Am J Nucl Med Mol Imaging 2021;11(1):1-9
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0126562

Original Article

^{18}F-FDG-PET/CT in the assessment of atherosclerosis in lung cancer

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Received September 22, 2020; Accepted December 6, 2020; Epub February 15, 2021; Published February 28, 2021

Abstract: The aim of this study was to assess the risk of atherosclerosis in patients with lung cancer compared to patients with extrapulmonary malignancies using ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). We hypothesized that patients with lung cancer would demonstrate increased FDG uptake in the thoracic aorta compared to patients with extrapulmonary cancers. Thirty-four lung cancer patients (21 male, 13 female, 64.1 ± 12.9 yo) were retrospectively compared to seventy-eight patients with extrapulmonary malignancies (46 male, 32 female, 59.6 ± 12.8 yo). Average maximum standardized uptake value (avgSUVmax) and maximum target-to-blood pool ratio (TBRmax) were measured by mapping regions of interest of the ascending aorta, aortic arch, and descending aorta. Two-tailed Student's t-test was used to assess the differences in avgSUVmax and TBRmax between the two groups and between smokers and non-smokers. Age and gender distribution between the groups were not statistically different. AvgSUVmax and TBRmax were statistically significant increase in lung cancer patients compared to extrapulmonary cancer patients in the ascending aorta, aortic arch, and descending aorta, suggesting a lung cancer-associated increased risk of atherosclerosis development. AvgSUVmax was not significantly different between smokers and non-smokers in all sections of the thoracic aorta. Moving forward, large, prospective studies that directly compare PET data between different malignancies of different stages will help determine the role of FDG-PET/CT in assessing paraneoplastic vascular disease.

Keywords: Atherosclerosis, FDG-PET/CT, lung cancer, CVD, Aorta

Introduction

Atherosclerosis (AS) is a progressive arterial disease characterized by the development and accumulation of fat-laden plaques within the arterial wall [1]. It is the leading cause of cardiovascular disease (CVD) such as myocardial infarction, ischemic stroke, and peripheral arterial disease [2, 3]. It has been accepted that there is an intimate relationship between cancer and AS; several studies have highlighted several important shared molecular pathways such as inflammation, oxidative stress, and cell proliferation in both of their pathogenesis [4-6]. Studies have also found that cancer patients have an increased risk of developing atherosclerotic CVD [7-9]. Furthermore, among cancer patients, the risk of AS-related CVD varied according to the location of the primary malignancy with lung cancer observed to be one of the cancers at highest risk [10, 11]. Therefore, early detection of AS in cancer patients, especially those with lung cancer, may lead to earlier interventions in high risk patients.

Computed tomography (CT) has been used to image vasculature changes, severity of luminal stenosis, and plaques in AS [12]. However, CT detects macro-level functional and structural changes that occur late in the progression of AS. Positron emission tomography/computed tomography (PET/CT), on the other hand, has the ability to visualize the molecular changes that precede the changes detected by other imaging modalities, allowing for early detection of AS [1].

Table 1. Types of primary malignancies diagnosed in patients

Cancer Types	Number of patients
Lung cancer	34
GI cancer (5 esophageal, 4 stomach, 3 colon, 1 dual esophageal/stomach, 1 non-specific, 4 pancreatic, 1 liver, 3 rectal, 1 anal)	23
Hematopoietic malignancy (17 lymphoma, 2 multiple myeloma, 1 thrombocytopenia)	20
Gynecologic cancers (5 uterine, 4 ovarian, 1 vulva)	10
Head and Neck cancer (3 parotid, 1 thyroid, 3 throat, 1 mouth, 1 tonsil)	9
Breast cancer	5
Bladder cancer	2
Mesothelioma	2
Other (2 mediastinal, 4 melanoma, 1 brain)	7
Total	112

^{18}F-fluorodeoxyglucose (FDG)-PET/CT has been used to monitor inflammatory processes such as AS. FDG is a radiotracer that preferentially localizes to extensive metabolic processes; in AS, FDG is taken up in atheromatous plaques by activated macrophages, which can be visualized on PET/CT images [13, 14]. Furthermore, the intensity of FDG uptake correlated with the severity of AS progression and is a strong predictor of vascular events, supporting FDG-PET/CT as a prognostic tool in the evaluation of AS [1, 15, 16].

The aim of this study was to investigate the differential risk of AS severity based on the location of the primary tumor. As atherosclerotic CVD is seen in higher rates in lung cancer [17, 18], we hypothesized that the uptake of FDG and thus risk of AS in the thoracic aorta would be higher in lung cancer patients compared to that of extrapulmonary cancers.

Methods

Subject population

Retrospective data from cancer patients with whole-body FDG-PET/CT imaging performed at the Hospital of the University of Pennsylvania between March 2012 to December 2014 were included in this study. The lung cancer group included 34 patients (28 smokers, 5 non-smokers, 1 unknown smoking history) and the extrapulmonary cancer group included 78 patients (33 smokers, 45 non-smokers) (**Table 1**). Patients with non-specific malignancies, concurrent pulmonary and extrapulmonary malignancies, or prostate cancer were not included. Smoking history was classified as smokers, who had a smoking history, and non-smokers, who never had a smoking history. One patient did not have any reported information on smoking and was not included.

Study design

For all patients, FDG-PET/CT was performed on integrated PET/CT scanners at the Hospital of the University of Pennsylvania (GEMINI TF; Philips Healthcare & Biograph mCT; Siemens & Discovery ST; GE & Ingenuity TF; Philips Healthcare). PET/CT images were acquired in accordance with international guidelines [19, 20]. and the institution PET/CT protocol, including quality control, calibration and harmonization of PET/CT scanners and validation of SUV measurements. Patients fasted for at least 6 hours and serum glucose levels were immediately measured prior to FDG injection. All scans were performed from the base of the skull to the upper thigh at 60 minutes after intravenous injection of 15 mCi FDG for Gemini TF, Biograph mCT, and Ingenuity TF or 1 mCi/10 kg for Discovery ST. Three acquisition protocols were used for Gemini TF, Biograph mCT, and Ingenuity TF: one for BMI under 30, another for BMI between 30 and 35, and the third BMI over 35; the CT settings were 50, 100 and 150 mAs respectively and all at 120 kVp. For the PET acquisitions, the time per bed was 1.5, 2, and 3 minutes, respectively. One acquisition protocol was used for Discovery ST: CT setting was 80 mA at 120 kVp and PET acquisition was 2 minutes to 2.5 minutes per bed.

Data processing differed based on manufacturer. For the Gemini-TF and Ingenuity TF, reconstruction algorithm BLOB-OS-TF was used with 3 iterations and 33 subsets; the time of flight kernel width was set to 23.0 cm. For the

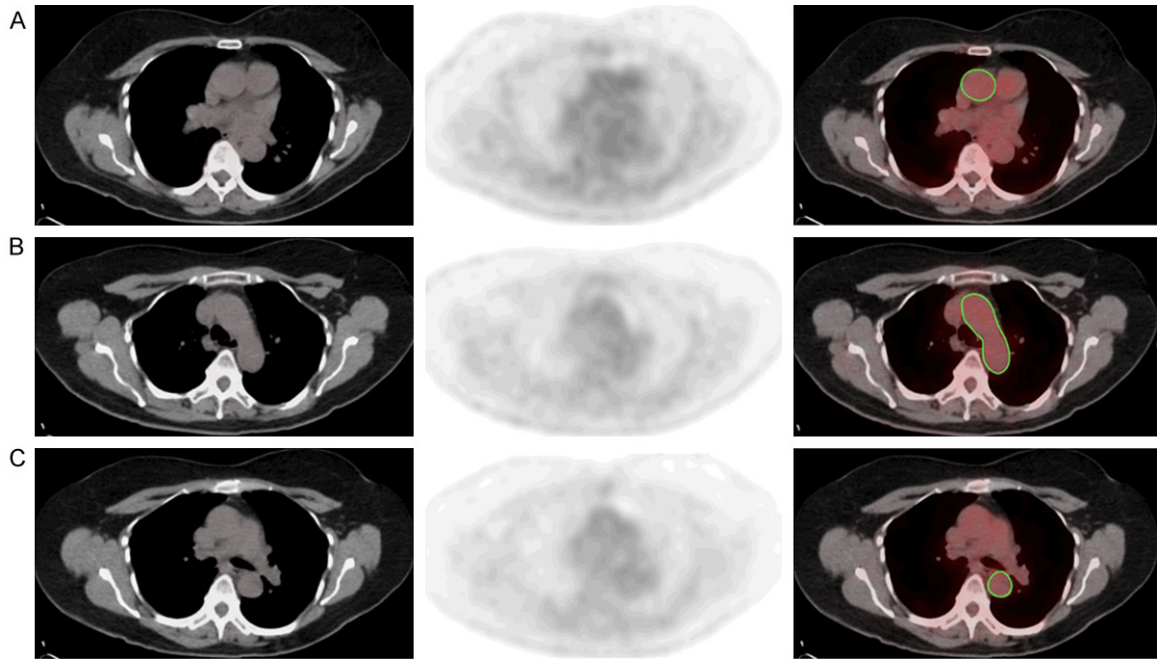

Figure 1. CT image, PET image, and fused PET/CT image with a sample region of interest (ROI) of the (A) ascending aorta (B) aortic arch (C) descending aorta from one of the patients with lung cancer. The above images demonstrate the method in which ROIs were delineated on fused PET/CT for each section of the aorta in all patients. Abbreviations: LC, lung cancer; EPC, extrapulmonary cancer; AA, ascending aorta; AoA, Arch of Aorta; DA, descending aorta; *, significant at $P<0.05$.

Biograph mCT, reconstruction protocol OP-OSEM was used with 2 iterations and 21 subsets, images were corrected for time of flight and point-spread function, and a Gaussian postfilter with a fundamental limits of spatial resolution of 3.0 mm. For Discovery ST, 2 iterations, 28 subsets, and 6 mm post filter was used.

Low-dose CT imaging was done for attenuation correction and anatomic correlation, and PET imaging was corrected for scanner dead time, scattering, and random coincidences. Voxel size was 4 mm × 4 mm with images reconstructed to 3 mm thick slices.

Image analysis

OsiriX MD software v.10.0.2 (DICOM viewer and image-analysis program, Pixmeo SARL; Bernex, Switzerland) was used to analyze the FDG-PET/CT images. Manual regions of interest (ROIs) were delineated on fused PET/CT images to measure global uptake in the ascending aorta, aortic arch, and descending aorta (**Figure 1**). Average max standardized uptake value (avgSUVmax) was calculated for each scan. FDG uptake within each trans-axial slice was calculated by multiplying the slice ROI area by the SUVmax.

ROIs of the aortic arch were delineated beginning at the most superior slice of the aorta to the most inferior slice in which the ascending and descending aortas are not distinct. 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 aorta was quantified from the inferior-most slice of the aortic arch to the superior limit of the uppermost kidney.

To correct for blood pool activity, maximum target-to-background ratio (TBRmax) was calculated by dividing the avgSUVmax of the aorta by average mean standardized uptake value (avgSUVmean) from the superior vena cava (SVC). The avgSUVmean was determined by placing a circular ROI within the SVC on 6 to 8 contiguous slices.

Statistical analysis

A two-tailed t-test in STATA software (Stata/IC Version 10.1, StataCorp, College Station, TX) was used to evaluate avgSUVmax, TBRmax,

Table 2. Subject characteristics of the lung cancer group and extrapulmonary cancer group

	Lung cancer	Extrapulmonary cancer
Age	64.1 ± 12.9	59.6 ± 12.8
Male	21	46
Female	13	32
Smoker	28	33
Non-smoker	5	45
Unknown smoking history	1	0

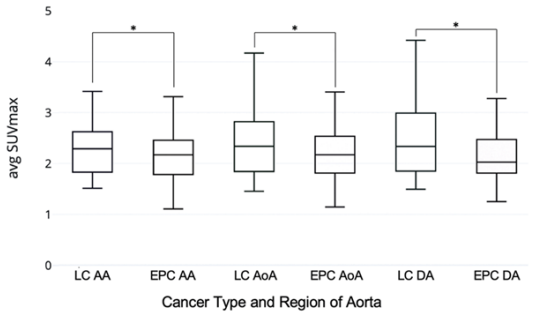

Figure 2. Box-and-whisker plots of average maximum standardized uptake value (avgSUVmax) of the ascending aorta, aortic arch, and descending aorta between 34 lung cancer patients and 78 extrapulmonary cancer patients. Abbreviations: LC, lung cancer; EPC, extrapulmonary cancer; AA, ascending aorta; AoA, Arch of Aorta; DA, descending aorta; *, significant at P<0.05.

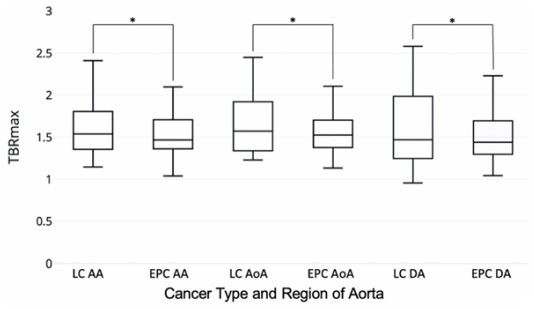

Figure 3. Box-and-whisker plots of maximum target-to-blood pool ratio (TBRmax) of the ascending aorta, aortic arch, and descending aorta between 34 lung cancer patients and 78 extrapulmonary cancer patients. Abbreviations: NS, non-smoker; S, smoker; AA, ascending aorta; AoA, Arch of Aorta; DA, descending aorta.

and age between lung cancer patients and extrapulmonary cancer patients and between smokers and non-smokers. A chi-square test of independence was used to evaluate the distribution of gender between lung cancer and extrapulmonary cancer groups. Fisher's exact test was used to evaluate the distribution of scanners between the two groups. A *p*-value less than 0.05 was defined as statistically significant.

Results

The lung cancer group included 32 patients, 21 male and 13 female patients, of which 28 reported a smoking history, five denied any smoking history, and one did not has any documented smoking history. The average age in the lung cancer group was 64.1 years. In the extrapulmonary cancer group, there were 78 patients with 46 male and 32 female patients. Thirty-three of the patients in the extrapulmonary cancer group had a reported smoking history and 45 denied any smoking history. The average age in this extrapulmonary cancer group was 59.6 years. Demographic characteristics and scanner distribution are summarized in **Table 2** and Supplementary Table 1. Age (P=0.10), gender (P=0.78), and scanner distribution (P=0.37) were not statistically significant between the two groups (P>0.05). AvgSUVmax and TBRmax were compared between lung cancer patients and extrapulmonary cancer patients (**Figures 2**, **3**). Lung cancer patients were observed to have a statistically significant increase in the ascending aorta, aortic arch, and descending aorta for avgSUVmax and TBRmax (**Tables 3**, **4**). In the ascending aorta, avgSUVmax and TBRmax were 2.41 and 1.77 respectively for the lung cancer group and 2.15 and 1.54 respectively for the extrapulmonary cancer group. In the arch of the aorta, avgSUVmax and TBRmax were 2.98 and 2.45 respectively for the lung cancer group and 2.20 and 1.58 respectively for the extrapulmonary cancer group. In the descending aorta, avgSUVmax and TBRmax were 2.47 and 1.95 respectively for the lung cancer group and 2.15 and 1.57 respectively for the extrapulmonary cancer group. When comparing smoking history in the entire patient population, an increase in avgSUVmax was demonstrated for smokers compared to non-smokers in all regions of the thoracic aorta. AvgSUVmax in the ascending aorta, arch of aorta, and descending aorta for the smoking group was 2.31, 2.63, and 2.34 respectively and for the non-smoking group it was 2.14, 2.23, 2.11 respectively. While FDG uptake was higher in smokers compared to non-smokers,

Table 3. Average SUVmax of 34 lung cancer patients and 78 extrapulmonary cancer patients in the ascending aorta, aortic arch, and descending aorta

	Lung cancer	Extrapulmonary cancer	*P*-value
Ascending Aorta	2.41 ± 0.90	2.15 ± 0.47	0.046
Aortic Arch	2.98 ± 2.20	2.20 ± 0.54	0.004
Descending Aorta	2.47 ± 0.80	2.15 ± 0.52	0.012

Table 4. TBRmax of 34 lung cancer patients and 78 extrapulmonary cancer patients in the ascending aorta, aortic arch, and descending aorta

	Lung Cancer	Extrapulmonary cancer	*P*-value
Ascending Aorta	1.77 ± 0.73	1.54 ± 0.27	0.013
Aortic Arch	2.45 ± 3.75	1.58 ± 0.34	0.043
Descending Aorta	1.95 ± 1.33	1.57 ± 0.57	0.037

the increase was not statistically significant; the *P*-values were 0.15 for the ascending aorta, 0.12 for the arch of aorta, and 0.06 for the descending aorta. Similarly, when comparing avgSUVmax among smokers and nonsmokers within the lung cancer group and extrapulmonary group, individually, higher values were seen in smokers compared to nonsmokers but the increase was not statistically significant (**Table 5**; **Figures 4**-**6**).

Discussion

In this study, FDG uptake in the ascending aorta, arch of aorta, and descending aorta in lung cancer patients were significantly higher compared to extrapulmonary cancer patients, indicating that lung cancer has an increased risk of AS among cancer patients. Additionally, FDG uptake was not significantly different in smokers compared to non-smokers among the studied patients. To our knowledge, no other studies have compared the aortic FDG uptake among cancer types. Previous studies have observed the association between type of cancer and end AS-related outcomes; however, little has been done on the association of type of cancer to FDG uptake, which is believed to be an early marker of AS.

Cancer and AS both share significant molecular pathways in their pathogenesis, and several studies have observed that the presence of cancer or AS will predispose an individual to the other. Recently, Lau *et al.* found an independent correlation between cardiovascular risk and the risk of future cancer from the Framingham Heart Study; elevated BNP, increased 10-year ASCVD score, and the development of CVD increased the risk of subsequent cancer in previously healthy patients [21]. Whitlock *et al.* noticed an association between a diagnosis of cancer with development of coronary artery calcification [8]. Furthermore, a difference in AS risk based on the location of primary malignancies has been demonstrated in several studies, in which lung cancer had the highest risk of CVD. Navi *et al.* reported that lung cancer patients had the greatest excess risk of arterial thromboembolism (ATE) and 6-month cumulative incidence of myocardial infarction and ischemic stroke [11]. Also, Oren & Herrmann highlighted how lung cancer maintained a 2.5-fold increased relative risk of ATE 12 months after diagnosis while most cancers begin to show a decrease in excess risk of ATE after 6 months [10]. These findings are indicative of the increased risk of AS in lung cancer patients and the need to further investigate this association.

In addition to lung cancer there are several other cancers that are also considered to be at high risk of AS. Breast cancer, malignant melanoma, and non-Hodgkin lymphoma were observed to have a higher risk of CVD among cancer types [7]. Patients with malignancies in the small intestine, kidney, liver, blood had the higher standardized incidence ratios for coronary heart disease [9]. Arterial thromboembolism was seen in higher rates among hospitalized cancer patients with leukemia, prostate, or colon cancers [22]. Prostate cancer also has a strong association to AS; in a recent population-based study, Liu *et al.* observed that prostate cancer patients, along with lung cancer patients, had the highest prevalence of cardiovascular comorbidities [17]. Raynor *et al.* further noted that prostate cancer had a significantly higher 18-F-NaF uptake; thus, prostate cancer patients were not included in the analysis [23]. While the previously mentioned studies have highlighted other cancers associated with AS-related conditions, lung cancer was still among the highest, if not the highest, rates for the various types of CVD in these studies and future studies must be conducted on the deter-

Table 5. Average SUVmax of 61 smokers and 50 non-smokers in the thoracic aorta

		Smokers	Non-smokers	*P*-value
All patients	Ascending Aorta	2.31 ± 0.20	2.14 ± 0.12	0.1520
	Aortic Arch	2.63 ± 0.44	2.23 ± 0.15	0.1209
	Descending Aorta	2.34 ± 0.19	2.11 ± 0.13	0.0621
Lung cancer	Ascending Aorta	2.46 ± 0.37	2.26 ± 0.66	0.6431
	Aortic Arch	3.11 ± 0.93	2.46 ± 0.74	0.5533
	Descending Aorta	2.46 ± 0.31	2.34 ± 0.91	0.7691
Extrapulmonary cancer	Ascending Aorta	2.18 ± 0.19	2.12 ± 0.12	0.5867
	Aortic Arch	2.21 ± 0.20	2.20 ± 0.15	0.9452
	Descending Aorta	2.23 ± 0.23	2.09 ± 0.13	0.2317

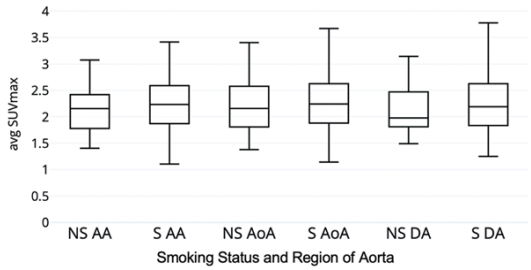

Figure 4. avgSUVmax of 61 smokers and 50 non-smokers in the ascending aorta, arch of aorta, and descending aorta of the patient population. Abbreviations: NS, non-smoker; S, smoker; AA, ascending aorta; AoA, Arch of Aorta; DA, descending aorta.

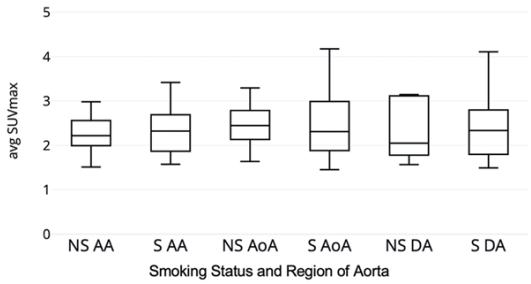

Figure 5. avgSUVmax of 61 smokers and 50 non-smokers in the ascending aorta, arch of aorta, and descending aorta of lung cancer patients. Abbreviations: NS, non-smoker; S, smoker; AA, ascending aorta; AoA, Arch of Aorta; DA, descending aorta.

mining the differential effect of cancer site on AS.

FDG-PET/CT offers an important benefit of visualizing inflammatory processes early in their progression. In AS, FDG-PET/CT can identify the metabolic changes due to AS in at-risk CVD patients prior to the structural and functional consequences of AS visualized by other imaging modalities [24]. FDG is of particular interest in the thoracic aorta as AS in the thoracic aorta is a strong marker for generalized AS and subsequent vascular events [25]. Routine PET/CT scans that monitored aortic FDG uptake was observed to predict CVD incidents and their potential timing in previously healthy patients [26]. Likewise, among cancer patients, increased aortic FDG uptake was determined to be a strong predictor of subsequent vascular events among cancer patients [16]. While AS has been studied in cancer patients, there has been no studies to our knowledge that has assessed the risk of AS between different cancer types. As previously mentioned, with the frequency of CVD varying according to the site of cancer and FDG uptake being able to predict future CVD events, FDG-PET/CT can potentially characterize the early risk of AS based on type of cancer and allow early preventative interventions against those at high risk for CVD.

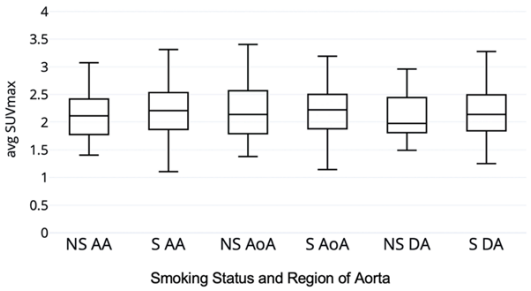

Figure 6. avgSUVmax of 61 smokers and 50 non-smokers in the ascending aorta, arch of aorta, and descending aorta of extrapulmonary cancer patients.

Cigarette smoke is the most significant modifiable risk factor in the development of AS [27, 28]. These effects may be visualized by molecular imaging. Blomberg *et al*. utilized FDG-PET/

CT to demonstrate that smoking history is associated with increased uptake within atherosclerotic plaques [29]. Cigarette smoke is also among the leading risk factors contributing to lung cancer, head and neck cancers, renal cell carcinoma, and other malignancies [30, 31]. Lung cancer in particular has been associated with increased risk for CVD, including coronary heart disease and stroke; however, the exact mechanism behind this relationship is not understood [32]. In our study, smoking history did not demonstrate a statistically significant effect on the FDG uptake for the thoracic aorta for both lung cancer and extrapulmonary cancer groups. However, a higher proportion of smokers comprised the lung cancer group compared to the extrapulmonary cancer group; as such, future studies need to be performed to ascertain the differential effects of cigarette smoke and lung cancer on the extent of AS.

While this study observed an increased risk in lung cancer among other cancer patients, several limitations should be noted. First, in our study there was no healthy control group to demonstrate that the cancer patients had AS despite it being widely known that cancer has a role in AS development. Additionally there is a bias when comparing the effects of smoking as 45 non-smokers were from the extrapulmonary cancer group while only 5 were from the lung cancer group. Another limitation was the lack of clinical and medical history of patients such as cancer stage, type of therapy received, and if the patient developed AS later on. Photon therapy has been demonstrated to induce vascular inflammation in the aorta, potentially increasing FDG uptake in lung cancer patients [33]. Previous history of CVD is also another limitation that should be noted. A review by Paulmier *et al.* indicated that cancer patients with a prior cardiovascular event had higher arterial FDG uptake compared to cancer patients with no prior cardiovascular event [34]. We did not have information on the patient's CVD history and thus its effect is unknown in our study. Lastly, age has been shown to have a strong correlation to increased FDG uptake in the aorta [35, 36]. Age was shown to have an impact on the co-prevalence of CVD and cancer in a study by Kreatsoulas *et al.* as prevalence increased twofold in patients over 74 years old compared to those 65 to 74 years old [37]. In our study, the groups were not age-matched, but there was no significant difference in the average age between the groups. These limitations show that cancer, while an important risk factor, is not the only risk factor that can contribute to the development of AS, and further trials are necessary to truly understand the impact of cancer on AS.

The aim of this study was to compare the FDG uptake in the aorta of lung cancer patients and extrapulmonary cancer patients to evaluate the relative risk of AS in lung cancer patients. The assessment showed a significant increase in FDG uptake in lung cancer patients, suggesting an increased risk of AS and subsequent CVD. Future prospective studies with a larger number of subjects are needed to confirm this finding, which can improve the early detection and treatment of AS among cancer patients.

Disclosure of conflict of interest

None.

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Supplementary Table 1. PET/CT scanner distribution of the lung cancer and extrapulmonary cancer groups

	Lung Cancer	Extrapulmonary cancer
Gemini TF; Philips	21	46
Biograph; Siemens	11	25
Discovery ST; GE	1	7
Ingenuity TF; Philips	1	0
Total	34	78