Original Article

Predictors of Myocardial Ischemia in Preoperative Oncology Patients Who Underwent Fluorodeoxyglucose-Positron Emission Tomography Study

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Abstract

Background: Coronary artery calcification (CAC) can be visually estimated on computed tomography (CT) attenuation correction (CTAC) of positron emission tomography (PET). The visual estimation of CAC from CTAC scans performed for PET/CT is comparable to the standard CAC score scan. Myocardial perfusion imaging (MPI) with single-photon emission CT (SPECT) is commonly performed for risk stratification before oncologic surgery. **Objective:** We investigated the value of visual estimation of CAC from CTAC of PET/CT as well as other factors such as coronary artery disease (CAD) risk factors and type of cancer as predictors of MPI ischemia. **Methods:** Retrospectively, we identified 268 patients who underwent PET/CT and MPI for preoperative cardiac evaluation. Visual estimation of CAC was performed and classified into four categories. **Results:** The results of visual CAC were as follows: 47.8% – zero CAC, 32.8% – mild CAC, 14.2% – moderate CAC, and 5.2% – severe CAC. The majority of patients (85.8%) had normal MPI, whereas 14.2% were abnormal. There was a strong association between ischemia on MPI and CAC seen on CTAC ($P < 0.01$), dyslipidemia ($P < 0.01$), family history of CAD ($P < 0.05$), smoking ($P < 0.01$), and type of malignancy ($P < 0.01$). **Conclusion:** A strong association exists between visual estimation of CAC on CTAC and MPI. Zero is highly associated with normal MPI, but moderate-to-severe CAC is associated with abnormal MPI, in addition smoking, dyslipidemia, and certain cancer are associated with ischemic MPI; subsequently, preoperative cardiac testing is warranted in these subsets of patients.

Keywords: *Cancer surgery, coronary artery calcification, coronary artery calcium score, coronary artery disease, myocardial perfusion imaging, preoperative evaluation, single-photon emission computed tomography*

Introduction

The use of positron emission tomography/computed tomography (PET/CT) in the management of cancer patients is increasing. Current clinical oncology utilities of PET/CT include many indications, such as initial disease staging, selecting optimal treatment approaches, early treatment response assessment, restaging and detection of recurrent cancer, tumor detection and differential diagnosis of benign and malignant tumors, and radiation treatment planning.[1-3] The CT component of PET/CT is used for attenuation correction (CTAC) and for improved localization of abnormal 18F-fluorodeoxyglucose (FDG) uptake. A CTAC scan can detect findings unrelated to primary cancer.[4-7] Coronary artery calcification (CAC) is one of several incidental findings that can be detected in routine PET/CT in patients with cancer; other non-FDG findings of potential clinical significance include pulmonary nodules, pleural effusion, and vascular aneurysm.[8] CAC burden obtained by traditional Agatston Calcium scoring CT (CSCT) is a strong and independent predictor of cardiovascular events.[9,10] A prior study revealed a high degree of correlation between visually estimated CAC and Agatston score.[11] In a similar study, it was found that the visual estimation of CAC in CTAC correctly classified 71% of the CAC score in the same category and 94% within one category.[12] Myocardial perfusion imaging (MPI) with single-photon emission CT (SPECT) has been widely used for the detection of coronary artery disease (CAD).[13-15] MPI is commonly performed for risk stratification in patients with cancer prior to oncologic surgery. There are several factors, such as age and gender, and CAD risk factors such as family history, dyslipidemia, smoking,

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and type of cancer that might affect MIP findings. Thus, we undertook this study to investigate the value of visual estimation of CAC from the CTAC component of PET/CT as well as other factors such as patient demographics, CAD risk factors, and type of cancer as predictors of MPI finding in the preoperative evaluation of cancer patients, as the presence or absence of CAC could help to risk stratify patients before surgery in patients who did not undergo traditional coronary artery calcium score scanning.

Methods

Study population

Retrospectively, we identified 268 patients who had undergone FDG-PET/CT between January 2017 and March 2019 for clinically indicated reasons such as initial cancer staging, assessment response for therapy, and cancer restaging. All of these patients underwent SPECT for preoperative cardiac evaluation within 3 months of each other. The exclusion criteria included unstable patients, patients with a known history of CAD, prior myocardial infarction, prior coronary revascularization, a history of congestive heart failure, diagnostic Q wave on baseline electrocardiogram (ECG), and patients with known cardiomyopathy. The patients' demographics and clinical data included age, sex, the presence of diabetes, hypertension, dyslipidemia, and family history of coronary artery disease (CAD). Age, as a risk factor, was defined as younger than 45 years for males and 55 years for females. Diabetes mellitus (DM) was self-reported by patients under antidiabetic therapy. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or being under antihypertensive therapy. Dyslipidemia was characterized by fasting serum low-density lipoprotein cholesterol level ≥140 mg/dl or being under lipid-lowering therapy. A family history of CAD was accepted as positive if the father or a first-degree male relative had CAD before 55 years of age and if the mother or a first-degree female relative had CAD before 65. The study was approved by our institutional review board, and patient consent was waived.

Determination of coronary artery calcification

We retrospectively reviewed the CT component of PET/CT study on dedicated commercial software using a soft-tissue window. Several consecutive axial images were reviewed. Visualization of the left main coronary artery, proximal and mid-segments of left anterior descending (LAD) artery, left circumflex (LCX) artery, and right coronary artery (RCA) can be evaluated in all studies. However, visualization of distal segments was not possible in some patients due to cardiac and breathing motion. The visual scale for CAC scoring was evaluated for the presence or absence of CAC, and subsequently, patients with CAC were subdivided into mild, moderate, and severe classes. Mild CAC was identified as a few scattered foci of calcification in a single coronary artery; moderate CAC was identified as multiple foci of calcification in two or more coronary arteries; and severe CAC was shown by diffuse severe triple coronary artery distribution [Figure 1a-d]. CT scans were scored by a single trained reader blinded with SPECT images. Interobserver agreement was high for all CAC categories; in case of disagreement among readers, the images were reviewed and reported based on a consensus interpretation.

Single-photon emission computed tomography acquisition and analysis

Patients underwent rest-stress myocardial perfusion studies with either a separate day protocol or a same-day protocol. The choice of tracer and same-day or separate-day protocol was based on logistical requirements. The rest dosage in patients who underwent a separate day rest-stress protocol was 1100 megabecquerel (MBq) of either technetium-99m (Tc-99m) sestamibi or tetrofosmin. The stress dose in patients who underwent the rest-stress same-day protocol was 1100 MBq mCi of either Tc-99m sestamibi or tetrofosmin. Tc-99m sestamibi or Tc-99m tetrofosmin was injected during peak pharmacological vasodilatation, with adenosine (140 μg/kg/min) or dipyridamole. The acquisition parameters and postprocessing were performed according to the most recent guidelines of the American Society of Nuclear Cardiology for nuclear cardiology procedures.[16] All images were reoriented in short, vertical, and horizontal views utilizing AutoSPECT (Cedars-Sinai Medical Center, Los Angeles, California) for visual interpretation by an experienced nuclear medicine physician. In the visual analysis, the 17 segments were scored for perfusion defects on a 4-point system (0 = normal, 1 = mild, 2 = moderate,

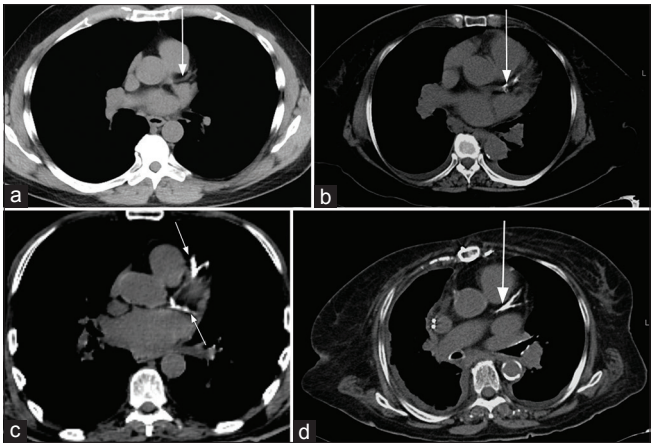

Figure 1: (a) Axial computed tomography attenuation correction image shows zero (arrows) coronary artery calcification. (b) Axial computed tomography attenuation correction shows few foci of calcification in the Left anterior descending coronary artery, consistent with mild coronary artery calcification (arrow). (c) Axial computed tomography attenuation correction image shows multiple foci of calcification in the left anterior descending artery and left circumflex artery, consistent with moderate coronary artery calcification (arrow). (d) Axial computed tomography attenuation correction image shows severe diffuse coronary calcification, consistent with severe coronary artery calcification (arrow)

and 3 = severe) for both the stress and rest images. The reader made the final determination of an abnormal SPECT study by comparing both the perfusion and functional data. The perfusion defects represented by the perfusion scores at stress and rest were used to form the interpretation of the studies.[16] An apical, anterior wall, and septal defect was considered LAD artery distribution; lateral wall defect indicated LCX artery distribution; and inferior wall defect indicated RCA distribution.

Fluorodeoxyglucose-positron emission tomography/computed tomography imaging

All patients fasted for at least 6 h before PET/CT studies. 370–740 MBq (10–20 mCi) of ^{18}F-FDG was injected intravenously and scanning started 60 min later. No intravenous contrast was administered. The studies were acquired on a hybrid PET/CT scanner (GE, Discovery, Wisconsin, USA). All patients were in a supine position. CT images were acquired from head to mid-thigh. CT images were acquired from head to mid-thigh as well using standard parameters: 10 Kvp, current 180 mA, pitch of 0.981:1, and single round tube rotation of 0.85. CT data were used for attenuation correction, and PET images were reconstructed using the Ordered-Subsets Expectation Maximization; 2 iterations, 20 subsets, and a matrix size of 128 × 128 pixels were used in the reconstruction.

Statistical analysis

We used the SPSS v. 23 program (IBM Corp, New York, United States), Statistical Package for the Social Sciences. Continuous measurements were reported as means and standard deviations while categorical variables were reported as percentages, and inferential statistics to test the relationship between variables, through:

1. Chi-square test for independence: This test is applied to determine whether there is a significant association between two categorical variables from a single population
2. Spearman's rho correlation test: This test is applied to determine the relationship between two ordinal variables.

Results

Table 1 shows the demographic data of the patients (n = 268). About 56.3% of the total participants were male, whereas 43.7% were female. The largest age group in the sample was the group aged 61–70 years at 37.3% of the total. Fifty-three percent of patients had DM and 51.9% had hypertension. Almost no patients (98%) had a family history. Ninety-one percent were nonsmokers and 86.2% did not have dyslipidemia. Regarding type of malignancy, 16% of the patients had either breast or gastrointestinal/genitourinary (GI/GU). These were followed by 11.9% with head and neck, 4.1% with lymphoma, and 3.7% with lung. Around 48.1% of the patients had other types of malignancy [Table 2]. SPECT findings showed that 85.8% of the total patients were normal, whereas 14.2% were abnormal, as follows: 5.2% had LAD artery, 4.1% had RCA, 2.6% had LCX artery, and the fewest, 2.2%, had multivessel disease. The results of the visual assessment of CAC showed that the highest percentage (47.8%) had no calcium seen on CT, whereas 32.8% had mild CAC, 14.2% had moderate CAC, and the fewest (5.2%) had severe CAC [Table 3].

Association between single-photon emission computed tomography findings and coronary artery calcification findings

There was a correlation between SPECT and CAC findings on CTAC by Spearman's rho correlation test as ordinal variables. SPECT findings correlated positively with CAC seen on CTAC (r = 0.268, $P < 0.01$). For more details about the relations between SPECT and CAC findings, a Chi-square

Table 1: Demographic data of the sample study (n=268)

Demographic variables	n (%)
Gender	
Male	151 (56.3)
Female	117 (43.7)
Age (years)	
20-50	24 (9.0)
51-60	71 (26.5)
61-70	101 (37.7)
71 and above	72 (26.9)
Hypertension	
Yes	139 (51.9)
No	129 (48.1)
DM	
Yes	142 (53.0)
No	126 (47.0)
Dyslipidemia	
Yes	37 (13.8)
No	231 (86.2)
Family history	
Yes	4 (1.5)
No	264 (98.5)
Smoking	
Yes	24 (9.0)
No	244 (91.0)

DM: Diabetes mellitus

Table 2: Type of malignancy in the sample study (n=268)

Type of malignancy	n (%)
Head and neck	32 (11.9)
Breast	43 (16.0)
Lung	10 (3.7)
GI/GU	43 (16.0)
Lymphoma	11 (4.1)
Others	129 (48.1)
Total	268 (100.0)

GI/GU: Gastrointestinal and genitourinary

test was performed. Normal SPECT was associated with zero CAC on CTAC (45.1% of 85.7%). Severe myocardial ischemia (multivessel distribution) was associated with severe CAC, and this indicates a strong association between SPECT and CAC findings on CTAC ($P = 0.000 < 0.01$).

Association between single-photon emission computed tomography findings and demographics (gender and age)

The results of the Chi-square test showed that there was no statistically significant association between SPECT findings and gender ($P > 0.05$), whereas there was a strong, statistically significant association between SPECT findings and age ($P < 0.01$). All patients below 51 years of age had normal SPECT findings, whereas the higher age of the patients, the higher the abnormality of the SPECT, with the highest percentage found for LAD artery.

Association between single-photon emission computed tomography findings and risk factors

The results of the Chi-square test showed that there was no statistically significant association between SPECT findings and hypertension or DM ($P > 0.05$). However, there was a statistically significant association between SPECT findings and each of dyslipidemia ($P < 0.01$), family history ($P < 0.05$), and smoking ($P < 0.01$) [Table 4].

Table 3: Coronary artery calcification seen on computed tomography attenuation correction scan, sample study (*n*=268)

CAC seen on CTAC	*n* (%)
None	128 (47.8)
Mild	88 (32.8)
Moderate	38 (14.2)
Severe	14 (5.2)

CAC: Coronary artery calcification, CTAC: Computed tomography attenuation correction

Association between single-photon emission computed tomography findings and type of malignancy

The results of the Chi-square test showed that there was a strong, statistically significant association between SPECT findings and type of malignancy ($P < 0.01$). The frequency of abnormal SPECT was high in patients with lung cancer (four patients of ten or 40%) compared to patients with breast cancer (9%), head and neck (21%), and GI/GU (20%) [Table 5].

Binary logistic regression results

Binary logistic regression results indicated that smoking, dyslipidemia, and CAC on CT had significant effects on the SPECT findings with *P* values of 0.002, 0.01, and 0.01, respectively. There was no statistically significant effect for age, type of malignancy, or family history on the SPECT findings ($P > 0.05$).

Discussion

There was a strong, statistically significant association between visual estimation of CAC on CTAC of PET/CT and stress-induced myocardial ischemia on MPI in cancer patients who underwent PET/CT for routine oncological indications. A visual CAC score of zero was associated with normal MPI, whereas a high degree of visual CAC was associated with more severe ischemia (multivessel ischemia) on MPI. Our results are concordant with multiple studies. Berman *et al*. reported that ischemic

Table 4: Results of Chi-square test for association between single-photon emission computed tomography findings and risk factors

Risk factor (%)	SPECT (%)					χ^2, df, *P*
	Normal	Abnormal				
		Multivessel disease	LAD	LCX	RCA	
Hypertension						
Yes	42.2	1.9	3.0	1.9	3.0	6.216, 4, 0.184
No	43.6	0.4	2.2	0.7	1.1	
DM						
Yes	43.6	1.9	3.4	1.9	2.2	4.316, 4, 0.365
No	42.1	0.4	1.9	0.7	1.9	
Dyslipidemia						
Yes	9.0	0.7	1.5	1.1	1.5	16.352, 4, 0.003**
No	76.9	1.5	3.7	1.5	2.6	
Family history						
Yes	0.7	0.4	0.4	0.0	0.0	13.316, 4, 0.010*
No	85.1	1.9	4.9	2.6	4	
Smoking						
Yes	5.3	0.0	1.1	0.7	1.9	26.860, 4, 0.000**
No	80.6	2.2	4.1	1.9	2.2	

**Significant at the 0.01 level, *Significant at the 0.05 level. SPECT: Single-photon emission computed tomography, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: Right coronary artery, DM: Diabetes mellitus

Table 5: The relationship between type of malignancy and single-photon emission computed tomography

Cancer type	SPECT					Total
	Normal	Abnormal				
		Multivessel	LAD	LCX	RCA	
Head and neck						
Count	25	0	4	1	2	32
Percentage of total	9.3	0.0	1.5	0.4	0.7	11.9
Breast						
Count	39	0	1	2	1	43
Percentage of total	14.6	0.0	0.4	0.7	0.4	16.0
Lung						
Count	6	3	0	0	1	10
Percentage of total	2.2	1.1	0.0	0.0	0.4	3.7
GI/GU						
Count	34	1	4	3	1	43
Percentage of total	12.7	0.4	1.5	1.1	0.4	16.0
Lymphoma						
Count	8	1	0	0	2	11
Percentage of total	3.0	0.4	0.0	0.0	0.7	4.1
Others						
Count	118	1	5	1	4	129
Percentage of total	44.0	0.4	1.9	0.4	1.5	48.1

SPECT: Single-photon Emission Computed Tomography, Multivessel: Ischemia in multivessel coronary artery distribution, LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: Right coronary artery, GI/GU: Gastrointestinal and genitourinary

MPI was associated with a high likelihood of subclinical atherosclerosis by CAC but was rarely seen with a zero CAC score or even a CAC score lower than 100; in a majority of patients, a zero CAC and a CAC score of less than 100 obviated the need for subsequent noninvasive cardiac testing.[17] In a similar study, Matsuo *et al*. reported, in a population with predominately intermediate likelihood of CAD, that a zero CAC score had the possibility of excluding stress-inducible ischemia on MPI, but that ischemic MPI was associated with a high likelihood of subclinical atherosclerosis as detected by CAC.[18] Fathala *et al*. reported that visual detection of CAC on the CT component of PET/CT was associated with normal MPI, but the presence of CAC was associated with a high likelihood of ischemic MPI.[19] Based on our data and the results of these prior studies, it appears that a zero CAC or a low CAC score is associated with normal MPI and may obviate a need for further noninvasive cardiac testing in preoperative evaluation of oncologic patients.

In addition to visual estimation of CAC on CTAC, a strong association between stress-induced myocardial ischemia on MPI and patient sex, dyslipidemia, family history of CAD, and smoking was found, but interestingly, there was no association between patients' age or other CAD risk factors and myocardial ischemia. A strong and significant statistical association was noted between the type of malignancy and ischemic MPI. For example, there was a high frequency of abnormal MPI in patients with lung cancer: 40% of patients with lung cancer had ischemic MPI. This observation is concordant with prior studies that reported a strong association between lung cancer and cardiovascular disease (CVD); patients with lung cancer had an 89% increased risk of CAD compared to those without lung cancer.[20,21] Our results are also in agreement with prior studies that supported a high abnormal CAC score in lymphoma patients. In one, on a series of 47 Hodgkin's lymphoma patients treated with radiation, abnormal high CAC scores compared to published values were found.[22] In another small study of 9 lymphoma patients treated with mediastinal radiation an average 26 years prior, 6/9 were above the 90th percentile for age and gender[23] and only 20% of patients with head-and-neck and GI/GU cancer had ischemic MPI. However, ischemic MPI was not prevalent in patients with breast cancer, with only 9% having abnormal MPI. Although CVD is the leading cause of death in breast cancer survivors who are older than 65, the increased risk of CVD-related mortality cannot be explained by treatment-induced cardiotoxicity or radiation therapy complications.[24] In a multivariate binary logistic regression analysis, visual CAC on CTAC, smoking, and dyslipidemia were found to be strongly associated with stress-induced MPI, with *P* values of 0.002, 0.01, and 0.01, respectively.

The prognostic value of visually estimated CAC on enhanced nongated chest CT for nonfatal myocardial infarction and all-cause mortality has recently been investigated. It was found that among patients with no known CAD who underwent nongated nonenhanced chest CT for pulmonary-related indications, visually detected CAC was a strong independent predictor for nonfatal MI and all-cause mortality.[25] Calcium scanning from nongated CT studies in a preliver transplant showed that calcium scanning from nongated CT may be integrated into a preoperative algorithm to rule out obstructive CAD and helped to avoid further noninvasive testing in this group of patients.[26] However, there are some limitations of visually estimated CAC on CTAC compared to standard CSCT. Visually estimated CAC in CTAC may be underestimating the extent of CAC due to factors such as blurring of coronary arteries, the gap between image data caused by a cardiac motion artifact, partial average effects caused by slice thickness, and low image resolution. By contrast, overestimating of CAC may occur due to high noise level, slice duplication, and erroneous detection of calcium other than coronary calcification, such as valve calcification or metal implants.[27,28]

Study limitations

The present study has limitations worth discussing. First, visual estimation of CAC was not correlated with standard CSCT, and CT component of PET/CT was obtained without ECG gating. Subsequently, distal segments of coronary artery could not be evaluated for calcification; however, there was an excellent agreement between both readers in visual estimation of CAC. Second, the images included in the study were obtained from a single hospital using a scanner from a single vendor. Further studies are needed to evaluate whether the results generalize to multicenter settings. Finally, the study was conducted as a retrospective study, and we do not have a correlation with coronary angiography or surgical outcome.

Conclusion

Our results revealed a strong association between visual estimation of CAC on CTAC of PET/CT in oncology patients and ischemia on preoperative MPI. It appears that zero or low CAC is associated with normal MPI, and further, cardiac evaluation in those patients is probably not indicated, as the likelihood of ischemic MPI is very low. On the other hand, patients with moderate or severe CAC are associated with a high likelihood of ischemia on preoperative MPI. In cancer patients who did not undergo standard coronary artery calcium score scanning, visual estimation of CAC on CTAC may be used to assess the degree of coronary artery atherosclerosis and may guide further investigation, such as preoperative MPI. Patients with lung cancer, male patients with a history of dyslipidemia, and active smokers will benefit from further cardiac evaluation with stress MPI.

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Conflicts of interest

There are no conflicts of interest.

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