Lung Cancer Patients May Have Higher Aortic Wall Inflammation on ^{18}F-FDG PET/CT Compared to non-lung Cancer Patients.

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ABSTRACT:

Purpose: Our aim is to investigate the role of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in assessing atherosclerosis (AS) risk in lung cancer patients compared to patients with other types of cancer. **Methods:** This prospective study enrolled 60 cancer patients (30 lung cancer and 30 non-lung cancer) who were referred for ^{18}F-FDG PET/CT. The aortic average max standardized uptake value (average SUV max) was calculated by drawing ROIs on the entire aorta (ascending, arch, descending thoracic and abdominal aorta till iliac bifurcation). The maximum target-to-blood pool ratio (TBR max) is calculated by dividing aortic avg SUV max by the regional blood pool average mean standardized uptake value (avg SUV mean) of superior vena cava (SVC), and inferior vena cava (IVC). TBR max was the primary outcome variable that was compared between the two cancer cohorts. Also, MVA (multivariate analysis) was performed for factors that showed significance in UVA (univariante analysis) including sex and smoking. **Results:** All aortic segments of lung cancer patients apart from the ascending aorta showed significantly higher TBR max: the aortic arch (P = 0.001), the descending thoracic aorta (P = 0.006), the abdominal aorta (P = 0.001), and the ascending aorta (P = 0.972). The lung cancer cohort has a higher proportion of men and smokers.

MVA analysis of TBR max of different aortic segments in respect to cancer type, sex and smoking status showed that for arch & abdominal aorta the highest odd ratio goes to lung cancer not male sex or smoking status, which indicate that lung cancer has the highest contribution in increased TBR max, though the absolute p value did not reach typical significant level of 0.05. **Conclusions:** TBR max of the majority of aorta segments tend to increase in lung cancer patients compared to non-lung patients independent of other known atherosclerotic risk factors; this may signify a higher burden of inflammatory plaques.

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INTRODUCTION:

AS is a condition in which the vessel wall develops a lipid-rich atheroma. Critical adverse effects include myocardial infarction or stroke from a thromboembolism brought on by atheroma as well as arterial luminal constriction [1]. Neoplasms and cardiovascular disease (CVD) are the two major causes of death globally [2].

The shared molecular routes and events, like oxidative stress, inflammation, aberrant apoptosis, unchecked cell proliferation, and *vasodilation,* serve as the connecting thread between atherosclerosis and cancer [3].

In addition, the location of the original malignancy affected the risk of AS-related CVD in cancer patients, with lung cancer being one of the malignancies with the highest risk [4].

Computed tomography (CT) is used to scan plaques, luminal stenosis severity, and alterations to the vasculature in AS [5]. However, CT detects morphological changes that become detectable late in AS.

Positron emission tomography/computed tomography (PET/CT), on the other side, recognizes changes at the molecular level that occur too early before the changes recognized by other traditional diagnostic modalities, enabling the early recognition of AS [6].

Activated macrophages in atheromatous plaques take up fluorodeoxyglucose (FDG), which is utilized to monitor inflammatory conditions like AS [7, 8], Furthermore, ^{18}F-FDG PET/CT is a powerful predictor of vascular events, e.g. atherosclerotic plaque at the molecular level before they lead to clinically detectable symptoms, supporting its use as a predictive tool in the evaluation of AS because of the relation between FDG uptake and AS progression [6, 9, 10]. Our aim in this study was to detect the risk of (AS) in lung cancer patients in comparison to patients with other types of cancer using pre-therapy initial ^{18}F-FDG PET/CT and the impact of different atherosclerotic risk factors on TBR max.

MATERIALS and METHODS:

Patient selection: Between September 2021 and February 2022, 93 patients with primary malignant neoplasms proved by pathology were referred for ^{18}F-FDG PET/CT scans at the Nuclear Medicine Unit (NEMROCK Center), Kasr Alainy Hospital, Cairo University. Sixty patients were eligible to be in our study (30 lung and 30 non-lung cancer) after the exclusion of 13 patients who had received anti-cancer therapy and 20

patients who had ended their therapy regimens and were referred for the detection of viable recurrent disease. 32 men (53%); and 28 women (47%) were included. The patient's history of smoking, diabetes, hypertension, hyperlipidemia, and obesity has been disclosed, patients with a BMI > 30 were considered obese. Patients who had received chemotherapy or radiotherapy, were known to have cardiovascular disease or any vascular intervention, had malignant tumors with vascular invasion detected by radiological imaging, were pregnant women, or children under the age of 18 were excluded from the study. Imaging was performed using an integrated PET/CT scanner (Philips Ingenuity PET/CT system).

^{18}F-FDG PET/CT Imaging Protocol: PET images were acquired in 3D mode from the base of the skull to the mid-thigh and reconstructed in transverse, coronal, and sagittal planes using a 64-row multi-detector hybrid system (Philips - Ingenuity PET/CT system) with an axial FOV of 216 mm and a PET sensitivity of 7.6 counts per second /kBq. Patients are advised to refrain from excessive exercise for the previous 24 hours and too fast for at least six hours before administering the radiotracer.

Serum blood glucose levels were measured using a finger stick to ensure that they were under 200 mg/dl. All patients received 8.14 MBq of ^{18}F-FDG per kilogram of body weight by intravenous injection while being kept in a warm and serene atmosphere. Each patient had 18F-FDG PET CT imaging at a range of 60 +/- 10 minutes after the administration of ^{18}F-FDG [11].

For attenuation correction and anatomic correlation, unenhanced low-dose CT imaging was performed, and all Manufacturer-recommended PET image corrections were applied.

RESULTS:

^{18}F-FDG PET/CT Image analysis: All studies were analyzed using a workstation, which allows for 3D reconstruction of PET and CT images as well as quantitative and semi-quantitative measurements.

The entire aorta was examined, beginning at the ascending aorta and ending at the aortic bifurcation. Each PET scan was blinded for patient characteristics and reviewed by a nuclear medicine physician with three years of experience, who was overseen by two nuclear medicine consultants with ten years of experience.

The degree of global arterial ^{18}F-FDG uptake was quantitatively assessed following previously published methods [4]. Manual regions of interest (ROIs) were performed on aortic segments at fused PET/CT images using a free-hand polygon tool *(Figure 1)*.
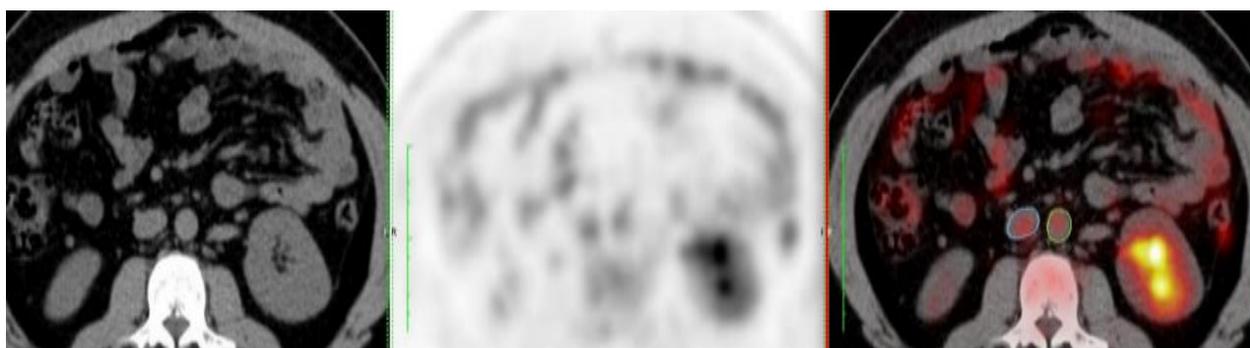

Figure (1): CT, PET and fused PET/CT images showing region of interest (ROI) in the abdominal aorta (green ROI) and IVC (blue ROI), it demonstrates the method in which ROIs were delineated on fused PET/CT for each aortic slice in all patients.

SUVmax was calculated for each aortic slice, and avg SUVmax was calculated for each aortic region. ROIs of the aortic arch were delineated starting at the highest cranial slice of the aorta to the lowest caudal slice, in which both the ascending and descending aortas are not distinguished. The ROIs of the ascending aorta were delineated starting from where the aorta arises from the heart to the inferior-most slice of the aortic arch. The descending thoracic aorta was quantified from the lowest slice of the aortic arch to the aortic hiatus in the diaphragm. The abdominal aorta was quantified from the aortic hiatus to the level of the aortic bifurcation.

To correct for background blood pool activity, the maximum target-to-background ratio (TBR max) for every aortic region was calculated. Drawing a circular ROI on five contiguous slices within each vessel (SVC and IVC) yielded the background average mean standardized uptake value (average SUV mean). As in the ascending aorta, the aortic arch and descending thoracic aorta were corrected by dividing the avg SUVmax of each aortic segment by (average SUV mean) from the SVC, and the abdominal aorta was corrected by dividing its average SUVmax by the average SUVmean of the IVC.

Statistical analysis:

Data management and analysis were performed using the Statistical Package for Social Sciences (SPSS) version 25. Numeric data and 18F-FDG PET/CT parameters (avg SUVmax and TBR max for the aorta and SUV mean for the vena cava vessels) were checked for normality and statistically described in terms of the mean (standard deviation).

Categorical data were described as numbers and percentages. The comparison of numeric data among two categories was performed using the independent Student's t-test, whereas Chi square or Fisher's exact tests were used for categorical data as appropriate. MVA was performed for factors that showed significance in UVA. All P-values are 2-tailed and were set significant at <0.05 level.

RESULTS:

Demographic data: The lung cancer group included 20 men (67%) and 10 women (33%) with mean age 58.3 ±9.9 years. The non-lung cancer group includes 12 males (40%) and 18 females (60%) with a mean age 59.9 ± 12.4 years having different primary tumor sites; including breast , GIT, Hematopoietic, Gynecologic, Head & neck as well as squamous cell carcinoma in the external ear, the most prevalent is breast cancer (37%), both groups had equivalent risk factors for atherosclerosis, such as hyperlipidemia, hypertension, diabetes mellitus, smoking, and obesity; however, the lung cancer cohort has more men and more smokers, with 20 males (67%) and 17 smokers (56.7%) in the lung cancer group compared to 12 males (40%) and 9 smokers (30%) in the non-lung cancer group, (***Table 1***) represents the different AS risk factors in both cohorts.

Table (1): As risk factors per tumor group (n=60).

Factor	Lung		
Sex			
Male	20 (66.7%)	12 (40%)	0.038 [b] *
Female	10 (33.3%)	18 (60%)	
Smoking status			
Smokers	17(56.7%)	9 (30%)	0.037 [a] *
Non-Smoker	13 (34.3%)	21 (70%)	
Hypertension			
Hypertensive	10 (33.3%)	9 (30)	0.781 [a]
Non-hypertensive	20 (66.7%)	21(70)	
Diabetes mellitus			
Diabetic	4 (13.3%)	3 (10)	1.000 [b]
Non-diabetic	26 (86.7%)	27 (90)	
Hyperlipidemia			
Hyperlipidemic	16 (53.3%)	11 (36.7)	0.194 [a]
Non-Hyperlipidemic	14 (46.7%)	19 (63.3)	
Obesity (BMI>30)			
Obese	15 (50%)	16 (53.3)	0.796 [a]
Non-Obese	15 (50%)	14 (46.7)	

¹⁸F-FDG PET/CT quantitative data: TBR max parameters were higher in the lung cancer group compared to non-lung cancer group in all aortic regions with the exception of the ascending aorta. In the ascending aorta, the TBR max was 1.8 for the lung cancer group and 1.8 for the non-lung cancer group. Regarding the aortic arch, the TBR max was 1.9 for the lung cancer group and 1.7 for the non-lung cancer group. In the descending thoracic aorta, the TBR max was 1.6 for the lung cancer group and 1.5 for the non-lung cancer group, while in the abdominal aorta, the TBR max was 1.4 for the lung cancer group and 1.3 for the non-lung cancer group *(Figure 2 and Table 2)*.

Table (2): TBR max parameters of aortic segments in relation to atherogenic risk factors.

Characteristic	n	Ascending TBR $_{max}$	Aortic Arch TBR $_{max}$	Thoracic TBR $_{max}$	Abdominal TBR $_{max}$
Sex					
Male	32	1.8 (0.2)	1.8 (0.2)	1.6 (0.2)	1.4 (0.2)
Female	28	1.8 (0.2)	1.8 (0.2)	1.5 (0.2)	1.3 (0.1)
	p	0.864	0.695	0.139	**0.041**[*]
Cancer Type					
Lung cancer	30	1.8 (0.3)	1.9 (0.2)	1.6 (0.2)	1.4 (0.2)
Extra-pulmonary cancers	30	1.8 (0.2)	1.7 (0.1)	1.5 (0.2)	1.3 (0.2)
	P	0.972	**<0.001**[*]	**0.006**[*]	**<0.001**[*]
Smoking status					
Smokers	26	1.8 (0.2)	1.9 (0.2)	1.6 (0.2)	1.4 (0.2)
Non-Smoker	34	1.8 (02)	1.8 (0.2)	1.5 (0.2)	1.3 (0.1)
	P	0.641	0.484	0.342	0.130
Hypertension					
Hypertensive	19	1.8 (0.2)	1.8 (0.2)	1.5 (0.2)	1.4 (0.2)
Non-Hypertensive	41	1.8 (0.2)	1.8 (0.2)	1.6 (0.2)	1.3 (0.1)
	P	0.232	0.541	0.377	0.307
Diabetes					
Diabetic	7	1.8 (0.1)	1.8 (0.1)	1.5 (0.1)	1.3 (0.1)
Non-diabetic	53	1.8 (0.2)	1.8 (0.2)	1.6 (0.2)	1.4 (0.2)
	P	0.826	0.555	0.706	0.233
Hyperlipidemia					
Hyperlipidemic	27	1.8 (0.2)	1.8 (0.2)	1.5 (0.2)	1.4 (0.2)
Non-Hyper-lipidemic	33	1.8 (0.2)	1.8 (0.2)	1.6 (0.2)	1.3 (0.1)
Obesity (BMI>30)					
Obese	31	1.8 (0.2)	1.8 (0.2)	1.5 (0.2)	1.4 (0.2)
Non-Obese	29	1.8 (0.2)	1.8 (0.2)	1.6 (0.2)	1.3 (0.2)

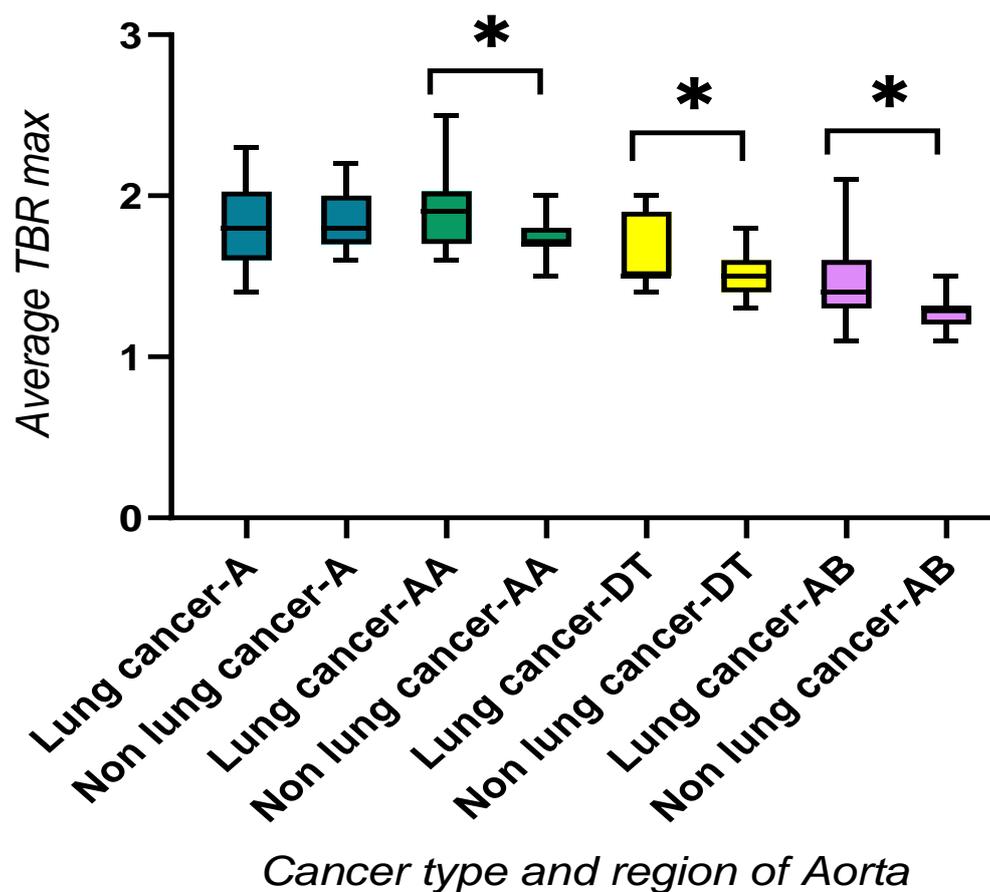Numbers are given as mean (SD). The asterisk '*' means statistically significant value

Figure (2): Box plots for average TBR max per cancer group; lung cancer (n=30) and non-lung cancer: (n=30) for each aortic region (A: Ascending, AA, Aortic arch, DT: Descending Thoracic, and AB: Abdominal). * Statistically significant at $p < 0.05$ level.

Then, a multivariable logistic regression method was used to analyze the factors contributing to increased TBR max, with TBR max as the dependent variable and factors that showed significance in UVA including cancer type, sex and smoking, as the predictors. In the multivariable analysis, lung cancer demonstrated the highest odds ratio for elevated TBR max of the aortic arch and abdominal aorta compared to sex and smoking status, though the absolute p value did not reach typical significant level of 0.05 (*Table 3*).

Table (3): MVA Analysis of TBR of different segments of the aorta in respect to cancer type, sex and smoking status.

	Ascending		Arch		Thoracic		Abdominal	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Lung Cancer (vs. non-lung cancer)	0.98 (0.85-1.13)	0.76	1.16 (0.96-1.41)	0.12	1.02 (0.91-1.15)	0.70	1.08 (0.98-1.2)	0.12
Male (vs. female)	1.18 (0.96-1.46)	0.11	1.00 (0.75-1.32)	0.98	1.05 (0.89-1.25)	0.54	1.05 (0.91-1.22)	0.49
Smoker (vs. non-smoker)	0.98 (0.79-1.21)	0.84	0.98 (0.74-1.3)	0.88	0.96 (0.81-1.15)	0.66	1 (0.86-1.16)	0.98

Regarding the risk variables discussed for atherosclerosis development, neither the lung nor the non-lung cancer groups showed a statistically significant influence of smoking, hyperlipidemia, hypertension, diabetes mellitus, or obesity on the FDG uptake at any aortic segment except the abdominal aorta, where TBR max was significantly higher in men *(Table 2)*.

DISCUSSION:

Because AS is an inflammatory disorder caused by lipid retention in the arterial wall, the risk of cardiovascular events increases as the disease progresses [12]. Concurrent cardiovascular disease and neoplasms are not uncommon; 4-10% of patients with chronic ischemic heart disease have a cancer history [2]. Multiple studies have found a link between lung cancer and CVD: lung cancer patients have a 66% increased risk of CVD and an 89% increased risk of coronary artery disease alone when compared to non-lung cancer patients [13]. Many other malignancies, in addition to lung cancer, are also thought to have a significant incidence of AS. Among cancer types, it was found that non-Hodgkin lymphoma, breast cancer, and malignant melanoma have a higher risk of CVD [12]. In this study, patients with lung cancer were having higher aortic wall FDG uptake compared to patients with other cancer types yet both groups are statistically different in number of smokers and male gender being more in lung cancer group, so MVA was done and showed that lung cancer has the highest contribution in elevation of TBR max, this may suggest that lung cancer may have more risk of AS among cancer patients. This finding seems to be independent of gender and smoking. AS can result in ischemic diseases including

myocardial infarction and stroke, which are thought to be responsible for the deaths of 10 million people annually [13]. Although stress perfusion imaging has a high predictive power of cardiac ischemia, and clinical evaluation of patients using scoring systems such as the Framingham Risk Score and Systemic Coronary Risk Evaluation are used to estimate the pre-test likelihood of having atherosclerosis, direct imaging of atherosclerosis is best for an early diagnosis [16]. CT and structural imaging provide important information about the structure and morphology of plaques, identify only macroscopic changes that happen later in the disease course, when the changes are typically irreversible. Contrarily, molecular imaging techniques like PET have the advantage of spotting microscopic alterations that enable treatment of these plaques before they undergo irreversible modifications. FDG is one of the tracers that are most frequently employed in PET imaging of atherosclerosis [14]. According to findings in the literature, ^{18}F-FDG PET/CT may alter the landscape for the early detection of people at risk for cardiovascular events and may help with the development of preventative interventions to reduce vascular damage and enhance patient outcomes.

Increased FDG uptake in major arteries was found to be a reliable indicator of future vascular events in a retrospective analysis of 932 asymptomatic individuals who underwent whole-body FDG PET for cancer [10]. Numerous studies have found that having either cancer or atherosclerosis predisposes a person to developing the other since they both share important biological pathways in their etiology [4], *Roubn and Cordero* demonstrated that up to one in ten people with ischemic heart disease have a history of cancer, while one in thirty people with ischemic heart disease have a new cancer [2]. Furthermore, routine ^{18}F-FDG PET/CT scans monitoring FDG uptake of aorta were found to predict cardiovascular disease occurrences and timing in patients who were not previously known to have cardiovascular disease [15, 16]. In our work, we use average TBR max as a metabolic metric to assess FDG uptake in aortic segments, Despite the fact that maximum standardized uptake value (SUVmax) is more commonly used to measure FDG uptake in atherosclerotic plaque, it has many limitations, including the fact that it does not demonstrate the lesion's overall activity if the tracer distribution within a lesion is not uniform, and that image noise and spill-in of adjacent activity due to partial volume effect can affect SUVmax accuracy , yet the advantage of SUVmax, being reproducible, convenient and widely used. TBR max is recommended over SUVmax because it reduces errors of quantification due to patient weight, radiotracer dose, and imaging time-point errors by dividing the average SUV max of each aorta area by the average SUV mean of the regional blood pool [17]. Additionally, TBR values show excellent intra- and inter-reader agreement in individuals who had two ^{18}F-FDG PET/CT imaging tests separated by two weeks [18]. When comparing TBR max of the FDG uptake between thirty patients with lung cancer and thirty patients with other types of cancer who came for initial PET/CT assessment, there was increase in FDG uptake in lung cancer patients compared to non-lung cancer patients in all segments of the aorta except the ascending aorta, Our results are in agreement with (*Koa, et al*) who suggested that the risk of atherosclerosis was higher in lung cancer patients in comparison to other patients with different primary malignancies other than lung cancer. They analyzed 34 lung cancer patients (21 males and 13 females) compared to 78 patients with non-lung malignancies (46 males and 32 females), Avg.

SUVmax and TBR max of the FDG uptake at different aortic segments showed a statistically significant increase in patients with lung cancer compared to non-lung cancer patients, Our patients didn't receive any anti-tumor therapy before the scan and came for initial staging, none of them having any history of cardiovascular disease [4]. Additionally, several studies have examined how the location of original malignancies affects the risk of atherosclerosis, with lung cancer having the highest risk compared to other malignancies as 280,000 matched pairs of cancer patients and control individuals, patients with cancer had a greater 6-month cumulative incidence of arterial thromboembolism, with lung cancer having the highest risk [19]. Many solid tumors including lung cancer have cholesterol crystals which trigger IL-1β production in atherosclerotic plaques is present in these tumors. These findings may elucidate shared risks and the co-occurrence of tumors and atherosclerotic cardiovascular disease [20]. Regarding risk factors for atherosclerosis that might affect the assessment of FGD uptake, including smoking, diabetes, hypertension, hyperlipidemia, and obesity, in our study TBR max showed no significant increase in the lung cancer group nor in the non-lung cancer group. (**Koa, et al**) agreed with our results as smoking history was higher in lung cancer group However, the thoracic aorta of both the lung cancer and extra-pulmonary cancer groups did not reach a statistically significant level [4]. But, when discussed FDG uptake in 82 patients with a history of coronary artery disease (CAD) revealed that smoking and hypertension can cause a significant increase in whole vessel TBR max values [21]. Also, increased in diabetic patients [22], Furthermore, in diabetic patients [23], it was discovered that the presence of diabetes had no significant impact on FDG uptake in any arterial region and explained that diabetic subjects in the study may not have higher FDG uptake than non-diabetics due to effective medical therapy or the competitive effect of hyperglycemia on FDG uptake. Furthermore, some diabetic medications, such as glita-zones, have anti-inflammatory properties [23]). All diabetic, hypertensive and hyperlipidemia patients included in this study were controlled on medical treatment as well as the majority of our cases are non-diabetic (53 non-diabetics compared to 7 diabetics), so our results could be considered biased.

CONCLUSIONS:

Our research has shown that people with lung cancer have a higher risk of developing atherosclerosis than those with other forms of cancer. Though uptake time is not considered optimal for vascular wall delineation, this opportunistic information may be used to tailor specific interventions. Further validation of the current findings in larger cohort including a cancer-free group and Study more risk factors for atherosclerosis (e.g effects of different anti-cancer therapies are warranted). Our investigation was constrained by the small sample size of the study population, the mismatch in the proportion of males and females as well as smokers and non-smokers across both cohorts, and the lack of a control group. Our advantages included a single-center trial design, uniform FDG doses prior to FDG PET/CT, and scanning patients with the same scanner.

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