Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 126–134, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.05.004

CLINICAL INVESTIGATION **Head and Neck**

COGNITIVE FUNCTIONING AFTER RADIOTHERAPY OR CHEMORADIOTHERAPY FOR HEAD-AND-NECK CANCER

Hui K. Gan, M.B.B.S.,* Lori J. Bernstein, Ph.D.,† Jennifer Brown, M.A.,* Jolie Ringash, M.D.,‡ Mehrdad Vakilha, M.D.,‡ Lisa Wang, M.Sc.,§ David Goldstein, M.D.,¶ John Kim, M.D.,‡ Andrew Hope, M.D.,‡ Brian O'Sullivan, M.D.,‡ John Waldron, M.D.,‡ Albiruni R. Abdul Razak, M.D.,* Eric X. Chen, M.D.,* and Lillian L. Siu, M.D.*

Departments of *Medical Oncology, †Psychosocial Oncology, ‡Radiation Oncology, §Biostatistics, and ¶Otolaryngology, Princess Margaret Hospital, Toronto, ON, Canada

Purpose: To perform a comprehensive cognitive function (CF) assessment in patients who were relapse free after curative intent radiotherapy (RT) or chemoradiotherapy for squamous cell carcinoma of the head and neck.

Methods and Materials: Patients underwent neuropsychological tests to assess their objective CF; completed questionnaires to assess subjective CF, quality of life, and affect; and underwent blood tests to assess hematologic, biochemical, endocrine, and cytokine status. Retrospectively, the dosimetry of incidental radiation to the brain was determined for all patients, and the dose intensity of cisplatin was determined in those who had undergone chemoradiotherapy.

Results: A total of 10 patients were enrolled (5 treated with radiotherapy only and 5 with radiotherapy and cisplatin). The mean time from the end of treatment was 20 months (range, 9–41). All patients were able to complete the assessment protocol. Of the 10 patients, 9 had impaired objective CF, with memory the most severely affected. The severity of memory impairment correlated significantly with the radiation dose to the temporal lobes, and impaired dexterity correlated significantly with the radiation dose to the cerebellum, suggesting that these deficits might be treatment related. Patients receiving cisplatin appeared to have poorer objective CF than patients receiving only RT, although this difference did not achieve statistical significance, likely owing to the small sample size. Consistent with the published data, objective CF did not correlate with subjective CF or quality of life. No association was found between objective CF and patients' affect, hematologic, biochemical, endocrine, and cytokine status.

Conclusion: Neuropsychological testing is feasible in squamous cell carcinoma of the head-and-neck survivors. The findings were suggestive of treatment-related cognitive dysfunction. These results warrant additional investigation.

Squamous cell carcinoma of the head and neck, Radiotherapy, Chemotherapy, Cognitive dysfunction, Neuropsychological testing.

INTRODUCTION

The global annual incidence of squamous cell carcinoma of the head and neck (SCCHN) has been >500,000, with annual mortality >300,000 (1). Radiotherapy (RT) has often been administered with a curative intent when surgery was not possible or if organ preservation was desirable (2). For locoregionally advanced disease, concurrent platinum-based chemotherapy (*e.g.,* cisplatin) has provided an absolute survival improvement of 6.5% compared with RT alone but with increased acute toxicity (2, 3). One alternate approach, usually for patients unable to tolerate platinum-based chemotherapy, has been to administer RT with antibodies antagonizing the epidermal growth factor receptor, such as cetuximab (2, 4). Compared with RT alone, RT with cetuximab has been shown to improve survival in patients with locally advanced SCCHN without a significant increase in acute toxicity (5). The results are awaited from trials directly comparing RT with concurrent cisplatin vs. chemoradiotherapy with concurrent anti-epidermal growth factor receptor antibodies. Finally, altered fractionation RT remains an alternative for these patients, with a survival advantage of 8% when the radiation dose has been intensified

Reprint requests to: Lillian L. Siu, M.D., Department of Medical Oncology, Princess Margaret Hospital, 610 University Ave., Suite 5-718, Toronto, ON M5G 2M9 Canada. Tel: (416) 946-2911; Fax: (416) 946-4467; E-mail: lillian.siu@uhn.on.ca

Preliminary results presented at American Society of Clinical Oncology 2009 meeting.

Supported by the Canadian Institutes of Health Research.

Conflict of interest: none.

Received Feb 8, 2010, and in revised form April 28, 2010. Accepted for publication May 3, 2010.

by hyperfractionation compared with standard fractionation (6).

It is likely that SCCHN patients are at risk of cognitive dysfunction because of their tumor or its treatment. Data exist regarding other cancers (*e.g.,* breast cancer [7–11], small-cell lung cancer [12–16], brain tumors [17–25], and nasopharyngeal cancer [26–28]) to show that these diseases, and the treatments administered for them, have been associated with cognitive dysfunction. Although the mechanisms by which tumors might directly cause cognitive dysfunction are not well understood, a number of mechanisms have been postulated, including derangements of cytokine production (29). Although the same mechanisms might be relevant in SCCHN patients (*e.g.,* SCCHN patients also have derangements of cytokines [29, 30]), these patients might be especially susceptible to cognitive dysfunction. In particular, the high prevalence of alcohol abuse in this patient population puts them at a greater risk of cognitive problems before treatment (31). Any pre-existing cognitive dysfunction might then be exacerbated by incidental RT to the brain during treatment or the neurotoxic effects of concurrent systemic chemotherapy.

We report on the first study in which patients who are relapse free after RT -based treatment for SCCHN were assessed using a comprehensive battery of neuropsychological (NP) tests, questionnaires (examining the subjective cognitive symptoms, quality of life [QOL] and affect), and blood tests.

METHODS AND MATERIALS

The present prospective trial enrolled patients who were relapse free after definitive RT, either alone or with concurrent cisplatin (100 mg/m^2 on Days 1, 22, and 43). Eligible patients were aged $\geq$18 years and had an Eastern Cooperative Oncology Group performance status of 0–2, bilirubin less than the upper limit of normal, liver function tests within 2.5 times the upper limit of normal, creatinine within 2 times the upper limit of normal, and provided written informed consent. Ineligible patients included those who had been receiving psychotropic medications (*i.e.,* opioids, anxiolytics or antidepressants), had nasopharyngeal tumors, had received chemotherapy or cranial RT for conditions other than SCCHN, had uncontrolled infection or severe medical comorbidities, had been diagnosed with other malignancies within 5 years (except for adequately treated nonmelanomatous skin cancer or cervical carcinoma *in situ)*, or could not complete the assessment protocol because of insufficient English skills or deafness. The institutional ethics board approved the present study, which was in accordance with the Helsinki Declaration (2000).

During a 2-hour session, patients underwent NP testing of intelligence (Wechsler Adult Intelligence Scale-III [32] or Wechsler Abbreviated Scale of Intelligence Vocabulary and Matrix Reasoning subtests [33] split half versions) and to assess functioning in the domains of language (Delis-Kaplan Executive Function System Verbal Fluency Test [34]; Boston Naming Test [35] split half version), memory encoding and retention (Hopkins Verbal Learning Test–Revised [36]; Brief Visuospatial Memory Test–Revised [37]), attention (Wechsler Adult Intelligence Scale-III Digit Span subtest [32]), processing speed (Trail Making Test Part A [38]; Delis-Kaplan Executive Function System Color Naming and Word Reading [34]), executive function (Trail Making Test Part B [38]; Delis-Kaplan Executive Function System Stroop Color Word Interference Test Inhibition and Switching [34]), and motor skills (grooved pegboard test of manual dexterity [39]). The patients were concurrently assessed for self-reported cognitive symptoms (Functional Assessment of Cancer Therapy [FACT]–cognitive function [Cog] [40, 41]), QOL (FACT–head-and-neck cancer [42]), fatigue symptoms (FACT-fatigue [43]), anxiety symptoms (Hospital Anxiety and Depression Scale [44]), and depression symptoms (Hospital Anxiety and Depression scale). Patients provided blood for the measurement of hemoglobin, creatinine, bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, thyroid-stimulating hormone, triiodothyronine, thyroxine, follicle-stimulating hormone, luteinizing hormone, and estrogen/testosterone. Vitamin B_1, vitamin B_{12}, folate, and albumin were measured as surrogate markers of nutritional status. The plasma levels of 10 cytokines (interleukin [IL]-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor-α, interferon-γ, and granulocyte-macrophage colony-stimulating factor) were also assessed using the LiquiChip Human 10-cytokine kit (Qiagen, Valencia, CA), according to the manufacturer's instructions.

The total dose of cisplatin received by patients was retrospectively determined from the patients' charts and pharmacy records. Similarly, the mean and maximal radiation dose received by the whole brain and specific substructures therein was determined by retrospective review of the archived intensity-modulated RT plans.

Statistical analysis

The NP test data were normalized to z-scores using age and education normative data. A z-score of 0 equates to test results equivalent to those obtained by the 50th percentile of a demographically matched group. A z-score of +1.0 or −1.0 corresponds to results that are one standard deviation better or worse, respectively. A global cognitive function score was derived by averaging the z-scores of all cognitive domains, except for the intelligence quotient (IQ) and manual dexterity. To assess whether each patient had experienced any change in cognitive function after treatment of SCCHN, the z-score for each cognitive domain was compared with the z-score for IQ. The IQ is stable during an adult's lifetime, preserved even with aging and after medical illness and is an accepted predictor of how patients should perform in other cognitive domains when assessed using NP tests (45). For example, a patient with an IQ z-score of +1.0 should have a z-score of approximately +1.0 on a test of verbal memory. A z-score that is significantly lower than +1.0 would suggest a decline in verbal memory in that patient. A comparison of the nonparametrically distributed z-scores was performed using the Kruskal-Wallis test with post hoc pairwise comparisons using the Mann-Whitney U test. The difference between the z-score for a cognitive domain and the z-score for the IQ was termed the ''difference score'' for that domain. A global difference score (GD score) was calculated by averaging all difference scores. All comparisons of normally distributed data were performed using t tests. Correlations between variables were tested using one-sided Kendall's tau. All other p values are two-sided, unless otherwise indicated.

RESULTS

A total of 18 eligible patients were approached for enrolment, with 8 patients declining (2 because of work commitments and 6 because of the inconvenience of an extra

Table 1. Patient demographics

Pt. No.	RT (Gy/fx)	Total cisplatin dose (mg)	Age (y)	Gender	Site	TNM stage	Follow-up (mo)	Current ethanol intake (drinks/wk)	Nicotine exposure (pack years)	Education (y)
1	60/25	0	66	Male	Larynx	T1N0M0	12	2	45*	15
2	60/25	0	66	Male	Larynx	T2N0M0	10	25†	40	6
3	64/20 BID	0	61	Male	Larynx	T2N1MO	12	0	10	18
4	64/20 BID	0	60	Male	Hypopharynx	T2N0M0	35	0	0	18
5	60/25	0	57	Male	Pharynx	T2N0M0	13	4	20	12
6	70/35	600	57	Male	Pharynx	TisN2M0	30	21	15*	12
7	70/35	480	58	Female	Pharynx	T2N2M0	41	0†	0	15
8	70/35	495	52	Male	Pharynx	T3N2M0	9	0†	0	15
9‡	70/35	432	47	Female	Pharynx	T4N1M0	25	4	12*	18
10	70/35	540	57	Male	Pharynx	T3N2M0	16	14	10	16

Abbreviations: Pt. No. = patient number; RT = radiotherapy; BID = twice daily.
* Current smoker.
† Self-reported alcohol abuse/dependency in the past.
‡ See also Fig. 2A.

hospital visit). The demographic data of the 10 enrolled patients (5 who underwent RT alone and 5 who underwent chemoradiotherapy) are listed in Table 1. All patients were caucasian and were relapse free after a mean follow-up of 20 months (range, 9–41). As expected, the patients who had undergone chemoradiotherapy had more advanced disease than those who had only received RT. All chemoradiotherapy patients received the three planned doses of cisplatin (mean dose administered, 509 mg). All 10 patients completed a full course of RT using computed tomography planning, intensity-modulated RT, and daily image guidance. The only intensity-modulated RT constraint applied routinely to the brain structures during planning related to the brainstem dose. The absolute point maximal dose was limited to 54, 45, and 40 Gy, and $\leq$0.1 cm^3 of brainstem was permitted to receive $\leq$50, 40, and 38 Gy, respectively, for plans delivering 70, 60, and 64 Gy, respectively (64 Gy in 40 fractions within 4 weeks, accelerated hyperfractionation) total dose. The prescribed dose/fractionation schedules are also listed in Table 1.

NP testing results

All patients completed the assessment protocol within the prescribed 2 h. The results of the NP tests are listed in Table 2 (z-scores) and Fig. 1 (difference scores and GD scores). The study population scored well on IQ, with a mean z-score of +1.15 and 80% of the patients having a z-score >+1.0 (Table 2). In contrast, evidence was found of cognitive dysfunction in multiple domains. The mean z-scores for all cognitive domains (except for language) and for global cognitive function were significantly lower than expected from the patient IQ (Table 2). The magnitude of the observed cognitive deficits is shown in Fig. 1. The most severely affected cognitive domain was memory. No significant correlation was

Table 2. Z-Scores for individual patients

		Cognition							
Pt. No.	IQ	Language	Memory encoding	Memory retention	Attention	Processing speed	Executive function	Global cognition	Manual dexterity
1	−1.00	−0.59	−2.61	−0.42	−0.62	−0.09	−0.89	−0.87	−1.32
2	−0.50	−2.94	−0.59	−2.05	−0.27	−0.19	−0.67	−1.12	−0.52
3	+1.88	0.89	−0.15	+0.51	+1.36	+1.05	+1.12	+0.79	+0.27
4	+1.99	0.55	−0.15	+0.94	+1.01	+0.49	+0.38	+0.54	−0.86
5	+1.88	0.72	−1.60	+0.48	+0.37	+0.32	+0.79	+0.18	−0.64
6*	+1.17	0.18	−0.37	−0.62	+1.04	+0.12	−0.33	0.00	−1.33
7*	+1.88	0.55	−0.86	−0.51	+0.03	+0.29	+0.28	−0.04	−1.26
8*	+1.36	−0.04	+0.37	+0.41	−0.85	−0.68	−0.16	−0.16	+0.17
9*	+1.16	0.06	−1.31	−0.79	+0.24	−0.23	+0.30	−0.29	−1.64
10*	+1.70	2.09	+1.11	+0.55	+1.36	+0.31	+1.02	+1.07	−1.04
Mean†	+1.15	+0.15	−0.62	−0.15	+0.37	+0.14	+0.19	+0.01	−0.81
p‡	NA	.063	.003	.007	.035	.0185	.0147	.0115	NA

Abbreviations: Pt. No. = patient number; IQ = intelligence quotient; NA = not applicable.
* Chemoradiotherapy patient.
† For all 10 patients.
‡ Kruskal-Wallis p = .024; p values from post hoc pairwise comparisons of mean values using Mann-Whitney U tests between individual cognitive domains vs. IQ.

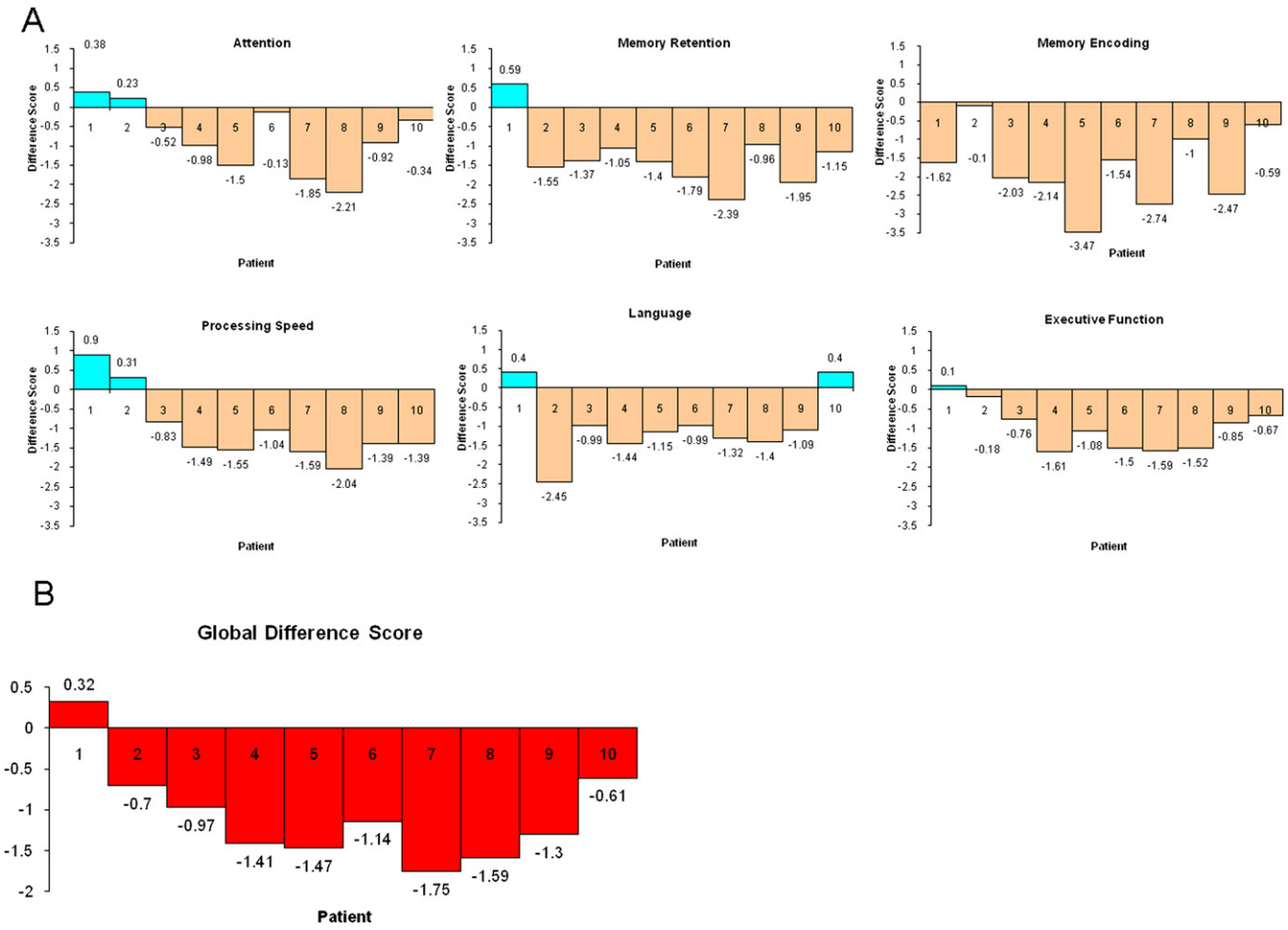

Fig. 1. Difference scores for individual patients. For each patient, (A) difference score (D-score) for each cognitive domain and (B) global difference score shown. Score of 0 represents performance at level expected from intelligence quotient subtests; score of −1.0 represents underperformance by one standard deviation (SD) and score of +1.0 represents overperformance by one SD.

found between the GD scores and interval from treatment completion for SCCHN.

Etiology of cognitive dysfunction

To determine whether incidental RT received by the brain might have contributed to the cognitive dysfunction shown by the NP data, the radiation dosimetry to the brain was determined for each patient (Table 3) and also for the group (Fig. 2). The mean dose to the whole brain was low (range, 0.14–4.83 Gy for the 10 patients; Table 3), with the average value for the group 2.8 Gy (Fig. 2B). The data for the mean dose to the substructures of the brain are also shown in Fig. 2B. Although the mean radiation dose to the brain and its component lobes was usually small, the maximal dose received by focal areas of the brain (specifically the temporal lobes, occipital lobes, and cerebellum) was often substantially greater (Table 3 lists the data for individual patients and Fig. 2C shows the data averaged for the entire group). We tested for the possibility that cognitive functions ascribed to the more heavily irradiated lobes might show a dose-deficit relationship. The resulting analysis found a statistically significant correlation between increasing radiation doses to the temporal lobes, which are important in memory function, and worse performance on tests of memory encoding (r^2 = 0.26, p = .030; Fig. 2D). Similarly, a statistically significant correlation was found between increasing radiation doses to the cerebellum, which is important for coordination, and manual dexterity on the Pegboard test (r^2 = 0.154, p = .045).

Given that one-half the patient sample had undergone chemoradiotherapy and one-half had not, we had an opportunity to examine the contribution of chemotherapy to cognitive function. The demographics of the chemoradiotherapy group were similar to those of the RT-only group, except for the nonsignificant differences in IQ (z-scores +1.45 vs. +0.85 respectively, p = .42). Despite the slightly more favorable characteristics of the chemoradiotherapy group, a trend was seen for the chemoradiotherapy group to have greater cognitive dysfunction, which was numerically evident but not statistically significant (GD score, −1.28 compared with −0.84, p = .29).

None of the other factors examined appeared to contribute to the observed NP test results. Because anxiety, depression, and fatigue can contribute to cognitive disturbance, we screened for these using the Hospital Anxiety and Depression

Table 3. Radiation dosimetry to brain for individual patients

Pt. No.	Mean dose (Gy) to whole brain	Maximal dose (Gy)								
		Whole brain	Frontal lobe	Parietal lobe	Temporal lobe	Occipital lobe	Thalamus	Pituitary	Hypothalamus	Cerebellum
1	1.36	36.05*	<1.00	<1.00	1.53	<1.09	1.00	1.05	1.13	36.05*
2	< 1.00	1.65	<1.00	<1.00	<1.00	<1.00	<1.00	<1.00	<1.00	<1.00
3	2.14	40.64*	1.86	<1.00	6.54	7.59	1.57	3.92	3.70	32.74*
4	1.74	38.99*	1.25	<1.00	3.61	9.22	1.75	2.15	1.95	37.76*
5	3.55	51.33*	2.02	<1.00	46.99*	27.11*	1.93	3.78	2.64	48.45*
6†	2.85	45.84*	1.93	<1.00	5.29	10.98*	2.18	2.96	3.30	45.84*
7†	4.07	51.76*	2.80	<1.00	11.36*	19.01*	2.41	3.74	3.32	51.76*
8†	2.71	44.28*	1.83	<1.00	3.80	3.28	1.43	2.66	2.10	44.28*
9†	4.83	57.77*	2.22	<1.00	40.08*	28.47*	2.60	3.64	3.58	57.77*
10†	4.27	54.42*	2.31	<1.00	30.54*	9.13	2.31	3.75	3.15	46.31*

Abbreviation: Pt = patient.
* Radiation dose ≥10 Gy.
† Chemoradiotherapy patient.

and FACT-F questionnaires (Table 4). No evidence was seen of anxiety, depression, or fatigue in the study participants. Also, no gross or consistent abnormalities were found in the patients' hematologic, biochemical, or endocrine laboratory test results (Table 5). No patients showed evidence of nutritional deficiency according to the surrogate markers tested, and no patient had abnormal elevations of any of the 10 cytokines tested (data not shown). Also, no evidence

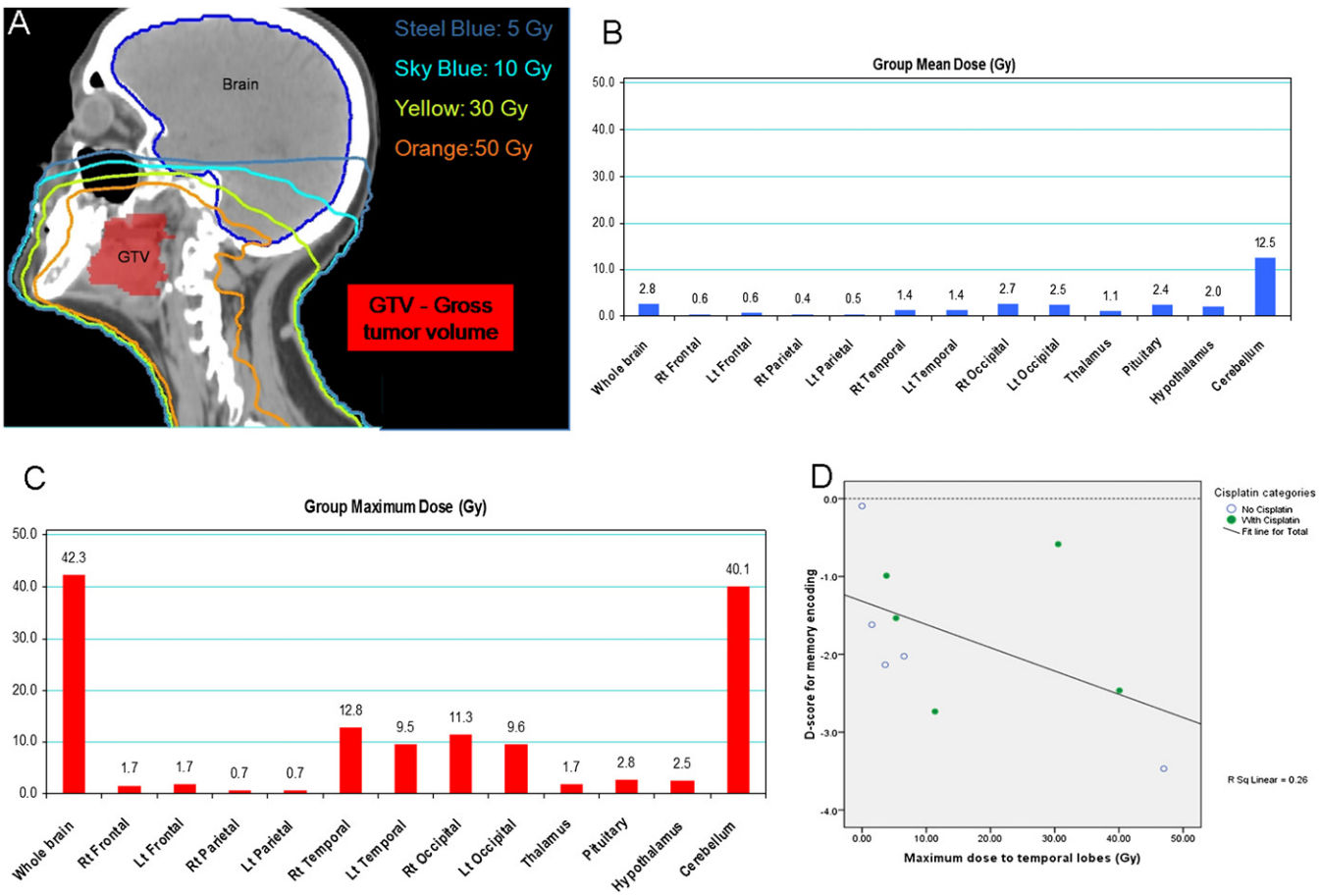

Fig. 2. (A) Sagittal computed tomography slice through mid-orbit showing isodose curves for Patient 9. (B, C) Graphs quantifying incidental radiation received by group (n = 10), showing (B) data regarding mean doses received and (C) data regarding maximal doses received. (D) Correlation between maximal radiation dose to temporal lobes and difference score for memory encoding. Radiotherapy-only patients indicated by empty circles and chemoradiotherapy patients indicated by solid green circles.

Table 4. Questionnaire data

Pt. No.	HADS anxiety score* (range, 0–21)	HADS depression score* (range, 0–21)	FACT-F† (range, 0–156)	FACT-H&N† (range, 0–152)	FACT-Cog† (range 0–188)
1	1	2	136	121	143
2	1	0	152	146	175
3	6	5	138	124	181
4	8	5	115	123	143
5	5	4	112	103	144
6‡	7	4	105	103	148
7‡	0	1	128	130	78
8‡	8	7	106	108	164
9‡	2	1	97	102	170
10‡	2	2	150	139	156

Abbreviations: Pt. No. = patient number; HADS = Hospital Anxiety and Depression Scale; FACT-F = Functional Assessment of Cancer Therapy-fatigue; FACT-H&N = FACT-head and-neck cancer; FACT-Cog = FACT-cognitive function.

* Score 0–7, no evidence of anxiety or depression; score 8–10, doubtful case; score 11–21, clinically significant case of anxiety or depression.

† For FACT-F, FACT-H&N, and FACT-Cog, higher scores equate with less fatigue, less impairment in quality of life, and fewer cognitive complaints, respectively.

‡ Chemoradiotherapy patient.

was found of cerebral ischemia or cranial vessel abnormalities.

Patient-reported symptoms

Patients' general and tumor-specific QOL was assessed using the FACT-H&N questionnaire (Table 4). Because higher scores on this scale correspond to better QOL, it was clear that the patients in the present study generally had good physical QOL. The only severe disease-specific symptoms patients reported were dry mouth (40%), an inability to swallow naturally and easily (10%), an inability to eat the foods they liked (10%), and dissatisfaction with their appearance (10%). Patients' self-reported cognitive symptoms were assessed using the FACT-Cog questionnaire (Table 4). Again, given that higher scores correlate with fewer problems, the patients in the present study were reporting few cognitive symptoms. No significant correlation was seen between the patient scores on the FACT-Cog and their GD scores.

Table 5. Patient laboratory results

Pt. No.	Hemoglobin*	Creatinine†	Liver function tests‡	Thyroid function tests§	Sex hormones¶
1	WNL	WNL	WNL	G1 hypothyroid‖	WNL
2	WNL	WNL	WNL	WNL	WNL
3	WNL	WNL	WNL	WNL	WNL
4	WNL	WNL	G1, ↑LFT results#	WNL	↑FSH, ↓testosterone**
5	G1, ↓Hb††	WNL	WNL	WNL	WNL
6‡‡	WNL	WNL	WNL	G1 hypothyroid§§	WNL
7‡‡	WNL	WNL	WNL	WNL	WNL
8‡‡	WNL	WNL	WNL	WNL	↑FSH¶¶
9‡‡	WNL	WNL	G1, ↑LFT results‖‖	WNL	WNL
10‡‡	G1, ↓Hb##	G1, ↑creatinine***	WNL	WNL	WNL

Abbreviations: Pt. No. = patient number; WNL = within normal limits; G1 = Grade 1 Common Toxicity Criteria, version 3, abnormality; LFT = liver function test; FSH = follicle-stimulating hormone; Hb = hemoglobin; TSH = thyroid-stimulating hormone; AST = aspartate transaminase; ALT = alanine transaminase; ALP = alkaline phosphatase

* Normal: males, >140 g/L; females, >120 g/L.

† Normal: males, >110 μmol/L; females, >98 μmol/L.

‡ Normal: aspartate transaminase ≤35 U/L, alanine transaminase ≤40 U/L, alkaline phosphatase ≤110 U/L, bilirubin ≤22 μmol/L.

§ Normal: thyroid-stimulating hormone 0.35–4.94 mIU/mL; triiodothyronine 2.6–5.7 pmol/L; thyroxine 9–19 pmol/L.

¶ Normal: follicle-stimulating hormone 1.4–13.6 IU/L; luteinizing hormone 1.1–8.8 IU/L.

‖ TSH 7.31mIU/L, thyroxine 8 pmol/L.

AST 38 U/L, ALT 70 U/L, ALP 169 U/L.

** FSH 15 IU/L and free testosterone 26.9 pnol/L

†† Hb 138 g/L

‡‡ Chemoradiotherapy patient.

§§ TSH 9.53 mIU/L.

¶¶ FSH 19 IU/L.

‖‖ ALP 152 U/L.

Hb 138 g/L.

*** Creatinine 113 mmol/L.

DISCUSSION

The present study is the first one to assess SCCHN survivors after radiation-based, organ-preservation therapy using a comprehensive assessment protocol of NP tests, questionnaires, and blood tests. To date, the few studies that directly examined cognitive function in SCCHN survivors focused on subjective cognitive symptoms using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item cancer-specific module (46–48). SCCHN survivors treated with RT were more likely to report cognitive symptoms than were patients treated with surgery only (48). Only one study has previously assessed objective cognitive function in SCCHN patients, but this was limited to an assessment of executive function only (49).

Our results are concerning, because they are suggestive of cognitive dysfunction in most SCCHN survivors. Furthermore, the degree of cognitive impairment seen in our study was moderately large. For 70% of patients, the estimated decline in cognitive performance across the cognitive domains as a whole was at least one standard deviation (Fig. 1B). Thus, most patients who would be expected to perform at the 80th percentile were only performing at the 50th percentile. Although we did not examine the functional implications of this cognitive dysfunction in our study, the limited published data would suggest that such cognitive dysfunction would result in adverse functional outcomes. Yuen *et al.* (50, 51) found that SCCHN survivors had inferior driving performance compared with controls without SCCHN (50), and 27% of SCCHN patients were unable to drive or drove only in a restricted capacity after treatment of SCCHN (51). Treatment-related cognitive dysfunction was probably contributory, because a subsequent study showed that an increasing radiation dose to the brain correlated with impaired objective cognitive function, which in turn negatively affected driving performance (49). Information from the breast cancer data have also suggested that cognitive dysfunction could contribute to post-treatment unemployment (10). The socioeconomic relevance of this is clear, given that 19–52% of patients who were employed before treatment of SCCHN were unemployed or disabled after treatment, with the risk tripled if patients had undergone chemotherapy as a part of their treatment (52, 53).

We hypothesized that some of the cognitive dysfunction seen in the present study was directly related to the cancer treatment with RT and likely also to the chemotherapy. Although direct RT to the brain in high doses has been shown to cause neurologic changes and cognitive dysfunction in patients with other cancers (17–28), our study results suggest that even the incidental RT received by the brain during treatment of SCCHN could contribute to cognitive dysfunction. Although the mean radiation dose to the whole brain was low in our patients, we found that small-volume, focal areas within the temporal lobes, occipital lobes, and cerebellum were frequently irradiated to relatively high levels. Furthermore, plausible and significant negative correlations were found between the radiation dose and cognitive performance. Specifically, an increasing radiation dose to the temporal lobes was significantly associated with worse memory performance and increasing cerebellar irradiation was significantly associated with worse motor coordination. The medial temporal region, which is crucial for the acquisition and retention of new memories, is thought to be particularly susceptible to vascular injury such as that caused by RT (54).

Similarly, our results were suggestive that chemotherapy use was associated with worse cognitive dysfunction, with the lack of statistical significance likely the result of the relatively small sample size. This is consistent with the published data regarding the neurotoxic effects of cisplatin. Cisplatin given intravenously has been associated with histologic abnormalities in the brain (55), encephalopathy (56–58), seizures (59, 60). and transient cortical blindness (59, 60). The use of RT concurrently with cisplatin might increase the risk because concurrent RT could disrupt the blood–brain barrier and allow cisplatin to enter the central nervous system more readily (57).

In contrast to the objective cognitive deficits, patients reported preserved QOL in a SCCHN-specific questionnaire (FACT-H&N) and minimal symptoms in a cognition-specific questionnaire (FACT-Cog). This lack of correlation between the NP test results and the FACT-Cog results was not unexpected. Although the reasons are unclear, multiple studies have shown that patients' subjective cognitive symptoms do not correlate with objective cognitive function (7, 8, 61–64). Thus, questionnaires of cognitive symptoms are not appropriate substitutes for NP testing as a method of measuring objective cognitive performance, because these two assessment approaches appear to capture different aspects of patient cognition.

Although provocative, the interpretation of these data must be tempered by the limitations of our cross-sectional study. The sample size was small. Furthermore, although the use of the current IQ as a predictor of performance in other cognitive domains is an accepted technique used in clinical neuropsychological assessments (45), future studies might benefit from directly comparing the post-treatment results with readings obtained before treatment.

CONCLUSION

The present study results have provided the first data using a comprehensive NP testing protocol in SCCHN survivors, with the results showing that most of these patients had evidence of objective cognitive dysfunction in multiple cognitive domains. This is concerning because cognitive dysfunction is likely to negatively affect patients' lives. Larger prospective trials are clearly required, preferably in which patients undergo a comprehensive baseline NP assessment before treatment, followed by serial assessments thereafter. In addition to groups treated with RT alone or with chemoradiotherapy, it would be relevant to assess the cognitive effects of RT administered with concurrent anti-epidermal growth factor receptor antibodies.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, *et al*. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med* 2008;359:1143–1154.
3. Pignon JP, le Maitre A, Maillard E, *et al*. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4–14.
4. Bernier J, Bentzen SM, Vermorken JB. Molecular therapy in head and neck oncology. *Nat Rev Clin Oncol* 2009;6:266–277.
5. Bonner JA, Harari PM, Giralt J, *et al*. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567–578.
6. Bourhis J, Overgaard J, Audry H, *et al*. Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. *Lancet* 2006;368:843–854.
7. Hermelink K, Untch M, Lux MP, *et al*. Cognitive function during neoadjuvant chemotherapy for breast cancer: Results of a prospective, multicenter, longitudinal study. *Cancer* 2007; 109:1905–1913.
8. van Dam FS, Schagen SB, Muller MJ, *et al*. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy. *J Natl Cancer Inst* 1998;90:210–218.
9. Von Ah D, Harvison KW, Monahan PO, *et al*. Cognitive function in breast cancer survivors compared to healthy age- and education-matched women. *Clin Neuropsychol* 2009;23:661–674.
10. Wefel JS, Lenzi R, Theriault RL, *et al*. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: Results of a prospective, randomized, longitudinal trial. *Cancer* 2004;100:2292–2299.
11. Wefel JS, Lenzi R, Theriault R, *et al*. ''Chemobrain'' in breast carcinoma?: A prologue. *Cancer* 2004;101:466–475.
12. Cull A, Gregor A, Hopwood P, *et al*. Neurological and cognitive impairment in long-term survivors of small cell lung cancer. *Eur J Cancer* 1994;30A:1067–1074.
13. Grosshans DR, Meyers CA, Allen PK, *et al*. Neurocognitive function in patients with small cell lung cancer: Effect of prophylactic cranial irradiation. *Cancer* 2008;112:589–595.
14. Johnson BE, Patronas N, Hayes W, *et al*. Neurologic, computed cranial tomographic, and magnetic resonance imaging abnormalities in patients with small-cell lung cancer: Further follow-up of 6- to 13-year survivors. *J Clin Oncol* 1990;8:48–56.
15. Komaki R, Meyers CA, Shin DM, *et al*. Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. *Int J Radiat Oncol Biol Phys* 1995;33:179–182.
16. van Oosterhout AG, Boon PJ, Houx PJ, *et al*. Follow-up of cognitive functioning in patients with small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1995;31:911–914.
17. Bosma I, Douw L, Bartolomei F, *et al*. Synchronized brain activity and neurocognitive function in patients with low-grade glioma: A magnetoencephalography study. *Neuro-Oncology* 2008;10:734–744.
18. Kramer JH, Crowe AB, Larson DA, *et al*. Neuropsychological sequelae of medulloblastoma in adults. *Int J Radiat Oncol Biol Phys* 1997;38:21–26.
19. Laack NN, Brown PD, Ivnik RJ, *et al*. Cognitive function after radiotherapy for supratentorial low-grade glioma: A North Central Cancer Treatment Group prospective study. *Int J Radiat Oncol Biol Phys* 2005;63:1175–1183.
20. Correa DD, Shi W, Thaler HT, *et al*. Longitudinal cognitive follow-up in low grade gliomas. *J Neurooncol* 2008;86:321–327.
21. Klein M, Heimans JJ, Aaronson NK, *et al*. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: A comparative study. *Lancet* 2002;360:1361–1368.
22. Surma-aho O, Niemela M, Vilkki J, *et al*. Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. *Neurology* 2001;56:1285–1290.
23. Postma TJ, Klein M, Verstappen CC, *et al*. Radiotherapy-induced cerebral abnormalities in patients with low-grade glioma. *Neurology* 2002;59:121–123.
24. Moretti R, Torre P, Antonello RM, *et al*. Neuropsychological evaluation of late-onset post-radiotherapy encephalopathy: A comparison with vascular dementia. *J Neurol Sci* 2005, 229–230:195–200.
25. Armstrong CL, Hunter JV, Ledakis GE, *et al*. Late cognitive and radiographic changes related to radiotherapy: Initial prospective findings. *Neurology* 2002;59:40–48.
26. Hua MS, Chen ST, Tang LM, *et al*. Neuropsychological function in patients with nasopharyngeal carcinoma after radiotherapy. *J Clin Exp Neuropsychol* 1998;20:684–693.
27. Lam LCW, Leung SF, Chan YL. Progress of memory function after radiation therapy in patients with nasopharyngeal carcinoma. *J Neuropsychiatry Clin Neurosci* 2003;15:90–97.
28. Lee PW, Hung BK, Woo EK, *et al*. Effects of radiation therapy on neuropsychological functioning in patients with nasopharyngeal carcinoma. *J Neurol Neurosurg Psychiatry* 1989;52:488–492.
29. Seruga B, Zhang H, Bernstein L, *et al*. Cytokines and their relationship to the symptoms and outcome of cancer. *Nat Rev Cancer* 2008;8:887–899.
30. Pries R, Nitsch S, Wollenberg B. Role of cytokines in head and neck squamous cell carcinoma. *Exp Rev Anticancer Ther* 2006; 6:1195–1203.
31. McCaffrey JC, Weitzner M, Kamboukas D, *et al*. Alcoholism, depression, and abnormal cognition in head and neck cancer: A pilot study. *Otolaryngol Head Neck Surg* 2007;136:92–97.
32. Weschler D. WAIS-III: Weschler Adult Intelligence Scale. 3rd ed. New York: Psychological Corporation; 1997.
33. Weschler D. WASI: Weschler Abbreviated Scale of Intelligence. New York: Psychological Corporation; 1999.
34. Delis DC, Kaplan E, Kramer JH. DKEFS: Delis-Kaplan Executive Function System. New York: Psychological Corporation; 2001.
35. Kaplan EF, Goodglass H, WeintraubBNT- S II. The Boston Naming Test. 2nd ed. New York: Lea & Febiger; 2000.
36. Brandt J, Benedict RHB. HVLT-R: Hopkins Verbal Learning Test-Revised. Odessa, FL: Psychological Assessment Resources; 2001.
37. Benedict RHB. BVMT-R: Brief Visuospatial Memory Test-Revised. Odessa, FL: Psychological Assessment Resources; 1997.
38. Reitan RM. The Halstead-Reitan Neuropsychological Test Battery. Tucson, AZ: Neuropsychology Press; 1985.
39. Klove H. Grooved Pegboard Test. *Med Clin North Am* 1963;46: 1647–1658.
40. Lai JS, Butt Z, Wagner L, *et al*. Evaluating dimensionality and scalability of a perceived cognitive function item bank for adult cancer patients. Gaithersburg, MD: All PROMIS Conference; 2006.
41. Jacobs SR, Jacobsen PB, Booth-Jones M, *et al*. Evaluation of the functional assessment of cancer therapy cognitive scale with hematopoietic stem cell transplant patients. *J Pain Symptom Manage* 2007;33:13–23.
42. Ringash J, Bezjak A. A structured review of quality of life instruments for head and neck cancer patients. *Head Neck* 2001;23:201–213.

43. Yellen SB, Cella DF, Webster K, *et al*. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13:63–74.
44. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–370.
45. Lezak M, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed. New York: Oxford University Press; 2004.
46. van der Schroeff MP, Derks W, Hordijk GJ, *et al*. The effect of age on survival and quality of life in elderly head and neck cancer patients: A long-term prospective study. *Eur Arch Otorhinolaryngol* 2007;264:415–422.
47. Abendstein H, Nordgren M, Boysen M, *et al*. Quality of life and head and neck cancer: A 5 year prospective study. *Laryngoscope* 2005;115:2183–2192.
48. Chaukar DA, Walvekar RR, Das AK, *et al*. Quality of life in head and neck cancer survivors: A cross-sectional survey. *Am J Otolaryngol* 2009;30:176–180.
49. Yuen HK, Sharma AK, Logan WC, *et al*. Radiation dose, driving performance, and cognitive function in patients with head and neck cancer. *Radiother Oncol* 2008;87:304–307.
50. Yuen HK, Gillespie MB, Barkley RA, *et al*. Driving performance in patients with cancer in the head and neck region: A pilot study. *Arch Otolaryngol Head Neck Surg* 2007;133: 904–909.
51. Yuen HK, Gillespie MB, Day TA, *et al*. Driving behaviors in patients with head and neck cancer during and after cancer treatment: A preliminary report. *Head Neck* 2007;29:675–681.
52. Taylor JC, Terrell JE, Ronis DL, *et al*. Disability in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2004; 130:764–769.
53. El-Deiry M, Funk GF, Nalwa S, *et al*. Long-term quality of life for surgical and nonsurgical treatment of head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2005;131:879–885.
54. Abayomi OK. Pathogenesis of cognitive decline following therapeutic irradiation for head and neck tumors. *Acta Oncol* 2002; 41:346–351.
55. el-Shazly MO, Afify MM, el-Dieb MK. Histopathological study into side-effect toxicity of some drugs used in treatment of cancer. *Arch Exp Veterinarmed* 1989;43:319–326.
56. Vihinen PP, Katka KM, Johansson RK, *et al*. Acute reversible encephalopathy after repeated low-dose cisplatin infusions and concomitant radiotherapy for cancer of the tongue. *Acta Oncol* 2003;42:237–239.
57. Gorman DJ, Kefford R, Stuart-Harris R. Focal encephalopathy after cisplatin therapy. *Med J Aust* 1989;150:399–401.
58. Kondo K, Fujiwara M, Murase M, *et al*. Severe acute metabolic acidosis and Wernicke's encephalopathy following chemotherapy with 5-fluorouracil and cisplatin: case report and review of the literature. *Jpn J Clin Oncol* 1996;26:234–236.
59. Berman IJ, Mann MP. Seizures and transient cortical blindness associated with cis-platinum (II) diamminedichloride (PDD) therapy in a thirty-year-old man. *Cancer* 1980;45:764–766.
60. Cattaneo MT, Filipazzi V, Piazza E, *et al*. Transient blindness and seizure associated with cisplatin therapy. *J Cancer Res Clin Oncol* 1988;114:528–530.
61. Shilling V, Jenkins V, Morris R, *et al*. The effects of adjuvant chemotherapy on cognition in women with breast cancer—Preliminary results of an observational longitudinal study. *Breast* 2005;14:142–150.
62. Cimprich B, So H, Ronis DL, *et al*. Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. *Psychooncology* 2005;14:70–78.
63. Schagen SB, van Dam FS, Muller MJ, *et al*. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer* 1999;85:640–650.
64. Castellon SA, Ganz PA, Bower JE, *et al*. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol* 2004;26:955–969.