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Original Article

Chemotherapy-induced coronary arteries calcium score deterioration as detected with unenhanced CT portion of FDG PET/CT

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Abstract: This study aims to detect the potential impact of chemotherapy on the coronary calcium scoring (CCS) in lymphoma patients undergoing FDG-PET/CT at baseline and for therapy response using the CT portion of the exam to calculate the CCS. One hundred twelve lymphoma patients were included in the study based on having both baseline and at least 2 post-chemotherapy scans. The unenhanced CT portions of the scans were reviewed to measure the CCS which was then extracted using the Toshiba Vital Program. Agatston scores were assessed as category 1 with zero CCS unit and categories 2 to 5 having more than >1, 11, 101, and 400 CCS units respectively. For statistical analysis, paired T-Tests were used to compare results. The overall changes in total coronary artery calcium (CAC) from baseline to last treatment showed a statistically significant increase in CAC with an average increase of at least 35% in the CAC score. We also compared the overall changes in CAC with patients having category 1 and 2 Agatston at baseline and found no statistical increase in CAC post-chemotherapy. Additionally, we compared the overall changes in CAC with patients having category 3 and 4 Agatston at baseline and found statistically significant increase in CAC post-chemotherapy. In lymphoma patients, chemotherapy may cause worsening of CCS and this can serve as an early indicator of chemotherapy-induced cardiac toxicity. When present, such CCS deterioration can be detected by the unenhanced CT portion of routine oncologic FDG PET/CT scans.

Keywords: Atherosclerosis, calcium score, lymphoma, PET/CT

Introduction

Lymphoma is the most prevalent blood cancer with approximately 74,240 new non-Hodgkin lymphoma (NHL) cases, and 8,260 new Hodgkin lymphoma (HL) cases diagnosed in 2017 [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL (30%-58%) and commonly occurs in adults above 64 years of age [2]. Among the new NHL cases, the incidence rate in males was higher (19.5 per 100,000 individuals) compared with females (5.9 per 100,000 individuals). In addition, the number of new cases of HL was 2.9 per 100,000 men and 2.3 per 100,000 women per year. The number of deaths was 5.9, and 0.3 per 100,000 men and women per year in NHL and HL, respectively [1].

Positron emission tomography/computed tomography (PET/CT) is a standard imaging modality for interim, restaging and post-treatment assessment of FDG avid subtypes of lymphoma [3-5]. According to the *national comprehensive cancer network* (*NCCN*) guidelines, PET/CT is now considered as a standard part of post-treatment response evaluation for patients with aggressive NHL and HL [6]. Patients with B cell lymphoma are treated with a combination of chemotherapy, including cyclophosphamide, doxorubicin, vincristine, prednisone as well as immunotherapy with rituximab [7]. Many studies have shown that despite the favorable outcomes of immunochemotherapy, cancer survivors are at risk for the development of several adverse effects that may lead to unfavorable outcome to cancer patients [8]. Cardiomyopathy

is one of the major harmful outcomes of chemotherapy, which may lead to serious morbidity or mortality [9]. Among the different chemotherapy regimens associated with chemotherapy-induced cardiotoxicity (CIC), anthracyclines have been reported to be the most common cause of end-stage heart failure [10]. These cardiotoxic effects can occur immediately or several weeks to months after chemotherapy administration [11]. Detection of subclinical CIC through resting left ventricular ejection fraction using multigated acquisition (MUGA) scan or echocardiographic fractional shortening has been shown to be suboptimal [12]. Several hypotheses have been proposed to explain the underlying pathogenetic mechanism. Free-radical-mediated myocyte damage, adrenergic dysfunction, intracellular calcium overload, and the release of cardiotoxic cytokines may all contribute to CIC [12]. Studies also have shown that preexisting cardiovascular disease, including coronary atherosclerosis, can increase the risk of heart failure in patients undergoing chemotherapy treatment [13].

Coronary artery calcium (CAC) scores determined by computed tomography (CT) allows for early detection and quantification of coronary calcification and has been proposed as an alternate approach for stratification of global cardiac risk, evaluation of chest pain patients and prediction of future cardiac events [14]. The amount of calcium deposition is an independent risk factor for major adverse events such as myocardial infarction and cardiac death [15, 16]. Coronary artery calcium (CAC) is a low-cost and low-radiation test that non-invasively allows direct visualization of coronary atherosclerosis. It is an established predictor of future major adverse atherosclerotic cardiovascular events. Recently published data from the PROMISE study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) showed that a CAC of 0 can safely exclude future cardiovascular events in symptomatic patients with suspected Coronary artery disease (CAD) and that most events occurred in patients with positive CAC scans [17]. The CAC is derived from the Agatston score which is a semi-automated tool able to quantify the extent of coronary artery calcification detected on an unenhanced CT scan. It is calculated using a weighted value assigned to the highest density of calcification in a given artery which is multiplied by the area in square millimeters of the calcification [18].

Obtaining the CAC score does not need to be extracted from a dedicated CT examination. Hybrid imaging (SPECT/CT and PET/CT) is becoming standard in most nuclear medicine facilities in the United States. For example, extracting the CAC score from the low-dose CT portion of SPECT/CT used for attenuation correction during the Myocardial perfusion images (MPI) is a feasible method to calculate CAC compared to standard CT [19]. In addition, we previously validated that extracting the CAC score from low-dose unenhanced CT portion of PET/CT is reliable when compared to the standard diagnostic CT in calculating CAC scores [20].

While many studies have shown that the use of external beam radiation as a part of cancer management may induce atherosclerosis and lead to potential high-risk adverse reaction, the impact of chemotherapy on coronary atherosclerotic calcification has yet to be studied [21-23]. In this study, we aim to evaluate whether chemotherapy can worsen coronary calcification detected by CAC scores using the unenhanced low-dose CT portion from the PET/CT in lymphoma patients.

Material and methods

Patient selection

The university institutional review board (IRB) has approved this retrospective study and waived individual informed patient consent. One-hundred and twelve lymphoma patients were selected for the study. All patients underwent a baseline ^{18}F-FDG PET/CT scan and at least one subsequent restaging scan after chemotherapy within 3 ± 1 year. A total of 443 ^{18}F-FDG PET/CT scans were retrospectively reviewed. None of our selected patients were exposed to thoracic radiation therapy or had a history of hemodialysis.

All cases underwent clinical evaluation and assessment of pre-clinical atherosclerosis. Clinical evaluation included major cardiovascular risk factors (hypertension, diabetes, and smoking), type of Lymphoma, and bulky/non-bulky disease.

PET/CT scanning

All ^{18}F-FDG PET/CT scans in our clinical studies were performed using a PET/CT scanner (Gemini TF; Philips Medical Systems) with an

Table 1. Patient characteristics

	Overall	Baseline Calcium Score				*p*-value
		0 (n=78)	1-100 (n=7)	101-400 (n=12)	>400 (n=15)	
Sex						0.64
Male	58	39	3	6	10	
Female	54	39	4	6	5	
DM						0.47
No	84	59	6	8	11	
Yes	17	9	1	3	4	
Missing/NA*	11	10	0	1	0	
Hypertension						0.002*
No	58	48	2	3	5	
Yes	43	20	5	8	10	
Missing/NA*	11	10	0	1	0	
Smokes						0.39
No	40	28	2	7	3	
Current	15	9	1	1	4	
Former	41	26	4	3	8	
Missing/NA*	16	15	0	1	0	
Dialysis						.008*
No	99	68	7	11	13	
Yes	2	0	0	0	2	
Missing/NA*	11	10	0	1	0	
Bulky						0.89
No	78	53	5	8	12	
Yes	11	7	1	1	2	
N/A	21	16	1	3	1	
Recurrence						0.06
No	66	47	6	7	6	
Yes	35	20	1	5	9	
N/A	10	10	0	0	0	
Type of Lymphoma						0.44
DLBL	68	45	6	9	8	
Marginal	11	8	0	1	2	
T-Cell	8	5	0	0	3	
HL	10	9	0	0	1	
AITL^	1	1	0	0	0	
Burkitt^	3	2	1	0	0	
Gray Zone^	1	0	0	1	0	
Mantle^	1	0	0	0	1	
SLL^	1	0	0	0	0	

^Combined into one group for statistical test, *Not included in the chi-square test. Numbers are presented in the tables.

axial co-scan range of 193 cm. As is the institutional protocol, all patients were instructed to fast at least 4 hours prior to receiving the radiopharmaceutical injection. Blood glucose level was <200 mg/dl in all patients. On the day of the exam, intravenous injection of 5.18 MBq/kg (0.14 mCi/kg) of ^{18}F-FDG was administered. For the uptake phase, patients sat in a quiet room without talking for approximately 60 minutes.

CT scanning

The CT component of the PET/CT scanner consisted of a 64 slice multidetector helical CT with a gantry port of 70 cm. The parameters of CT detectors were set as follows for 20-21 bed acquisitions: 120-140 kV and 33-100 mAs (based on body mass index), 0.5 s per CT rotation, pitch of 0.9, and 512 × 512 matrix data were used for image fusion and the generation of the CT transmission map. The CT images were obtained without oral or IV contrast administration according to the standard PET/CT protocol at our institution.

Coronary artery calcium score

Low-dose, non-contrast raw CT images were reconstructed from the selected PET/CT scans using the Toshiba Vital program (VitreaCore program, version 6, 7 1030, 1). The calcium score of calcified plaques appearing on CT slices of the four main coronary arteries (left main coronary, left anterior descending, circumflex, and right coronary arteries) was calculated by multiplying the area of the calcification by its density. The total artery calcium score was calculated by the sum of all individual calcium scores. Based on the total Agatston score, patients were divided into four groups (0; 1-100; 101-400; >400) and further into three groups (0, >0 and all patients) [24].

Statistical analysis

Participant characteristics are reported as mean (SD) for continuous variables, frequen-

Table 2. Paired t-tests for baseline calcium scores

	Baseline Mean (SD)	End Mean (SD)	t-value	*p*-value
Overall, n=112	233.69 (663.74)	424.13 (1178.53)	-3.01	0.003*
BL Calcium =0, n=78	0 (0)	32.67 (186.37)	-1.55	0.13
1-100, n=7	43.86 (35.51)	452.29 (89.74)	-1.19	0.28
101-400, n=12	208.42 (98.99)	439.17 (226.34)	-3.74	0.003*
>400, n=15	1557.67 (1133.04)	2434.60 (2292.06)	-2.25	0.04*

*Not included in the chi-square test.

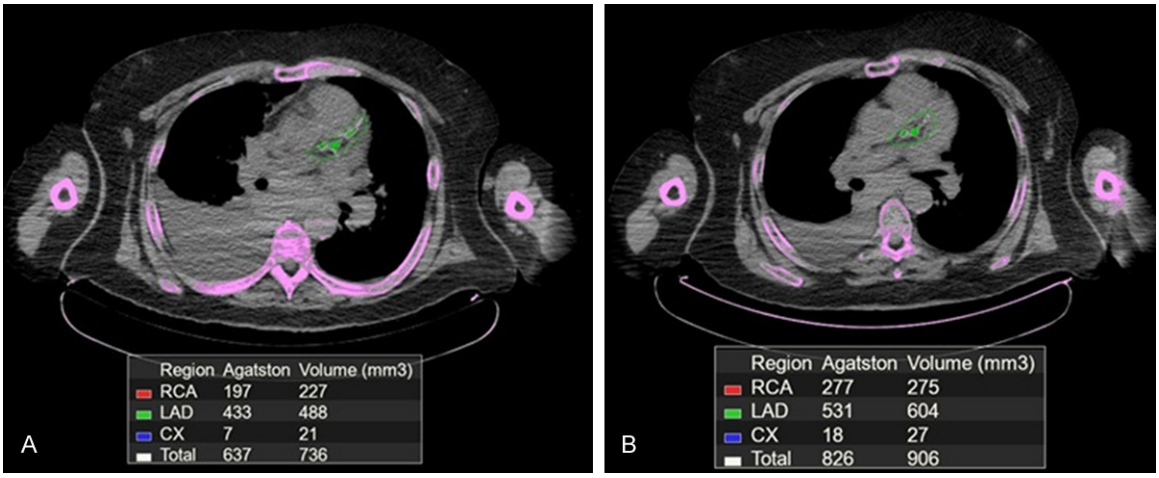

Figure 1. 63-year-old male with DLBCL. Image was measured using Toshiba Vital program. Green areas show regions of coronary calcification in the LAD territory and pink areas denote normal bone. Baseline CT image (A) from PET/CT shows a total Agatston score of 637. Six month follow-up CT image (B) from PET/CT shows a total Agatston score of 817. Of note, the RCA, CX and total regions are not displayed in this image.

cies (%) for categorical variables. Paired t-tests were conducted to examine differences in calcium scores between baseline and post-chemotherapy measurements for the group as a whole and for each Agatston category. IBM SPSS Statistics version 23 was used to conduct all analyses. Statistical significance was set at $P<0.05$.

Results

One-hundred and twelve lymphoma patients (M=58, F=54) were included in the study. Among these patients, 56 of them are current or former smokers, 17 are diabetic, 43 have a known history of hypertension, and 2 of them undergo hemodialysis treatment (**Table 1**). Sixty-five present of our patient population were diagnosed with Diffuse B-Cell Lymphoma (DBCL) and 31% had recurrent disease.

We identified that the overall changes in total CAC from baseline to last treatment showed a statistically significant increase in CAC (P= 0.003) with an average increase of at least 35% in the CAC score. We also compared the overall changes in CAC with patients having category 1 and 2 Agatston at baseline and found no statistical increase in CAC post-chemotherapy (P=0.13, P=0.28 respectively). Additionally, we compared the overall changes in CAC with patients having category 3 and 4 Agatston at baseline and found statistically significant increase in CAC post-chemotherapy with P= 0.003, P=0.04 respectively (**Table 2**).

For example, a 63-year-old male diagnosed with DLBCL has Agatston score of 637 extracted from his initial (pre-treatment) PET/CT CAC. A 6 month follow-up post-treatment PET/CT was performed and showed an Agatston score of 817 (**Figure 1**). In contrast, a 59-year-old male with an initial Agatston score of 0, extracted from his initial (pre-treatment) PET/CT CAC, has no significant deposition of calcium in his coronary arteries with an Agatston score of 0 at his 8 month follow-up post-treatment PET/CT (**Figure 2**). Both patients were matched in gender, social history (smoking) and comorbidities.

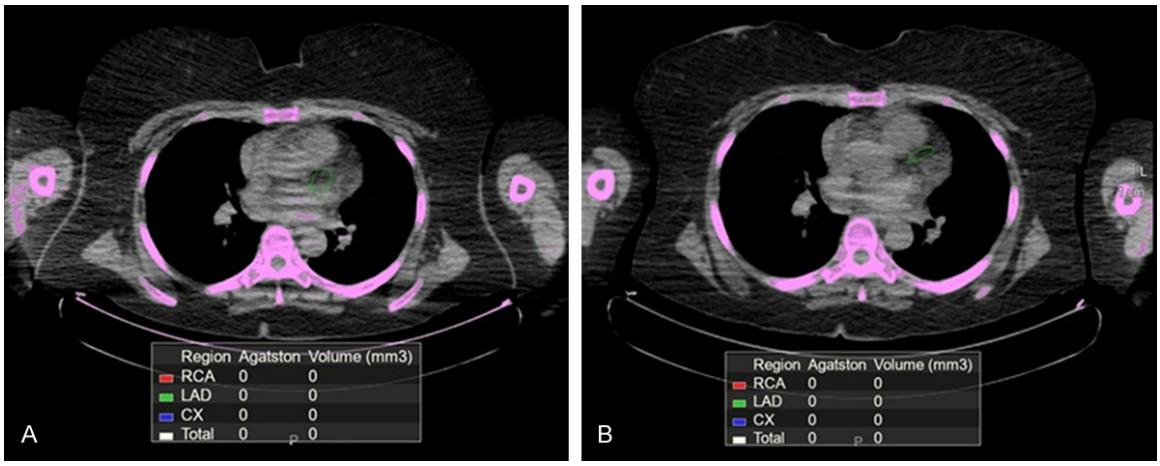

Figure 2. 59-year-old male with DLBCL. Image was measured using Toshiba Vital program. Green circle shows measured area of LAD with no calcification. Baseline CT image (A) from PET/CT shows a total Agatston score of 0. Eight month follow-up CT image (B) from PET/CT also shows a total Agatston score of 0. Of note, the RCA, CX and total regions are not displayed in this image.

Discussion

In the United States, the number of new cases diagnosed with different types of lymphoma is over 80,000 cases per year [1]. Based on the National Cancer Institution (NIH) statistics, the percentage of survival among these patients has exceeded 70% in 5 years [1]. However, cancer survivors are at risk to develop serious, life-altering adverse effects as a result of their cancer treatment [25]. Although acute tissue injuries during chemotherapy can be reversible, chronic tissue injuries after chemotherapy can evolve into lifelong secondary morbidities [8]. An early detection of these tissue injuries could enable rescue interventions and prevent lifelong morbidity. Anthracyclines are among the most commonly used class of chemotherapy in the management of lymphoma patients. Studies have shown that the use of anthracyclines is limited by dose-dependent cardiotoxicity, which can result in heart failure either during treatment or years after the completion of therapy [26]. It is believed that anthracycline cardiotoxicity is related to direct injury to the cardiomyocytes due to a combination of free radicals and intracardiac metabolic derangements [27]. Other studies showed that chemotherapy may increase cardiac events in patients with underlying CAD [13].

In this study, we aimed to evaluate the feasibility of using the low-dose non-contrast CT scan used in FDG-PET/CT to calculate and extract CAC. We hypothesize that chemotherapy could induce calcium deposition in the coronary arteries which may contribute to cardiomyopathy related to chemotherapy.

Integrated whole body PET/CT has become a preferred imaging modality for initial staging and restaging for lymphoma [4]. The use of FDG-PET/CT imaging in the management of lymphoma patients has been markedly expanded in the last decade [28]. At our institution, we have utilized the use of the low-dose non-contrast CT portion of the FDG-PET/CT to extract CAC. We were able to prove that CAC extracted from PET/CT is reliable when compared to the standard CT.

We have reviewed pre-therapy, follow-up and post-therapy PET/CTs of 112 lymphoma patients and used the CT portion of the PET/CT to extract the CAC. We have identified all cardiovascular risk factors including age, diabetes mellitus (DM), hypertension (HTN), history of smoking and end-stage renal disease (ESRD). Numerous studies pointed to age, DM, and ESRD as the primary factors associated with the presence of arterial calcification [29, 30]. Male gender, however, was not found to be an important contributing factor. The frequency of hypertension and DM did not differ significantly between different Agatston groups. We have limited our study for patients who underwent full treatment within 4 years from the baseline study to avoid age-related atherosclerotic cal-

cium deterioration. We have also excluded all patients who underwent external radiation therapy, as many studies have proven that radiation therapy may worsen atherosclerotic changes [24].

In our study, the overall CAC has significantly increased between the baseline pre-treatment PET/CTs and last post-therapy PET/CTs. However, based on Agatston score grouping, patients with a baseline Agatston score of 1, (no-calcium deposition in their coronary arteries) have no significant increase in the calcium deposition post-chemotherapy. Furthermore, patients with Agatston score in groups 3 and 4 have significant increase in their coronary arteries calcification. To the best of our knowledge, this may be the first study to identify chemotherapy as an independent potential cause for worsening in coronary atherosclerosis.

Our study was limited to evaluation of the clinical significance of increased CAC to a patient's cardiovascular disease. We were also limited in evaluating which type of chemotherapy may contribute the most in this significant deterioration of the CAC. We were limited to a single institution with a single fixed PET/CT camera. In addition, the lack of a control group without lymphoma or chemotherapy limits our findings. A prospective multi-institute study would be able to better assess different cameras, various types of chemotherapies and also compare results with a control group.

Our data provides evidence that chemotherapy may worsen calcium deposition in the coronary arteries which may significantly contribute in serious cardiovascular comorbidities. Given that FDG PET/CT is the standard of care in the management of cancer patients, information regarding CAC at baseline and post-therapy can easily be extracted from the CT portion the PET/CT without an additional dedicated CT scan. Such information may provide early signs for chemotherapy induced cardiotoxicity than the frequently used MUGA scan and can avoid additional cost and radiation exposure from a dedicated cardiac examination. Furthermore, information regarding an abnormal CAC at the time of the baseline PET/CT scan may contribute to the selection of less cardiotoxic chemotherapeutic agents for certain NHL subtypes, potentially without compromising malignancy control.

Disclosure of conflict of interest

None.

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