Brain Imaging and Behavior
DOI 10.1007/s11682-015-9393-5

ORIGINAL RESEARCH

Brain damage following prophylactic cranial irradiation in lung cancer survivors

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Abstract Long-term toxic effects of prophylactic cranial irradiation (PCI) on cognition in small cell lung cancer (SCLC) patients have not yet been well-established. The aim of our study was to examine the cognitive toxic effects together with brain structural changes in a group of long-term SCLC survivors treated with PCI. Eleven SCLC patients, who underwent PCI≥2 years before, were compared with an age and education matched healthy control group. Both groups were evaluated using a neuropsychological battery and multimodal structural magnetic resonance imaging. Voxel-based morphometry and Tract-based Spatial Statistics were used to study gray matter density (GMD) and white matter (WM) microstructural changes. Cognitive deterioration was correlated with GMD and Fractional Anisotropy (FA). Finally, we carried out a single-subject analysis in order to evaluate individual structural brain changes. Nearly half of the SCLC met criteria for cognitive impairment, all exhibiting a global worsening of cognitive functioning. Patients showed significant decreases of GMD in basal ganglia bilaterally (putamen and caudate), bilateral thalamus and right insula, together with WM microstructural changes of the entire corpus callosum. Cognitive deterioration scores correlated positively with mean FA values in the corpus callosum. Single-subject analysis revealed that GMD and WM changes were consistently observed in nearly all patients. This study showed neuropsychological deficits together with brain-specific structural differences in long-term SCLC survivors. Our results suggest that PCI therapy, possibly together with platinum-based chemotherapy, was associated to permanent long-term cognitive and structural brain effects in a SCLC population.

Keywords Prophylactic cranial irradiation · Cognitive deterioration · Small cell lung cancer · Diffusion tensor imaging · Voxel-based morphometry

Electronic supplementary material The online version of this article (doi:10.1007/s11682-015-9393-5) contains supplementary material, which is available to authorized users.

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Published online: 27 May 2015

Introduction

Small cell lung cancer (SCLC) constitutes nearly 15 % of all newly diagnosed cases of lung cancer (Johnson et al. 1990; Riaz et al. 2012). Despite treatment advances, SCLC is difficult to cure as it has a high tendency to develop distant metastasis. Nearly 10 % of patients present brain metastases at the time of the initial diagnosis and an additional 40–50 % will develop brain metastases during the course of their disease (Johnson et al. 1990). In this setting, the use of prophylactic cranial irradiation (PCI) has demonstrated a reduction in the incidence of brain metastases, a prolonged disease-free survival and an improvement in overall survival in limited and extensive SCLC patients who have previously responded to chemoradiation therapy (Auperin et al. 1999; Meert et al. 2001; Slotman et al. 2007). Moreover, PCI has also been explored in non-SCLC populations, demonstrating an increased disease-free survival interval but without an improvement in overall survival (Lester et al. 2005).

Cranial irradiation is known to carry transient or permanent neurotoxic effects that can lead to subcortical dementia (Giglio and Gilbert 2003; Sheline et al. 1980). The pathophysiology underlying these radiation-induced toxic effects is not yet fully understood. Traditionally, cranial irradiation has been related to the impairment of brain endothelial and oligodendrocyte progenitor cells, all together resulting in acute demyelination and late onset white matter necrosis. However, recent preclinical studies revealed that radiation injury involves a complex and dynamic interaction between multiple cell types. Specifically, brain radiation seems to decrease hippocampal neurogenesis, inducing changes in neuronal function (particularly in synaptic plasticity) and eliciting neuroinflammatory responses (Greene-Schloesser et al. 2013).

Long-term cognitive toxic effects of PCI in SCLC patients have not yet been well-established. Studies focused on PCI-associated cognitive neurotoxic effects are limited and contradictory (Arriagada et al. 1995; Ball and Matthews 1995; Crossen et al. 1994; Cull et al. 1994; Fonseca et al. 1999; Gondi et al. 2013; Gregor et al. 1997; Grosshans et al. 2008; Komaki et al. 1995; Parageorgiou et al. 2000; Roman and Sperduto 1995; van Oosterhout et al. 1995; Welzel et al. 2008a). Retrospective neuropsychological studies demonstrated cognitive deficits in SCLC survivors who underwent PCI between 2 and 13 years prior to assessment (Crossen et al. 1994). However, some prospective studies demonstrated that a high proportion of SCLC patients were impaired at baseline before PCI, presented a decline 1–2 months following PCI (Welzel et al. 2008a) but seemed to recover in the long-term follow-up (Arriagada et al. 1995; Gregor et al. 1997; Grosshans et al. 2008; Komaki et al. 1995; Parageorgiou et al. 2000; van Oosterhout et al. 1995; Welzel et al. 2008a). Furthermore, most of these studies presented limited neuropsychological evaluations (Arriagada et al. 1995; Ball and Matthews 1995; Crossen et al. 1994; Cull et al. 1994; Fonseca et al. 1999; Gondi et al. 2013; Gregor et al. 1997; Komaki et al. 1995; Roman and Sperduto 1995; van Oosterhout et al. 1995), they did not conduct magnetic resonance imaging (MRI) in all cases to rule out asymptomatic brain metastases (Ball and Matthews 1995; Crossen et al. 1994; Cull et al. 1994; Komaki et al. 1995; Roman and Sperduto 1995; van Oosterhout et al. 1995) and no control groups, such as chemotherapy-treated or healthy matched individuals, were included (Arriagada et al. 1995; Ball and Matthews 1995; Crossen et al. 1994; Cull et al. 1994; Fonseca et al. 1999; Gregor et al. 1997; Grosshans et al. 2008; Komaki et al. 1995; Parageorgiou et al. 2000; Roman and Sperduto 1995; van Oosterhout et al. 1995).

Newly developed neuroimaging techniques, such as voxel-based morphometry (VBM) (Ashburner and Friston 2000; Sarkamo et al. 2014; Simo et al. 2015) and Diffusion Tensor Imaging (DTI) (Molinuevo et al. 2014; Smith et al. 2006; Tuomiranta et al. 2014), can identify subtle gray (GM) and white (WM) matter changes and are able to detect structural differences before other gross variation become evident using conventional MRI. For this reason, these new MRI techniques are currently used to study cognitive functioning in cancer (Kaiser et al. 2014; Simo et al. 2013) and neurodegenerative diseases (Acosta-Cabronero et al. 2010). Concerning PCI studies, to the best of our knowledge, only some short-term (1 or 1.5 months) prospective neuroimaging studies using DTI in an SCLC population— which found that SCLC patients exhibited widespread WM changes following PCI therapy— have been published (Welzel et al. 2008b; Chawla et al. 2015).

The aim of our study was to describe the long-term cognitive toxic effects, together with their relation to GM and WM microstructural changes, in a long-term SCLC survivor group treated with PCI.

Materials and methods

Patients

Patients with histologically or cytologically confirmed SCLC (either limited or extensive disease) diagnosed between January 2005 and December 2010 at ICO Duran i Reynals-Hospital Universitari de Bellvitge and ICO Girona-Hospital Doctor Josep Trueta were reviewed. Patients were eligible if a) they had received a platinum-based chemotherapy regimen and/or thoracic radiation, with documented evidence of disease stabilization or tumor response, and b) if they had undergone PCI at least 2 years before the start date of the study (Fig. 1). Exclusion criteria were severe concomitant illness or psychiatric disorder with a negative impact on cognitive functioning, or any contraindication to undergo an MRI scan. Age and education-matched healthy controls (HC, $n=11$) who

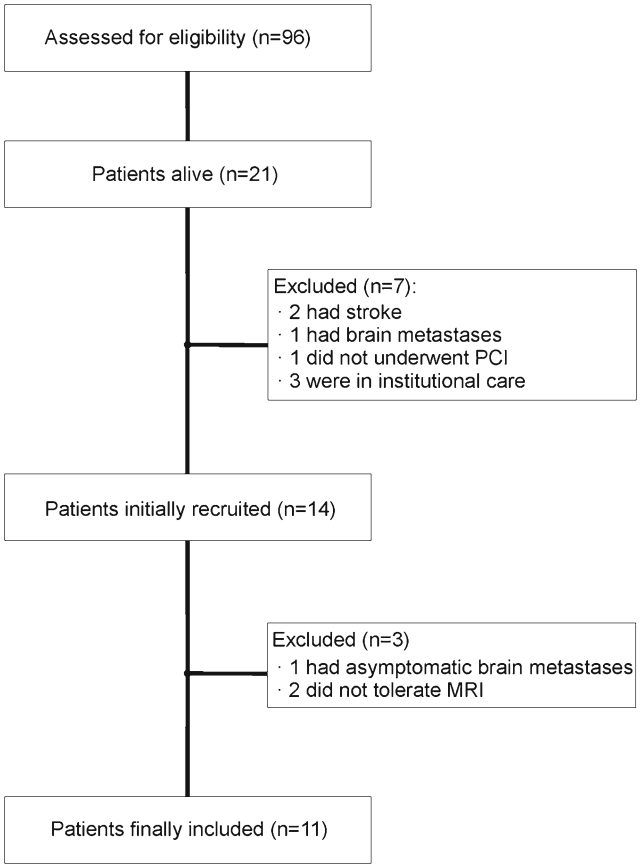

Fig. 1 Flow chart. Scheme of the enrollment of patients in the present study. *The three patients who were in institutional care met criteria for cognitive impairment based on their medical files

met the same inclusion (except for cancer diagnosis) and exclusion criteria were recruited through community advertisements.

Demographic, clinical, cancer- and cancer therapy-related variables were collected. Because the presence of extrapyramidal symptoms have been associated with subcortical dementia and might contribute to a potential disability (Engelman et al. 2015), we studied the presence of extrapyramidal symptoms and signs in our patient sample by using the Hoehn and Yahr scale (Hoehn and Yahr 1967). This staging system ranges from 1 to 5; in our sample, patients without parkinsonism features were classified as 0. Furthermore, patients were classified into two groups based on vascular risk factors: low-risk (if the patient had none or one risk factor) and high-risk (if the patient had two or more risk factors) (Welzel et al. 2008b). In addition, due to the fact that different PCI doses had been used (Le Pechoux et al. 2009), SCLC patients were classified into two groups depending on the total accumulated radiation dose received: low-dose (25Gy total dose in 2.5Gy daily fractions) and high-dose (including 30 or 36Gy total dose in 3 or 2Gy daily fractions). The study protocol was approved by the local Ethical Commission and written informed consent was obtained from all participants.

Neuropsychological assessment

All patients were evaluated using a dementia screening test, the Mattis Dementia Rating Scale-2 (Mattis 1988), and a complete battery of eight neuropsychological tests, which were classified in the following cognitive domains: (i) general estimation of intelligence quotient (Spanish version of the WAIS-III -Wechsler Adult Intelligence Scale III-: Vocabulary subtest) (Wechsler 1997), (ii) language processing (Boston Naming Test) (Kaplan et al. 1983), (iii) verbal fluency (Phonemic and Semantic variants) (Peña-Casanova 2005), (iv) processing speed and executive functions (Trail Making Test part A and part B, and part B minus part A) (Reitan 1992), (v) attention and working memory (WAIS-III digit span subtest) (Wechsler 1997), (vi) visuospatial abilities (first copy of the Rey-Osterrieth Complex Figure or ROCF) (Pena-Casanova et al. 2009), (vii) visual memory (delayed memory of the ROCF) (Meyers and Meyers 1995), and (viii) verbal memory (Auditory Verbal Learning Test -AVLT-, which is divided in: (i) immediate recall (trial A1 and B), (ii) learning curve (trial A1 to A5), and (iii) long-term memory recall (short-delay -trial A6- and long-delay -trial A7-) (Schmidt 1996). The Beck Depression Inventory test was also administered (Beck et al. 1961).

Raw cognitive test scores were compared with the validated Spanish normative values, corrected for age and education, and converted into z-scores. Cognitive impairment was defined as a Mattis Dementia Rating Scale-2 raw score below 123 (Mattis 1988) or one of all of the aforementioned tests with z scores ≥ two standard deviations below the sample mean or two tests with z scores ≥ one and half standard deviations below the sample mean (Wefel et al. 2004). Beck Depression Inventory was considered abnormal if the score was ≥13 (Lasa et al. 2000).

Statistical analysis

All statistics were performed with SPSS 18.0 (SPSS, Chicago, IL). Fisher's exact or U-Mann–Whitney analysis were used to assess clinical and disease-related differences between groups. A pairwise *T*-test analysis was used to assess differences between groups concerning neuropsychological results. For the evaluation of the AVLT learning curve, a repeated measures ANOVA design was used. Statistical significance for all the mentioned tests was assessed at $P<0.05$.

MRI acquisition

Images were acquired on a 3T MRI scanner (Siemens Magnetom Trio) with a 32-channel phased-array head coil. All images were acquired over a 1-month and a 6-month interval for patients and controls, respectively. Conventional high-resolution structural images were obtained using an MPRAGE

- Magnetization Prepared Rapid Gradient Echo - sequence (240 slices, TR=2300 ms, TE=2.98 ms, 1 mm isotropic thickness). A DTI sequence was acquired using a diffusion tensor spin echo-planar imaging sequence (2.5×2.5×2.5 mm voxel size, matrix of 96×96, 55 slices with no gap, TE=98 ms, TR=9600 ms, Echo Planar Imaging factor=96, field of view=240 mm, bandwidth=1022 Hz, *b*-value=1000 s/mm). One single run of 64 diffusion-weighted directions with one non-diffusion-weighted volume was acquired.

Finally, in order to rule out potential brain metastases and to control for silent strokes, a Fluid Attenuation Inversion Recovery (FLAIR) (64 slices, TE=145 ms, TR=9000 ms, voxel size 1.0×0.9×2.0 mm) sequence was also acquired. We qualitatively evaluated the presence of white matter hyperintensities on FLAIR images using a 4-point rating scale (Wahlund et al. 2001). The assigned values for this rating scale are: 0 for no lesions, 1 for focal lesions, 2 for beginning confluence of lesions and 3 for diffuse involvement of the entire regions with or without involvement of U fibers.

T1-VBM processing and analysis

Morphometric analysis was carried out using VBM (Ashburner and Friston 2000). T1-weighted data were processed using MATLAB version 7.8.0 (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM8; The Welcome Department of Imaging Neuroscience, London). Specifically, Unified Segmentation (Ashburner and Friston 2005) and Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) registration method (Ashburner 2007) were applied to the structural images to achieve spatial normalization into Montreal Neurological Institute (MNI) space. Normalized GM images were smoothed with an isotropic spatial filter (8 mm). GM Density (GMD) images were entered into a second-level analysis in order to compare patient and control groups. Total Intracranial Volume was included as nuisance variable in order to correct for global differences in GMD (Pell et al. 2008). Results are reported at a $P \leq 0.05$ Family Wise Error-corrected threshold at the cluster level, with an auxiliary threshold of $P<0.001$ at the voxel level.

Additionally, to study the effect of cognitive deterioration on GMD, we carried out a Spearman's correlation analysis between the general cognitive deterioration score of the Mattis Dementia Rating Scale-2 and the individual mean GMD maps of the patients. Specifically, a mask for each significant cluster yielded by the GMD group analysis was defined and was applied to each individual image. Then a mean GMD value for each individual and each cluster was calculated. Correlations between these values and each patient's cognitive score (Mattis Dementia Rating Scale-2 score) were computed.

Diffusion MRI processing and analysis

Data was corrected for eddy current distortions and head motion by means of FMRIB's Diffusion Toolbox (FSL5.0.2, www.fmrib.ox.ac.uk/fsl/) (Jenkinson et al. 2012). For each subject, the gradient matrix was then rotated using the fdt_rotate_bvecs program which is part of the FSL distribution (Leemans and Jones 2009) and brain extraction was performed (Smith 2002). Then, diffusion tensors were reconstructed using Diffusion Toolkit 0.6.2.2 (Ruopeng Wang, Van J. Wedeen, trackvis.org/dtk, Martinos Center for Biomedical Imaging, Massachusetts General Hospital), which uses a least-square estimation algorithm. Finally, Fractional Anisotropy (FA), Radial Diffusivity (RD), Axial Diffusivity (AD) and Mean Diffusivity (MD) maps for each subject were calculated using the eigenvalues (1, 2, and 3) extracted from the diffusion tensors.

A voxel-wise comparison between patients and controls for all DTI indexes was performed using Tract-Based Spatial Statistics (TBSS; Smith et al. 2006). First, FA maps were registered to the MNI FMRIB58_FA template using FNIRT (Andersson et al. 2007a, b). The resulting registration parameters were also applied to the AD (λ1), RD (λ2+λ3/2) and MD (λ1+λ2+λ3/3) maps. Then, skeletons that corresponded to the center of the major white-matter tracts were created. In order to compute voxel-wise statistics the resulting subject-specific FA, AD, RD and MD skeletons were fed into a two-sample *t*-test. Results are reported at a Family Wise Error-corrected $P<0.05$ value using threshold-free cluster enhancement and a nonparametric permutation test with 5000 permutations (Nichols and Holmes 2002). Additionally, in order to study the effect of cognitive deterioration on WM microstructure we carried out a Spearman's correlation analysis between the cognitive deterioration score of the Mattis Dementia Rating Scale-2 and the individual mean FA values of the patients. Specifically, a mask for each significant cluster yielded by the FA group analysis was defined and then applied to each individual image. Then a mean FA value for each individual and each cluster was calculated. Correlations between these values and each subject's Mattis Dementia Rating Scale-2 score were then computed.

Single subject analysis

An additional fine-grained analysis was carried out as a mean to evaluate each patient's structural damage separately using appropriate single-case statistical procedures. Thus, each patient's whole-brain FA skeleton and smoothed GMD images were compared to those of the control group through a modified version of the independent samples *t*-test, which accounts for the limited size of the control group, and was developed to be used in clinical practice and single case research (Crawford et al.

1998). This method allowed a comparison between an individual patient's test score against norms derived from the control sample and has previously been applied in several MRI studies to obtain an statistically sound comparison between single-subject structural MRI information and a control group (Gillebert et al. 2014; Tuomiranta et al. 2014). Results are reported at an uncorrected $P<0.05$ with a cluster extent of 50 contiguous voxels.

Results

A total of 96 patients diagnosed with SCLC between 2005 and 2010 were identified, from which 21 (22 %) were alive. Eleven of these patients were eventually enrolled in the study (see Fig. 1). Clinical and demographic characteristics of the cohort are described in Table 1. There were no significant differences between patients and control groups concerning age, gender, education or grouped vascular risk factors. However, Performance Status was clearly worse in SCLC patients (U(21)=22, Z=−3.10, $P<0.002$) and, as expected, smoking history showed a significant difference between SCLC and HC (Fisher exact test, $P<0.03$). Half of the SCLC group ($n=6$) exhibited extrapyramidal symptoms and signs (U(21)=27, Z=−2.77, $P<0.006$), and in 4 of these 6 SCLC patients the Hoehn and Yahr scale pointed to a mild to moderate disability (grade 3 of the mentioned scale) (Hoehn and Yahr 1967).

Median time since PCI treatment for the whole treated cohort was 3.1 (range: 2–10) years. Regarding the accumulated radiation dose received, the median time since PCI for patients treated with low-dose (25Gy) and high-dose (30 and 36Gy) was 2.3 (range 2–10) and 3.1 (range 2.4–6) years, respectively (U(10)=13, Z=−0.36, $P>0.05$).

Neuropsychological data

Long-term survivors scored significantly worse than the HC group on most of the neuropsychological domains including: (i) language processing (naming), (ii) verbal fluency, (iii) processing speed and executive functions, (iv) visuospatial abilities, (v) visual memory and (vi) verbal memory. Regarding the Auditory Verbal Learning Test (AVLT) learning curve, patients showed a clear impairment in their capacity to recall words (Group effect, F(1.19)= 6.9, $P<0.017$) (see Table 2 and Fig. 2). However, SCLC patients showed no significant difference compared to the HC group in the Beck Depression Inventory test (Fisher exact test, $P>0.15$).

The neuropsychological assessment revealed that nearly half of the SCLC survivors met the criteria for cognitive impairment (45 %, $n=5$). In an exploratory subanalysis, these cognitively impaired SCLC patients did not significantly differ in terms of PCI doses nor in other demographic or treatment-related characteristics, such as median time since PCI therapy, from non cognitive-impaired patients (see Supplementary Table S1). However, the comparison between non cognitive-impaired SCLC patients ($n=6$) and the HC group demonstrated significant differences in neuropsychological tests involving processing speed and executive functions (Trail Making Test part A -t(15)=2.9, $P<0.01$-, part B -t(14)=2.2, $P<0.05$-) and verbal fluency (Phonemic verbal fluency, $P<0.001$). Additionally, no

Table 1 Clinical and disease-related characteristics of the entire cohort

	SCLC ($n=11$)	HC ($n=11$)	p-value
Age - years	68 (57–77)	65 (53–74)	0.51
Gender[&]			
Male	10 (91)	10 (91)	1.0
Female	1 (9)	1 (9)	
Education (years)*	7.27±6	9±3.52	0.08
Smoking[&]	11 (100)	6 (54.5)	**0.03**
Alcohol[&]	2 (18)	4 (36)	0.36
HT[&]	4 (36)	4 (36)	1.0
DM type II[&]	3 (27)	1 (9)	0.58
Dyslipidemia[&]	5 (45.5)	7 (64)	0.39
Vascular risk factors[&]			
Low-risk (0 or 1)	4 (36)	6 (54.5)	0.39
High-risk (≥2)	7 (64)	5 (45.5)	
PS	2 (1–3)	1 (1–1)	**0.002**
Hoehn and Yahr scale	1 (0–3)	0 (0)	**0.006**
Tumor stage[&]			
Limited-disease	10 (91)		
Extensive-disease	1 (9)		
Chemo type[&]			
CDDP-based	8 (73)		
CBDCA-based	2 (18)		
CDDP/CBDCA combination	1 (9)		
Number of chemo cycles	4 (4–5)		
Time from PCI (years)	3.13 (2–10)		
PCI doses[&]			
24-25Gy	5 (45.4)		
30Gy	2 (18.2)		
36Gy	4 (36.4)		

Statistically significant results are marked in bold

median (range); *(mean±SD); [&] n (%)

Abbreviations: *SCLC* small cell lung cancer patients, *HC* healthy controls, *HT* hypertension, *DM type II* diabetes mellitus type II, *PS* Eastern Cooperative Oncology Group-ECOG Performance Status, *CDDP* cisplatine, *CBDCA* carboplatine, *PCI* prophylactic cranial irradiation. Statistically significant results are marked in bold

Table 2 Neuropsychological data (z scores)

	SCLC (n=11)	HC (n=11)	p-value
Cognitive impairment[&]	5 (45)	0 (0)	**0.035**
Mattis Dementia Rating Scale-2	139 (90–144)	144 (142–144)	**0.004**
BDI (≥13)[&]	4 (36)	1 (9)	0.15
Estimated verbal IQ*			
WAIS-III Vocabulary sub-test	0.42±0.99	1.09±1.21	0.17
Language*			
Brief Spanish adaptation of the Boston Naming Test	−0.27±0.99	0.76±0.94	**0.023**
Verbal fluency*			
Semantic fluency	−0.57±0.86	0.30±0.48	**0.008**
Phonemic fluency	−1.09±0.63	0.15±0.46	**0.0001**
Processing speed/executive functions*			
Trail Making test A (TMT-A)	−1.11±0.78	0.21±0.70	**0.001**
Trail Making test B (TMT-B)	−1.24±0.87	−0.12±0.60	**0.015**
TMT-B minus TMT-A (in seconds)**	159±77	72±42	**0.006**
Attention/working memory*			
WAIS-III Digits sub-test	−0.03±0.77	0.33±0.86	0.30
Visuospatial abilities*			
ROCF first copy	0.22±1.68	1.00±0.77	0.22
Visual memory*			
ROCF delayed	0±1.10	1.06±0.78	**0.030**
Verbal memory*/**			
AVLT immediate recall (A1)	2.40±1.58	4.36±1.75	**0.014**
AVLT immediate recall (B)	2.70±1.50	4.36±1.03	**0.007**
AVLT short-delay recall (A6)	4.00±3.56	−6.91±1.97	**0.039**
AVLT long-delay recall (A7)	3.50±3.24	−6.91±2.34	**0.012**

Statistically significant results are marked in bold

median (range); *(mean±SD); [&] n (%);** Raw scores are used

Abbreviations: *SCLC* small cell lung cancer patients, *HC* healthy controls, *BDI* Beck Depression Inventory test, *IQ* Intelligence Quotient, *WAIS-III* Wechsler Adult Intelligence Scale-III, *ROCF* Rey-Osterrieth Complex Figure, *AVLT* Auditory Verbal Learning Test

differences were found between low and high dose PCI group concerning neuropsychological results.

Neuroimaging findings

Voxel-based morphometry

The statistical analysis revealed differences in GMD between groups, mainly in the bilateral basal ganglia. Specifically, SCLC patients showed a significant decrease in mean GMD compared to the HC group in the thalamus, putamen, and posterior caudate bilaterally, and the right insula (see Supplementary Table S2 and Fig. 3a). No regions exhibited less GMD in the HC group compared to the patient group. Furthermore, FLAIR images of both groups showed no stroke-like GM lesions in the cortex or basal ganglia. Correlations between average GMD values of the clusters showing differences and the Mattis Dementia Rating Scale-2 scores were not significant.

Diffusion tensor imaging and WM changes

Median rating scale of WM hyperintensities using FLAIR images was 2 (0–3) for SCLC survivors and 0 (0–1) for control subjects. WM hyperintensities significantly differed between groups (Mann–Whitney U-test; p 0.002).

SCLC patients showed decreased FA values compared to the HC group in the white matter tracts involving the entire corpus callosum (CC), including the genu, the body and the splenium (see Fig. 3b). No other regions resulted significantly different between groups. No significant decreased FA values were observed in the HC group compared to the patient group. The correlation between the average FA values of the only cluster at the corpus callosum showing differences and the cognitive deterioration score (Mattis Dementia Rating Scale-

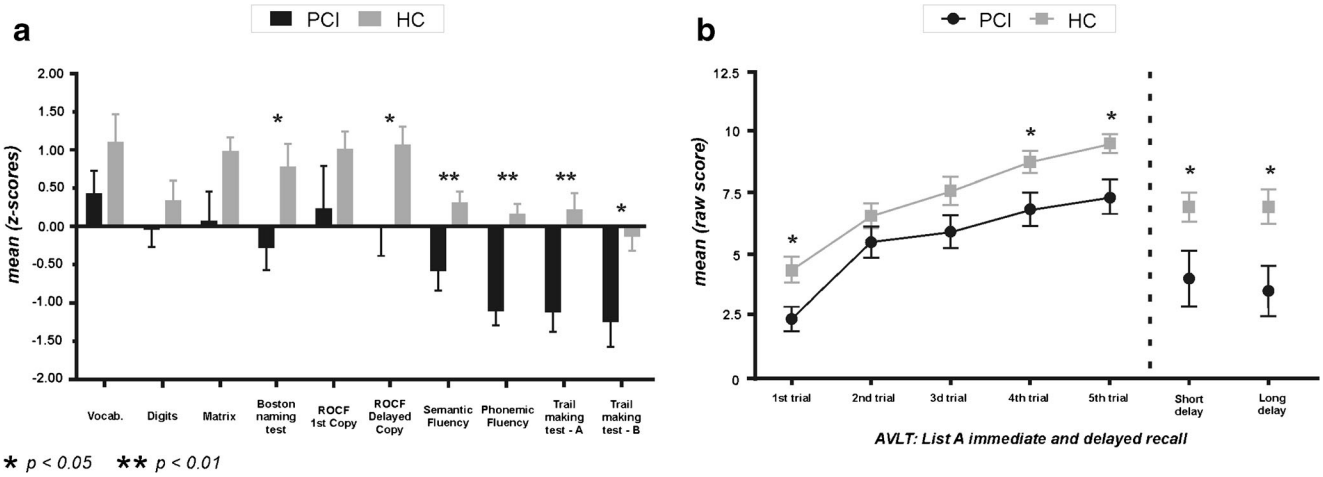

Fig. 2 Neuropsychological results. **a** Bar charts show mean and standard error of the neuropsychological testing for both groups. *PCI* prophylactic cranial irradiation group; *HC* healthy control group; *Vocab*. WAIS-III Vocabulary sub-test; *ROCF* Rey-Osterrieth Complex Figure. **b** Mean and standard error of the AVLT list A are displayed in the line chart. Learning curve (A1 to A5) is displayed on the left of the dashed line, while long-term memory recall (short-delay: A6, long-delay: A7) is displayed on the right. Significant differences (*T*-test *p*-value): * $P<0.05$ and ** $P<0.01$

2) revealed a significant positive correlation ($r=0.82$, $P<0.002$). This correlation was of the utmost importance as it shows how larger cognitive deterioration values (lower scores in the dementia scale) were associated to lower FA values (decreased white matter integrity) in the CC (see scatter plot in Fig. 3c). AD, RD and MD showed no significant differences between groups.

Single subject analysis

The analysis comparing each patient's FA and GMD maps against the control group revealed that 10 of 11 SCLC patients showed FA decreases in the CC (see single-patient contrasts in Fig. 4) and that all SCLC patients showed less GMD in the basal ganglia (including putamen, posterior caudate) and the thalamus bilaterally and right insula. These results were similar to those from the whole group analysis (11 SCLC versus 11 HC) confirming the reliability of the findings at single-patient level. This analysis also rules out the possibility that the group-results observed could have been affected by large effects observed only in some participants, thus affecting the statistical analysis.

Discussion

In this study we document long-term neuropsychological and structural brain changes in a cohort of SCLC patients treated with PCI. Our results revealed that long-term SCLC survivors following PCI and chemotherapy exhibited an overall significant cognitive deterioration. These cognitive deficits were accompanied by several structural differences, including GM decreases mainly in bilateral basal ganglia and WM microstructural changes in the CC. These structural findings were observed both at the group and at the single-patient level, in which nearly each patient presented structural deficits in the basal ganglia, thalamus and CC. More important, cognitive deterioration in the patient sample was strongly associated to the white-matter changes observed in the CC. All together, these neuropsychological and structural imaging findings show that SCLC patients following PCI therapy and chemotherapy, present long-term detrimental cognitive toxic effects.

Interestingly, long-term effects of whole-brain radiation therapy in patients with brain metastasis or primary central nervous system lymphoma have been increasingly recognized (Marsh et al. 2010). Cognitive symptoms include moderate to severe deficits in verbal memory and executive functions (Giglio and Gilbert 2003), together with a progressive subcortical dementia that usually comes with gait alterations and extrapyramidal symptoms (Marsh et al. 2010). Hence, although it seems clear that whole-brain radiation therapy has deleterious effects on cognitive functioning, the extent of PCI-associated cognitive toxicity in long-term SCLC survivors has been scarcely studied (Arriagada et al. 1995; Ball and Matthews 1995; Crossen et al. 1994; Cull et al. 1994; Fonseca et al. 1999; Gregor et al. 1997; Grosshans et al. 2008; Komaki et al. 1995; Parageorgiou et al. 2000; Roman and Sperduto 1995; van Oosterhout et al. 1995; Welzel et al. 2008a, b). This limited evidence is probably due to the fact that most of the studies were designed to evaluate the impact of PCI on survival, and thus cognitive assessment was frequently reported as a secondary point. The SCLC population does however present some of the potential risk factors that have been associated with the development of radiation-induced cognitive impairment: they are usually elders, previously treated with chemotherapy and they frequently carry

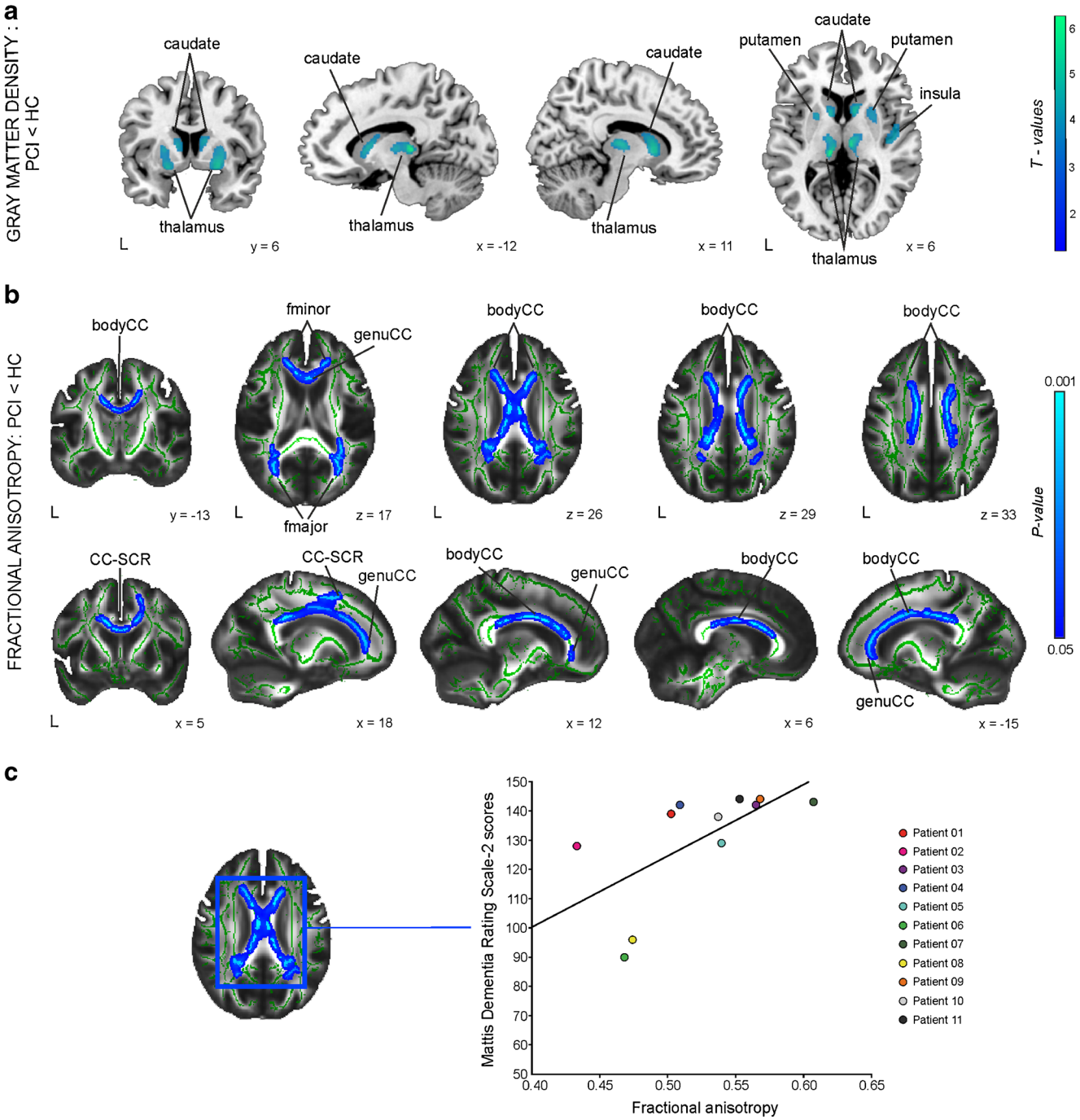

Fig. 3 Group differences for regional Gray Matter Density (GMD) and Fractional Anisotropy (FA) between groups. **a** Significant decreases in GMD for the prophylactic cranial irradiation (PCI) group compared with controls are reported at a $P<0.05$ FWE-corrected threshold at the cluster level. Results are displayed on a T-map and superimposed on a canonical T1 template. Neurological convention and MNI coordinates are used. *GMD* gray matter density; *PCI* prophylactic cranial irradiation group; *HC* healthy control group. **b** Statistical maps showing reduced FA (*blue*) in the PCI group compared with HC are reported over a mean skeleton (*green*) and the FMRIB58_FA template. Results are shown at a FWE-corrected $p<0.05$ threshold. Neurological convention and MNI coordinates are used. *PCI* prophylactic cranial irradiation group; *HC* healthy control group; *BodyCC* body of the corpus callosum; *Fminor* forceps minor; *genuCC* genu of the corpus callosum; *CC-SCR* corpus callosum-superior corona radiata. **c** Scatter plot displaying the relationship between the areas showing differences in FA (mainly corpus callosum) in the PCI group and the cognitive deterioration scores (Mattis Dementia Rating Scale-2 score; $r=0.82$, $P<0.002$)

some vascular risk factors (Welzel et al. 2008b). In order to control for some of these risk factors, an age- and education-matched HC group was included. As expected, only smoking was significantly different between patients and controls; a

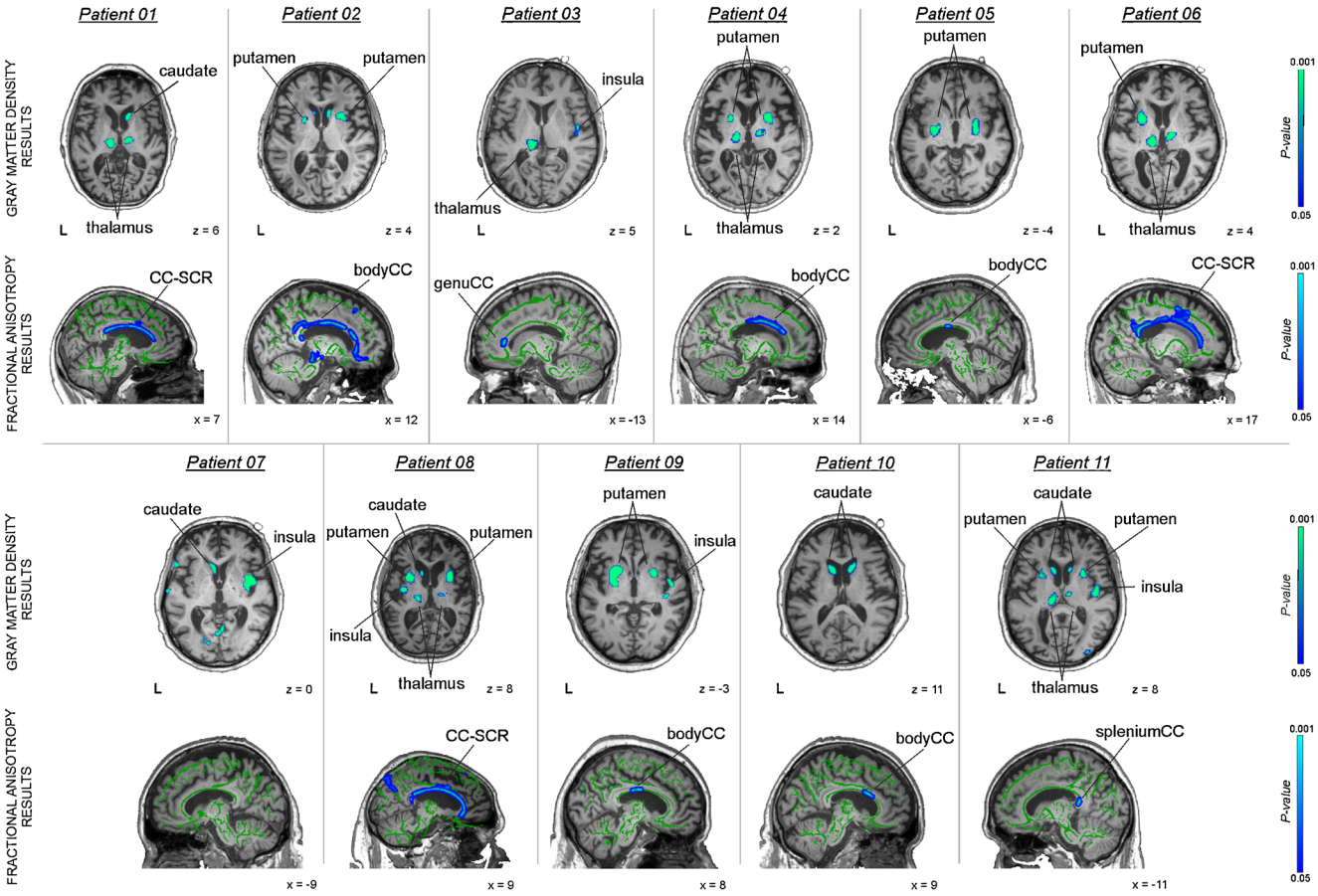

Fig. 4 Single subject analysis for regional Diffusion Tensor Imaging (DTI)-Fractional Anisotropy (FA) and Gray Matter Density (GMD). Statistical maps showing reduced FA (*blue*) of small cell lung cancer (SCLC) single patients compared to the healthy control (HC) group are reported over a mean skeleton (*green*) and superimposed to each individual normalized T1 image. Results are shown at a $P<0.05$ uncorrected threshold with 50 voxels of spatial extent. Neurological convention and MNI coordinates are used. *BodyCC* body of the corpus callosum; *SpleniumCC* splenium of the corpus callosum; *genuCC* genu of the corpus callosum; *CC-SCR* corpus callosum-superior corona radiata

higher proportion of SCLC patients had a smoking history. Importantly, cigarette smoking has been associated with an increased risk of silent cerebral infarctions (Howard et al. 1998). In our study, FLAIR images showed no GM lesions suggesting the presence of silent cerebral infarcts. Thus, although cigarette smoking significantly differed between groups, it did not have a significant impact on GM structural changes in our study.

As a result, and in agreement with the whole-brain radiation therapy studies (Marsh et al. 2010), long-term SCLC survivors in our cohort exhibited a global worsening of cognitive functioning, being most of the neuropsychological domains impaired. In addition, almost half of the long-term SCLC survivors (45 %) met criteria for cognitive impairment. These cognitively impaired SCLC patients did not significantly differ from non cognitive-impaired patients neither in terms of PCI doses nor in other demographic or treatment-related characteristics, such as median time since PCI therapy. Concerning the underlying structural neuroimaging findings, we found brain-specific structural damage following PCI that was not only restricted to WM tracts but also affects GM structures, supporting the idea that the underlying mechanisms of radiation-induced cognitive impairment involve multiple cell types (Greene-Schloesser et al. 2013). Long-term SCLC survivors showed decreased WM microstructural changes in the entire CC when compared with HC. Interestingly, the CC, the largest fiber bundle in the human brain interconnecting the two cerebral hemispheres and integrating motor, sensory, and cognitive processes, has recently been described as one of the most radiation-sensitive structures of the brain (Chapman et al. 2013). Emerging evidence suggests that damage in the CC, whose integrity is crucial for optimal brain functioning and cognition, directly contributes to a decline in cognitive functioning of aging adults (Voineskos et al. 2012), in neurodegenerative disorders (Wang et al. 2006) and also in long-term childhood acute lymphoblastic leukemia survivors treated with PCI (Khong et al. 2006; Reddick et al. 2006). The present results also show a close relationship between

cognitive function and the CC, as WM microstructural changes in this region were correlated with cognitive deterioration. This implies that patients with worse global cognitive functioning (those with lower scores in the Mattis Dementia test) showed WM microstructural changes (lower mean FA values) in this region. Hence, this further points out that cognitive deterioration exhibited by the patients is associated to the amount of microstructural damage to white matter fibers in the CC.

Similarly, we found a decrease of GMD in bilateral basal ganglia, bilateral thalamus and right insula. The basal ganglia are strongly connected with the cerebral cortex and the thalamus, integrating the corticostriatal circuits. These circuits have been functionally related to planning and modulation of motor pathways, visuospatial functions and to a variety of cognitive processes involving executive functions (Alexander et al. 1986). These GM findings might explain the presence of extrapyramidal signs and symptoms in the SCLC group (Noback et al. 2005). Moreover, the thalamus and the insula are both brain regions that exert a complex integrative function (Cauda et al. 2012; Herrero et al. 2002). Importantly, although these specific GM changes have also been described in long-term cancer survivors of childhood leukemia exposed to cranial irradiation (Porto et al. 2008), our study is the first to report basal ganglia damage associated with radiation in an adult cancer population. Additionally, GM changes did not correlate with overall cognitive deterioration score. In contrast to WM results, there is scarce evidence of the GM damage following PCI (Porto et al. 2008) and how this contributes to the neurocognitive effects observed. We believe that if GM deficits in basal ganglia have an impact on cognitive functioning in SCLC survivors, it would be minor in comparison to the contribution of WM damage.

The mechanism behind regional damage in GM and WM structures following chemotherapy and radiation is still unclear. Recent studies using DTI have demonstrated that regional brain white matter structures varied greatly in their response to chemoradiation (Chapman et al. 2013). The deep location of both GM and WM structures, which implies a low capillary density and less blood flow (Nonaka et al. 2003; Hodges et al. 1998), might represent an increased vulnerability to the toxic effects of chemoradiotherapy. This might explain why a whole brain radiation therapy is associated to more focal WM and GM injuries to brain structures. In comparison to other studies of childhood leukemia survivors where WM microstructural damage to other tracts in addition to CC was reported following PCI (Chapman et al. 2013, Schuitema et al. 2013, Aukema et al. 2009), our study showed a focal CC WM damage in SCLC survivors compared to the HC group. One possible explanation is that chilhood leukemia survivors in contrast to SCLC patients are treated with intravenous chemotherapy, known to cross the blood brain barrier as metrotrexate, or directly with intrathecal metrotrexate that has been associated with WM microstructure changes.

Brain specific damage following cranial irradiation is a major issue, and many recent clinical trials have employed selective sparing of critical brain regions in an effort to reduce late cognitive toxicities. One of the most commonly 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 and the subgranular zones within the dentate gyrus of the hippocampus (Wan et al. 2013). Recently, conformal avoidance of the hippocampus during whole brain radiation therapy has been associated with preservation of verbal memory (Gondi et al. 2014). Yet, based in our neuroimaging results, sparing only the limbic system or the neural stem cell areas may not prevent SCLC survivors from developing long-term neurocognitive deficits as the main affected areas appear to extend well beyond the aforementioned regions.

Although our study included a small sample size, which could be considered an important limitation, the natural aggressive history of this disease makes this a relevant long-term SCLC group studied with a fine-grained neuroimaging evaluation. Furthermore, the usual recommendation of performing all neuroimaging studies in the same MRI in order to avoid technical confounding factors, further limits the possibility to extend the study to other centers. In addition, the single-patient analysis revealed that nearly all patients, when individually compared to the HC group, showed decreased FA and GMD in the same areas found at the whole-group analysis. Interestingly, the three patients with larger cognitive deterioration (based on the Mattis Dementia Rating Scale-2, see Fig. 3c) also showed the largest WM changes in the CC (lower FA values) in the single-subject analysis.

Aside from the sample size, our study presents some other potential limitations. Firstly, the total accumulated PCI dose in our cohort was heterogeneous. This is a result of the fact that the optimum dose of PCI for SCLC was not established until 2009 (Le Pechoux et al. 2009). Prior to this, radiation schedules of 36 or 30 Gy, which were based on meta-analysis suggesting that the risk of brain metastases might be reduced with higher PCI doses, were frequently used (Auperin et al. 1999; Le Pechoux et al. 2011; Wolfson et al. 2011). Considering this, differences between cognitive and non-cognitive impaired patients concerning radiation doses were explored. Although no significant results were found between high and low radiation groups, the small number of our cohort might have limited the power to detect small changes between groups. Secondly, all SCLC patients in our cohort were also treated with a platinum-based chemotherapy regimen. Chemotherapy has previously been associated with cognitive and structural brain changes in many cancer survivors and could therefore appear to be a contributing factor to the identified deficits in this study (Simo et al. 2013). However, most of the previous chemotherapy-related studies performed in long-term breast cancer survivors found subtle cognitive

deficits and structural brain changes predominantly in frontal regions (Correa et al. 2013; Deprez et al. 2011; Inagaki et al. 2007; McDonald et al. 2013). Indeed, our research group also conducted a neuropsychological and neuroimaging study on SCLC patients following a platinum-based chemotherapy prior to PCI. We found that SCLC patients just following chemotherapy showed cognitive deficits together with brain changes in structures integrating the paralimbic system (Simo et al. 2015). Although the inclusion of a cohort of SCLC survivors that only underwent chemotherapy and not PCI would have been helpful to delineate the effects of chemotherapy from more general PCI-related changes, unfortunately only those SCLC patients who have not responded to first-line therapy and therefore have worse prognosis and short-term life expectancy, do not undergo PCI treatment (Auperin et al. 1999; Slotman et al. 2007). Hence, despite the fact that the cognitive deficits and selective brain damage found in the present study (in agreement with previous observed radiation-associated deficits) suggest that PCI therapy may be the main contributing factor responsible for the observed cognitive and structural brain changes, given the lack of longitudinal data and the impossibility to recruit a SCLC group only treated with chemotherapy, the contribution of platinum-based chemotherapy to the reported findings cannot be ruled out.

In conclusion, SCLC survivors exhibit a spectrum of neurocognitive deficits together with brain-specific structural changes, thus showing permanent long-term toxic effects. Additionally, this cognitive deterioration appears to be directly associated to the amount of microstructural damage to white matter fibers in the CC. These findings suggest that new radiation approaches, which avoid only hippocampal structures, may not prevent SCLC patients from developing cognitive deficits in the future and that novel procedures must be developed.

Compliance with Ethical Standards

Conflict of interest Marta Simó, Lucía Vaquero, Pablo Ripollés, Josep Jové, Rafael Fuentes, Felipe Cardenal, Antoni Rodríguez-Fornells, and Jordi Bruna reviewed and approved the manuscript content and there is no conflict of interest.

Ethical Statement All procedures performed in this study, which involve human participants, were in accordance with the ethical standards of the local Ethical Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants included in the study (both patients and healthy controls).

Funding This work was supported by Fundació Marató-TV3 [Acquired Spinal Cord and Brain Injuries Program (2012–2014) awarded to ARF] and the Catalan Government [Generalitat de Catalunya, 2009 SGR 93 to ARF]. Marta Simó was a recipient of a Rio Hortega research contract (code: CM11/00256) from the Carlos III National Health Institute (Spanish Government).

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