6. Rousseau F, Extra JM, Culine S, *et al.* Phase I and pharmacologic study of Taxotere, a new taxol analog. *Eur J Cancer* 1991, 27(suppl. 2), 1238.
7. Tomiak E, Piccart MJ, Kerger J, *et al.* A phase I study of Taxotere (RP 56976, NSC 628503) administered as a one hour intravenous infusion on a weekly basis. *Eur J Cancer* 1991, 27(suppl. 2), 1184.
8. Pazdur R, Newman RA, Newman BM, *et al.* Phase I trial of Taxotere: five-day schedule. *J Natl Cancer Inst* 1992, **84**, 1781–1788.
9. Burris H, Irvin R, Kuhn J, *et al.* Phase I clinical trial of taxotere administered as either a 2-hour or 6-hour intravenous infusion. *J Clin Oncol* 1993, **11**, 950–958.
10. Wanders J, Van Oosterom A, Gore M, *et al.* Taxotere toxicity: protective effects of premedication. *Eur J Cancer* 1993, **29**(suppl. 6), 1148.
11. Schrijvers D, Wanders J, Dirix L, Prove A, Vronk I, Van Oosterom A, Kaye S. Coping with toxicities of docetaxel (Taxotere™). *Ann Oncol* 1993, **4**, 610–611.

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Neurological and Cognitive Impairment in Long-term Survivors of Small Cell Lung Cancer

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Despite its effectiveness in reducing the rate of brain metastases, the role of prophylactic cranial irradiation (PCI) in the management of small cell lung cancer (SCLC) remains controversial because of concern about radiation-induced neurological morbidity. In order to evaluate morbidity and its impact on quality of life 64 patients surviving ≥2 years in remission were recalled for assessment. 52 had received PCI. Most of the patients were well: 95% had performance status ≤1 and nine out of 37 neurological examinations were abnormal. On neuropsychometric testing, only 19% of patients performed at the level expected for their age and intellectual ability on all four tests used. Fifty-four per cent of patients were impaired on two or more of the tests, suggesting a significant degree of measurable cognitive dysfunction. The number of patients who had not received PCI was insufficient for comparative analysis with the number who had, but among those treated with PCI, patients receiving 8 Gy in 1 fraction appeared less impaired than those receiving higher radiation doses in multiple fractions. The study showed that neuropsychometric testing is acceptable to patients, can be administered by non-psychologists in the clinic and is sensitive to otherwise undetected deficits of cognitive function in this patient population. Prospective evaluation of PCI should include neuropsychometric testing.
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INTRODUCTION

THE ROLE of prophylactic cranial irradiation (PCI) in the management of small cell lung cancer (SCLC) remains controversial [1]. Cerebral metastases are a common problem in SCLC with estimates of cumulative risk around 50% at 2 years [2]. When they occur, cerebral metastases cause greater deterioration in performance status and require more time in hospital than is the case for relapse at other sites [3], although it is not clear what influence the presence of actively-treated brain metastases exert on length of survival [4, 5]. Data on the effect of therapeutic irradiation of brain metastases have recently been reviewed [1] with the tentative conclusion that more than two thirds of irradiated patients had some improvement in their symptoms, while 40% achieve clinically complete remission. However, Lucas *et al.* [6] reported complete neurological recovery in only 20% of their series while 53% failed to achieve any significant benefit from their palliative irradiation.

PCI significantly lowers the incidence of cerebral metastases [7], thereby reducing the risk of the associated morbidity and social consequences. Howver, PCI has no demonstrable survival effect and is potentially curative only in the few patients whose non-central nervous system (CNS) disease has been eradicated by systemic treatment [8–10]. Radiation dose–response data for the eradication of subclinical CNS involvement do not exist.

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The published rates of CNS relapse after different PCI schedules are not analysed using life-table methods [11–17]. Commonly used schedules of PCI reduce the average lifetime frequency of cranial relapse from 22 to 6%, but median survival times are short and permanent sterilisation of CNS disease cannot be assumed.

Assessing the value of PCI to SCLC patients involves weighing potential tumour control against the morbidity associated with treatment. Of particular concern is the risk of late radiation injury to the brain [18] which can occur a few months to 10 or more years after therapy. It is irreversible, progressive and sometimes fatal. The most prominent clinical feature of this radiation damage is impaired mental function. The evidence of the extent and degree of neuropsychological morbidity following PCI remains controversial.

The methodological pitfalls of existing PCI studies have recently been reviewed [1] and the findings are summarised in Table 1. Typically, data are derived from case note review augmented by more detailed assessment of a small number of long-term survivors. Studies vary both in the neurological functions tested and the assessment methods used. There are differences both within and between studies in important treatment variables (i.e. neurotoxic chemotherapy, radiation schedule, timing of PCI relative to chemotherapy), making the interpretation of outcome data still more difficult. Relatively few have employed standardised neuropsychological testing [22–25] although this is known to be the most sensitive way of examining brain function [28], and diametrically opposed conclusions have been drawn from different studies [26, 27]. It is generally felt that neuropsychometric methods are time consuming and

Table 1. Assessment of neurotoxicity following treatment for SCLC

Reference no.	Treatment	n*	Assessment method	Findings	Conclusion
19	IC ± PCI ± MTX	16	CNE, EEG, CT brain scan	PCI 9/13—abnormal CT No PCI 2/3—abnormal CT	No contraindications to PCI
20	IC + PCI	16	CNE	NED 4/10 had neurological problems	PCI + nitrosoureas associated with neurological morbidity
21	IC + PCI ± MC	18	I, CNE	14/18 neurological problems (2 institutionalised, 6 grossly impaired)	Significant risk of neurological morbidity after treatment for SLCC
22	IC ± PCI	20	I, CNE, MSE, NPT, CT brain scan	75% neurological complaints 65% abnormal CNE 60% abnormal MSE 75% abnormal NPT 75% abnormal CT	Neurological abnormality common in long-term survivors; more marked with high-dose chemotherapy during cranial irradiation or with large RT fractions
23	IC + PCI	38	CNE, CT brain scan	Brain irradiated 14/20 had abnormal CT scan 3/20 CNS neurotoxicity	Chronic CNS neurotoxicity a problem after brain irradiation and chemotherapy in long-term survivors of SCLC—higher risk with methotrexate and procarbazine
24	IC ± PCI	21	CNE, MSE (I, NPT for 5 patients)	PCI 12/14—memory loss No PCI 0/7—no memory loss 5/5 attention and mental control impaired	Treatment of SCLC is associated with neuropsychological morbidity
25	IC + PCI	12	I, CNE, MSE, NPT, CT brain scan	3 borderline dementia 2/3 post-treatment neurological symptoms 7 neuropsychological impairment + 3 borderline All CT scans showed atrophy	Risk/benefit ratio for PCI unfavourable: failed to prevent brain relapse in 1/5 and associated with neuropsychological impairment for the majority
26	IC + PCI	16	CNE CT brain scan	PCI 7/11—memory deficits and ataxia NO PCI 0/5—no significant CNS toxicity	Question the role of PCI because of high incidence of CNS toxicity and infrequent incidence of isolated CNS recurrence with no PCI
27	IC + PCI	58	Questionnaire ($n = 14$)	PCI 9/48 neurological complications, 2 dementia No PCI 1/10 dementia, 1 brain embolism	PCI effective in reducing frequency of CNS metastases. Adverse effects only for a minority. Continue to use PCI.

IC, induction chemotherapy; PCI, prophylactic cranial irradiation; MTX, methotrexate; EEG, electroencephalography; CT, computed tomography; MSE, mental state examination; NED, no evaluable disease; MC, maintenance chemotherapy; CNE, clinical neurological examination; I, interview; NPT, neuropsychological testing; RT, radiotherapy; SCLC, small cell lung cancer. *Number of long-term survivors of SCLC evaluated.

difficult to perform, making them unsuitable for use with large numbers of patients in multicentre studies.

The aims of this study were: (1) to assess systematically the prevalence of neurological and neuropsychological morbidity in a larger than previously reported sample of long-term survivors of SCLC treated in a number of European centres; and (2) to test the feasibility and usefulness of formal neuropsychological assessment by non-psychologists in general oncological practice.

PATIENTS AND METHODS

SCLC patients alive and in remission >2 years following induction treatment were identified from four databases (EORTC, Manchester, Glasgow and Edinburgh). 64 patients were reviewed: 33 men and 31 women. The median age at assessment was 61 years (range 38–76). The majority (61/64) had limited disease at diagnosis. They were treated using different chemotherapy and radiation protocols. The majority, 52 patients (80%), received PCI of whom 24 patients treated in Manchester received 8 Gy in 1 fraction and the remainder received conventional radiation schedules, most commonly at 30 Gy in 10 fractions (18 patients).

26 patients received PCI concurrently with chemotherapy. The median time from diagnosis to PCI was 189 days. The induction chemotherapy schedules used included a number of well-known neurotoxic agents (i.e. doxorubicin, methotrexate, platinum, lomustine) and 11 patients had received two or more of these drugs.

Demographic data collected included educational level. The majority, 52/64, had completed the legally required period of normal secondary schooling, 12/64 had received tertiary education. No evidence of gross premorbid cognitive impairment was elicited.

Patients were recalled for clinical assessment, neurological examination, computed tomography (CT) scan, neuropsychometric testing and quality of life (QL) assessment.

Neuropsychometric testing

Estimates of premorbid intellectual function could be derived for native English-speaking patients using the National Adult Reading Test (NART) [29].

A brief battery of standard neuropsychometric tests was selected to enable testing to be carried out by non-experts in clinical settings across Europe. Traditional verbal memory tests, e.g. list learning, could not be included because of the lack of validated translations. Tests were selected which use visually presented materials requiring verbal, graphic and constructional responses to sample patients cognitive functioning.

The following tests were administered in all centres. The criteria applied to the interpretation of scores obtained by this patient sample are specified in each case with reference to published comparative data.

(*a*) *Williams delayed recall test* [30]. This is a screening test for memory disorder in which patients' scores can be compared with age-related cut-offs to identify impairment. For patients aged <50 years, Williams interprets a score >10 as indicative of organic impairment. For patients aged 50–60 years and those aged >60 years cut-off scores of 15 and 20, respectively, were applied.

96) *Digit symbol* [31]. This timed coding task from the Wechsler Adult Intelligence Scale (WAIS) assesses psychomotor performance and is sensitive to organic brain damage. Age-scaled scores are available and a score ≤7 is indicative of impairment, i.e. ≥1 S.D. below the mean.

(*c*) *Complex figure test* [32]. This test was devised to investigate perceptual organisation and visual memory in brain-damaged subjects. Taylor's scoring system was applied [33] in which drawings are scored for accuracy in 18 separate units and a wide disparity between copy (C) and recall (R) scores (i.e. R≤C/2) suggests impairment.

(*d*) *Trails A and B* [34]. Performance on these timed tests of visuomotor and conceptual tracking is vulnerable to brain damage and age. Age-related percentile scores are available. Scores ≤25th percentile of age-related norms are regarded as impaired [35].

Quality of life

The Rotterdam Symptom Checklist (RSCL) [36] is a brief self-report questionnaire covering physical symptoms and psychological distress, which has been used in studies of SCLC patients [37]. Items refer to the patient's experience over the past week and are scored on a four-point scale (not at all = 0 to very much = 3). The eight-item functional status scale was also administered.

The Hospital Anxiety and Depression Scale (HADS) [38] is a well-known screening measure and was included because high levels of anxiety and depression are known to impair performance on neuropsychological testing.

Statistical methods

Socio-demographic and treatment variables were examined for their effect on the results of psychometric tests: sex, marital status, education, performance status (0/1 or >1), neurological abnormalities (none/some), RSCL functional status (0/1 or >1), initial chemotherapy (one neurotoxic drug/multiple drugs), PCI regime (no PCI, 1 fraction and >1 fraction), time from diagnosis to PCI (no PCI/≤189 days/>189 days), time from PCI to assessment (no PCI/≤201 weeks/>201 weeks), and five continuous variables: age at assessment, time since diagnosis in years, HADS anxiety, HADS depression, psychological distress.

Association between psychometric test scores and sociodemographic and treatment variables was examined using Wilcoxon (dichotomous variables) and Kruskal–Wallis (categorical variables) tests. For continuous variables, Spearman rank correlation was calculated. The cut-off level for statistical significance was taken as 5%.

Multivariate analysis was limited by the sample size, distribution of variables and the problem of missing values. Neuropsychometric test scores were classified as 'impaired' or 'not impaired' and the probability of impairment was modelled using multiple logistic regression. Backwards stepwise regression was used to determine the final model. Only variables significant at the 5% level were retained in the model at each step. The following variables were investigated: PCI treatment (yes versus no), PCI regimen categorised as standard regimes versus the rest (i.e. no PCI + 8 Gy in one fraction), time since PCI, initial chemotherapy, HADS anxiety and depression, age at assessment, education, sex, marital status. Apart from the PCI regime, they were coded as described before.

RESULTS

Clinical data

Full assessment data were not available for all patients (Table 2). ECOG performance status (PS) [39] was recorded for 38

Table 2. Data set available from 64 patients

	n		n
Clinical testing			
ECOG performance status	38	Clinical examination	38
WHO toxicity	61	CT brain scan	20
Neurological testing			
Delayed recall	64	Complex figure	60
Digit symbol	64	Trails	62
Quality of life			
RSCL	40	HADS	64

RSCL, Rotterdam Symptom Checklist; CT, computed tomography; HADS, Hospital Anxiety and Depression Scale.

patients; 28 had PS = 0, 9 PS = 1 and 1 had PS = 3. Thirty-seven neurological examinations were carried out and 28 were normal. Cognitive deficits were found in 4 patients (11%). 6 patients (16%) had ataxia and 2 (5%) peripheral neuropathy. WHO toxicity [40] assessed in 61 patients was generally mild. Only 5 (8%) had significant (≥ grade 3) toxicity: 4 had permanent alopecia and 1 peripheral neurotoxicity.

Eight of 20 (40%) CT brain scans carried out at the time of the study assessment were normal. The commonest abnormality was atrophy in 9 patients (45%). Periventricular hypodensity, characteristic of late radiation damage was found in 4 patients (20%). Median time from diagnosis to PCI was 189 days and the median time from PCI to assessment was 202 weeks (range 95–513).

Neuropsychometric testing

Estimates of premorbid intelligence quotient (IQ) based on the NART were available for 31 English-speaking patients. Estimated mean IQ was 102 (S.D. = 12, range 85–128).

59 patients completed all four neuropsychometric tests. 48 (81%) were impaired in their performance on at least one test, 54% on two or more (Figure 1).

10 out of 64 (16%) patients completing the delayed recall test gave an impaired performance relative to William's normative data.

Age-scaled scores obtained from the general population on the digit symbol test have a mean of 10 (S.D. = 3). Forty-five per cent of this sample were impaired. The mean age-scaled score achieved was 7.8 (S.D. = 2.7).

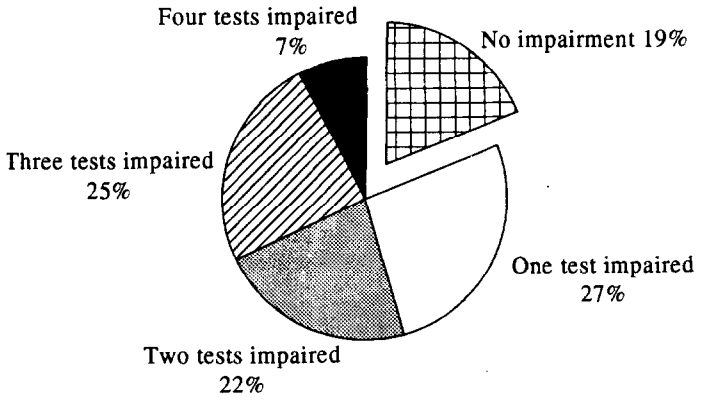

Figure 1. Impairment of performance on neuropsychometric tests.

The average adult score for accuracy of copying the complex figure is 32 and 42% of the sample achieved this or better. However, less than 20% of the sample achieved the average score for anticipated recall which is 22.

Drawing a complex figure from memory caused most difficulty, with 41/60 (68%) impaired, relative to their own ability to copy the figure.

Performance on both trails A and B were slow with median times, respectively, of 65 and 133.5 s. In a normal sample of this age the expected medians would be 48 and 119 s.

No association was seen between clinical abnormalities on neurological examination and psychometric deficits on testing. Patients with CT abnormalities performed less well in trails A ($P = 0.037$). The relationship between patients' performance on testing and educational level, anxiety/depression and known treatment-related risk factors is shown in Table 3. The relatively small number of patients who had not received PCI ($n = 13$) made comparison difficult and no statistically significant differences in scores were observed between those who did and did not have PCI, although on the Williams delayed recall test, for example, all 10 patients with impaired scores had received PCI.

In the logistic regression analysis, scores on Williams delayed recall test depended on therapy and time since diagnosis. Performance was poorer with longer time from PCI. The estimated change in the odds ratio (OR) when time from diagnosis is increased by1 year is 1.53. Patients receiving standard PCI regimes were more likely to be impaired in their performance than those who had no PCI or 8 Gy in a single fractions (Table 4).

Performance on the digit symbol test was related to educational attainment, therapy and mood (Table 5). Patients who were anxious and/or depressed as assessed by the HADS performed poorly. The analysis including depression scores gave the same result as that shown in Table 5 for anxiety. Better educated patients also performed better. With respect to the effect of therapy the number of patients without PCI was too small to observe significant differences in performance between this group and the different PCI regimes, but when only patients who received PCI were included in the analysis patients receiving only 8 Gy in 1 fraction were less likely to give an impaired performance than those receiving higher radiation doses (Williams test OR = 4.91, $P = 0.18$; digit symbol OR = 5.82, $P = 0.02$).

For the complex figure test and trails A there were no variables associated with impairment at the 5% level and for trails B impairment was significantly related to age ($P = 0.01$) and HADS depression ($P = 0.04$).

Quality of life

The RSCL was not administered in Manchester for logistic reasons but HADS data are available for the whole sample. 2 of 40 patients completing the RSCL had no complaints on the physical scale. The mean number of physical complaints reported on the RSCL was five per patient, two or three of which were rated moderate to severe. The most common complaints were also the most likely to be rated moderate to severe. Of 39 patients, 25 (64%) complained of tiredness, 23 (59%) of lack of energy and 21 (54%) each of difficulties with sleeping and with concentration. More than one-third of those completing the RSCL also reported persistent dry mouth, tingling hands and/or feet, pain and burning eyes.

Only 30 patients completed the functional status grid. 18

Table 3. Univariate analysis psychometric test scores with sociodemographic and treatment variables

Test variable	Delayed Williams recall	Digit symbol	Complex figure	Trails A	Trails B
Wilcoxon test*					
Education	1.21	2.37	1.64	−2.69	−1.98
	$P = 0.23$	$P = 0.02$	$P = 0.10$	$P = 0.007$	$P = 0.05$
Initial chemotherapy	1.67	−2.23	−2.21	2.31	1.68
	$P = 0.09$	$P = 0.02$	$P = 0.03$	$P = 0.02$	$P = 0.09$
Kruskal–Wallis test†					
Time from diagnosis to PCI	7.89	3.81	1.13	7.74	6.37
	$P = 0.02$	$P = 0.15$	$P = 0.57$	$P = 0.02$	$P = 0.04$
Time since PCI	6.51	2.57	1.85	2.63	3.16
	$P = 0.04$	$P = 0.28$	$P = 0.40$	$P = 0.27$	$P = 0.21$
PCI regime	9.01	4.58	1.27	6.48	5.94
	$P = 0.01$	$P = 0.10$	$P = 0.53$	$P = 0.04$	$P = 0.05$
Spearman correlation					
HADS anxiety	0.07	−0.37	0.08	0.08	0.08
	$P = 0.58$	$P = 0.01$	$P = 0.54$	$P = 0.53$	$P = 0.54$
HADS depression	0.08	−0.35	0.05	0.16	0.23
	$P = 0.53$	$P = 0.01$	$P = 0.70$	$P = 0.21$	$P = 0.07$

PCI, prophylactic cranial irradiation; HADS, Hospital Anxiety and Depression Scale. *Z statistic. †χ^2 statistic on two degrees of freedom.

Table 4. Multiple regression Williams delayed recall test

Variable	Coefficient	S.E.	P	Odds ratio	95% CI for odds ratio
Time since diagnosis	0.43	0.21	0.05	1.53	100–2.33
PCI regime	2.75	1.14	0.02	15.67	1.61–152.76

PCI, prophylactic cranial irradiation.

(60%) reported no functional impairment while 3 (10%) were significantly impaired, with the remainder reporting some difficulty in daily activities, e.g. housework, climbing stairs.

Patients' scores on the psychological distress subscale of the RSCL were not significantly different from the normative data reported on Watson *et al.* [41] for disease-free cancer patients off treatment (Table 6). The proportions of patients achieving borderline or higher scores (≥8) on the HADS are significantly lower than published data for SCLC patients undergoing or recently completing active treatment [37].

DISCUSSION

The assessment of late morbidity in patient groups with short, median and long-term survival requires multicentre collaboration if sufficient numbers of patients are to be collected for meaningful analysis. This necessitates aggregation of patients treated on different treatment protocols, often with incomplete or suboptimal assessment data. Our study encountered some of the problems reported previously [1].

Patients surviving in remission for a minimum of 2 years following completion of treatment were selected for this study. Following earlier conflicting reports [25, 26], we were interested both in the prevalence of CNS morbidity in this population and in the feasibility of using neuropsychometric methods to assess cognitive impairment in this context. The aim was to provide the background for the prospective controlled trial (now underway) which is needed to address the causative relationships between disease and treatment-related variables and outcome.

Table 5. Multiple regression analysis: digit symbol

Variable	Coefficient	S.E.	P	Odds ratio	95% CI for odds ratio
PCI regime	1.24	0.61	0.04	2.47	1.03–11.67
Eduction	−1.92	0.87	0.03	0.15	0.03–0.83
HADS anxiety	0.18	0.08	0.03	1.19	1.02–1.40

PCI, prophylactic cranial irradiation; HADS, Hospital Anxiety and Depression Scale.

Table 6. Psychological distress

RSCL—psychological scale	*n*	Mean	S.D.	Median
SCLC	40	12.0	5.0	10.0
Control: cancer patients, disease-free off treatment [39]	67	12.4	4.3	12.0

HADS	*n*	Normal	Border line (8–10)	Case level (≥11)
Anxiety	64	81%	8%	11%
Depression	64	85%	11%	4%
Control: anxiety and/or depression—SCLC patients on or recently completed treatment [37]	274	42%	22%	36%

RSCL, Rotterdam Symptom Checklist; SCLC, small cell lung cancer; HADS, Hospital Anxiety and Depression Scale.

Using clinical assessment and standardised, validated scales of toxicity and performance status, the majority of these long-term survivors (75%) reviewed here were well. On clinical examination, cognitive deficits were apparent in 11% with a further 16% having ataxia which could be attributed to late CNS toxicity. This is at the low end of the frequency and severity range reported in the literature [19, 21–26], where up to 85% of patients have been found to have clinically detectable problems [22, 23].

CT abnormalities, mainly cerebral atrophy, were found in 60% of patients studied, which is similar to previously reported figures [19, 22]. The availability of CT scans for only one third of patients in this study precluded further analysis of the relationship between CT and clinical abnormalities. Whilst it is possible that some of the patients without recent CT scans harboured subclinical brain metastases [42], this does not compromise this study's objective of describing the prevalence of CNS morbidity and its relationship to quality of life in this population. The cumulatively rising incidence of CNS relapse will underestimate the true magnitude of this problem in a patient population with limited follow-up [43]. A balance between available patient numbers and ultimate relapse rate needs to be achieved.

The major interest of this study, however, lies in patients' psychometric performance, subjectively reported symptoms and quality of life.

The dominant complaints of persistent tiredness and lack of energy have been previously reported among long-term survivors of other malignancies [44]. More than half (21/39) of the subjectively reported concentration difficulties were not related to performance on objective testing. Studies of subjective and objective assessments of cognitive impairment generally find them only weakly related [45]. Until recently, there has been a lack of objective tests using the skills of everyday life on which the subjective report is based. A closer correspondence is evident when verbal rather than visual memory tasks are employed [46]. This cross-cultural study used visual test materials to reduce problems of verbal translation in order to assess memory and speed of response. Sustained attention was not explicitly tested so the lack of correspondence between patients' self reports of concentration difficulties and their test performance is not altogether surprising. However, this should be considered in the design of any future study. Patients complaining of tiredness were more likely to have impaired neuropsychometric scores, particularly on the delayed recall test. The majority of assessed patients had normal functional ability (ECOG performance status = 0), but 1 patient was in bed for a significant proportion of the time and limited in self-care and mobility. 2 other patients were unable to manage stairs or heavy chores but were otherwise active. A further 9 patients reported some difficulty with everyday activities. Functional impairment was not related to increasing age.

The prevalence of case level anxiety and depression, as detected by the HADS, was significantly lower than reported by Hopwood and Thatcher [37] in a group of SCLC patients still receiving or only just completing treatment. Thirty-six per cent of their 274 patients were found to have an affective disorder, with a further 22% scoring in the borderline range, i.e. possible cases. Although the majority of our sample (82–85%) was not emotionally distressed, the relevance of such screening is seen in the significant relationship between abnormal HADS scores and performance on the Digit Symbol test ($P = 0.01$).

Available measures did not allow a reliable estimate of premorbid IQ for all patients but data obtained suggested a normal distribution of premorbid intellectual ability with an average IQ comparable to that of the general population.

The absence of appropriate controls or of premorbid test data for the patients undergoing testing is a commonly occurring problem in the assessment of neuropsychological deficits. Although test performance can be interpreted with respect to normative standards, these are not always as adequate as one would wish and are commonly expressed in different forms for different tests. In interpreting this data we have used the best comparison standards available in the literature and, where performance is expected to decline with age, we have used age-related comparisons.

On this basis, 16% of the patients showed impaired delayed recall; 37% were impaired on Trails B and 46% on Digit Symbol, and 68% had difficulties in reproducing a complex figure accurately from memory. More than half of the patients (54%) were impaired on half or more of the tests used. Descriptive data, therefore, suggest a significant degree of measurable cognitive dysfunction in this group. This was largely undetectable from conventional clinical assessment and did not adversely impact on patients' quality of life.

Univariate analysis confirmed the complex array of factors which influence psychometric performance, e.g. age, education, emotional state and some treatment-related factors. The number

of patients who had not received PCI was too small for statistically significant differences to be seen between their scores and those of patients receiving PCI, but other treatment-related variables were associated significantly with impairment of higher mental function on testing. The data suggest that patients treated with standard PCI schedules were more likely to suffer neuropsychometric impairment than those receiving 8 Gy or less. The well-known association between radiation fraction size and neurotoxicity may, therefore, be over-riden by the low total dose used in this schedule. It is not clear from this study whether this less toxic regimen is as effective as regimens employing higher doses of radiation but it warrants prospective assessment in a randomised trial against a standard radiation schedule.

Although the input of a trained psychologist is required for the selection of appropriate methods and the interpretation of abnormal results, it is characteristic of psychometric testing that the procedure to be followed is standardised and clearly specified. Thus, non-psychologists can be trained to administer these tests satisfactorily for use in a research setting. The selection of neuropsychological tests for this study was influenced by the need to select brief measurements which could be applied cross-culturally, if necessary on the basis of only written procedural instructions to those administering the tests. This multicentre study showed that neuropsychometric testing is acceptable to patients and feasible for clinical staff to administer under such conditions. The data thus derived was considerably more complete and more informative than standard clinical assessment.

It has long been recognised that the overall value of PCI in the management of SCLC can only be determined by a prospective randomised clinical trial. This study demonstrates that it is feasible to incorporate neuropsychometric testing which is sensitive to otherwise undetectable morbidity. Four large multicentre prospective studies of PCI are underway [1] and prospective assessment of neurotoxicity and quality of life is an intrinsic part of two of them.

1. Kristjansen PEG, Kristensen CA. The role of prophylactic cranial irradiation in the management of small cell lung cancer. *Cancer Treatment Rev* 1993, **19**, 3–16.
2. Pedersen AG. Diagnosis of CNS metastases from SCLC. In Hansen HH, ed. *Lung Cancer: Basic and Clinical Aspects*. Boston, Martinus Nijhoff Publishers, 1986, 153–182.
3. Felleti R, Souhami R, Spiro SG, *et al.* Social consequences of brain or liver relapse in small cell carcinoma of the bronchus. *Radiother Oncol* 1985, **4**, 335–339.
4. Van Hazel GA, Scott M, Eagan RT. The effect of CNS metastases on the survival of patients with small cell cancer of the lung. *Cancer* 1983, **51**, 933–937.
5. Hirsch FR, Paulson OB, Hansen HH, Olesen Larsen S. Intracranial metastases in small cell carcinoma of the lung. *Cancer* 1983, **51**, 529–533.
6. Lucas CF, Robinson B, Hoskin PJ, Yarnold JR, Smith IE, Ford HT. Morbidity of cranial relapse in small cell lung cancer and the impact of radiation therapy. *Cancer Treat Rep* 1986, **70**, 565–570.
7. Bleehen NM, Bunn PA, Cox JD, *et al.* Role of radiation therapy in small cell anaplastic carcinoma of the lung. *Cancer Treat Rep* 1983, **67**, 11–19.
8. Rosen ST, Makuch RW, Lichter AS, *et al.* Role of prophylactic cranial irradiation in prevention of central nervous system metastases in small cell lung cancer. *Am J Med* 1983, **74**, 615–624.
9. Aroney RS, Aisner J, Wesley MN, *et al.* Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma. *Cancer Treat Rep* 1983, **67**, 675–682.
10. Rosenstein M, Armstrong J, Kris M, *et al.* A reappraisal of the role of prophylactic cranial irradiation in limited small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1992, **24**, 43–48.
11. Cox JD, Petrovich Z, Paid C, Stanley K. Prophylactic cranial irradiation in patients with inoperable carcinoma of the lung. *Cancer* 1978, **42**, 1135–1140.
12. Beiler DD, Kane RC, Berneth AM, Cashdollar MR. Low dose elective brain irradiation in small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 1979, **5**, 941–945.
13. Aisner J, Whiteacre M, Van Echo DA, Wiernik PH. Combination chemotherapy for small cell carcinoma of the lung: Continuous versus alternating non cross resistant combinations. *Cancer Treat Rep* 1982, **66**, 221–230.
14. Jackson DV, Richards II F, Cooper MR, *et al.* Prophylactic cranial irradiation in patients with inoperable carcinoma of the lung. *J Am Med Assoc* 1987, **237**, 2730–2733.
15. Maurer HL, Tulloh M, Weiss RB, *et al.* A randomised combined modality trial in small cell carcinoma of the lung. *Cancer* 1980, **45**, 30–39.
16. Seydel HG, Creech R, Pagano M, *et al.* Combined modality treatment of small cell undifferentiated carcinoma of the lung. A cooperative study of the RTOG and ECOG. *Int J Radiat Oncol Biol Phys* 1981, **7** (suppl. 1), 41.
17. Hirsch FR, Hansen HH, Paulson OB. Development of brain metastases in small cell anaplastic carcinoma of the lung. In Kay J, Whitehouse J, eds. *CNS Complications of Malignant Disease*. New York, Macmillan, 1979, 175–184.
18. Valk PE, Dillon WP. Radiation injury of the brain. *Am J Radiol* 1991, **156**, 689–706.
19. Catane R, Schwade JG, Yarr I, *et al.* Follow up neurological evaluation in patients with small cell lung carcinoma treated with prophylactic cranial irradiation and chemotherapy. *Int J Radiat Oncol Biol Phys* 1981, **11**, 105–109.
20. Ellison N, Bernath A, Kane R, Porter P. Disturbing problems of success: clinical status of long term survivors of small cell lung cancer (SCLC). *ASCO Abstr* 1982, C-579, 149.
21. Looper JD, Ginhom LH, Garcia SA, Homback NB, Vincent B, Williams SD. Severe neurologic problems following successful therapy for small cell lung cancer. *ASCO Abstr* 1984, C-903, 231.
22. Johnson BE, Becker B, Goff WB, *et al.* Neurologic neuropsychologic and computer cranial tomography Scan abnormalities in 2 to 10 year survivors of small cell lung cancer. *J Clin Oncol* 1985, **3**, 1659–1667.
23. Lee JS, Umsa Wasdi T, Lee YY, *et al.* Neurotoxicity in long term survivors of small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1986, **12**, 313–321.
24. Twijnstra A, Boon PJ, Lormans ACM, Ten Velde GPN. Neurotoxicity of prophylactic cranial irradiation in patients with small cell carcinoma of the lung. *Eur J Cancer Clin Oncol* 1987, **23**, 983–986.
25. Laukkanen E, Klonoff H, Allan B, Graeb D, Murray N. The role of prophylactic brain irradiation in limited stage small cell lung cancer: clinical, neuropsychologic and CT sequelae. *Int J Radiat Oncol Biol Phys* 1988, **14**, 1109–1117.
26. Fleck JF, Ginhom LH, Lauer RC, Schultz SM, Miller ME. Is prophylactic cranial irradiation indicated in small cell lung cancer? *J Clin Oncol* 1990, **8**, 209–214.
27. Lishner M, Feld R, Payne DG, *et al.* Late neurological complications after prophylactic cranial irradiation in patients with small cell lung cancer: the Toronto experience. *J Clin Oncol* 1990, **8**, 215–221.
28. Lezak MD. Neuropsychological asssessments in behavioural toxicology—developing techniques and interpretive issues. *Scand J Work Environ Health* 1 1984, **10**, 25–29.
29. Nelson HE. *The National Adult Reading Test (NART)*. Manual NFER. Windsor, Nelson.
30. Williams M. The measurement of memory in clinical practice. *Br J Soc Clin Psychol* 1986, **7**, 19–34.
31. Wechsler D. *Wechsler Adult Intelligence Scale: Manual Psychological Corporation*. New York, 1955.
32. Osterrieth PA. Le test de copie d'une figure complexe. *Arch de Psychologie* 1944, **30**, 206–356.
33. Taylor EM. Scoring system for the Rey complex figure. In Lezak MD, ed. *Neuropsychological Assessment*, 2nd edition. New York, Oxford University Press, 1983, 400–401.
34. Reitan RM. Validity of the trail making test as an indication of organic brain damage. *Perceptual Motor Skills* 1958, **8**, 127–130.
35. Lezak MD. *Neuropsychological Assessment*, 2nd edition. New York, Oxford University Press, 1983, 556–559.
36. de Haes JCJM, Van Knippenberg FCE, Neijt P. Measuring psychological and physical distress in cancer patients: structure and

application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990, 62, 1034–1038.
37. Hopwood P, Thatcher N. Preliminary experience with quality of life: evaluation in patients with lung cancer. *Oncology* 1990, 4, 158–162.
38. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983, 67, 361–370.
39. Zubrod CG, Scheiderman M, Frei E, *et al.* Cancer—appraisal of methods for the study of chemotherapy of cancer in men: thiophosphoramide. *J Chron Dis* 1960, 11, 7–33.
40. World Health Organisation. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, WHO Offset Publ. 48, 1979.
41. Watson M, Law M, Maguire GP, *et al.* Further development of a quality of life measure for cancer patients: the Rotterdam Symptom Checklist (revised). *Psycho Oncol* 1992, 1, 35–44.
42. Hirsch FR, Paulson OB, Hanson HH. Intracranial metastases in small cell carcinoma of the lung. *Cancer* 1982, 50, 2433–2437.
43. Souhami RL, Law K. Longevity in small cell lung cancer. *Br J Cancer* 1990, 61, 584–589.
44. Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D. Psychosocial problems among survivors of Hodgkin's disease. *J Clin Oncol* 1986, 4, 805–814.
45. Lincoln NB, Tinson DJ. The relation between subjective and objective memory impairment after stroke. *Br J Clin Psychol* 1989, 28, 61–65.
46. Sunderland A, Harris JE, Baddeley AD. Do laboratory tests predict everyday memory? A neuropsychological study. *J Verbal Learning and Verbal Behav* 1983, 22, 341–357.

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Paclitaxel (Taxol) Induces Cumulative Mild Neurotoxicity

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Paclitaxel (Taxol), a new antineoplastic drug, has been reported to be neurotoxic at doses above 200 mg/m² per course. It is uncertain whether neurotoxicity is related to cumulative amounts of paclitaxel. Neuropathy was prospectively assessed in 18 patients with breast cancer, receiving between two and eight courses of 135 or 175 mg/m² of paclitaxel. Vibratory perception thresholds (VPT) and tendon reflex scores were proportionally related to the corresponding cumulative amounts of paclitaxel ($P = 0.002$; $P = 0.0003$). The amounts of paclitaxel administered between the first and last assessments (175–1225 mg/m²) were related to concomitant changes in VPT ($P = 0.034$). Paclitaxel had no clear neurotoxic threshold; if present, it lies below 540 mg/m². Rather, VPT appeared to increase 0.1 μm per 400 mg/m² over the entire range of 175–1225 mg/m² of paclitaxel. Clinical neuropathy prevailed in 0/8 patients at screening and in 5/10 patients at the final assessment ($P = 0.029$). Neuropathy never exceeded grade 1. Thus, although neurotoxicity of paclitaxel is frequent and cumulative, it remains mild or subclinical up to at least 1400 mg/m² administered over eight cycles.

Key words: breast carcinoma, neuropathy, neurotoxicity, paclitaxel, vibration threshold
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INTRODUCTION

THE ROLE of paclitaxel (Taxol) as a new antineoplastic agent has not been fully established, but it seems promising in the treatment of a variety of tumours, including ovarian, breast, head and neck and non-small cell lung cancer [1–3]. The main side-effects of paclitaxel are anaphylactoid reaction, granulocytopenia and polyneuropathy. The neuropathy has been characterised as being predominantly sensory, and both axonal and demyelinating [4]. Neuropathy has usually been observed at doses per course of 200–600 mg/m² or higher [1, 3–7]. It has been suggested that neuropathy is rare at below 200 mg/m² per course [8, 9] and that paclitaxel can safely be administered up to 250 mg/m² per cycle [6].

It thus appears that paclitaxel may have cumulative neurotoxicity. In various malignant diseases, neuropathy frequently was found at the highest doses [10]. Others reported that the occurrence of neuropathy appears to be associated with the area under the concentration–time curve of paclitaxel [11]. In one report, the neuropathy was worse with cumulative amounts higher than 600 mg [7]. In this study, however, patients were treated not only with paclitaxel, but also with cisplatin, which is well-known to be neurotoxic up to 4 months after cessation of