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Impact of Prophylactic Cranial Irradiation and hippocampal sparing on 18F-FDG brain metabolism in Small Cell Lung Cancer Patients

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préparée sous la direction du Professeur Niklaus Schaefer
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et présentée à la Faculté de biologie et de médecine de
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DOCTEUR EN MEDECINE

par

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Médecin diplômée de la Confédération Suisse
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Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Résumé en français

L'irradiation prophylactique cérébrale augmente la survie globale de patients traités pour un carcinome pulmonaire à petites cellules. Malheureusement ce traitement est également associé à une atteinte cognitive, notamment dû à l'irradiation des hippocampes, structures cérébrales particulièrement radiosensible et impliqué dans la genèse de mémoire. Récemment, des techniques de radiothérapie par modulation d'intensité (RTMI) permettent l'irradiation de l'encéphale en totalité (EIT), tout en épargnant les hippocampes. Notre étude a pour but d'étudier l'impact de l'irradiation cérébrale prophylactique (ICP) sur le métabolisme cérébral et le potentiel bénéfice de l'épargne hippocampique en utilisant la tomographie par émission de positrons (TEP)/ Tomodensitométrie (TDM) au ^{18}F-Fluoro-Deoxy-Glucose (^{18}F-FDG).

Pour ce faire, nous avons rétrospectivement inclus 22 patients ayant effectué un TEP/TDM avant et après ICP dans notre centre. L'ICP a été effectué selon le schéma classique de 25 Gy en 10 fractions de 2.5 Gy. 50% des patients avait bénéficié d'une épargne hippocampique. Les TEP/TDM ont été effectués en moyenne 145 jours avant et 383 jours après irradiation cérébrale. Les TEP/TDM cérébraux ont ensuite été automatiquement segmentés en 12 régions basées sur l'atlas combined-AAL issu du programme MI-Neurology de Syngo.via (Siemens Healthineers). Pour chaque région un ratio (SUVR) a été calculé en utilisant le tronc cérébral comme référence (SURV = SUV moyen / SUV moyen du tronc cérébral). Les SUVR avant et après PCI ont ensuite été comparés en utilisant un test Wilcoxon avec un seuil de significativité de $p<0.05$.

L'irradiation cérébrale a entrainé une diminution significative du métabolisme cérébral de manière diffuse notamment au niveau des ganglions de la base (1.40±0.12 vs 1.34±0.13, p=0.004), des régions centrales (1.34±0.13 vs 1.29±0.12, p=0.001), du cortex cingulé (1.33±0.11 vs 1.25±0.13, p<0.001), du corpus striata (1.42±0.12 vs 1.36±0.14, p=0.003), du cortex frontal (1.24±0.14 vs 1.27±0.13, p<0.001), du cortex pariétal (1.36±0.15 vs 1.30±0.12, p=0.001), du cortex occipital (1.50±0.15 vs 1.44±0.15, p=0.002), du precuneus (1.48±0.15 vs 1.42±0.14, p=0.001), du cortex temporal latéral (1.35±0.12 vs 1.29±0.11, p=0.001) et du cervelet (1.27±0.10 vs 1.23±0.09, p<0.001). Toutefois, nous n'avons pas mis en évidence d'altération significative du métabolisme des cortex temporaux médiaux, qui contiennent les hippocampes (1.05±0.09 vs 1.01±0.08, p=0.09). Une analyse de sous-groupe a montré que seuls les patients ayant reçu une irradiation de l'encéphale standard présentent une baisse du métabolisme hippocampique (1.04±0.10 vs 0.98±0.08, p=0.033). Les patients ayant bénéficié de l'épargne hippocampique présentent une préservation du métabolisme des régions épargnées : 1.02±0.05 vs 1.01±0.08, p=0.78. De surcroit, la variation métabolique des hippocampes est plus marquée chez la patient ayant reçu une irradiation standard, -5% vs -1.3% pour ceux ayant bénéficié de l'épargne hippocampique. A noter que le dose moyenne reçu par les hippocampes épargnés était de 12.2 Gy, soit une diminution de 50% par rapport à la dose de prescription.

Notre étude démontre que l'irradiation prophylactique cérébrale induit une baisse diffuse du métabolisme cérébrale, mais que l'épargne hippocampique entraine une préservation de l'activité métabolique des régions épargnées. Une baisse de 50% de dose prescrite au niveau des hippocampes est suffisante pour observer ce bénéfice.

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Original Article

Impact of prophylactic cranial irradiation and hippocampal sparing on ^{18}F-FDG brain metabolism in small cell lung cancer patients

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ABSTRACT

Background and purpose: Prophylactic cranial irradiation (PCI) in small-cell lung cancer (SCLC) patients improves survival. However, it is also associated with cognitive impairment, although the underlying mechanisms remain poorly understood. Our study aims to evaluate the impact of PCI and potential benefit of hippocampal sparing (HS) on brain metabolism assessed by ^{18}F-Fluoro-Deoxy-Glucose Positron Emission Tomography/Computed Tomography (^{18}F-FDG PET/CT).

Materials and methods: We retrospectively included 22 SCLC patients. 50% had hippocampal-sparing (HS) PCI. ^{18}F-FDG PET/CT was performed 144.5 ± 73 days before and 383 ± 451 days after PCI. Brain ^{18}F-FDG PET scans were automatically segmented in 12 regions using Combined-AAL Atlas from MI-Neurology Software (Syngo.Via, Siemens Healthineers). For all atlas regions, we computed SUV Ratio using brainstem as a reference region (SUVR = SUVmean/Brainstem SUVmean) and compared SUVR before and after PCI, using a Wilcoxon test, with a level of significance of $p < 0.05$.

Results: We found significant decreases in ^{18}F-FDG brain metabolism after PCI in the basal ganglia ($p = 0.004$), central regions ($p = 0.001$), cingulate cortex ($p \leq 0.001$), corpus striata ($p = 0.003$), frontal cortex ($p \leq 0.001$), parietal cortex ($p = 0.001$), the occipital cortex ($p = 0.002$), precuneus ($p = 0.001$), lateral temporal cortex ($p = 0.001$) and cerebellum ($p \leq 0.001$). Conversely, there were no significant changes in the mesial temporal cortex (MTC) which includes the hippocampi ($p = 0.089$). The subgroup who received standard PCI showed a significant decrease in metabolism of the hippocampi ($p = 0.033$). Contrastingly, the subgroup of patients who underwent HS-PCI showed no significant variation in metabolism of the hippocampi ($p = 0.783$).

Conclusion: PCI induced a diffuse decrease in ^{18}F-FDG brain metabolism. HS-PCI preserves metabolic activity of the hippocampi.

Lung cancers are among the most lethal cancers worldwide with over 50% death rate at 1 year and less than 18% survival at 5-year [1,2]. Recently, the addition of immunotherapy to some treatment regimens has improved survival, particularly in "extensive stage" small cell lung cancer (ES-SCLC) [3]. Indeed, there are two main subtypes of lung cancer: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) representing 85% and 15% of all lung cancer, respectively [4]. SCLC is characterized by its high sensitivity to chemotherapy, rapid evolution and a tendency to metastasize early. Indeed, though only 10% of SCLC patients present with brain metastases (BM) at diagnosis, it increases to 50% after 2 years and 65% at autopsy [5,6]. The use of prophylactic cranial irradiation (PCI) has reduced the incidence of BM, prolonged disease-free survival, and improved overall survival in patients with the so-called "limited-disease" SCLC and who previously responded to chemoradiation therapy [5,7-9].

However, radiotherapy (RT) to the brain is associated with transient or permanent neurotoxic effects that are not fully understood [10,11]. Studies have demonstrated that cranial RT impairs both brain endothelium and oligodendrocyte progenitor cells, leading to acute demyelination and ultimately to white matter necrosis [12]. Moreover, some brain regions seem to be more radiosensitive than others, such as it is for the hippocampus. Indeed, new neurons and glia are produced throughout adult life from neural stem cell precursors in the hippocampus, and these cells play an important role in brain injury repair [13]. In this setting, modern intensity-modulated radiotherapy (IMRT) techniques have been used to

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develop hippocampal-sparing whole brain RT (HS-WBRT) [13,14]. Hippocampal metastasis are a rare occurrence [15]. HS-WBRT aims to prevent adverse cognitive effects of cerebral irradiation and allows for the preservation of radiosensitive, memory-specific part of the hippocampus [13,14], while maintaining intracranial efficacy.

The impact of PCI, and more generally WBRT, on the development of neurocognitive deficits – notably memory decline – and the worsening of patient-reported quality of life have increasingly been studied and recognized [16-19]. The increase in long-term cancer survivors prompts the implementation of specific measures to limit those adverse effects. Yet, although many studies have shown that hippocampal sparing preserve neurocognitive functions while maintaining intracranial control, this technique is not a gold standard [20-23].

Many neuroimaging studies have evaluated the effects of WBRT including PCI on brain structures and functions in order to elucidate the underlying mechanisms of cognitive decline related to brain irradiation [11,12,21,24-26]. Magnetic resonance imaging (MRI) studies demonstrated a reduction in brain volume following WBRT, occurring as early as 6 months after WBRT and resulting in a maximum reduction usually less than 10% of the baseline volume [21,24,26]. Popp and colleagues retrospectively compared WB and hippocampal atrophy following WBRT and HS-WBRT using MRI, showing a relative preservation of hippocampal volume in patients benefitting from HS [27]. A few functional neuroimaging studies, using Positron Emission Tomography (PET) or functional Magnetic Resonance Imaging (fMRI), have helped elucidate the possible changes of functional activation patterns related to PCI [28]. To the best of our knowledge, there are only two PET studies with conflicting results assessing the impact of PCI on ^{18}F-FDG (^{18}F-Fluoro-Deoxy-Glucose) brain metabolism [29,30].

Our retrospective study aims to evaluate the impact of prophylactic cranial irradiation and potential benefit of HS on ^{18}F-FDG brain metabolism in SCLC patients.

Material and methods

Patient population

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its last amendments or comparable ethical standards. The Ethics Committee Vaud (CER-VD) approved this retrospective study protocol. We included patients who did not explicitly refuse the retrospective use of their data for research, as per local legislation.

From January 2010 to August 2018, 45 consecutive patients with biopsy-proven SCLC and a staging PET/CT, who received first-line chemoradiotherapy (for limited-stage disease) or in complete response after first line chemotherapy (for extensive-stage disease) followed by prophylactic WBRT were eligible. We excluded 16 patients who did not have a follow-up PET/CT after PCI. Two patients who refused the use of their data for research and 5 patients with incomplete data were also excluded. In total, 22 patients were retrospectively included in our study (Appendix A). None had brain metastases or any other intracranial pathology, based on brain MRI. Chemotherapy regimen consisted of platinum based antineoplasic drug (either cisplatin or carboplatin) associated with etoposide.

All included patients underwent ^{18}F-FDG PET/CT at our institution before and after PCI, as part of standard-of-care assessment of tumor response. The ^{18}F-FDG PET/CT scans nearest to the prophylactic-WBRT were selected. Patients who developed BM before receiving the second PET/CT were not included.

Radiotherapy planning

All radiation treatments were planned and delivered in the same institution. Planning CT was acquired with 2 mm slice thickness in treatment position with a 3 point thermoplastic mask. Bilateral hippocampal contours were manually delineated by a trained radiation oncologist in the HS-PCI subgroup using non-elastic registration of brain MRI and CT planning image. Treatment planning relied on IMRT technique. Dose covering 95% (D95) of the planning target volume (PTV) was at least 95% of the prescribed dose, and no more than 107%, as per institution guidelines. Our institution's HS protocol was based on RTOG 0933 guidelines (33) with the following modification: dose covering 100% of the hippocampi (D100%) equal to 10 Gy to ensure proper coverage of the PTV, maximum dose (Dmax) must be less than 15 Gy and mean dose (Dmean) must be less than 13 Gy. Hippocampal avoidance region (HAR) was generated by a 5 mm automatic expansion of hippocampal contours. Adequate positioning was ensured by daily image-guided radiotherapy (IGRT). A standard PCI dose of 25 Gy in 10 fractions of 2.5 Gy was prescribed. One fraction was delivered per day, 5 days per week.

PET/CT acquisitions

All PET/CT were performed in the same institution on a GE Discovery 690 TOF PET/CT camera (GE Healthcare, Waukesha, MI, USA), except for two patients who had their PET/CT on a GE Discovery LS PET/CT (GE Healthcare, Waukesha, MI, USA). Patients observed a fasting period of at least 4 hours before PET/CT. Blood glucose level was measured before the injection of 3.5 MBq/kg of ^{18}F-FDG. Patients were excluded if glucose level was >12 mmol/L. Whole-body images were acquired 60 minutes after radiotracer injection according to standard oncologic protocol (2 min per bed position).

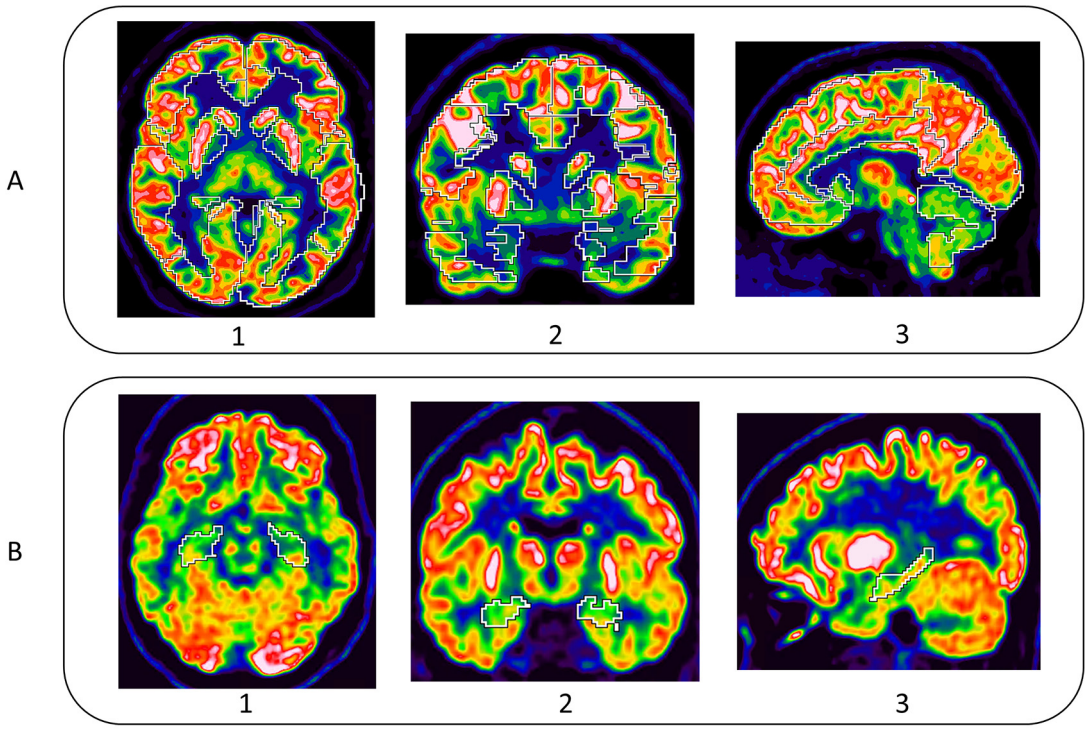
PET/CT analyses

Patient PET/CT scans were evaluated by one radiation oncologist and by one experienced nuclear medicine physician. All the ^{18}F-FDG PET scans were first analysed visually. Subsequently, we performed semi-quantitative analysis. Brain ^{18}F-FDG PET were automatically segmented into 11 regions using Combined-AAL Atlas from MI-Neurology Software (Syngo.Via, Siemens, Erlangen, Germany) into the bilateral following cerebral regions of interest (ROIs): frontal cortex, central regions, anterior cingulate cortex, lateral parietal cortex, precuneus/posterior cingulate cortex, mesial temporal cortex (MTC), lateral temporal cortex, occipital cortex, basal ganglia, corpus striata, pons and cerebellum (Fig. 1). The hippocampi were also extracted using the same program (Fig. 1). SUVmean was automatically extracted from all these bilateral ROIs, and then used to calculate SUVR, using brainstem as reference region (SUVR = SUVmean/Brainstem SUVmean). There was no registration or segmentation failure with the automated MI-Neurology software.

Statistical analysis

All values were expressed as mean ± standard deviation (SD). All data were processed using SPSS® v. 24.0 software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The level of significance was set for $p < 0.05$.

For each ROI, we compared SUVR before and after PCI, using a non-parametric test for paired groups (Wilcoxon test).



Legend: PET: positron emission tomography

Fig. 1. Illustration of the combined-AAL atlas (A) and hippocampi (B) automatic segmentation used for semi-quantitative analysis of PET images (1: axial plan; 2: coronal plan; 3: sagittal plan).

Results

Twenty-two consecutive patients with biopsy-proven SCLC were retrospectively included. The mean age was 64.4 years-old (range 50–79), with a female/male ratio of 0.36. Nineteen patients out of 22 (86%) had limited-stage SCLC, and 3 out of 22 (14%) had extensive-stage SCLC. Eight patients (36%) received immunotherapy after PCI (most commonly Ipilimumab associated with Nivolumab), 7 of them had received HS-PCI.

Mean follow-up was of 39 months (range 4.6–77.2) for our entire cohort, 37 months for the standard PCI subgroup and 49 months for the HS-PCI subgroup. At the moment of analysis, only 8 patients (32%) were still alive, 6 of which had received HS-PCI (p = 0.18). Six (27%) patients developed BM despite PCI, on average 32.6 months after cerebral radiation (range 9.3–48.1), none were localized in the hippocampi. Half of the patients who developed BM had received HS-PCI (p = 1.0). Twenty-one patients had cerebral imaging as part of their follow-up of which 17 were by MRI. Last MRI check-up was on average 35.4 months (range 4.2–82.2) after the end of radiotherapy. MRI description of white matter lesions or diffuse cerebral atrophy were found in 9 patients, 5 of which had undergone HS-PCI. Table 1 summarizes the characteristics of the study population.

Eleven patients out of 22 (50%) underwent HS-PCI. Dose distributions for standard and HS-PCI are shown in Fig. 2. The mean planned total dose to the brain (WB including the hippocampi) was of 24.9 Gy for our entire cohort, 24.7 Gy and 25.4 Gy for the HS-PCI and standard PCI subgroup, respectively (Table 1). Mean planned total dose to the hippocampi was of 12.2 Gy in the HS-PCI subgroup, which represents a 49% decrease (Table 1). Dose volume histograms (DVH) of the hippocampi for all 11 patients are included in Appendix B.

The mean time-lapse between PET/CT acquisition and PCI was 143.5 days before PCI (range 13–354) and 382 days after PCI (range 21–1516). The mean blood glucose measured before injection of ^{18}F-FDG injection was 6.0 mmol/L (range 4.6–9.6) on the pre-PCI PET/CT scan and 5.6 mmol/L (range 4.4–7.6) on the post-PCI PET/CT scan. ^{18}F-FDG PET/CT scans were acquired on average 64 ± 6 minutes after injection for pre-PCI PET/CT (range 56–75 minutes) and 62 ± 9 minutes for post-PCI PET/CT scan (range 48–92 minutes). On paired comparison, neither the injected activities for pre-PCI and post-PCI PET/CTs (p = 0.51) nor the mean time-lapse between injection and acquisition (p = 0.57) or the mean blood glucose level (p = 0.18) were significantly different. These data are summarized in Table 2.

On visual analysis, both pre-PCI and post-PCI ^{18}F-FDG PET/CT scans were normal.

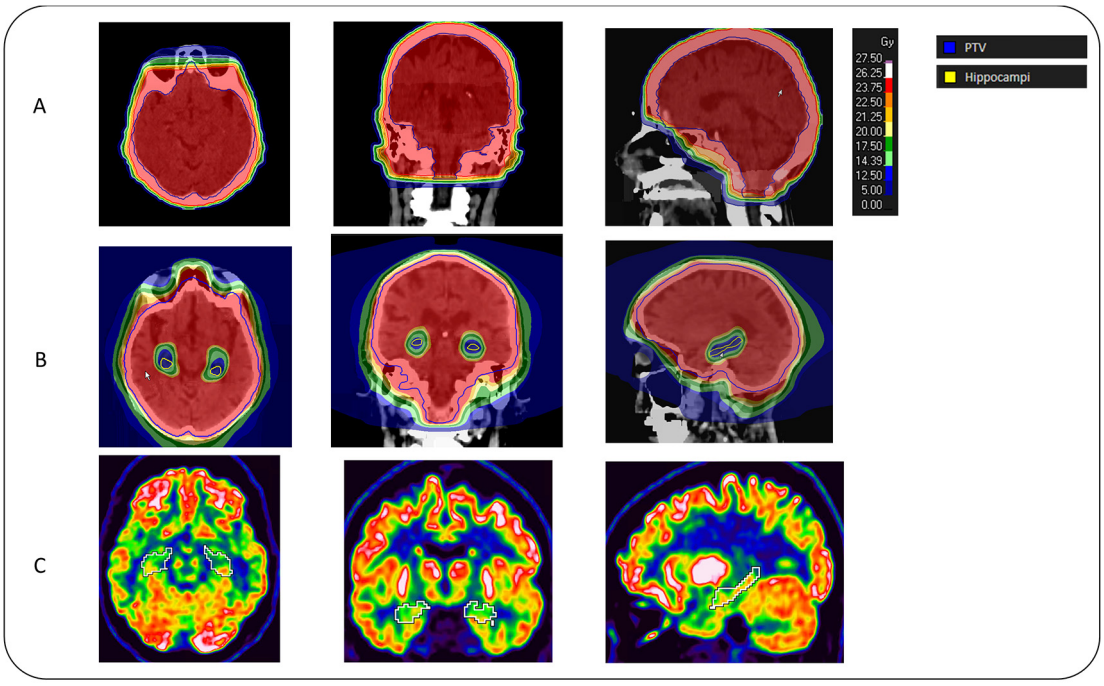
For semi-quantitative analysis, among the regions most commonly used for normalization [32], the brainstem was defined as reference region because it did not present significant variation before and after PCI (SUVmean: 4.70 ± 1.42 vs 4.9 ± 0.9, p = 0.53).

After PCI, there was a significant decrease of regional SUVR in basal ganglia (1.40 ± 0.12 vs 1.34 ± 0.13; −4.3% variation, p = 0.004), central regions (1.34 ± 0.13 vs 1.29 ± 0.12; −3.7% variation, p = 0.001), cingulate cortex (1.33 ± 0.11 vs 1.25 ± 0.13; −6.0% variation p < 0.001), corpus striata (1.42 ± 0.12 vs 1.36 ± 0.14; −4.2 % variation, p = 0.003), frontal cortex (1.34 ± 0.14 vs 1.27 ± 0.13; −5.2% variation, p < 0.001), parietal cortex (1.36 ± 0.15 vs 1.30 ± 0.12; −4.4%, p = 0.001), the occipital (1.50 ± 0.15 vs 1.44 ± 0.15; −4.0% variation, p = 0.002), precuneus (1.48 ± 0.15 vs 1.42 ± 0.14; −4.1% variation, p = 0.001), lateral temporal cortex (1.35 ± 0.12 vs 1.29 ± 0.11; −4.4% variation, p = 0.001) and cerebellum (1.27 ± 0.10 vs 1.23 ± 0.09; −3.1% variation, p < 0.001) as summarized in Fig. 3. Conversely, there were no significant changes in

Table 1
Patients Characteristics (n = 22).

Characteristics	Entire Cohort (n = 22)	Standard PCI (n = 11)	HS-PCI (n = 11)	p-Value
Age (years)				
Mean (Range)	65 (50–79)	64 (52–74)	65 (50–79)	0.85
Gender				
Male/Female	14/8	7/3	5/5	0.66
Stage of disease				
Limited /Extensive	19/3	9/1	8/2	1.00
Mean delay between PCI and PET Acquisition (days)				
Before PCI (Mean (Range))	143.5 (72–354)	151.6 (13–354)	135.5 (27–226)	0.80
After PCI (Mean (Range))	382 (21–1332)	386 (21–1516)	378 (26–1332)	0.90
Survival status				
Alive/Dead	8/14	2/9	6/ 5	0.18
Metastasis after PCI				
Yes /No	6/16	3/8	3/8	1.00
Planned dose (Gy)				
Whole brain (Mean (Range))	24.9 (24.6–25.5)	25.4 (25.2–25.5)	24.7 (24.6–24.8)	-
Hippocampi (Mean (Range))	NA	NA	12.2 (9.9–16.9)	-

PET: positron emission tomography; PCI: prophylactic cranial irradiation; HS: hippocampal sparing; Gy: Gray; NA: not applicable.



Legend: PCI: Prophylactic cranial irradiation ; HS: Hippocampal sparing ; PET: positron emission tomography ; PTV: Planning target volume

Fig. 2. Three-plane illustration of PCI dose distribution without (A) and with (B) HS, and corresponding hippocampi automatic segmentation (C) used for semi-quantitative analysis of PET images.

Table 2
PET characteristics (n = 22).

Characteristics (Mean ± SD)	Pre-PCI PET/CT	Post-PCI PET/CT	p-Value
Injected dose (MBq/kg)	254 ± 56.0	246 ± 70.4	0.51
Post-injection time (minutes)	63.7 ± 6.0	62.2 ± 9.0	0.57
Glycemia (mmol/L)	6.0 ± 1.2	5.6 ± 0.7	0.18

PET/CT: positron emission tomography/computed tomography; SD: standard deviation; PCI: prophylactic cranial irradiation.

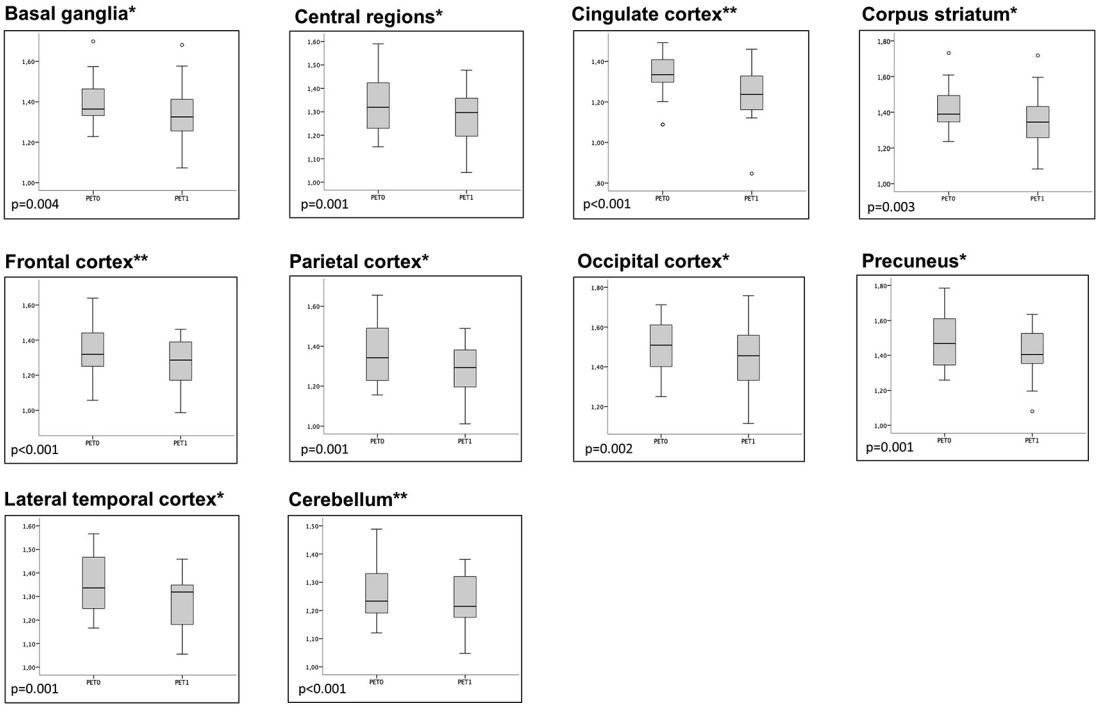
the mesial temporal cortex (MTC) which includes the hippocampi (1.05 ± 0.09 vs 1.01 ± 0.08, −3.8% variation, p = 0.089) (Fig. 4).

Subgroup analysis was performed for the hippocampi. In patients who received HS-PCI hippocampal metabolic activity was preserved, with no significant variation (1.02 ± 0.05 vs 1.01 ± 0.08; −1.3% variation, p = 0.783) (Fig. 4). In patients receiving standard PCI, on the other hand, the hippocampi show a significant decrease in metabolism (1.04 ± 0.10 vs 0.98 ± 0.08; −5% variation, p = 0.033) (Fig. 4).

Discussion

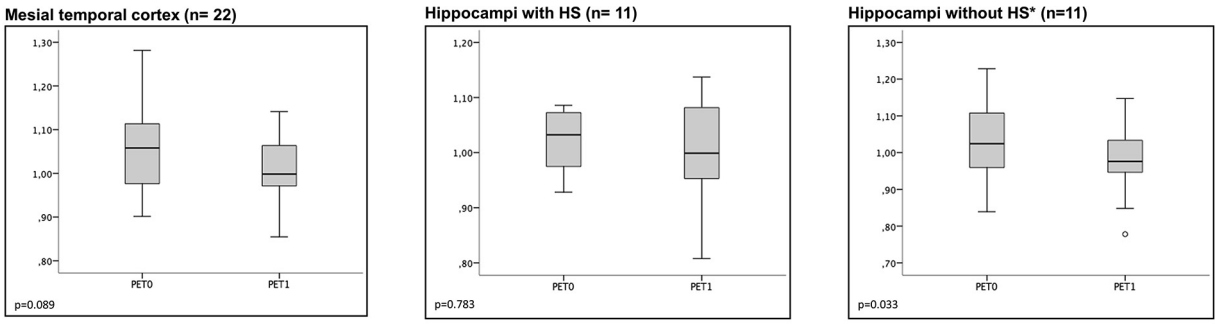
Our study showed that PCI induced a diffuse decrease in cerebral glucose metabolism. Subgroup analysis of patients who underwent HS-PCI showed that HS preserves metabolism of the hippocampi, unlike the standard PCI group, which showed decreased hippocampal metabolism.

To our knowledge, this retrospective cohort study has the largest population for which ^{18}F-FDG PET/CT was used to evaluate the impact of PCI on cerebral metabolism. Our results are consistent with the mechanisms of radiation toxicity, and the known characteristics of ^{18}F-FDG uptake as a marker of neuronal integrity



Legend: SUVR: Standardized uptake value ratio ; PCI: Prophylactic cranial irradiation ; *: p<0.01, **: p<0.001

Fig. 3. Box plot comparison of SUVR for each region of the combined-AAL Atlas before and after PCI (n = 22).



Legend: SUVR: Standardized uptake value ratio ; PCI: Prophylactic cranial irradiation ; HS: Hippocampal sparing ; *: p<0.05

Fig. 4. Box plot comparison of SUVR before and after WBRT for the mesial temporal cortex in our entire cohort and for the hippocampi in the subgroup of patients receiving HS-PCI and standard PCI.

[33,34]. They are also congruent with previous studies done with different imaging techniques [27]. Interestingly, our results differ from the study by Eshghi et al., which is the only other study evaluating the ^{18}F-FDG brain metabolism after PCI on humans [29]. Indeed, they showed both increased and decreased cerebral glucose metabolism in different brain compartments approximately 3 months after PCI in 13 patients. They postulated that asymmetrical differences in cerebral metabolism reflect functional changes due to chemotherapy and PCI, and found that, in 12/13 patients, the frontal lobe was most commonly affected [29]. However, they did not explain why some patients showed an increase while others presented with a decrease in metabolism for the same brain compartment. Similarly, Robbins et al. studied the impact of PCI on ^{18}F-FDG uptake and cognitive impairment on non-human primates [30]. They showed a decrease in metabolism in the cuneate and prefrontal cortex, and an increase in the cerebellum and thalamus [30]. A direct comparison with our study is difficult, although non-human primate brains have similarities with human brains, the response mechanism to radiation might be different. In addition, Robbins et al. used a different radiation regimen of 40 Gy in two 5 Gy fractions per week for 4 weeks. Radiation toxicity is modulated by total dose and fractionation, and differences in the radiation protocol may also explain some of the dissimilarities.

Our study demonstrated that HS preserves hippocampal metabolic activity. Patients who underwent HS-PCI present a non-significant variation of −1.4% in the hippocampi, whereas patients receiving a full irradiation dose to the hippocampi, showed a significant variation of −5%.

Our study is the first to show metabolic preservation of hippocampal activity in patients receiving HS using ^{18}F-FDG PET/CT. Dose to the hippocampi may be reduced up to 80% by implementing HS-PCI according to some studies [31]. Such steep reduction in hippocampal radiation poses the risk of decreased PTV coverage and therefore increased risk of intracranial progression in the spared brain tissue, which will extend beyond the delineated hippocampi. The HIPPORAD trial, a phase II study aiming to compare

the impact of HS on neurocognitive function in patients with multiple BM treated by WBRT and simultaneous integrated boost (SIB) versus HS-WBRT + SIB, is ongoing. Their dose constraints (D98% $\leq$ 9 Gy and D2% $\leq$ 17 Gy) for the HS-WBRT arm lead them to a hippocampal Dmean $\leq$ 10 Gy ([35]). In our case, dose to the hippocampi was reduced by approximately 50% (Dmean = 12.2 Gy) with no compromise on PTV coverage. This reduction was sufficient to preserve hippocampal metabolic activity.

None of our patients underwent standardized neurocognitive evaluation, and no clinical implications may be directly drawn from our results regarding the neurotoxocity of PCI and potential neurocognitive benefit of HS. However, some studies have shown direct correlation between hippocampal hypometabolism and cognitive decline, mild cognitive impairment (MCI) and even Alzheimer's disease (AD) [36-38]. Our results suggest that HS, by conserving hippocampal metabolism, may preserve cognitive function, this requires a prospective evaluation to be confirmed.

The impact of cerebral radiation on cognitive function has been the subject of several studies [33,39,40], with discordant results due to the presence of many confounding factors including inhomogeneous populations, and a wide variability of interval between radiation and cognitive evaluation. Nonetheless, it is widely assumed that PCI leads to some degree of neurocognitive loss largely due to hippocampi radiation, a highly radiosensitive structure responsible for memory formation [41]. This has encouraged the development of HS-PCI, but HS is also the centre of controversy. Indeed, although it may seem like an elegant and attractive alternative to standard PCI, and has shown some promise in a phase II study [31], there is no consensus on its clinical impact and needs further confirmation from a phase III study. Two recently published phase III studies evaluated HS's clinical benefit, and results are contradictory. Indeed, Brown et al.'s phase III trial evaluated the impact of HS during WBRT in preserving neurocognitive function, with results favoring HS [42]. On the other hand, Belderbos et al.'s single-blinded phase III trial [43], did not show any neurocognitive benefit of HS. Our results add to the heated debate amongst radiation oncologists over the toxicity of PCI and the potential clinical benefit of HS.

All patients analyzed in our study received multimodal treatment for SCLC including chemotherapy and chest radiation (either concurrently or as consolidative treatment) prior to PCI. Our entire cohort received the same systemic regimen of platinum-based chemotherapy in association with etoposide. Chemotherapy is known to have neurotoxic side effects which may alter cognitive function [44-46]. The extent to which this neurotoxicity participates to our observations is unclear. A third of our patients received immunotherapy, which may also impact our results, although to date very little is known about potential neurotoxic effects of such treatments [47].

Our study's results and interpretation were affected by its retrospective design and the small cohort. Indeed, all patients underwent a standard oncological acquisition protocol PET/CT instead of a dedicated ^{18}F-FDG cerebral acquisition protocol. Some patients had brain MRI follow-up using standard oncological procedure, neither adequate nor aimed at hippocampal analysis which would have enabled us to draw parallels with our observations. Another limitation is the variability of interval between the end of radiation therapy and the second PET/CT was wide. Indeed, although most patients underwent the second PET/CT within a year after PCI, 8 patients had a longer time lapse between the end of radiation and the second PET/CT (up to three years). This is noteworthy because cerebral radiation toxicity is often described in three phases: acute, occurring days to weeks after radiation exposure; early delayed occurring 1–6 months after; and late, over 6 months after [12]. The physiopathology behind these different stages may differ, hence causing variations in cerebral metabolism, and some degree of recovery in cognitive function has even been described [48]. Large variation of time between radiation and PET/CT did not alter our observations, and cerebral glucose metabolism remained diffusely reduced, even with longer intervals. Our results suggest that cerebral radiation has a long-term effect on cerebral glucose metabolism.

Conclusion

In conclusion, our retrospective study of brain metabolism using ^{18}F-FDG PET/CT in SCLC patients who underwent PCI showed that cerebral irradiation leads to a diffuse decrease in cerebral ^{18}F-FDG uptake. A 50% decrease in radiation dose delivered to the hippocampi during HS-PCI preserves the metabolic activity of that area.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.02.016.

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