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Pilot Study: Regional Changes in Brain ^{18}F-FDG Uptake After Prophylactic Cranial Irradiation and Chemotherapy in Small Cell Lung Cancer May Reflect Functional Changes

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Pilot Study: Regional Changes in Brain ^{18}F-FDG Uptake After Prophylactic Cranial Irradiation and Chemotherapy in Small Cell Lung Cancer May Reflect Functional Changes

Objective:

Chemotherapy followed by prophylactic cranial irradiation (PCI) is associated with increased survival in patients with small cell lung cancer (SCLC) but is associated with fatigue and cognitive impairment. This retrospective study evaluated regional differences in fluorodeoxyglucose (^{18}F-FDG) uptake of the brain before and after PCI. The null hypothesis was that direct toxic effects on the brain from PCI and chemotherapy are symmetric, thus asymmetric deviations may reflect functional changes due to therapy.

Materials and Methods:

Electronic medical records from 2013-2016 were reviewed for patients with SCLC, MRI of brain negative for metastasis, and ^{18}F-FDG-positron emission tomography/computed tomography (PET/CT) scans pre- and post PCI. As standard of care, patients received first-line chemotherapy or chemoradiation to the thorax followed by PCI. The ^{18}F-FDGPET/CT scans closest in temporal proximity before and after PCI were selected. Sixteen patients met these initial criteria. Commercially available PET software (MIM) was utilized to register and subtract the PET scans pre-and post PCI to obtain difference maps. Occipital and cerebellar regions were excluded from the final statistical analysis given known high variability and misregistration. The Chi-square test was used to analyze the data.

Results

Two patients had ^{18}F-FDG uptake differences only in occipital and cerebellar regions. The software registration failed on one patient's scans. Therefore, thirteen patients were included in the final analysis. Nine of thirteen patients demonstrated significant unilateral changes in only one region of the brain, and three of thirteen showed significant changes unilaterally in two regions. The Chi-square test revealed a significant unilateral regional difference on the patient level ($X^2 = 6.24$, $p = 0.025$). The most commonly affected brain region was the frontal lobe.

Conclusion

Significantly more patients had unilateral rather than bilateral regional differences (both increases and decreases) in ^{18}F-FDG uptake in the brain pre-and post PCI. This suggests that differences in unilateral distribution are related to functional changes, since direct toxicity alone from PCI and chemotherapy would be symmetric. The frontal region was the most commonly affected, suggesting a potential contributing etiology for cognitive impairment and decreased executive function after therapy.

Introduction

Approximately 5-10% of patients with lung cancer are diagnosed with high-grade malignancy small cell lung cancer (SCLC). SCLC originates from neuroendocrine cells in the bronchus (*1*). The greatest risk factor for this type of lung cancer is smoking. Treatments for SCLC are limited. Depending on tumor stage and individual factors, surgical resection, chemotherapy or chemotherapy combined with radiotherapy to the thorax are considered. Platinum-based chemotherapy remains the standard first-line chemotherapy in limited as well as extensive stage disease (*2*,*3*).

A recent meta-analysis demonstrated a relative risk of approximately 45% for developing brain metastasis within one year after diagnosis for SCLC, plus a decreased incidence of brain metastasis after PCI (*4*). Multiple studies reported increased survival after prophylactic cranial irradiation (PCI) in patient with SCLC; however, controversy does exist in the literature with one studying show similar outcomes of PCI versus a strategy of close observation with MRI (*5*-*7*). Additionally, cognitive impairment has been observed after chemotherapy, especially when combined whole brain radiation therapy (*8*-*9*). A MRI study on patients with SCLC who received chemotherapy and PCI showed an association between long-term cognitive effects and structural brain changes (*10*).

This retrospective pilot study is the first to evaluate regional differences in fluorodeoxyglucose (^{18}F-FDG) uptake of the brain in SCLC patients before and after PCI (all patients had already received first-line chemotherapy). The null hypothesis was that direct toxic effects on the brain from chemotherapy and whole brain irradiation are symmetric. Hence, asymmetric differences of ^{18}F-FDG uptake in the brain may represent functional changes as consequences of the therapy.

Methods

Patient selection

This retrospective study was approved by the institutional Human Subjects Protection Program. From 2013 to 2016, the electronic medical record database was searched for patients with biopsy proven SCLC, who received standard of care first-line chemotherapy followed by prophylactic cranial irradiation (PCI) with 25 Gy in 10 fractions at 2.5 Gy per daily fraction. Patients were excluded if they had brain metastases or any other intracranial pathology, which could alter ^{18}F-FDG uptake. All included patients had fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scans performed at our institution pre and post PCI as part of standard of care assessment of tumor response. The^{18}F-FDG PET/CT scans closest in temporal proximity before (about 2 months) and after (about 3 months) PCI were selected. All ^{18}F-FDG PET/CT scans at our facility extend from vertex to thigh. 27 patients with SCLC were treated over this time period, and 16 patients met the inclusion criteria.

PET/CT scanning

A minimum of 4 hours fasting prior to intravenous (IV) administration of ^{18}F-FDG was standard for all patients. Fingerstick blood glucose levels were measured before IV injection of ^{18}F-FDG at a weight-based dose of 3.7 MBq (0.1 mCi)/kg with a range of 185 MBq (5 mCi) to 370 MBq (10 mCi). After injection of ^{18}F-FDG, the patients sat quietly awake for approximately 60 min. ^{18}F-FDG PET/CT was performed from vertex to thighs using a General Electric 690 time-of-flight PET/CT scanner. A low dose CT scan was obtained without IV contrast and with oral contrast before the PET acquisition. The acquisition time was 2.5 minutes per bed position, and 7-8 bed positions were used depending on the height of the patient. The PET data were

reconstructed using an ordered-subsets expectation maximization algorithm (28 subsets, 2 iterations).

Analysis of PET/CT scans

The two most recent ^{18}F-FDG PET/CT scans before (about 2 months) and after (about 3 months) PCI were analyzed. The brain portions of the scans were saved as separate files and analyzed using commercially available software (MIM © 2017 MIM Software Inc.). MIM-neuro, quantitative analysis brain software, was used to register and subtract the brain PET scans (pre- and post PCI) and obtain difference maps. The baseline scan was first registered to a template image in order to define the whole brain outline region. A mutual information-based algorithm was then used for image co-registration. Registration was performed using the Assisted Alignment method, and the alignment was manually corrected as necessary. The two images were auto normalized within the whole brain outline region, and subsequent z-score analysis was restricted to this region. For PET subtraction analysis z-scores, the mean and standard deviation were calculated for all voxels contained within the brain mask contour on the subtraction data. In MIMneuro, The z-score analysis window displays regions with low metabolism/perfusion and regions with increased metabolism/perfusion. Regions are displayed in the hyper or hypo z-score list if the region is unilaterally hyper or hypo, even if the entire bilateral region is not hyper or hypo (MIM © 2017 MIM Software Inc.). For each patient, areas of the brain with differences greater than a z-score of +/- 2.5 were recorded. Each area of significant difference was categorized into one of five lobar regions (frontal, parietal, temporal, occipital or cerebellar) by the software program. The occipital region was excluded from the final analysis given the known high variability in this region from visual stimulation. The cerebellar region was also excluded due to misregistration of brain to bone.

Statistical analysis

The data were analyzed using single variable Chi-square tests to determine if the distribution demonstrated significant changes occurring in only one region (asymmetric) of the brain or bilaterally (symmetric).

Results

Sixteen patients with biopsy proven SCLC met the inclusion and exclusion criteria. The software registration failed for one patient, and two patients had ^{18}F-FDG uptake differences only in occipital and cerebellar regions. Thus, 13 patients were included in the final analysis for regional cerebral differences. The mean age was 65 years (range 49-78), 6/13 (46%) were female, and 5/13 (38%) had limited stage and 8/13 (62%) had extensive stage SCLC. Table 1 provides the characteristics of the study population.

The average blood glucose measured before injection of ^{18}F-FDG on the pre-PCI ^{18}F FDG-PET/CT was 117 mg/dl (range 83-281 mg/dl) and on the post-PCI ^{18}F FDG-PET/CT was 98 mg/dl (range 80-121 mg/dl). The mean of the differences of blood glucose subtracting post from pre-PCI on an individual basis was 19 mg/dl with standard error of 14 mg/dl. The average uptake time of ^{18}F-FDG for pre PCI ^{18}F-FDG PET/CT was 62 minutes (range 49-70 minutes) and for post PCI ^{18}F-FDG PET/CT was also 62 minutes (range 51-75 minutes).

Statistically significant increases or decreases in regional cerebral FDG uptake pre-PCI compared to post-PCI were found in 13 patients. Nine of thirteen patients (69%) demonstrated significant unilateral changes in only one region of the brain (Fig.1), and three of thirteen (23%) showed significant changes unilaterally in two regions. Only one patient showed bilateral changes (frontal). Therefore, twelve of thirteen (92%) patients showed unilateral regional changes. Overall a Chi-square test for unilateral regional differences on the patient level was

significant ($X^2 = 6.24$, $p = 0.025$). Eight patients showed significant positive z-score differences ($z \geq 2.5$) and 3 displayed negative z-score differences ($z \leq -2.5$). Two patients demonstrated negative as well as positive z-score differences in different regions. The most commonly affected cerebral region was the frontal lobe in 8 of 13 (62%) patients. Five patients showed significant differences in the parietal lobe and 3 in the temporal lobe (Table 2).

Discussion:

To the best of our knowledge, this retrospective pilot study is the first to investigate regional increases or decreases in ^{18}F-FDG uptake of the brain pre- and post-PCI in patients with SCLC (all previously treated with first-line chemotherapy). If changes in FDG uptake were solely due to direct cellular toxicity from systemic chemotherapy and/or whole brain irradiation and not due to functional changes, one would expect to see symmetric differences in ^{18}F-FDG uptake in the brain pre- and post-radiation. However, significantly more patients had unilateral (92%) rather than bilateral (8%) regional uptake differences. The Chi-square test for unilateral regional difference on the patient level was significant ($p = 0.025$). The percentage of asymmetric regional differences in ^{18}F-FDG uptake in the cerebrum after chemotherapy and PCI suggests that functional brain changes related to PCI are likely common. The frontal lobe was the most commonly affected cerebral region.

Horky et al. found decreased glucose metabolism in both gray and white matter structures associated with chemotherapy for small cell lung cancer, and the frontal cortex was more affected (*11*). In breast cancer patients, Silverman et al. used a combination of [O-15] water and ^{18}F-FDG PET to reveal changes in activity of frontal cortex 5-10 years after completion of chemotherapy (*12*). This result in the frontal region may suggest an etiology for cognitive impairment after therapy, also referred to as “chemo-brain.” Prior studies in SCLC have also

shown that first-line chemotherapy followed by PCI was associated with development of cognitive impairment (*9,10*). Commonly reported cognitive dysfunctions include decreased attention, loss of concentration and impaired memory (13).

A limitation of this pilot study is the relatively small sample size. However, our results are in line with the above cited studies and thus together do support the hypothesis that asymmetric differences of FDG uptake in the brain may represent functional changes as consequences of PCI post chemotherapy. These results justify assessing functional changes in the brain by ^{18}F-FDG PET/CT in a larger, prospective study which would allow for correlation of ^{18}F-FDG PET/CT parameters (by region and direction of change) with cognitive testing and quality of life assessments. This analysis could also be performed for patients with different types of cancers and therapies, which may allow separation of the effects of chemotherapy from radiation therapy. Another possible limitation is that despite instructions to sit quietly, patients may have been active during the FDG uptake period.

Conclusion: This retrospective pilot study of SCLC patients who underwent chemotherapy followed by PCI found unilateral increases and decreases in ^{18}F-FDG uptake of the brain pre-and post PCI. Importantly, asymmetric rather than symmetric regional differences were observed which suggests functional changes after PCI since direct toxicity alone from PCI and chemotherapy would be symmetric. The most commonly affected region was the frontal cortex, which may suggest an etiology for cognitive difficulties after therapy.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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Table 1: Overview of patient characteristics

Total (n = 13)		
Characteristic		
Age (years)	**Mean (range)**	65 (49-78)
Gender	**Female**	6 (46%)
	Male	7 (54%)
Stage of the disease	**Limited**	5 (38%)
	Extensive	8(62%)

Table 2: Regional z-score differences for each patient

No. Patients (n=13)		**Z-Score ***
One cerebral region affected unilaterally		
1	R Frontal	+
2	R Frontal	+
3	R Frontal	-
4	L Frontal	+
5	R Frontal	-
6	L Temporal	+
7	L Temporal	+
8	R Parietal	+
9	R Parietal	-
Two cerebral regions affected unilaterally		
10	L Parietal	-
	R Frontal	+
11	L Frontal	+
	L Parietal	-
12	R Parietal	+
	L Temporal	+
One cerebral region affected bilaterally		
13	R Frontal	+
	L Frontal	+

***Z-Score: (+) =** $z \geq 2.5$, (-) = $z \leq -2.5$

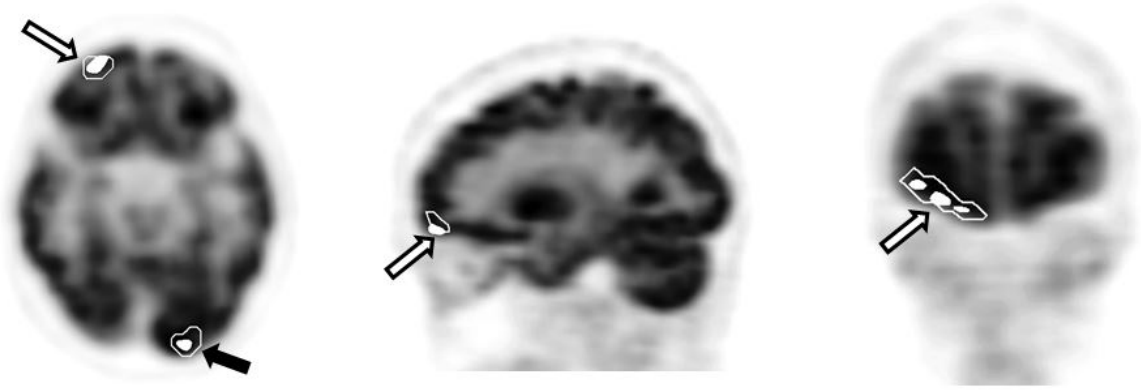

Figure 1:

Subtracted, pre and post PCI FDG-PET images using MIMneuro software are presented in the transaxial (left), sagittal (middle), and coronal (right) planes. A region of the right frontal lobe (white arrows) was calculated to have FDG uptake difference greater than Z-Score ≥ +2.5. A region of the left occipital lobe (black arrow) also demonstrated a difference after subtraction.