patient-reported outcomes, and further hormonal data will be reported subsequently, although no patient was recorded as receiving hormone therapy [19].

Data collection

The primary endpoints were six objective cognitive tasks measured using *CogHealth*: psychomotor function, visual attention/vigilance, complex decision making, visual attention, visual learning, and working memory [16]. Each task has a single outcome measure, which was selected drawn from a distribution, distributed normally, and which contains only a small probability of floor or ceiling effects and no restriction in the range of possible performance values. This short, 10-min speed and accuracy test, on-line pressing one of three computer keyboard keys limits patient burden, utilizing an interactive familiar playing-card system, where respondents have to recognise cards or match cards as quickly as possible. The familiarity with playing cards can aid in reducing respondents' test anxiety [5]. Practice tests help acclimatize patients, eliminating learning effects at baseline, and card tasks are randomized, limiting floor and ceiling effects. The unit of measurement is Log_{10} milliseconds where the speed of performance on each task is the mean of the log_{10} transformed reaction times of correct responses.

CogHealth is devised from a larger battery of tasks where sensitivity to change was initially assessed utilizing natural or enforced neurocognitive alterations (i.e. low-dose sedative medications, head injury, sleep deprivation, etc.). Tasks were removed if they were unstable, had low test-retest reliability, repeated assessments evidenced practice effects, or task sensitivity was inferior to detect cognitive change. Criterion validity was then assessed in samples with mild traumatic brain injury, schizophrenia and AIDS dementia complex [16].

Secondary psychological endpoints included three standardized patient self-report outcomes (PROs) with eight unique scales. The *Cognitive Failures Questionnaire* (*CFQ*) assessed self-perceived (subjective) cognitive dysfunction using a 25-item scale where respondents read questions and estimated the frequency of the occurrence using scales from 'very often' to 'never'. Examples of questions are 'do you forget appointments?' For this study, the timeframe was over the past week [20]. The *Functional Assessment of Chronic Illness Therapy-Fatigue* (*FACT-F*) is a 41-item scale which assesses QOL including physical, social/family, emotional and functional well-being—the elements of FACT-G, plus has a 13-item fatigue assessment [21]. Mood was assessed using the screening tool, the *Hospital Anxiety and Depression Scale* (*HADS*) for brevity [22].

Study coordinators recorded demographics, a checklist of 48 current symptoms, patient recruitment center, assessment dates and whether completed, patient ECOG performance status, disease status, treatment regimen, concomitant medications and any hormone replacement therapy (HRT) [23]. Laboratory tests included full blood exams (FBE), and relevant hormone assays such as testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), among other biomarkers.

Statistical considerations

Data were analysed using SAS 9.4, and the STROBE checklist was followed to report the study design [24]. Frequencies and descriptive statistics were utilized: to determine participants' naturally occurring group membership (surgery + chemotherapy, or surgery-only); to determine which patients had complete data for either of the amalgamated time points that maximized comparisons (baseline to follow-up); and finally, to characterize the sample (demographics and health-related data).

Customized linear mixed models (LMMs) were used to compare changes in the six objective cognitive function tasks and eight psychological assessments, from baseline through to follow-up.

To customize LMMs for the six objective cognitive tasks, baseline scores for the eight psychological scales (derived from the CFQ, FACIT-F and HADS, as known predictors of cognitive function) and three theoretical variables (age, patient performance status and testosterone level) were subjected to a series of stepwise backwards regression models to determine unique, significant covariates associated with the six tasks. For each task, any variable remaining significant in the final step of the model ($a = 0.05$) was then included as a covariate in the 'customized' LMM. For the eight psychological assessments, the same method was used for testing whether the theoretical variables (age, patient performance status and testosterone level) were significant covariates for each model.

A priori power analysis for this multidisciplinary collaboration was based on Cohen's recommendations (as variables are based in the behavioural sciences) and best estimates based on previous findings of chemotherapy impacting cognitive impairment to moderate degrees (effect sizes) or small magnitudes [24]. Planned recruitment of 77 patients in each group allowed for 20% attrition and anticipated 64 cases per group completing follow-up. This sample size achieves an 80% power for detecting moderate effects between groups (alpha = .05) [25]. All surgery + chemotherapy patients were accrued (with three cases not included at a later stage); however, recruitment of surgery-only patients was suspended at a given timepoint. Exact p values are reported throughout the paper, and 95% confidence intervals for group and time pairwise comparisons are provided in additional (Online Resources 1 and 2).

Results

From the 16 centres, of 145 chemotherapy-naïve patients, 43 did not provide sufficient data, and two patients with ample data commenced chemotherapy prior to baseline. Thus, 102 patients were compared from baseline (≤ 6 months post-orchiectomy/pre-chemotherapy) to follow-up (12–18 months post-baseline). Groups were determined by stage and included those treated with surgery + chemotherapy ($n = 61$) or surgery-only ($n = 41$). In the chemotherapy group, $n = 41$ (67.2%) received multi-agent cisplatin-based combination chemotherapy (BEP/EP) and $n = 20$ (32.8%) single-agent carboplatin (Table 1). The surgery-only group included seven (17.1%) patients due to commence radiotherapy, with two (0.05%) patients' adjuvant plans unknown at baseline (Table 1). For the purposes of this study, the two chemotherapy regimens were combined into one group, and radiotherapy patients remained classified as 'surgery-only' to test chemotherapy influences alone.

Additional LMMs between the two different chemotherapy regimens (multi-agent BEP/EP versus single-agent carboplatin), across the six objective cognitive function tasks, showed no significant interaction terms, suggesting that any significant main effects for group or time were not due to group membership. The only significant main effect was for change over time from baseline to follow-up for psychomotor function (Online Resource 3). Specifically, additional analyses showed that this effect was due to improvements in the BEP/EP chemotherapy group with psychomotor function improving from baseline to follow-up, $t(58) = 2.28$, $p = 0.03$, 95% CI 0.007–0.099. However, given there were only 20 patients in the single-agent carboplatin group, these results should be viewed with caution due to likely Type II error.

Customized LMMs for the six objective cognitive function tasks evidenced no significant differences between groups, over time for five of the six cognitive tasks, suggesting little evidence of objective cognitive dysfunction (Tables 2 and 3). Psychomotor function, however, was significantly worse in the chemotherapy group compared to the surgery-only group at baseline, with groups converging at follow-up (Fig. 1). The significant interaction effect suggested that the different trajectories over time were due to group membership, with only age included as a significant covariate (the older the patients, the worse their psychomotor function).

Other significant covariates included age for the visual attention task. Interestingly, performance status, testosterone levels and fatigue were all significant covariates for visual learning, despite no main or interaction effects for group or time. Thus, patients with higher levels of testosterone and those with less fatigue performed significantly better on this task. However, those with a poorer performance status also performed better. Given this task assesses the *accuracy of recognition speed* and not simply the speed of the reaction, these outcomes suggest that after controlling the variance associated with these theoretically driven variables, there was no evidence of significant cognitive dysfunction (Table 3).

For the eight psychological assessments, no significant covariates were identified to include in models. The only significant LMM was for physical well-being, where scores appeared significantly worse for the chemotherapy group compared to the surgery-only group, at baseline. Although both groups improved over time, greater improvement occurred in the chemotherapy group, with a significant interaction suggesting that group trajectories were due to group membership (Tables 2 and 3, Online Resource 4).

The CFQ scale assessed self-perceived (subjective) cognitive dysfunction, a superior assessment to that chosen in two-thirds of studies according to a recent systematic review [2]. There were no significant differences between the groups, over time (Fig. 2). The perception of 'chemobrain' did not

Table 1 Participant characteristics

Variable	Surgery + chemotherapy group $n = 61$	Surgery-only group $n = 41$
Age in years, median (range)	34.8 (26.9 to 39.5)	34.5 (27.9 to 40.5)
Histology, *n* (%)		
Pure seminoma	19 (46.3%)	30 (49.2%)
Non-seminoma/mixed	22 (53.7%)	31 (50.8%)
Treatment, *n* (%)		
Surgery	61 (100.0%)	41 (100.0%)
Chemotherapy	61 (100.0%)	–
Radiotherapy	–	7 (17.9%)[a]
Chemotherapy regimen, *n* (%)		
Multi-agent cisplatin-based[c] (BEP/EP)	41 (67.2%)	–
Single-agent carboplatin	20 (32.8%)	–
ECOG performance status[c], *n* (%)		
0 = fully active, able to carry on all pre-disease performance without restriction	57 (55.9%)	38 (37.3%)
1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	3 (2.9%)	3 (2.9%)
2 = ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	1 (1.0%)	0 (0.0%)

[a] Two participants did not provide data; therefore, the percentage of surgery-only patients who were having, had, or due to have radiotherapy is based on $n = 39$

[b] Multi-agent chemotherapy BEP/EP = combinations of cisplatin, and etoposide, and/or bleomycin

[c] ECOG = Eastern Cooperative Oncology Group's standardized measure of patient performance status [24]

significantly change from baseline to follow-up, although men who received chemotherapy appeared to have worse objective psychomotor function at baseline compared to the surgery-only group (Cohen's $d = 0.67$) (Fig. 1 and Table 3).

For the main effects of group and also time alone, at baseline, the chemotherapy group showed significantly higher anxiety than the surgery-only group, poorer functional well-being, and worse fatigue. No differences were evident at follow-up. For both groups, emotional well-being, functional well-being, and anxiety improved over time; the chemotherapy group showing greater improvements (see Tables 2 and 4, Online Resource 2 for pairwise comparisons for group and time, including 95% confidence intervals for additional information).

With groups combined, baseline scores on the six objective cognitive function tasks were correlated with subjective (self-reported) cognitive dysfunction. No significant relationships were found [2]. One exception was high visual learning outcomes which showed a small non-significant association with men's self-reports of low cognitive dysfunction ($r = -.19$, $p = 0.07$, $n = 97$). Also, there was a small association between men who perceived themselves to have good cognitive function (post-surgery/pre-chemotherapy and high performance on the visual learning task—the only CogHealth task to assess both speed and accuracy) ($r = -.19$, $p = 0.07$, $n = 97$). However, in the customised LMMs, visual learning or the one card learning task (OCL) had the highest number of significant covariates identified: patient performance status, fatigue and testosterone levels. And, after controlling for the three covariates, the final model had no significant interaction or main effects for group or time.

Discussion

This study shows no substantive difference in cognitive changes between a group of patients with testicular cancer who received chemotherapy and those treated with surgery alone. This suggests that in testicular cancer, cognitive change is not confined to the chemotherapy group as the term 'chemobrain' would suggest and other studies in testicular cancer show no difference in objective cognitive decline between patients receiving chemotherapy or not [2, 14, 15]. Baseline anxiety was worse in the chemotherapy group compared to the surgery-alone group. We hypothesise that the anxiety of the chemotherapy group was higher because of a somewhat more extensive disease, and the anticipation of adverse effects from chemotherapy

Amidi et al. used the two naturally occurring groups in testicular cancer: 22 who received chemotherapy, and 43 who received no adjuvant treatment and also tested 25 healthy controls. Comparative neuropsychological testing showed both cancer groups had higher rates of cognitive decline compared to healthy controls ($p < .05$), with a trend toward greater

Table 2 Descriptive statistics (means and standard deviations) for CogHealth and psychological variables, at baseline and follow-up, by group

Variable	Time: baseline (1) vs. follow-up (2)[a]	Surgery + chemotherapy group		Surgery-only group	
		n	M (SD)	*n*	M (SD)
CogHealth variables					
Psychomotor function	1	61	2.49 (0.12)	41	2.43 (0.08)
(Detection task; DET)	2	60	2.44 (0.08)	40	2.44 (0.08)
Visual attention/vigilance	1	61	2.70 (0.08)	41	2.68 (0.06)
(Identification task; IDN)	2	60	2.68 (0.06)	41	2.67 (0.07)
Complex decision making	1	61	2.82 (0.08)	41	2.80 (0.07)
(Matching task; MAT)	2	60	2.80 (0.07)	41	2.79 (0.08)
Visual attention	1	60	2.54 (0.10)	41	2.53 (0.09)
(Monitoring task; MON)	2	60	2.53 (0.09)	41	2.51 (0.10)
Visual learning	1	60	1.04 (0.14)	41	1.02 (0.15)
(One card learning task; OCL)	2	60	1.07 (0.14)	41	1.03 (0.16)
Working memory	1	61	2.83 (0.10)	41	2.82 (0.09)
(One back memory task; ONB)	2	60	2.83 (0.09)	41	2.81 (0.11)
Psychological variables					
Self-Perceived Cognitive Dysfunction (CFQ)	1	59	30.81 (10.33)	39	28.87 (10.98)
	2	59	32.19 (11.61)	39	30.31 (12.50)
Anxiety	1	61	6.16 (4.08)	40	4.13 (3.69)
(HADS)	2	59	4.72 (3.36)	40	3.25 (3.69)
Depression	1	61	3.05 (3.66)	40	2.10 (2.21)
(HADS)	2	59	2.09 (2.55)	40	1.80 (2.72)
Emotional well-being	1	61	18.88 (4.05)	41	20.52 (2.97)
(FACIT-F)	2	59	21.15 (2.47)	39	21.18 (3.09)
Functional well-being	1	61	21.31 (5.50)	41	23.63 (4.62)
(FACIT-F)	2	59	24.36 (4.00)	39	24.93 (3.62)
Physical well-being	1	61	23.62 (4.23)	41	25.83 (2.50)
(FACIT-F)	2	59	26.21 (2.01)	40	26.55 (2.17)
Social/family well-being	1	61	24.31 (4.09)	41	23.69 (4.65)
(FACIT-F)	2	59	24.38 (4.24)	40	23.88 (4.39)
Fatigue	1	61	41.93 (1.04)	41	45.24 (1.27)
(FACIT-F)	2	59	44.60 (1.06)	40	47.23 (1.28)

CFQ Cognitive Failures Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, measure of four core domains of QOL and fatigue

[a] Baseline (Time 1, ≤ 6 months post-surgery/pre-chemotherapy) versus follow-up (Time 2, 12–18 months post-baseline)

decline in the chemotherapy group compared to the controls ($p = .07$) [13].

Our study used the CogHealth tool, which has been shown to have construct validity when compared to other neuropsychological tests, as well as criterion validity in identifying affected patients, without cultural biases, and given that it is used serially, has no practice effects [16, 17, 26, 27]. It has been used to measure cognition in women with early stage breast cancer and more recently during therapy for childhood leukaemia [28, 29].

At baseline, men who received chemotherapy had worse objective psychomotor function than the surgical group, but there were no differences between groups over time for men's' subjective perceptions of cognitive ability. A large study of 666 testicular cancer patients who were treated with cisplatin-based chemotherapy reported that 19% recorded worsening of cognitive function when they compared baseline to 2-year post-chemotherapy. However, in that study, there was no comparison with patients who did not receive chemotherapy [30]. In 182 patients from a cross-sectional study, when comparisons could be made between those receiving chemotherapy, radiotherapy or no further treatment after surgery, approximately one third of patients in all treatment groups reported cognitive problems [12]. In 122 patients with testicular cancer where self-reported cognitive decline was compared between patients receiving no chemotherapy, one cycle of

Table 3 Objective cognitive function task comparisons for group differences (surgery + chemotherapy vs. surgery-only), over time (baseline to follow-up), and group by time (interaction effects), controlling for covariates

Cognitive function tasks[a]	Overall effects	*F*	*p*
Psychomotor function	Group	5.49	0.02
(Detention task; DET)	Time	2.02	0.16
	Group*time	4.91	0.03
	Age (covariate)	22.92	≤ 0.001
Visual attention/vigilance	Group	2.52	0.12
(Identification task; IDN)	Time	2.92	0.09
	Group*time	0.26	0.61
Complex decision making	Group	1.74	0.19
(Matching task; MAT)	Time	2.38	0.13
	Group*time	0.25	0.62
Visual attention	Group	2.24	0.14
(Monitoring task; MON)	Time	1.18	0.28
	Group*time	0.06	0.81
	Age (covariate)	31.28	≤ 0.001
Visual learning	Group	1.45	0.23
(One card learning task; OCL)	Time	0.76	0.39
	Group*time	0.16	0.69
	Testosterone (covariate)	5.25	0.03
	Fatigue (covariate)	10.54	0.002
	ECOG (covariate)	11.71	0.001
Working memory	Group	0.69	0.41
(One Back Memory Task; OBM)	Time	0.10	0.75
	Group*time	0.11	0.75

Group = main effect, comparison of surgery + chemotherapy and surgery-only groups; Time = main effect, comparing baseline to follow-up; Group*Time = interaction term, determining if different patterns of change were due to group membership; *F* value = variation among group means—the higher the value the larger the variance; *P* value = statistical significance considered < 0.05

[a] Cognitive function tasks assessed using CogHealth

chemotherapy and multiple cycles of chemotherapy, more patients reported cognitive decline between baseline and follow-up in the two chemotherapy groups compared to the non-chemotherapy group. In that study, the predictors of self-reported cognitive decline were psychological distress, fatigue, lower levels of education and the occurrence of Raynaud-like symptoms, but there was no correlation with objective neuropsychological test performance. This discrepancy between objective and subjective cognitive function remains even when change measures rather than static scores are used [31]. In a study of individual difference in self-reported attentional function in oncology patients receiving chemotherapy, those characteristics affecting baseline function were employment status, functional status, trait anxiety, depressive symptoms sleep disturbance, evening fatigue and morning energy, the latter also affecting the trajectory of attentional function which was worse in females [32].

With subjective symptoms, we have previously described a relationship between pre-treatment expectations and experiencing toxicities, and studies show that patients with pre-existing knowledge of the risk of cognitive dysfunction post-chemotherapy have more likelihood of reporting than toxicity [33–35]. Changing the information given to patients prior to treatment in breast cancer has been shown to modify subsequent cognitive complaints [35].

We did not attempt to look for mechanisms of cognitive decline in both chemotherapy and non-chemotherapy groups, but prior studies have examined the hypotheses that the inflammatory response to cancer may trigger neurotoxic cytokines which contribute to lower performance. In chemotherapy patients, greater cognitive decline has been associated with an increase in tumour necrosis factor alpha and APOE ε4 carriers perform worse with chemotherapy [13]. Voxel-based morphometry from the magnetic resonance imaging scans has revealed changes in cerebral grey matter, with prefrontal reduction more specifically seen in those who had received chemotherapy [13]. Of 69 patients with testicular cancer who had neuropsychological assessment after orchiectomy but prior to chemotherapy, 46% showed cognitive impairment, which is higher than would be expected in a healthy population [36].

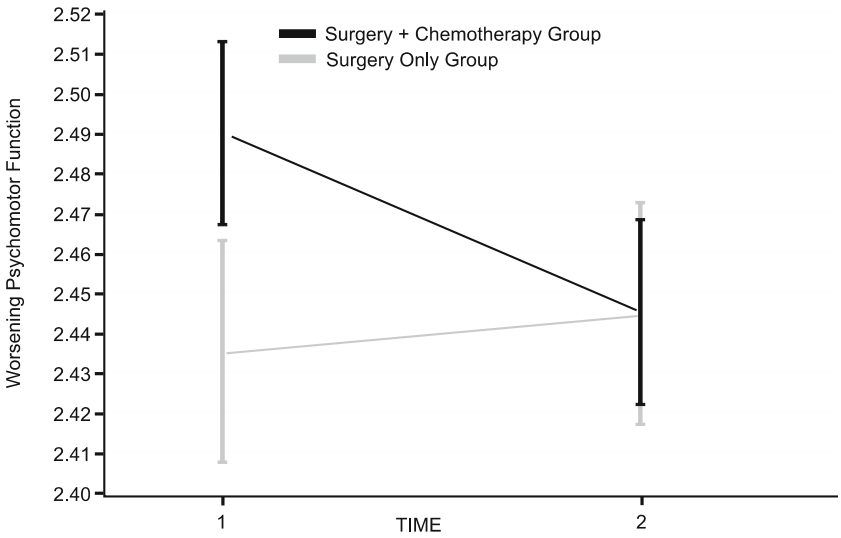

Fig. 1 Mean transformed log10 millisecond reaction times for objective psychomotor function comparing the surgery + chemotherapy and surgery-only group from baseline to follow-up

Surgery and anaesthesia have been associated with cognitive decline. Of 964 patients, cognitive decline, as measured by working memory, was statistically significantly different in patients receiving surgery than those not having surgery, with the number of operations and longer operations correlated with greater decline [37].

The impact of hypogonadism on cancer treatment-related cognitive dysfunction is unclear. Our study only recorded modest levels of biochemical hypogonadism which were unlikely to influence the outcome, so this is a question for future trials.

Our study shows improvement in cognitive function over time. There have been reports of self-rated cognitive function improving over 6 months in patients with breast cancer [38]. A study of objective cognitive dysfunction, in testicular cancer which showed no difference between those patients receiving chemotherapy and those who did not, unsurprisingly showed no negative effect of chemotherapy at 1 year [15]. A small study of testicular cancer survivors after surgery and chemotherapy or surgery alone, however, suggested that 10 years later, chemotherapy patients were at risk of long-term cognitive dysfunction, but this did not correlate with white matter changes on CT scans [11]. Clearly more long-term follow-up studies are required. Another study comparing testicular cancer patients who had received cisplatin chemotherapy to those who had not showed comparable patterns of change on cognitive data from 3 to 14 years. On functional magnetic resonance imaging, the chemotherapy group showed functional hyperconnectivity in multiple sites including the executive control network beyond 10 years and hypoactivation was found when performing the affective processing task. Hyperconnectivity may compensate for pathophysiological disturbances [39, 40].

More studies are required to assess predictive factors for both objective and subjective cognitive change and add information on management. Self-reported cognitive decline may

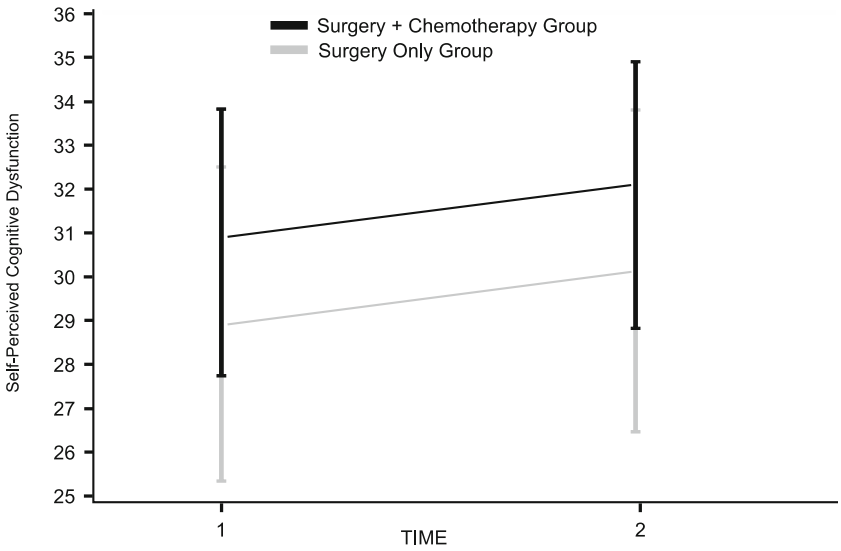

Fig. 2 Mean scores for self-perceived cognitive dysfunction comparing the surgery + chemotherapy group and the surgery-only group from baseline to follow-up

Table 4 Psychological assessment comparisons for group differences (surgery + chemotherapy vs. surgery-only), over time (baseline to follow-up), and group by time (interaction effects), controlling for covariates (if significant)

Psychological assessments	Overall effects	*F*	*p*
Self-perceived cognitive dysfunction	Group	1.34	0.25
	Time	0.72	0.40
	Group*Time	0.00	0.99
Physical well-being	Group	8.84	0.004
(FACIT-F)	Time	15.01	≤ 0.001
	Group*Time	4.79	0.03
Social/family well-being	Group	0.81	0.37
(FACIT-F)	Time	0.04	.083
	Group*Time	0.01	0.93
Emotional well-being	Group	3.19	0.08
(FACIT-F)	Time	9.79	0.002
	Group*Time	2.97	0.09
Functional well-being	Group	4.82	0.03
(FACIT-F)	Time	10.82	0.001
	Group*Time	1.75	0.19
Fatigue	Group	6.46	0.01
(FACIT-F)	Time	3.96	0.05
	Group*Time	0.09	0.77
Anxiety	Group	10.62	0.002
(HADS)	Time	4.66	0.03
	Group*Time	0.27	0.60
Depression	Group	2.17	0.14
(HADS)	Time	2.25	0.14
	Group*Time	0.62	0.43

Group = main effect, comparison of surgery + chemotherapy and surgery-only groups; Time = main effect, comparison of baseline to follow-up; Group*Time = interaction term, determining if different patterns of change were due to group membership; *F* value = variation among group means—the higher the value, the larger the variance; *P* value = statistical significance considered < 0.05

CFQ Cognitive Failures Questionnaire; *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, measure of four core domains of QOL and fatigue; *HADS* Hospital Anxiety and Depression Scale

well respond to cognitive behavioural or mindfulness therapy [5]. Other suggested treatments include commercial cognitive training programs, increasing physical activity, diet modification including omega 3 fatty acids with low sugar diets, psychostimulants and Pifithrin-μ for objective cognitive decline [40–44].

Limitations which provide challenges for future studies include the study not being powered to address any difference between the single agent chemotherapy, which was adopted mid-study, and the three-drug regimen, although we have provided an exploratory analysis added to the online resources. Attrition was an issue, but with an on-line measure, patients could complete the cognitive function tests and CFQ at the hospital or home; however, the surgery-only group had less follow-up contact than those receiving chemotherapy. There is also no attrition analysis for the 47 patients with insufficient data, but it is unlikely that any of these dropped out due to cognitive decline because there were no differences between groups over time in mens' perceptions of subjective cognitive dysfunction. We also know that the format of testing (paper vs on-line) can influence outcomes [45].

In summary, findings around changes in cognitive function following chemotherapy in this study of patients with testicular cancer differ from those reported in previous studies in breast cancer. Despite some differences at baseline between objective and subjective cognitive function, there are no substantive differences in either group persisting at 12 to 18 months post-baseline.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Within the authorship we have full control of the data which is held at COGState and the NHMRC data centre and we agree to allow the journal to review the data if requested.