COGNITIVE IMPAIRMENT INDUCED BY CHEMOTHERAPY AND RADIOTHERAPY. EVALUATION OF THE IMPACT AND IDENTIFICATION OF CLINICAL, NEUROPHYSIOLOGICAL AND FUNCTIONAL NEUROIMAGE RISK MARKERS

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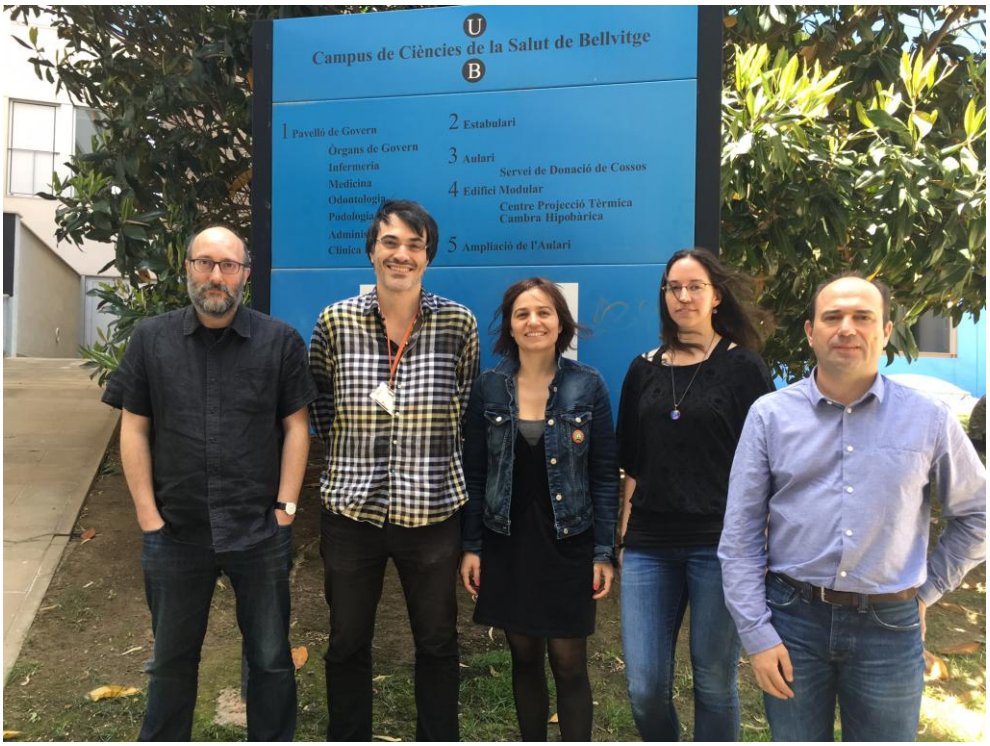

1. Summary

Lung cancer is the third most common cancer in the world and the most common cause of death from cancer worldwide. Classically, research in lung cancer has been focused on the development of new oncological therapies with the aim to increase overall survival or achieve cancer cure. In this sense, systemic chemotherapy together with thoracic radiation and more recently, prophylactic cranial irradiation, have been shown to reduce brain metastases and increase overall survival in a subgroup of small-cell lung cancer patients (SCLC). Radiation therapy is the application of ionizing radiation to treat cancer cells. The concept underlying PCI is to eliminate microscopic deposits of metastatic tumor within the brain and/or brainstem before they become clinically manifest.

Chemotherapy has recently been associated with cognitive impairment as well as with changes in brain structure in breast cancer population. In addition, cranial radiation in brain tumor population has also been associated with cognitive impairment or even dementia in long-term survivors. However, the impact of chemotherapy and/or cranial radiation on cognition and quality of life in lung cancer population is nowadays uncertain. Only a handful of studies have focused especially on the short and long-term cognitive toxic effects of these therapies of lung cancer population.

The aim of this work was to study the impact of both systemic chemotherapy and cranial radiation on cognition of lung cancer population, using (i) fine-grained neuropsychological assessment, (ii) neurophysiological-cognitive evoked related potentials (ERPs) and (iii) brain neuroimaging (structural and functional magnetic resonance imaging, MRI). Additionally, these techniques will help us to identify potential risk markers of cognitive impairment, facilitating the stratification of patients at baseline, before any treatment.

Study design

For this purpose, we designed a comparative longitudinal prospective study, composed of 3 cohorts of patients: Group A: healthy control subjects (HC), Group B: small cell lung cancer patients (SCLC) that received platinum-based chemotherapy and prophylactic cranial irradiation (PCI), and Group C: non small cell lung cancer patients (NSCLC) that received the same platinum-based chemotherapy as small cell lung cancer patients but without receiving PCI prophylactic cranial irradiation.

In Group A we recruited 22 healthy controls, 21 of whom completed the 3-month evaluation. In Group B we recruited 43 SCLC of whom 21 completed 3-month evaluation and finally in Group C we recruited 41 NSCLC patients of whom 13 completed the 3-month evaluation. Concerning recruitment of Groups B and C, although the number of patients designed in the project was initially recruited, we lost nearly 35% of the patients at 3-months and nearly 70% of patients at 9-months. The reasons were mainly systemic progression of the oncological disease or appearance of central nervous system progression. However, some of the patients were unable to tolerate MRI procedure, especially in Group C (the NSCLC group), mainly due to physical weakness. This was the reason why these patients were included just after the oncological diagnosis and before any therapy.

To date we have analyzed baseline and 3-month longitudinal data. The 3 groups included were studied at baseline and in the 3-month assessment using: i) a neurological examination, ii) a neuropsychological battery, iii) a multimodal neuroimaging including structural MRI: Voxel-Based Morphometry and Diffusion Tensor Imaging and functional MRI: Resting State Networks or memory paradigm and iv) a neurophysiologic-cognitive evoked related potentials (ERPs) study. Baseline cross-sectional analysis including neurological examination, neuropsychological assessment and structural neuroimaging resulted in our first work (**Study 1**). The analysis of 3-month longitudinal data resulted in a second work (**Study 3**, because it was finished and published chronologically before the Study 2. See Diagram 1). Currently we are finishing two more articles derived from the present experiment: one is focused on the analysis of the baseline (default mode) functional MRI (**Study 5**) and the other is the analysis of neurophysiologic-evoked cognitive potentials (ERPs) at baseline (**Study 4**). Finally, due to the difficulties in the long-term follow-up of SCLC patients, we decided to add a small sub-study with a very similar aim. We reviewed all SCLC patients

diagnosed in our hospital between 2000 and 2010 treated with PCI at least 2 years before. Of the 96 patients diagnosed between 2000 and 2010 only 21 were alive, of whom 14 agreed to participate in our MRI study. Eleven of these 14 patients were finally recruited (see **Study 2)**. We used the same methodology as described above for the assessment of this group of long-term survivals.

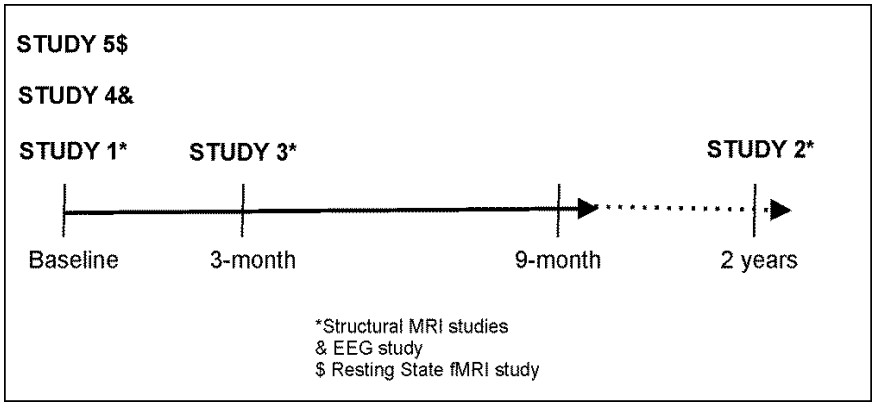

Diagram 1: chronologic scheme of the different studies included in this project.

2. Results

This project was divided in 3 studies:
In **Study 1**, nearly 40% of SCLC exhibited cognitive impairment 1-month following chemotherapy and prior to cranial radiation. These cognitive deficits were focused in visuospatial abilities and verbal fluency together with brain structural changes in bilateral temporal regions. Additionally, the NSCLC group, prior to receiving any chemotherapy, exhibited cognitive impairment in nearly 30% of the cases. Our study highlights that lung cancer patients at baseline, prior to receiving chemotherapy, exhibit cognitive impairment, and the addition of chemotherapy adds brain structural changes both in gray and white matter brain structures (see Figure 1A and 1B). Following chemotherapy, the SCLC received prophylactic cranial irradiation (**Study 3**). In study 2, we observed that SCLC patients 3-month following PCI showed cognitive worsening in verbal fluency together with important brain structural changes. Gray matter damage observed in the present study was initially related to chemotherapy, but then superimposed by PCI-specific damage in more medial and subcortical brain regions. Thus, PCI therapy seems to expand the cognitive and gray matter structural

deficits already observed following chemotherapy in SCLC, but adding a brain-specific white matter damage at 3-month follow-up (see Figure 1C and 1D).

Finally (**Study 2**), SCLC survivors (more than 2 years following PCI) that have been treated both with chemotherapy and PCI exhibit a spectrum of neurocognitive deficits (20% of them meet criteria for dementia) together with brain-specific structural changes, thus showing permanent long-term toxic effects. These cognitive deficits were accompanied by several structural differences, including gray matter decreases mainly in bilateral basal ganglia and white matter microstructural changes in the corpus callosum. Additionally, this cognitive deterioration appears to be directly associated to the amount of microstructural damage to white matter fibers (see Figures 1E and 1F).

See figure 1 for a review of the three studies.

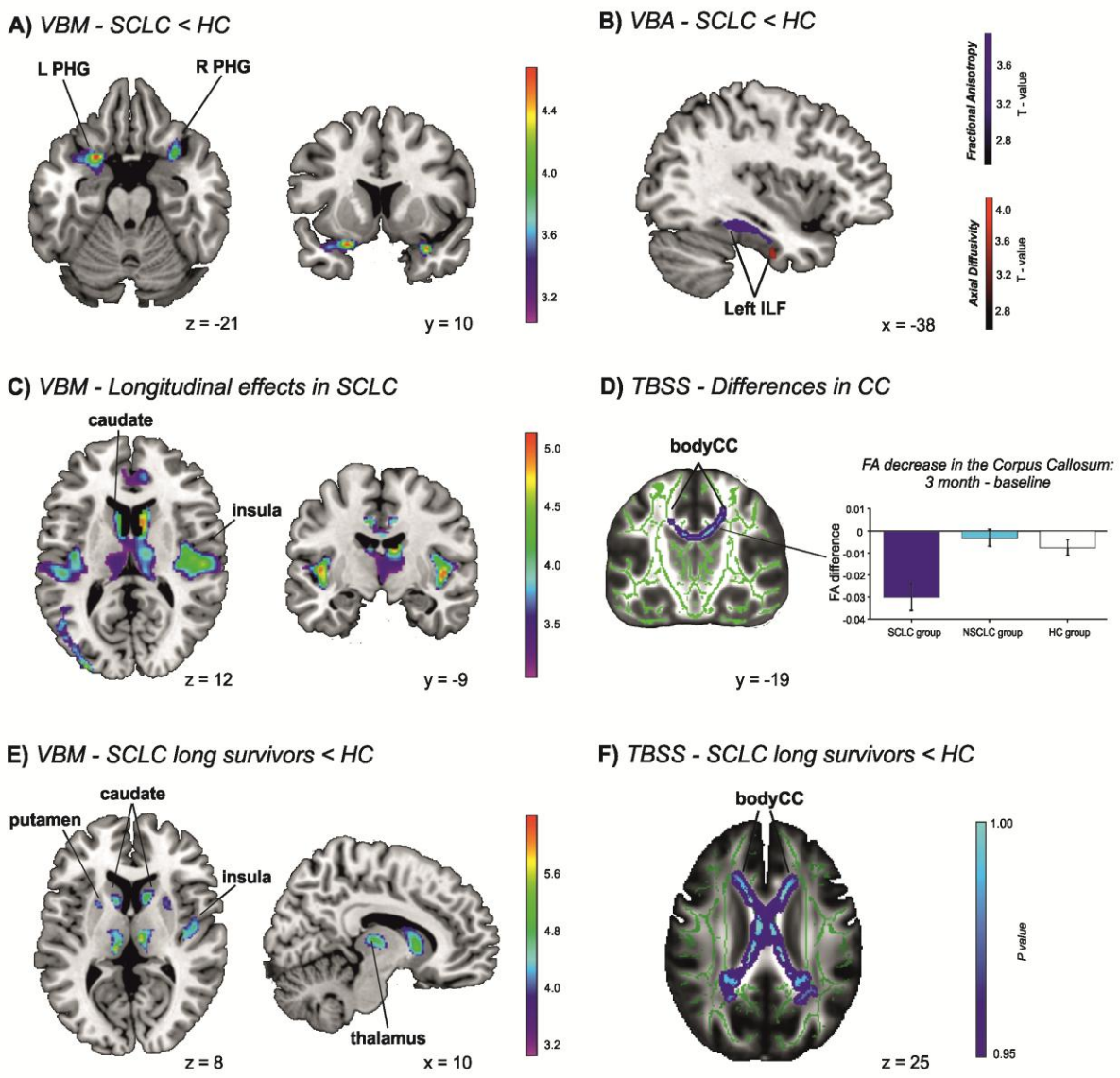

Figure 1: Summary of the results obtained from the different studies included in this project. In the two upper panels the results for the **First Study** are depicted, specifically the comparison between SCLC patients and healthy controls, both for gray matter (A) and for white matter (B). The central panels show the results from the **Third Study**: C) Longitudinal effects in gray matter in the SCLC patient group, and D) (longitudinal) differences in white matter in the three groups of participants. The lower panels show the comparison between the SCLC patient group and the healthy controls, both in gray matter (E) and in white matter (F), results from the **Second Study**. Abbreviations: bodyCC: body part of Corpus Callosum, L: left, R: right, PHG: parahippocampal gyrus, ILF: inferior longitudinal fasciculus, HC: healthy controls, SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer, TBSS: tract-based spatial statistics, VBA: voxel-based analysis (white matter), VBM: voxel-based morphometry (gray matter).

3. Relevance and potential implications in clinical practice

This work is the first to describe the impact of systemic chemotherapy and cranial radiation on cognitive functioning and brain structure of lung cancer population. The results of this project (Studies 1, 2 and 3) have added relevant evidence of the time and spatial extent of the underlying neural changes following chemotherapy and radiation in lung cancer population. Chemotherapy but especially cranial radiation seems mostly responsible for the moderate to severe cognitive deficits (nearly 20% of long-term survivors meet criteria for dementia) in long-term SCLC survivors. The brain structural changes induced by PCI are already seen at 3-month follow-up (following PCI). However, it is also important to note that 50% of long-term survivors, though exhibiting similar brain structural changes, did not present with cognitive deficits. This suggests that there is a subgroup of SCLC patients that are more vulnerable to neurotoxicity.

The results of this project will help clinicians to better advise SCLC patients about advantages and disadvantages of PCI. Although PCI has been shown to increase overall survival, SCLC patients should be informed about the risk of developing cognitive deficits or even dementia in the long-term follow-up.

Additionally, based on these results, we have planned new studies focused on the potential underlying mechanisms of neurotoxicity, using the methodology used in this study, with the aim of describing risk markers that allow us to identify, at baseline, which patients are at risk for cognitive impairment, with the aim to individualize oncological treatment in the future.

4. Publications (derived from this project)

Our research has resulted in several publications in high impact factor journals. The 3 studies explained in the results section were published in first quartile journals:

Study 1. Simó M, Root JC, Vaquero L, Ripollés P, Jové J, Ahles T, Navarro A, Cardenal F, Bruna J, Rodríguez-Fornells A. Cognitive and brain structural changes in a lung cancer population. **J Thorac Oncol. 2015 Jan;10(1):38-45. IP 5.3 Q1**

Study 2. Simó M, Vaquero L, Ripollés P, Jové J, Fuentes R, Cardenal F, Rodríguez-Fornells A, Bruna J. Brain damage following prophylactic cranial irradiation in lung cancer survivors. **Brain Imaging Behav. 2016: 10(1):283-95 IP 4.6 Q1**

Study 3. Simó M, Vaquero L, Ripollés P, Guturbay A, Jové J, Navarro A, Cardenal F, Bruna J, Rodríguez-Fornells A. Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer. **J Thorac Oncol. 2016;11(4):475-86. IP 5.3 Q1**

In addition, we published another 2 papers in relation with this project, also in high-impact factor journals:

Simó M, Ripollés P, Fuentemilla L, Vaquero L, Bruna J, Rodríguez-Fornells A. Studying memory encoding to promote reliable engagement of the medial temporal lobe at the single-subject level. **PLoS One. 2015 Mar 24;10(3):e0119159. IP 3.5 Q1**

Simó M, Rifà-Ros X, Rodriguez-Fornells A, Bruna J. Chemobrain: a systematic review of structural and functional neuroimaging studies. **Neurosci Biobehav Rev. 2013 Sep;37(8):1311-21. IP 10.2 Q1**

To date, we are finishing 2 more papers directly related with this project:

Study 4: Electrophysiological correlates of cancer and chemotherapy in a lung cancer population.

Study 5: Brain functional connectivity in lung cancer population: a pilot study

All these studies have been presented in international and national meetings:

- Alteraciones neuropsicológicas y neuroanatómicas secundarias a la Radioterapia Holocraneal Profiláctica en largos supervivientes de cáncer de pulmón de célula pequeña. Congreso Anual de la Sociedad Española de Neurología. Noviembre 2013. Barcelona.
- Brain damage following prophylactic cranial irradiation in lung cancer survivors. European Association of Neuro-Oncology (EANO) Meeting. October, 2014. Torino, Italy.
- Brain functional connectivity in lung cancer population: first results. Human Brain Mapping Organization (OHBM). June, 2014. Hamburg, Germany.

- Acute brain structural changes induced by chemotherapy in small cell lung cancer patients. International Cancer and Cognition Task Force (ICCTF) Congress. February 2014. Seattle. USA.
- Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer. Sociedad Española de Neurología (SEN). November, 2015. Valencia, Spain.
- Longitudinal brain changes associated with prophylactic cranial irradiation in lung cancer. International Cancer and Cognition Task Force (ICCTF) Congress. March 2016. Amsterdam.
- Brain functional connectivity in lung cancer population: a pilot study. International Cancer and Cognition Task Force (ICCTF) Congress. March 2016. Amsterdam.

  Finally, this project has been the basis for the PhD degree of Marta Simó, entitled: "Effects of chemotherapy and cranial radiation in brain structures and cognitive functions of lung cancer patients". The PhD dissertation presented on May 2015 has the qualification of Cum Laude by the University of Barcelona.