ORIGINAL ARTICLE

Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer

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ABSTRACT

Introduction: The toxic effects of prophylactic cranial irradiation (PCI) and platinum-based chemotherapy on cognition in the lung cancer population have not yet been well established. In the present study we examined the longitudinal neuropsychological and brain structural changes observed in patients with lung cancer who were undergoing these treatments.

Methods: Twenty-two patients with small cell lung cancer (SCLC) who underwent platinum-based chemotherapy and PCI were compared with two control groups: an age- and education-matched group of healthy controls (n = 21) and a group of patients with non-SCLC (NSCLC, n = 13) who underwent platinum-based chemotherapy. All groups were evaluated using a neuropsychological battery and multimodal structural magnetic resonance imaging: T1-weighted and diffusion tensor imaging at baseline (before PCI for SCLC and chemotherapy for NSCLC) and at 3 months after treatment. T1 voxel-based morphometry and tract-based spatial statistics were used to analyze microstructural changes in gray matter (GM) and white matter (WM). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core Questionnaire was also completed.

Results: Patients with SCLC exhibited cognitive deterioration in verbal fluency over time. Structural magnetic resonance imaging showed decreases in GM at 3 months in the right subcortical regions, bilateral insular cortex, and superior temporal gyrus in patients with SCLC compared with both control groups. Additionally, patients with SCLC showed decreases in GM over time in the aforementioned regions plus in the right parahippocampal gyrus and hippocampus, together with changes in the WM microstructure of the entire corpus callosum. These changes had a limited impact on responses to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core Questionnaire, however. Patients with NSCLC showed no cognitive or brain structural differences after chemotherapy.

Conclusions: This longitudinal study documents moderate neuropsychological deficits together with notable brain-specific structural changes (in GM and WM) in patients with SCLC after chemotherapy and PCI, suggesting that chemotherapy and especially PCI are associated with the development of cognitive and structural brain toxic effects.

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Introduction

Small cell lung cancer (SCLC) constitutes nearly 15% of all newly diagnosed cases of lung cancer. Standard therapy for patients with SCLC includes platinum-based chemotherapy and thoracic radiation.[1] Despite treatment advances, SCLC is difficult to cure as it has a high tendency toward development of distant metastasis, especially brain metastases. The use of prophylactic cranial irradiation (PCI) has reduced the incidence of brain metastases, prolonged disease-free survival, and improved overall survival (OS) in patients with SCLC who previously responded to chemoradiation therapy.[2,3] Specifically, the addition of PCI to the standard therapy has an absolute benefit in prolonging survival without disease progression at 6 months (8.8% and 7.9% for limited and extensive SCLC, respectively) and in increasing OS (5.4% at 3 years for limited SCLC and 13.8% at 1 year for extensive SCLC).[2,3] Thus, to date, only those patients with SCLC with a dismal prognosis are not eligible for PCI. Conversely, patients with non-SCLC (NSCLC) usually undergo similar platinum-based chemotherapy but not PCI.[4] In the NSCLC population, PCI has been shown to increase disease-free survival without an improvement in OS.[5]

With recent increases in the number of long-term cancer survivors, the potential contribution of chemotherapy and radiotherapy to the development of neurocognitive deficits and its impact on quality of life are increasingly being recognized.[6–8] However, chemotherapy-related cognitive research focused on the lung cancer population has been scarce. Early studies found that patients with NSCLC exhibited transient cognitive deficits soon after chemotherapy.[9–14] Other studies, focusing exclusively on patients with SCLC, found that nearly 60% to 90% of patients were cognitively impaired 1 to 5 months after concluding chemotherapy.[9–11,15,16] Although these results are suggestive, little is known about the underlying structural or functional brain alterations that might follow chemotherapy for lung cancer.

Additionally, the cognitive toxic effects of PCI in patients with SCLC have not been well established. Studies focusing on PCI-associated cognitive neurotoxic effects are limited and contradictory.[9,10,15,17–26] To the best of our knowledge, only a few short-term (1.5 months) prospective neuroimaging studies have been published, showing widespread changes in white matter (WM) shortly after PCI therapy.[11,27] However, the impact of these neurotoxic effects on self-reported quality of life measures described in patients with SCLC is minor and not significant at 3 months after PCI. [6]

The aim of our study was to examine the PCI-induced longitudinal cognitive toxic effects together with the structural changes in gray matter (GM) and WM in a group of patients with SCLC who were treated with platinum-based chemotherapy and PCI compared with those in an age- and education-matched group of healthy controls (HCs). Additionally, to control for the cognitive effects of chemotherapy, a group of patients with NSCLC who underwent the same platinum-based chemotherapy schedule was also recruited.

Materials and Methods

Patients

Patients were prospectively recruited from December 2010 to January 2014 from the Lung Cancer Unit-Institut Català d'Oncologia Duran i Reynals-Hospital Universitari de Bellvitge (n = 28) and from the Radiation Oncology Department-Institut Català d'Oncologia Badalona-Hospital Germans Trias i Pujol (n = 7). Patients were eligible if they had a histologically proven diagnosis of either SCLC or NSCLC; were between 40 and 70 years of age; and had no severe concomitant systemic illness, psychiatric disorder with a negative impact on cognitive function, or contraindication to magnetic resonance imaging (MRI). Patients were excluded if they had anti-Hu antibodies in their serum (to exclude paraneoplastic anti-Hu encephalitis),[28] evidence of brain metastasis on MRI, or disease progression. Patients with SCLC (n = 22) eligible to receive PCI at a total dose of 25 Gy (2.5 Gy per fraction) were enrolled 1 month after completion of chemotherapy and before PCI (baseline assessment). Patients with NSCLC (n = 13) eligible to receive platinum-based chemotherapy were enrolled in the study before the initiation of chemotherapy (baseline assessment). Both groups were evaluated at 3 months after completion of PCI in the group with SCLC and chemotherapy in the group with NSCLC (3-month assessment). The baseline analysis of this cohort (the group with SCLC 1 month after chemotherapy, the group with NSCLC before receiving chemotherapy, and the HC group) has been previously published.[29]

The NSCLC group was selected as a control for the evaluation of chemotherapy effects on patients with SCLC because patients with NSCLC presented a common organ location, had similar demographic and clinical features, and underwent the same platinum-based chemotherapy without PCI. Age- and education-matched HCs (n = 21) meeting the same inclusion (except for cancer diagnosis) and exclusion criteria were recruited through community advertisements. Vascular risk factors were collected and

patients were categorized as low-risk (no or one risk factor) or high-risk (two or more risk factors) groups.[11] Platinum-based chemotherapy type (cisplatin or carboplatin) and dose (in mg/m^2) received was also compiled. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL). One-way analysis of variance (ANOVA) and chi-square tests were used to test group differences with a critical p threshold of 0.05.

Standard Protocol Approvals

The study protocol was approved by the local ethical committee, and all participants were given and signed a written informed consent document.

Neuropsychological and Quality of Life Assessment

Patients were evaluated at baseline using the following battery: the vocabulary subtest of the Spanish version of the Wechsler Adult Intelligence Scale-III to estimate intelligence quotient, a verbal memory test (the Rey Auditory Verbal Learning Test [AVLT]), a test to measure visuospatial abilities and visual memory (the copy and delayed recall measures of the Rey-Osterreith Complex Figure Test [ROCF]), the Verbal Fluency Test (phonemic and semantic), a processing speed test (parts A and B of the Trail Making Test [TMT]), and the Beck Depression Inventory (BDI). At the 3-month evaluation, a different version of the ROCF and the Rey AVLT, together with the Verbal Fluency Vest (phonemic and semantic), TMT A and B, and BDI, were administered. Quality of life measures included the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core Questionnaire (QLQ-C30) and were administered at baseline and at the 3-month evaluations.[30]

Raw cognitive test scores were compared with the validated Spanish normative values, corrected for age and education, and converted into z values. The QLQ-C30 was scored according to methods described in the QLQ-C30 scoring manual (http://groups.eortc.be/qol/manuals). A repeated measures ANOVA with time (at baseline and at 3 months) as a within-subject factor and group (SCLC, HC, and NSCLC) as a between-subject factor was used to assess changes in cognitive test z values and quality of life results. Neuropsychological results are reported uncorrected for multiple testing, although the main group differences surviving a Bonferroni correction are also indicated (12 ANOVAs, $p < 0.00416$). Post hoc independent t tests between groups (calculated for those neuropsychological variables showing a main effect of group in the repeated measures ANOVA) are also reported after Bonferroni correction (three tests: SCLC versus NSCLC, SCLC versus HC, and HC versus NSCLC).

MRI Scan Acquisition

Participants underwent imaging on a 3-tesla MRI scanner (the Siemens Magnetom Trio Tim Syngo MR B17, Siemens, Erlangen, Germany) with a 32-channel phased-array head coil. High-resolution structural images were obtained using a T1-weighted magnetization-prepared, rapid-acquired gradient echo sequence (240 slices sagittal, repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, 1 mm isotropic voxels). A whole brain diffusion MRI sequence using diffusion tensor spin echo planar imaging was acquired as well (voxel size: 2.5 × 2.5 × 2.5 mm, matrix: 96 × 96 × 55, 2.5-mm-thick slices, no gap, TE = 98 ms, TR = 9600 ms, echo planar imaging factor = 96, field of view = 240 mm, bandwidth = 1022 Hz, echo spacing = 1.08 ms, b value = 1000 s/mm^2) in one single run of 64 diffusion-weighted directions and one non–diffusion-weighted volume. Image data quality for both T1 and diffusion images was visually assessed and no artifacts were detected. Finally, a fluid-attenuated inversion recovery sequence was also acquired (64 slices, 2.0 mm thick, TE = 145 ms, TR = 9000 ms, voxel size 1.0 × 0.9 × 2.0 mm) to exclude asymptomatic brain metastasis.

T1 Image Processing and Analysis. The methodology used was similar to that used in our previous works.[29,31–33] Morphometric analysis was carried out using the longitudinal processing stream in the Voxel-Based Morphometry 8 (VBM8) toolbox (http://dbm.neuro.uni-jena.de/vbm/) under the Statistical Parametric Mapping 8 (SPM8) software package (Version 8, Wellcome Department of Imaging Neuroscience, London, UK) and MATLAB (Version 7, Mathworks, Inc., Natick, MA). Follow-up T1 structural images were coregistered to baseline T1 images for each subject, bias-corrected, and segmented into GM, WM, and cerebrospinal fluid compartments using the Montreal Neurologic Institute (MNI) T1-weighted template and tissue probability maps. Then, the resultant subject-specific tissue probability maps (GM) were subjected to diffeomorphic anatomical registration using exponentiated Lie algebra to achieve spatial normalization by using a nonlinear registration to the MNI space. Diffeomorphic anatomical registration using exponentiated Lie algebra normalization alternates between computing an average template of GM segmentation from all subjects and warping all subjects' GM tissue maps into a better alignment with the template created.[31] Normalized images were modulated by their Jacobian determinants to identify regional differences in the volume of GM; "modulation" was used to try to compensate for the effect of spatial normalization.[33] Normalized and modulated images were smoothed using an isotropic Gaussian spatial filter (full width at half maximum = 8 mm) to accommodate for residual interindividual variability.

The individual smoothed GM volume (GMV) images were entered into a second-level analysis, specifically a three groups (SCLC, HC, and NSCLC) two times (baseline and 3 months) flexible factorial design within SPM8. In this step, an explicit mask with a threshold of 0.4 (i.e., only those voxels having a 40% probability of being GM were included) was also used to select only the most homogeneous voxels. After omnibus testing, pairwise *t* tests were performed at the group level to analyze within-group changes over time (baseline – 3 months). For all contrasts, a $p \leq 0.05$ familywise error (FWE)-corrected threshold at the cluster level was used with an auxiliary threshold of $p < 0.001$ at the voxel level and 50 voxels of spatial extent.

Additionally, to study the effect of cognitive deterioration on GMV, we carried out a Pearson's correlation analysis between the neuropsychological testing scores showing significant differences (see the Results section) and the individual mean GMV maps of patients. Specifically, a mask for each significant cluster yielded by the GMV group analysis was defined and applied to each individual image. For each participant, the mean GMV value within the aforementioned mask was then calculated at baseline and at 3 months. Finally, four correlations were computed: the difference in GMV between the 3-month follow-up and baseline was correlated with the difference in the four neuropsychological variables of interest that showed significant main group effects (phonemic fluency, TMT A, AVLT immediate recall [A1], and ROCF first copy) (see the Results section). These correlations were Bonferroni-corrected for multiple comparisons.

DTI Processing and Analysis. Diffusion tensor imaging (DTI) preprocessing was started by correcting for eddy current distortions and head motion using the Functional MRI of the Brain (FMRIB) group's Diffusion Toolbox (FDT;FSL5.0.1, www.fmrib.ox.ac.uk/fsl/). The gradient matrix was rotated using the *fdt_rotate_bvecs* software included in the FMRIB Software Library distribution. Brain extraction was performed using the Brain Extraction Tool, which is also part of the FMRIB Software Library software. The analysis was reconstructed the diffusion tensors by using the linear least-squares algorithm included in Diffusion Toolkit 0.6.2.2 (Ruopeng Wang, Van Wedeen, trackvis.org/dtk, Martinos Center for Biomedical Imaging-Massachusetts General Hospital). Finally, fractional anisotropy (FA) maps for each subject were calculated at baseline and 3 months. Tract-based spatial statistics (TBSS) of FA was performed.[34] Briefly, FA maps from all participants and sessions were registered to the FMRIB58_FA template using the nonlinear registration tool FNIRT (FMRIB's Nonlinear Image Registration Tool) and then averaged to create a mean FA volume. A mean FA skeleton was derived, and each participant's aligned FA data were then projected onto this skeleton. Once all skeletons were created, follow-up images were subtracted from the baseline images, creating baseline – 3 month skeletons.

To compute voxelwise statistics, these baseline – 3 months skeletons were entered into a one-way ANOVA with group as the between factor (group = SCLC, HC, NSCLC). The analysis implemented is equivalent to a three groups (SCLC, NSCLC, and HC) two times (baseline and 3 months) design. After interaction testing, pairwise *t* tests were performed at the group level to analyze within-group changes over time. Results are reported as an FWE-corrected value ($p < 0.05$) using threshold-free cluster enhancement and a nonparametric permutation test with 5000 permutations.[35]

Additionally, to study the effect of cognitive deficits on WM microstructure,[30] we carried out a Pearson's correlation analysis between the neuropsychological testing scores showing significant differences and individual mean FA values of the patients. Specifically, a mask covering the areas showing significant differences in the FA group analysis was defined (setting the threshold at a FWE-corrected $p < 0.01$; the mask included one cluster with maxima at the genu of the corpus callosum, see the Results section). For each participant, the mean FA value within the aforementioned mask was then calculated at baseline and at 3 months. Finally, as in the GMV analysis, four correlations were computed: the difference in FA between the 3-month follow-up and baseline was correlated with the difference in the neuropsychological variables of interest that showed significant main group effects (phonemic fluency, TMT A, AVLT A1, and ROCF first copy; see the Results section). These correlations were Bonferroni-corrected for multiple comparisons.

Results

Patient Characteristics

The study design is graphically explained in Figure 1. The final groups consisted of 22 patients in the SCLC group, 13 in the NSCLC group, and 21 in the HC group (characteristics of the entire cohort are described in Table 1). There were no significant differences between groups in terms of age, gender, education, or grouped vascular risk factors. However, smoking history showed a significant difference between patients with lung cancer and the HCs ($p < 0.0001$), but no differences were observed between the two cancer groups (SCLC and NSCLC, $p > 0.37$). The rates of type 2 diabetes mellitus (DM) and dyslipidemia were significantly different between groups. Type 2 DM showed a higher incidence in patients with NSCLC cancer compared with both the SCLC ($p < 0.03$) and HC ($p < 0.01$) groups. Conversely, dyslipidemia showed a lower incidence in the SCLC

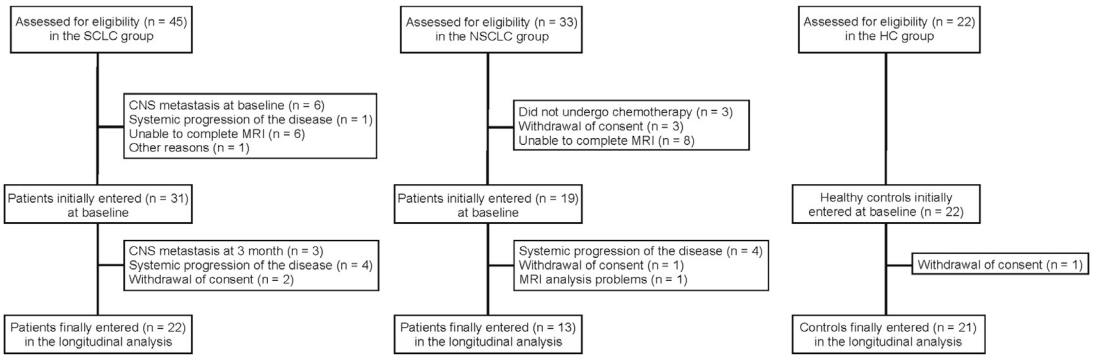

Figure 1. CONSORT flow diagram.

group compared with the NSCLC ($p < 0.03$) and HC ($p < 0.02$) groups. There were no significant differences concerning disease- or treatment-related characteristics between the two lung cancer groups.

Neuropsychological Assessment

No significant group × time interaction in any of the measures evaluated was found. However, there were main group effects for phonemic fluency [F(2,53) = 6.02,

Table 1. Baseline Demographics and Vascular Risk Factors of the Entire Cohort and Disease- and Treatment-Related Characteristics of the Patients

	SCLC Group (n = 22)	NSCLC Group (n = 13)	HC Group (n = 21)	*p* Value
Mean age ± SD, y	59.64 ± 4.84	59.92 ± 6.14	62.86 ± 7.91	0.22
Gender, n (%)				
Male	16 (73)	12 (92)	19 (90.5)	0.18
Female	6 (27)	1 (8)	2 (9.5)	
Median years of education (range)	8 (4-17)	10 (0-15)	8 (6-19)	0.61
Estimated mean verbal IQ ± SD	8.73 ± 3.55	9.54 ± 4.41	9.57 ± 3.94	0.22
Smoking, n (%)	22 (100)	12 (92)	11 (52)	**<0.01**
Alcohol, n (%)	7 (32)	3 (23)	10 (48)	0.31
HT, n (%)	6 (27)	5 (38.5)	8 (38)	0.70
T2DM, n (%)	3 (14)	6 (46)	2 (9.5)	**0.02**
Dyslipidemia, n (%)	4 (18)	7 (54)	11 (52)	**0.03**
Vascular risk factors, n (%)				
Low-risk (0-1)	12 (54.5)	2 (15)	9 (43)	0.07
High-risk (≥2)	10 (45.5)	11 (85)	12 (57)	
Median KPS (range)	80 (70-100)	90 (80-100)		0.08
Histological diagnosis, n (%)				
SCLC	22 (100)			
NSCLC				
Adenocarcinoma		7 (54)		
Squamous cell carcinoma		5 (38)		
Nonclassified		1 (8)		
Tumor stage, n (%)				
Limited disease	18 (82)			
Extensive disease	4 (18)			
IIB		1 (8)		
IIIA		5 (38)		
IIIB		7 (54)		
Chemotherapy type, n (%)				
CDDP-based	18 (82)	11 (85)		0.41
CBDCA-based	4 (18)	2 (15)		
Median no. chemotherapy cycles (range)	4 (1-6)	4 (3-4)		0.11
Mean CDDP dose ± SD, mg/m^2	287.5 ± 77	267.5 ± 45		0.44
Thoracic radiation therapy, n (%)	20 (91)	11 (85)		0.57

Note: Statistically significant results are marked in bold.
SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; HC, healthy control; SD, standard deviation; IQ, intelligence quotient; HT, hypertension; T2DM, type 2 diabetes mellitus; KPS, Karnosfky Performance Scale; CDDP, cisplatin; CBDCA, carboplatin.

Table 2. Neuropsychological Results

	SCLC Group			NSCLC Group			HC Group			RM ANOVA Main Group Effect
			Paired *t* Test			Paired *t* Test			Paired *t* Test	
	Baseline	At 3 mo	*p* Value	Baseline	At 3 mo	*p* Value	Baseline	At 3 mo	*p* Value	*p* Value
BDI ≥13, n (%)[a]	6 (12)	4 (9)	0.89	1 (2)	2 (4)	0.72	3 (6)	3 (6)	0.75	0.95
Verbal fluency										
Semantic fluency	0.06 (1.06)	-0.41 (1.02)	**0.03**	0.18 (0.94)	-0.26 (1.34)	0.32	0.40 (0.78)	0.16 (0.68)	0.18	0.19
Phonemic fluency	-0.32 (1.09)	-0.83 (1.17)	**0.03**	-0.03 (1)	-0.54 (1.24)	0.20	0.51 (0.68)	0.21 (0.95)	0.06	**0.004**[b,c]
Processing speed and executive functions										
Trail Making Test A	-0.33 (0.78)	-0.20 (1.14)	0.49	-0.18 (1.08)	0.09 (1.51)	0.61	0.35 (0.92)	0.62 (0.88)	0.06	**0.025**[b]
Trail Making Test B	-0.55 (0.94)	-0.12 (1.53)	0.05	-0.37 (1.20)	0 (1.29)	0.52	-0.03 (0.77)	0.35 (0.94)	**0.02**	0.29
Visuospatial abilities										
ROCF first copy	0.33 (0.76)	0.21 (1.18)	0.66	1.61 (1.22)	1.05 (1.45)	0.25	1.50 (1.04)	1.07 (1.14)	0.22	**0.0001**[c,d]
Visual memory										
ROCF delayed	0.60 (0.81)	0.40 (1.04)	0.33	0.61 (0.72)	0.54 (0.88)	0.76	0.77 (0.71)	1.07 (1.14)	**0.002**	0.17
Verbal memory[a]										
AVLT immediate recall (A1)	4.14 (1.93)	3.91 (1.72)	0.52	4.31 (1.44)	4.38 (1.32)	0.87	5.05 (1.69)	5.29 (1.79)	0.60	**0.037**[c]
AVLT immediate recall (B1)	4.68 (1.21)	3.86 (1.52)	**0.04**	4.54 (2.26)	3.77 (1.30)	0.22	5 (1.30)	5 (1.55)	1	0.08
AVLT learning curve (A5–A1)	5.82 (1.97)	4.95 (2.48)	0.17	5.46 (2.07)	5.77 (2.49)	0.70	5.38 (2.11)	5.57 (2.46)	0.70	0.94
AVLT short-delay recall (A6)	6.32 (2.51)	6.86 (3.44)	0.24	7.23 (3.47)	7.38 (2.06)	0.86	7.95 (3.04)	8.67 (2.69)	0.19	0.11
AVLT long-delay recall (A7)	6.82 (2.72)	6.64 (3.06)	0.77	6.69 (3.32)	6.54 (2.40)	0.86	7.95 (3.54)	8.19 (2.44)	0.67	0.18

Note: Statistically significant results are marked in bold. The paired *t* test and RM ANOVA between-group results are reported. p Values are reported Bonferroni corrected for groups comparisons but uncorrected for multiple testing.

[a]Except for items marked with a *b* (raw score), all results are *z* values and presented as means (standard deviations).

[b]Differences were significant between the SCLC and HC groups.

[c]Differences were significant between the SCLC group and both the HC and the NSCLC groups.

[d]Main group differences that were significant after Bonferroni correction.

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; HC, healthy control; RM ANOVA, repeated measures analysis of variance; mo, month; BDI, Beck Depression Inventory; ROCF, Rey-Osterrieth Complex Figure Test; AVLT, Auditory Verbal Learning Test.

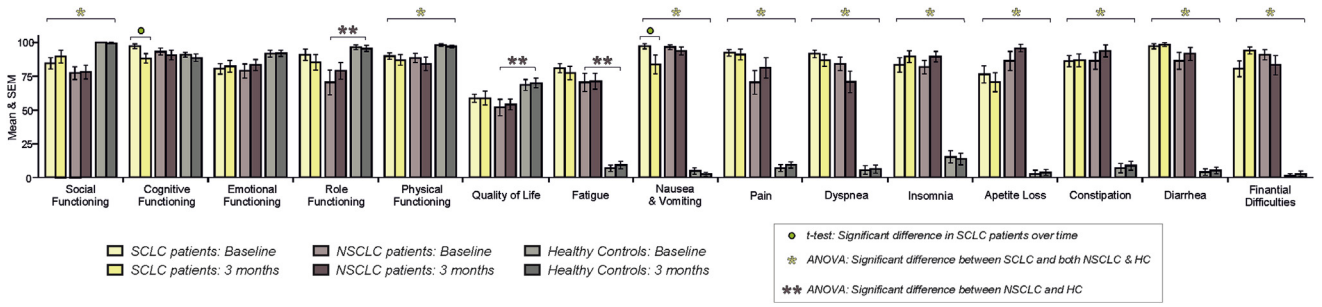

Figure 2. Quality of Life Questionnaire—Core Questionnaire (QLQ-C30) results.

$p < 0.004$], TMT A [$F(2,51) = 3.97$, $p < 0.025$], AVLT A1 [$F(2,53) = 3.51$, $p < 0.037$], and ROCF first copy [$F(2,52) = 9.85$, $p < 0.001$]. The Bonferroni post hoc analysis revealed that the SCLC group performed worse than the HC group in verbal fluency (phonemic fluency), processing speed (TMT A), and verbal working memory (AVLT A1). Moreover, the SCLC group also performed worse than the HCs and patients with NSCLC in visuospatial abilities (ROCF first copy). Further paired t test comparisons in each group showed that patients with SCLC deteriorated over time in verbal fluency (semantic and phonemic fluency, $p < 0.03$), whereas no significant changes were observed in the NSCLC group. The HC group showed an improvement over time in visual memory and processing speed because of learning effects (see Table 2). Group effects for phonemic fluency and ROCF first copy were still significant after application of a Bonferroni correction (12 ANOVAs, $p < 0.0041$). Additionally, no significant differences between groups were found for the difference in BDI scores between the baseline and the follow-up sessions [Kruskal-Wallis test, $H(2) = 0.10$, $p > 0.95$].

Quality of Life Measures

Overall, statistically significant group differences were observed for the QLQ-C30 in the corresponding ANOVA for most of the evaluated items (see Supplementary Table e-1 and Fig. 2). However, no significant group × time interaction was encountered. Further explorative paired t test comparisons in each group showed that the SCLC group deteriorated over time in terms of cognitive functioning ($p < 0.05$) and nausea ($p < 0.03$) whereas no significant changes over time were observed in the NSCLC and HC groups.

Structural Neuroimaging: VBM

Longitudinal assessment: group × time interaction. The VBM analysis revealed a significant group × time interaction for GMV in several brain regions (see Supplementary Table e-2 and Fig. 3). Specifically, patients with SCLC exhibited a significant decrease in GMV in the right thalamus, right caudate, bilateral insular cortex, and superior temporal gyrus at 3 months follow-up in comparison with the HC group. A significant decrease in GMV in the bilateral caudate and insula, left superior and middle temporal gyrus, and right cerebellum at 3 months follow-up was observed in patients with SCLC compared with patients with NSCLC. No other significant results were found in the group × time interaction analysis.

Longitudinal Assessment: Within-Group Analysis. Within-group longitudinal analysis yielded significant results in the SCLC group. Patients with SCLC showed a significant decrease in GMV over time in similar regions as in the aforementioned group × time interaction (right thalamus, right caudate, bilateral insular cortex, and superior and middle temporal gyrus). Furthermore, GMV decreases in the right parahippocampal gyrus and hippocampus were also found for the SCLC group. No significant differences were observed in the within-group longitudinal analysis in the HC and NSCLC groups. Additionally, the correlations between the average GMV values of all the clusters showing differences over time in the SCLC group and the four cognitive tests showing a main group effect were not significant.

Diffusion Tensor Imaging: TBSS Analysis

Longitudinal Assessment: Group × Time Interaction. No significant differences were found in the group × time interaction in the TBSS analysis. However, when using a more permissible p value ($p = 0.10$ FWE-corrected) and also holding at a $p = 0.001$ uncorrected threshold, we found a trend toward FA decreases mainly in the genu and body of the corpus callosum (CC) for the SCLC group compared with both the HC and NSCLC groups at 3 months follow-up. These interactions should be taken with caution as, although plausible, they only reflect a trend that did not survive a corrected threshold.

Longitudinal Assessment: Within-Group Analysis. The within-group longitudinal analysis showed a significant decrease ($p < 0.05$, FWE-corrected) in FA (changes in WM microstructure) in the CC at 3 months after PCI in the SCLC group. No significant differences were observed

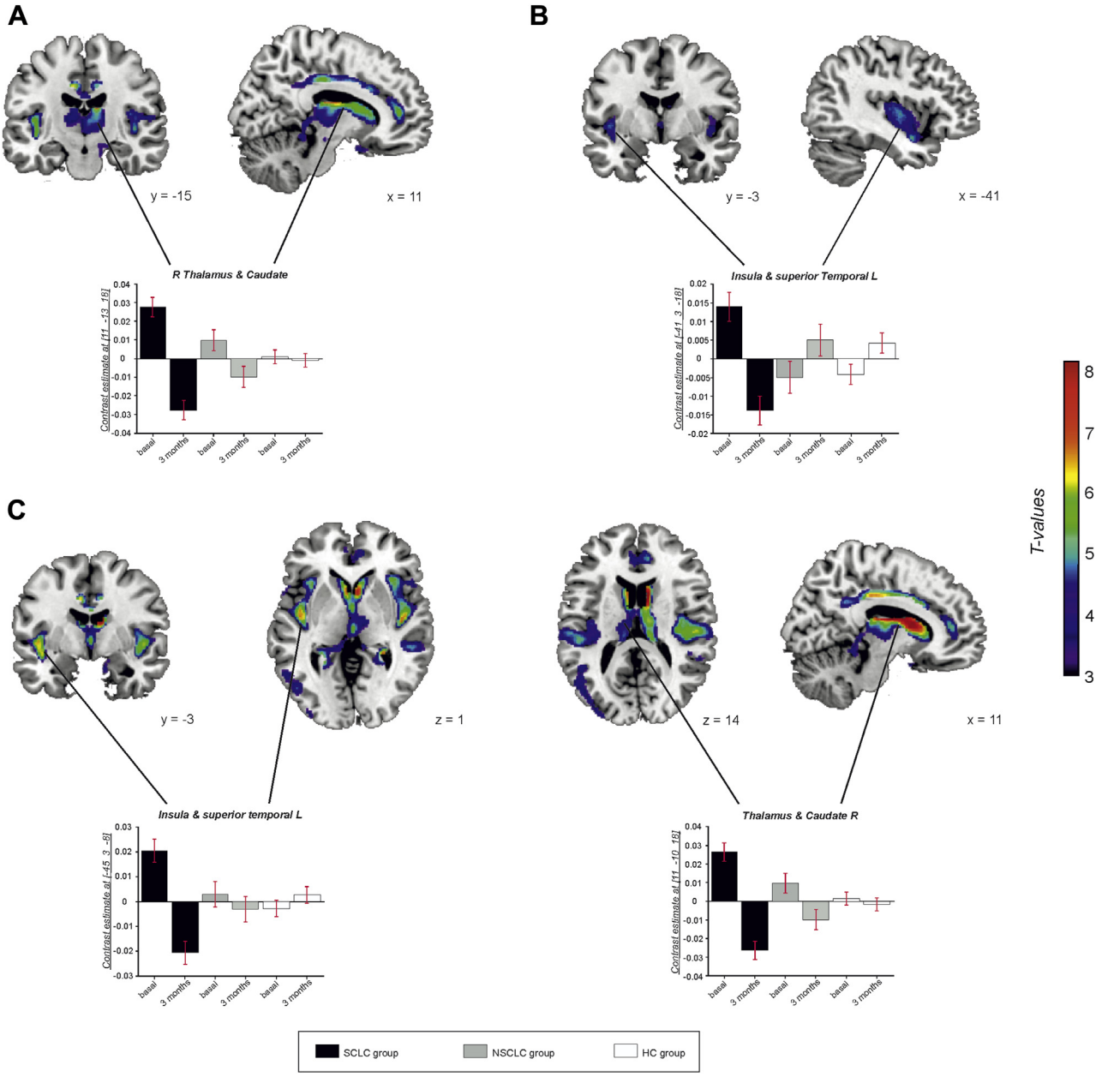

Figure 3. Regional gray matter volume (GMV) differences in the longitudinal voxel-based morphometry analysis. Results are displayed with a $p < 0.05$ familywise error–corrected threshold at the cluster level (using an auxiliary $p < 0.001$ threshold at the voxel level and 50 voxels of spatial extent) on a canonical T1 structural magnetic resonance imaging template. Neurological convention is used. Montreal Neurologic Institute coordinates are indicated at the bottom right of each slice. Bar plots show contrast estimates (amplitude of the effect at a given voxel) for all groups and times with standard error of the mean. Contrast estimates represent the mean-corrected parameter estimates of all effects of interest. Because of the mean correction, the bar plot shows the deviations of the contrast estimates from their mean. Therefore, a negative value does not necessarily mean that the contrast estimate is negative; rather, it may just be lower than the mean of all contrast estimates. (*A*) Group × time interaction analysis comparing patients with small cell lung cancer (SCLC) with healthy controls. This analysis revealed significant GMV decreases at 3 months in the right thalamus, right caudate, bilateral insular cortex, and superior temporal gyrus of patients with SCLC compared with healthy controls. (*B*) Group × time interaction analysis comparing patients with SCLC with patients with non-SCLC. This analysis revealed significant GMV decreases at 3 months in the bilateral caudate and insula, left superior and middle temporal gyrus, and right cerebellum in patients with SCLC compared with patients with non-SCLC. (*C*) Within-group longitudinal analysis of patients with SCLC. The analysis revealed differences in the GMV in the right thalamus, right caudate, bilateral insular cortex, and superior and middle temporal gyrus, as well as in the right parahippocampal gyrus and hippocampus of patients with SCLC over time (at baseline – 3 months).

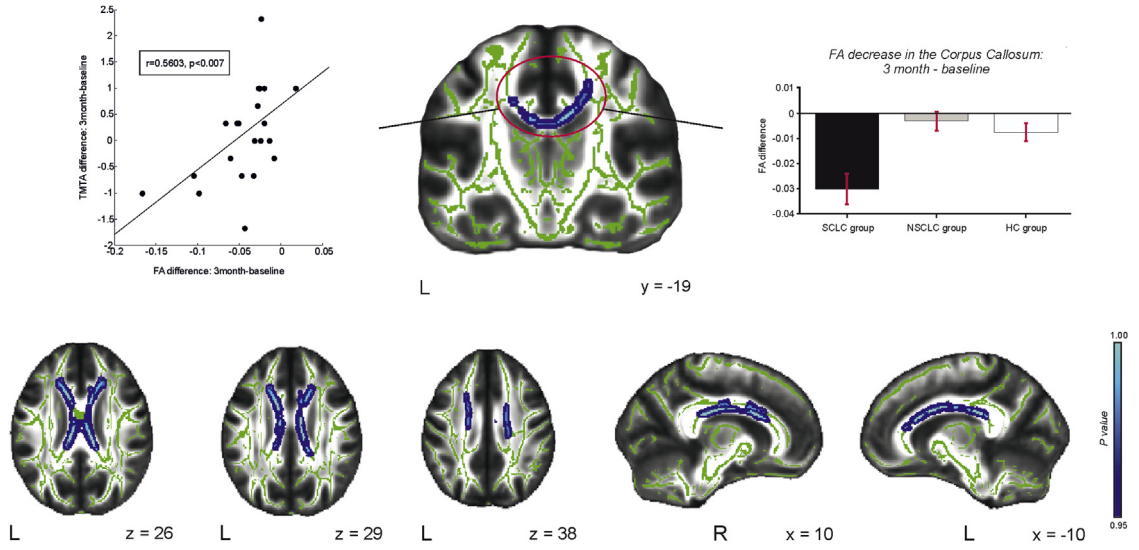

Figure 4. Regional diffusion tensor imaging differences for fractional anisotropy (FA) in the longitudinal (at 3 months – baseline) tract-based spatial statistics analysis for the small cell lung cancer (SCLC) group. The within-group longitudinal analysis in the SCLC group revealed that FA decreases in the entire corpus callosum at 3 months compared with baseline. Statistical maps (*blue*) showing reduced FA are displayed over a mean skeleton (*green*) and the FMRIB58_FA template for better visualization of the white matter pathways. The scatter plot displays the relationship between the areas showing differences in FA (maxima at the genu of the corpus callosum; baseline – 3 months) in the SCLC group and the Trail Making Test A (TMTA, 3 months – baseline). Bar plots show the mean difference (3 months – baseline) in FA within the main cluster at the corpus callosum for all groups with standard error of the mean. Results are shown at an FWE-corrected threshold ($p < 0.05$). Neurological convention and Montreal Neurologic Institute coordinates are indicated at the bottom right of each slice.

in the within-group longitudinal analysis for the HC or NSCLC groups.

Additionally, the correlation between the average FA values of the only cluster at the CC in the SCLC group and the four cognitive tests showing a main group effect revealed a significant positive correlation ($r = 0.56$, $p < 0.007$, Bonferroni-corrected for the four correlations computed) between FA decreases and deteriorated processing speed (TMT A). This correlation shows that slow processing speed was associated with changes in WM microstructure (lower FA values) in the CC (see Fig. 4).

Discussion

This is the first longitudinal study, to the best of our knowledge, to document neuropsychological and structural brain changes in the GM and WM of a group of patients with SCLC who were treated with PCI. Our results revealed that the SCLC group exhibited moderate cognitive worsening at 3 months after PCI treatment that was accompanied by large decreases in GM mainly in the caudate, insula, and superior temporal gyrus bilaterally in comparison with both the HC and NSCLC groups. Additionally, patients with SCLC showed GM decreases over time in the aforementioned regions and in the right parahippocampal gyrus and hippocampus. Regarding microstructural changes in WM, patients with SCLC showed less FA in the entire CC over time. These imaging findings were found only in patients with SCLC after radiation, suggesting that platinum-based chemotherapy and PCI therapy are associated with brain-specific structural changes in the SCLC population.

Cranial radiation toxicity has often been associated with cognitive dysfunction and radiation-induced leukoencephalopathy in patients with brain metastases and primary central nervous system lymphoma. Cognitive symptoms related to cranial radiation include deficits in verbal memory and executive functions, together with a progressive subcortical dementia that usually accompanies gait alterations and extrapyramidal symptoms.[36] Recent neuroimaging studies using DTI both in patients with brain tumors and in the SCLC population showed decreased FA in the CC after radiation.[32,37] In fact, the CC has recently been described as one of the most radiation-sensitive structures of the brain,[38] and the amount of microstructural damage to the WM fibers of the CC has been directly related to the cognitive deterioration found in long-term SCLC survivors.[32] Hence, the WM changes in the CC exhibited in the present study provide evidence that the damage to WM microstructure seen in long-term SCLC survivors occurs as early as 3 months after radiation therapy, and that these WM changes also correlated with cognitive deficits in processing speed.

Patients with SCLC present some of the potential risk factors that have been associated with the development of radiation-induced cognitive impairment: they are

usually elderly, have been previously treated with chemotherapy, and frequently carry vascular risk factors.[11,36] To control for these risk factors, we included an age and education matched HC group as well as an NSCLC group. Concerning vascular risk factors, as expected, a higher proportion of patients with lung cancer had a history of smoking than in the HC group. Smoking has been associated with an increased risk of cognitive decline or even dementia, as well as with structural brain differences in both WM and GM.[39] Additionally, smoking has also been associated with cerebrovascular damage induced by oxidative stress. This is of relevance especially because this pathological condition is also characterized by a loss of blood-brain barrier integrity. Both the increase in oxidative damage and the loss of blood-brain barrier integrity have been related to the pathogenesis of chemotherapy- and cranial radiation–induced cognitive impairment.[40,41] Additionally, DM and dyslipidemia occurred at a higher incidence in patients with NSCLC than in patients with SCLC, thus not appearing to be a confounding factor in the changes observed in SCLC.

In agreement with some previous neuropsychological studies in patients with lung cancer,[6,25,26,42–45] and although no significant group × time interaction was found, the SCLC group did exhibit a moderate decrease in cognitive functioning at follow-up, especially in verbal fluency (no differences between time points were found for the other groups). These relevant but minor cognitive deficits observed in the SCLC group complement our previous results in the same cohort,[28] in which almost 40% of the SCLC group examined 1 month after platinum-based chemotherapy and before PCI exhibited cognitive impairment. On the basis of these results, we hypothesize that significant cognitive changes may occur very soon after chemotherapy, leaving little room for further deterioration 3 months after PCI.

In regard to quality of life measures and in line with previous literature,[6] the main group differences between SCLC and both NSCLC and HC were only found in relation to selected symptoms and functioning scales (see Fig. 2).

Although there was no significant group × time interaction, patients with SCLC exhibited a limited but significant self-reported cognitive worsening 3 months after PCI. These results are in concordance with the results of a previous longitudinal study comparing quality of life measures in a SCLC population treated with PCI with those in a group of patients with SCLC who did not receive PCI. The results of this study showed that both groups exhibited a global worsening in quality of life and cognitive functioning at 3 months follow-up, but with small differences between groups.[6]

Concerning structural neuroimaging findings, we observed brain-specific structural damage after PCI that was not restricted to WM tracts but also involved GM structures. The GM alterations observed in this study were similar to those recently described by our group in an SCLC population 1 month after platinum-based chemotherapy and before PCI[29] (see Supplementary Fig e-1 for the imaging overlap between the studies). On the basis of these results, we suggest that the GM damage observed in the present study would be initially related to chemotherapy, especially affecting the bilateral insula, parahippocampal regions, and thalamus and would be then superimposed by PCI-specific damage in more medial and subcortical brain regions.

Thus, PCI therapy seems to expand the cognitive and GM structural deficits already observed after chemotherapy in patients with SCLC, but adding brain-specific WM damage exclusively in the CC at 3 months follow-up. One possible explanation for this difference is that although chemotherapy may induce chronic brain changes in the GM of the SCLC population, it seems to trigger transient WM changes that are replaced by specific radiation-induced WM damage. Indeed, animal models have associated the lower capillary density and blood flow of the CC with severe WM degradation after radiation.[46] This explanation is also supported by the fact that similar WM changes are seen in long-term SCLC survivors.[32] Interestingly, these chemotherapy-related changes did not appear after platinum-based chemotherapy in the NSCLC group. We speculate that this distinct response to chemotherapy might be related to an increased susceptibility of SCLC to platinum-based toxicity. The mechanisms underlying these toxic adverse effects are not fully understood. We hypothesize that the inflammatory response induced by SCLC might facilitate the access into the brain of both cancer-related cytokines[47] and platinum-based drugs by modifying some characteristics of the BBB.[48]

Brain-specific damage after cranial irradiation is a major issue, and many recent clinical trials have used selective sparing of critical brain regions in an effort to reduce late cognitive toxicities. One of the most frequently used strategies for reducing neurotoxicity while maintaining the efficacy of cranial radiation therapy is to avoid either the limbic circuit or the neural stem cell–specific areas, such as the subventricular zone and the subgranular zone within the hippocampus.[49] Recently, conformal avoidance of the hippocampus during whole brain radiation therapy failed to prevent cognitive decline, although it did show a significant reduction of cognitive deficits.[50] Yet, on the basis of our neuroimaging results, sparing only the limbic system or the neural stem cell areas may not prevent the development of neurocognitive deficits in patients with SCLC as the main affected areas appear to extend well beyond the aforementioned regions.

In conclusion, the SCLC group exhibited cognitive deficits together with brain-specific structural changes after platinum-based chemotherapy and PCI, compared with both the HC and NSCLC groups with a limited impact on their quality of life. Although chemotherapy might have a role in the cognitive and decreases in GM changes seen in patients with SCLC at baseline, our longitudinal results suggest that PCI-induced changes are mainly responsible for the brain structure and neuropsychological findings observed in the present study. On the basis of our results, patients with SCLC should be informed about the survival benefits of PCI and about the potential minor, but negative, effects of this therapy on cognitive functioning, with emphasis on their limited impact on quality of life. However, because of the permanent long-term cognitive and structural brain effects observed in our previous study of SCLC survivors treated with PCI,[32] we think that it is crucial to better identify upfront those patients in whom brain metastases will develop and those patients in whom they will not, so that we can safely avoid PCI in specific subgroups of patients and thereby elude the brain-toxic effects.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2015.12.110.

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