Am J Nucl Med Mol Imaging 2020;10(1):66-73
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0104699

Original Article

^{18}F-FDG-PET/CT in the quantification of photon radiation therapy-induced vasculitis

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Received November 9, 2019; Accepted February 25, 2020; Epub February 25, 2020; Published February 28, 2020

Abstract: Radiation therapy (RT) is an important component of care for head and neck cancers (HNC). Photon RT vasculitis is a complication of incidental dose delivery to nearby vascular structures. However, optimal methods for early diagnosis are not clearly established. The aim of this study was to evaluate ^{18}F-FDG-PET/CT in detecting radiation-induced vasculitis of the left common carotid (LCC) and the arch of the aorta (AoA) in patients treated for HNC. ^{18}F-FDG-PET/CT scans obtained before RT (Pre-RT) and 3 months after RT (Post-RT) were retrospectively reviewed in 30 HNC patients (25 males, 5 females; average age 57.9±8.1 years) treated with photon RT. All subjects underwent ^{18}F-FDG-PET/CT imaging 60 minutes after 5.0 MBq/kg ^{18}F-FDG injection. Average standard uptake values (Avg SUVmean) of the LCC and AoA were obtained by global assessment. A two-tailed paired t-test was used to assess the difference in Avg SUVmean between pre- and post-RT imaging. Subjects demonstrated significant increased Avg SUVmean within the LCC post-RT (pre = 1.42, post = 1.65, P<0.001), with a mean increase of 0.23 SUV. Similarly, subjects exhibited higher ^{18}F-FDG uptake in the AoA post-RT (pre = 1.44, post = 1.69, P<0.01), with a mean increase of 0.23 SUV. ^{18}F-FDG-PET/CT may be used to detect and quantify photon RT vasculitis in HNC patients. Further investigation is warranted to evaluate the clinical implications of this pathology and the role for alternative treatment strategies in minimizing tissue toxicity.

Keywords: PET/CT, ^{18}F-FDG, photon therapy, radiation therapy, vasculitis, head and neck cancer

Introduction

More than 680,000 patients are diagnosed globally with head and neck cancers each year [1]. The majority of patients receive photon radiotherapy (RT) as either definitive or adjuvant therapy. In head and neck malignancies, RT is a critical component of care, with treatment guidelines dependent largely on disease stage, site, and presentation [2-4]. Despite advancements in modern head and neck radiotherapy, including intensity modulated radiotherapy (IMRT), radiation can induce significant toxicities in normal tissues, which can override the benefits of metastatic control gained with RT [5].

In particular, prior studies have demonstrated an increased risk of vascular stenosis and cerebrovascular accidents following RT to the head and neck [6, 7]. Vasculitis can cause debilitating pathologies, including ischemia, hemorrhage, and tissue necrosis [8]. Abnormal blood flow in the carotid arteries may additionally lead to irreversible brain damage and potentially death [9, 10]. Thus, early identification of RT-induced vasculitis is crucial to optimizing patient outcomes and guiding clinical management following head and neck photon RT. However, optimal screening and intervention strategies to help mitigate this risk remain poorly defined [11]. Further investigation into how patients and providers can maximize the

Table 1. Patient characteristics

Distribution of Tumor	Grade	Age at Baseline	Sex	Race
Tongue (n = 13)	3: 2 4A: 9 4B: 2	61.3±6.9	M: 11 F: 2	W: 10 AA: 3
Nasopharynx (n = 3)	3: 1 4A: 2 4B: 0	58.0±3.1	M: 3 F: 1	W: 2 AA: 1
Oropharynx (n = 8)	3: 1 4A: 6 4B: 1	54.7±8.0	M: 8 F: 0	W: 7 AA: 1
Hypopharynx (n = 1)	3: 0 4A: 0 4B: 1	47.9	M: 1 F: 0	W: 0 AA: 1
Larynx (n = 5)	3: 2 4A: 3 4B: 0	57.1±12.1	M: 3 F: 2	W: 5 AA: 0
n = 30	3: 6 4A: 20 4B: 4	57.8±8.1	M: 25 F: 5	W: 24 AA: 6

M = male, F = female, W = white, AA = black or African American.

beneficial effects of photon RT while minimizing unfavorable side effects or the development of additional pathologies is paramount in the progression of cancer research.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a tracer for glucose metabolism, a process that is upregulated in tumor cells and inflammatory states [12]. ^{18}F-FDG-positron emission tomography/computed tomography (PET/CT) is a powerful imaging technique that has demonstrated high value in the management of head and neck malignancies [13]. Differentiation of residual disease from RT complications can be challenging with structural imaging techniques, like CT and MRI, due to loss of normal anatomy [14]. In contrast, ^{18}F-FDG-PET/CT evaluates metabolic activity as a marker of tumor cell viability, which overcomes the known limitations of structural imaging modalities [15].

Additionally, ^{18}F-FDG-PET/CT has demonstrated clinical utility in the diagnosis of vasculitis of varying severity [16]. As such, we predict that ^{18}F-FDG-PET/CT will be a useful imaging technique in head and neck photon RT patients, not only for the evaluation of tumor cell viability, but also for the identification of patients at risk for developing vasculitis, with the potential to diagnose subclinical disease before the damage becomes irreversible. Here, we aim to evaluate the role of ^{18}F-FDG-PET/CT imaging in the detection of vascular inflammation in the left common carotid artery (LCC) and the arch of the aorta (AoA) following photon RT for head and neck malignancies.

Methods

Study population

This study included 30 patients (25 males, 5 females; average age = 57.9±8.1 years) with head and neck cancer who were treated with photon RT at the University of Pennsylvania between 02/09/2010 and 11/27/2018. Information regarding additional diagnoses was unavailable and were not utilized in data acquisition. Only patients imaged with ^{18}F-FDG-PET/CT before RT and 3 months following photon RT, with both scans of an imaging quality able to identify and trace structures of interest, were included. All patients received weekly cisplatin and cetuximab chemotherapy concomitant to two sessions of photon RT. Patients only received photon RT targeted to the area where their tumors were located in their head and neck area. Patient demographics and tumor distribution are further described in **Table 1**. The study received Institutional Review Board approval and was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Image acquisition

All subjects underwent ^{18}F-FDG-PET/CT imaging 60 minutes after a dose of 5.0 MBq/kg ^{18}F-FDG injected intravenously. Each scan was obtained using the same protocol, and imaging was performed on hybrid PET/CT scanners with a comparable spatial resolution (Siemens 923/Biograph 64 mCT (Siemens Healthineers AG, Chicago, IL, USA); Philips Ingenuity TF/Gemini TF 16 (Philips Medical Systems, Andover, MA, USA)). Low-dose CT imaging was performed for attenuation correction and anatomic correlation. PET scans were corrected to account for scatter, attenuation, random coincidences, and scanner dead time.

^{18}F-FDG-PET/CT image analysis

OsiriX MD software v.10.0.2 (DICOM viewer and image-analysis program, Pixmeo SARL; Bernex, Switzerland) was used to analyze the ^{18}F-FDG-

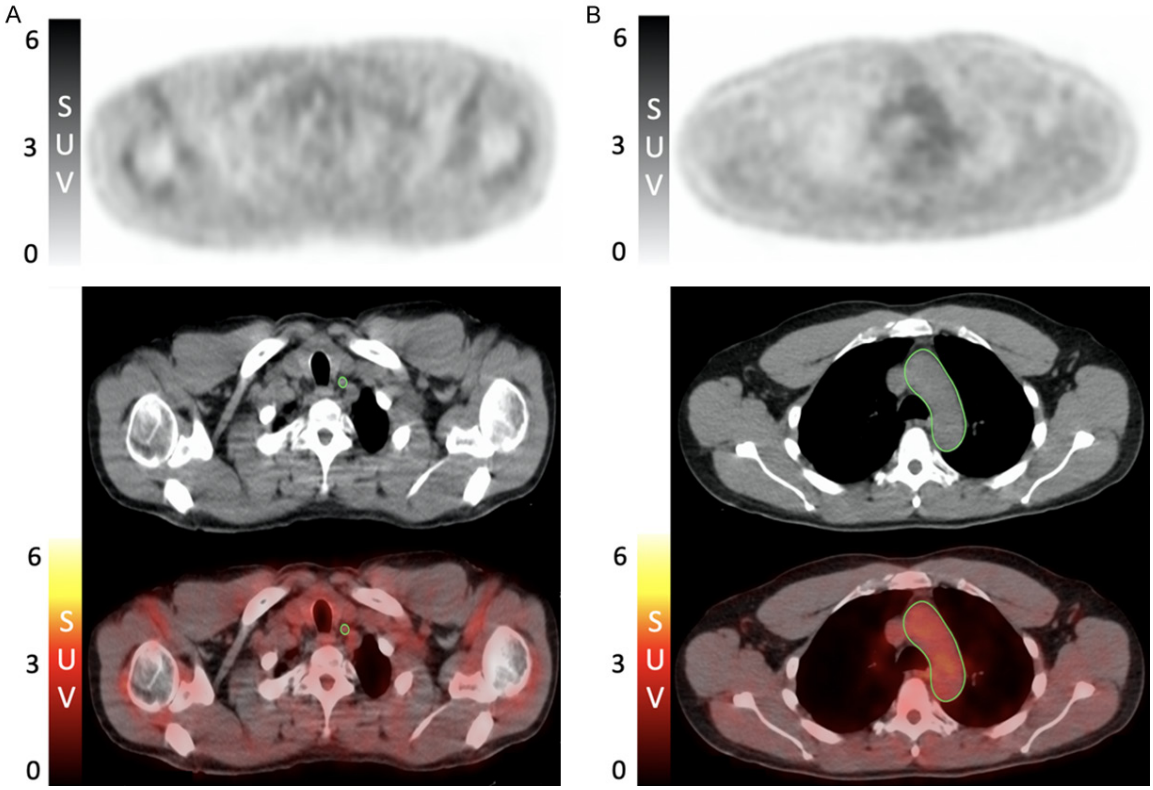

Figure 1. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) images of (A) the left common carotid artery and (B) the arch of the aorta. Top: PET, middle: CT, bottom: fused PET/CT. Indicated regions are highlighted in green to aid in visualization.

Table 2. Global ^{18}F-FDG uptake in the left common carotid and arch of the aorta of head-and-neck cancer patients before and 3 months after radiation therapy

	Pre-RT	Post-RT	*P*-value
LCC	1.42±0.26	1.65±0.26	0.0004
AoA	1.44±0.33	1.69±0.28	0.004

LCC = left common carotid artery, AoA = arch of the aorta, RT = radiation therapy.

PET/CT scans. Semi-quantification of ^{18}F-FDG uptake was calculated from regions of interest (ROIs) manually drawn around the LCC and AoA structures on axial PET/CT images (**Figure 1**).

LCC ROIs were drawn beginning inferiorly at the initial branch of the superior AoA. The bifurcation into the internal and external carotid arteries was defined as the superior border. AoA ROIs were drawn beginning just inferior to the branching of the brachiocephalic trunk. The split into the ascending and descending branches of the aorta was defined as the inferior border, to separate the AoA from other parts of the aorta. SUVmean and ROI volume were measured for each trans-axial slice. The tracer uptake in each slice was calculated by multiplying the slice SUVmean by the slice ROI volume. Avg SUVmean across all slices was used for statistical comparison.

Results

In the current study, 30 head and neck cancer patients were included for evaluation. Patient characteristics are shown in **Table 1**. The Avg SUVmean of the LCC and AoA measured by ^{18}F-FDG-PET/CT were compared pre- and post-RT (**Table 2**). Avg SUVmean was calculated for each subject pre- and post-photon RT. A two-tailed paired t-test in STATA software (Stata/IC Version 10.1, StataCorp, College Station, TX) was used to analyze the Avg SUVmean pre- and post-photon RT. A *p*-value of less than 0.05 was defined as significant. The mean increase in Avg SUVmean was calculated by subtracting pre-photon RT Avg SUVmean from post-photon

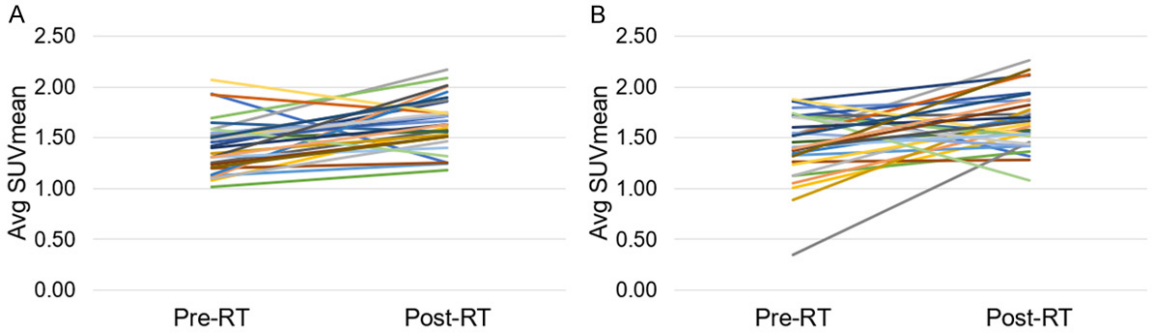

Figure 2. Change in ^{18}F-FDG average standardized uptake value mean (Avg SUVmean) from before radiation therapy (Pre-RT) to 3 months after radiation therapy (Post-RT) in (A) the left common carotid and (B) the arch of the aorta.

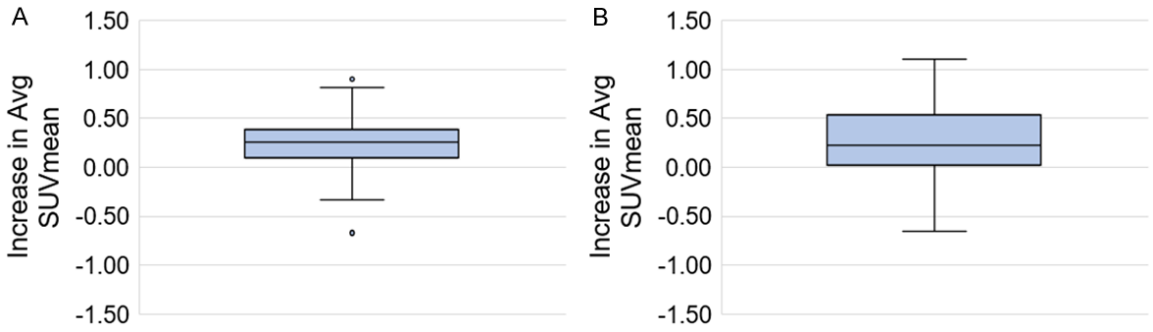

Figure 3. Box-and-whisker plot of difference (pre-radiation therapy minus 3-month-post-radiation therapy) in ^{18}F-FDG average standardized uptake value mean (Avg SUVmean) in (A) the left common carotid and (B) the arch of the aorta.

RT values for each patient, then taking the average.

Subjects demonstrated significant increased Avg SUVmean within the LCC post-RT (pre = 1.42, post = 1.65, P<0.001) (**Figure 2A**), with a mean difference of 0.229 SUV (**Figure 3A**). The increased ^{18}F-FDG uptake in the LCC demonstrates vascular inflammation after RT therapy.

Similarly, subjects exhibited higher ^{18}F-FDG uptake in the AoA post-RT (pre = 1.44, post = 1.69, P<0.01) (**Figure 2B**), with a mean difference of 0.233 SUV (**Figure 3B**). As was the case in the LCC, increased ^{18}F-FDG uptake in the AoA after RT is indicative of treatment-related vasculitis.

Discussion

Our study demonstrates a significant increase in the uptake of ^{18}F-FDG-PET/CT in the LCC and AoA of head and neck cancer patients following photon RT. Investigating the relationship between RT and vasculitis is a particularly important avenue of study. RT may have the potential to ameliorate tumors, but this benefit must be balanced against an increased risk of cardiovascular complications. To our knowledge, this is the first study that has assessed ^{18}F-FDG-PET/CT uptake in the LCC and AoA of head and neck cancer patients in order to better investigate this concept. Although the exact mechanism behind the correlation between photon RT and vasculitis is unknown, our findings suggest a relationship between photon RT and inflammatory responses in these vessels, which may influence health outcomes in patients. Particularly, because the AoA is out of the radiation field range for most head and neck cancer patients, this data may indicate the possibility of a larger systemic effect from photon RT on the vasculature of patients.

Data regarding vasculitis derived from PET/CT may provide additional clinically useful information for oncologists providing survivorship related care to patients previously treated for head and neck cancer. Severe vasculitis in the carotid arteries can lead to stenosis, which is associ-

ated with cognitive decline resulting from CVA and transient ischemic attack [17, 18]. As such, future studies should assess the effects that photon RT may have on morbidity and mortality.

^{18}F-FDG-PET/CT has demonstrated utility in the imaging of multiple pathologies, including cancer, neurodegenerative disorders, and cardiovascular abnormalities [19-21]. Particularly, ^{18}F-FDG-PET/CT can identify inflammation and diseased tissues within specific regions of interest, which makes it a powerful diagnostic tool. Several authors have shown that ^{18}F-FDG-PET/CT has diagnostic capabilities in recognizing infections or inflammation in the aorta, which our work has further confirmed [22, 23]. Kang *et al*. have also demonstrated that ^{18}F-FDG-PET/CT may be used to track the anti-inflammatory effects of a statin on atherosclerotic lesions in the carotid arteries, as well as the ascending thoracic aorta [24]. The clinical usefulness of ^{18}F-FDG-PET/CT to detect diseased tissues before, during, and after RT and/or chemotherapy in head and neck cancer patients has been explored in several studies [25, 26]. However, the inflammatory ^{18}F-FDG uptake in photon RT-induced vasculitis is valuable information that has not yet been extracted from PET images. Taken together, these previous studies support our use of ^{18}F-FDG-PET/CT in the present study. Our quantitative analysis has combined the diagnostic capabilities of ^{18}F-FDG-PET/CT in both cardiovascular disease and cancer to investigate the relationship between photon RT and vasculitis in head and neck malignancies.

Few authors have used ^{18}F-FDG-PET/CT to elucidate the association between cancer therapeutic avenues and cardiovascular events. Bauckneht *et al*. identified a left ventricular (LV) ^{18}F-FDG uptake increase from pre-treatment to 4-6 weeks after the completion of doxorubicin chemotherapy, which persisted to a 3-month follow-up, in patients with Hodgkin's disease [27]. Authors from the same research group found that this increase in LV ^{18}F-FDG-PET/CT uptake in Hodgkin's lymphoma patients is positively correlated with decreased left ventricular ejection fraction (LVEF) after 2 cycles and at the conclusion of doxorubicin chemotherapy when compared to LVEF before treatment (12). ^{18}F-FDG-PET/CT has also been used to study thyroid carcinoma patients whose thyrotropic hormones were suppressed, in order to identify a significant increase in arterial inflammation following radioiodine ablation therapy [28]. Moreover, Jahangiri *et al.* utilized ^{18}F-FDG-PET/CT to conclude that lung cancer patients treated with RT experienced increased inflammation in the AoA and ascending aorta [29]. While these authors have probed the possibility of a relationship between cancer therapies and arterial inflammation, existing research has largely overlooked the potential for vasculitis in head and neck cancer patients who receive photon RT. This has led to a gap in knowledge regarding the proper assessment of cardiovascular risk factors prior to and following photon RT in head and neck cancer.

There are several limitations to the present study. This is a retrospective analysis of a small sample, so future assessments of ^{18}F-FDG-PET/CT as an identifier of RT-induced vasculitis should be tailored towards larger prospective studies. Furthermore, because the full tumor stage, type of radiation field, and the exact dose of radiotherapy administered to patients were not available to be included in this study as defining parameters, a more detailed description of the patient cohort could not be established. In addition, the volume-based parameters utilized to obtain the ROIs are subject to the partial volume effect, which has the potential to skew the results due to overlap from neighboring structures and potential movement of patients during image acquisition [30-32]. This is due largely to the limited resolution of the technology utilized and possible human error. Such variance could explain the outlier observed in the data (**Figure 2B**). Nonetheless, additional variance due to anatomic differences or common carotid origin between subjects was minimized by assessing the LCC instead of the right common carotid [33]. Ideally, we would have preferred to have utilized scans generated with delayed imaging. The subjects who participated in this study received their scans 60 minutes after the introduction of ^{18}F-FDG administration. However, work by Blomberg *et al.* has suggested that a 180 minute delay between ^{18}F-FDG administration and imaging is more favorable for the quantification of vascular inflammation, particularly due to atherosclerotic plaque formation [34]. This is because blood-pool activity, which can disturb the ^{18}F-FDG signal in the wall of the arteries, gradually decreases with time [35]. Nonethe-

less, our results demonstrate the severity of the vasculitis in these patients, since a delay that was a third of what is considered optimal still generated statistically significant results in increased ^{18}F-FDG uptake.

Our study examines SUVmean to quantify inflammatory activity of the LCC and AoA, rather than SUVmax. The latter measurement may be more sensitive to changes; however, SUVmax is not as representative of disease activity [36]. In contrast, SUVmean is a more sensitive and specific measure of disease activity in vascular inflammation than SUVmax. As such, the present study utilizes a robust and reproducible methodology for the assessment of vasculitis in these patients.

Furthermore, this study examines only two time-points: pre- and 3-months-post photon RT. It would be beneficial to existing research to perform a longitudinal ^{18}F-FDG-PET/CT analysis of LCC and AoA vasculitis in these patients to assess the extent of vasculitis over time. Additional analysis, including correlating post-RT ^{18}F-FDG uptake to post-mortem histopathological markers of vasculitis, would further add evidence to the detrimental effects of photon radiation [37].

Finally, this study does not separate the effects of radiation from the effects of chemotherapy, which may have influenced the results. Additionally, chemotherapy may contribute to renal damage, which may cause a decreased glomerular filtration rate and resultant reduction in renal clearance of ^{18}F-FDG [38]. However, Akers *et al.* did not find a significantly affected ^{18}F-FDG distribution in patients with a disrupted renal function [39]. Additionally, ^{18}F-FDG-PET/CT has demonstrated utility in the assessment of leukemia treatment post-chemotherapy, suggesting that inflammatory chemotherapy effects are transient [40]. Finally, previous studies have examined the inflammatory effects of RT despite concomitant chemotherapy [41]. As such, we are confident that our results demonstrate the adverse effects of RT rather than chemotherapy. Moving forward, we anticipate additional studies to better characterize the differential effects of photon RT and chemotherapy.

Conclusion

We have demonstrated the potential application of ^{18}F-FDG-PET/CT for the diagnosis of radiation-induced vasculitis of the LCC and AoA in head and neck cancer patients. This study used volume-based parameters to quantify vascular ^{18}F-FDG uptake pre- and post-photon RT, revealing significant associations between photon RT and localized inflammation in the LCC and AoA. Future evaluation in large-scale trials would be useful for characterizing ^{18}F-FDG-PET/CT imaging in the diagnosis of photon RT-induced vasculitis and its potential role in elucidating toxicity benefits afforded by alternative treatment therapies.

Disclosure of conflict of interest

None.

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