

Predictive Value of Left Ventricular ^{18}F -FDG PET/CT Derived Parameters and Uptake Patterns for Chemotherapy-Induced Cardiotoxicity in Patients with Lymphoma

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Abstract

Background

Anthracycline-induced cardiotoxicity significantly impacts the survival and quality of life of lymphoma patients. Since traditional echocardiographic markers often detect injury only after irreversible damage, there is an urgent need for early biomarkers. We aimed to evaluate the predictive value of myocardial FDG uptake patterns and quantitative parameters from routine oncologic PET/CT for cancer therapy-related cardiac dysfunction (CTRCD).

Methods

This retrospective cohort study included lymphoma patients treated with anthracycline-based regimens at a single hospital between 2018 and 2024. Patients underwent FDG PET/CT at baseline and after chemotherapy. CTRCD was operationally defined using the LVEF-based component of the 2022 ESC cardio-oncology guidelines on follow-up echocardiography. Metabolic parameters including maximal standard uptake value (SUVmax), metabolic target volume (MTV), total lesion glycolysis (TLG), and visual uptake patterns were analyzed on pre and post-treatment PET scans.

Results

Post-treatment SUVmax, MTV, and TLG were significantly higher in patients who developed cardiotoxicity ($p = 0.04$, 0.017 , and 0.03 , respectively). Multivariate logistic regression identified post-treatment SUVmax ≥ 8.49 ($p = 0.018$) and a focal/diffuse uptake pattern ($p = 0.004$) as independent predictors of CTRCD. Notably, absent myocardial FDG uptake after treatment was observed only in patients without CTRCD in this cohort. Baseline PET parameters showed no significant predictive value ($p = \text{n.s.}$).

Conclusion

Routine post-treatment oncologic FDG PET/CT may provide exploratory information on myocardial metabolic changes associated with CTRCD in lymphoma patients receiving anthracycline-based chemotherapy. Elevated post-treatment SUVmax and focal/diffuse uptake patterns were associated with CTRCD, whereas absent myocardial FDG uptake after treatment was observed only in patients without CTRCD in this cohort. These findings should be considered hypothesis-generating and require prospective validation using standardized myocardial metabolic preparation and predefined imaging timepoints.

Introduction

Significant advancements in chemotherapeutic regimens, particularly the widespread use of anthracyclines, have markedly improved survival outcomes in patients with lymphoma over the past few decades [1, 2]. However, this clinical success is partially overshadowed by the risk of severe cardiovascular adverse events, among which heart failure and left ventricular (LV) dysfunction are the most concerning, directly impacting the quality of life and mortality of cancer survivors [3, 4]. Anthracycline-induced cardiotoxicity is generally dose-dependent and cumulative, resulting from irreversible cardiomyocyte injury driven by complex mechanisms including oxidative stress, mitochondrial dysfunction, and topoisomerase II β -mediated DNA damage [5, 6].

Currently, clinical monitoring of cardiotoxicity primarily relies on the assessment of LV ejection fraction (LVEF) via echocardiography or multigated radionuclide angiography (MUGA) [1, 7]. However, a decline in LVEF is often a late manifestation of myocardial injury, occurring only after compensatory mechanisms have been exhausted and structural damage has become irreversible [7, 8]. Global longitudinal strain (GLS) and cardiac biomarkers, such as troponin and BNP/NT-proBNP, may provide additional information for early detection and risk stratification of cancer therapy-related cardiac dysfunction. However, they are generally interpreted in combination with clinical and echocardiographic findings rather than as sole diagnostic criteria, and their routine availability may be limited in real-world oncology practice [9]. Hence, there is an urgent need for novel and practical biomarkers capable of identifying early pathophysiological changes before the onset of mechanical dysfunction [2, 10].

Whole-body ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is widely used for diagnosis, staging, and response assessment in patients with lymphoma [5]. Beyond tumor evaluation, FDG PET/CT provides a window into myocardial glucose metabolism [3], without additional cost, radiation, or procedural burden. The utilization of existing data from oncological FDG PET/CT can be a highly cost-effective tool for early risk stratification in patients undergoing anthracycline-based therapy.

This study aimed to evaluate myocardial FDG uptake patterns and quantitative PET/CT parameters from both baseline and post-treatment scans in patients with lymphoma and to identify significant imaging predictors of chemotherapy-induced cardiotoxicity.

Methods

Study Population and Design

This retrospective cohort study included patients aged ≥ 18 years diagnosed with lymphoma (including Hodgkin and non-Hodgkin subtypes) at 108 Military Central Hospital between October 2018 and December 2024. Eligible patients were those treated with first-line anthracycline-containing chemotherapy regimens who underwent baseline and post-treatment FDG PET/CT scans as part of their standard oncologic staging and response assessment. Post-treatment FDG PET/CT scans were performed after completion of the planned first-line chemotherapy regimen as part of routine oncologic

response assessment, generally within 3–6 weeks after the last chemotherapy cycle, rather than after a fixed interim number of cycles. Follow-up transthoracic echocardiography was performed for the assessment of CTRCD at least 6 months after completion of chemotherapy. No patient underwent an earlier-than-scheduled post-treatment PET/CT because of suspected disease progression.

Patients were excluded if they had: (1) a documented history of coronary artery disease, heart failure, severe valvular disease, or baseline LVEF < 50% ; (2) suspected or confirmed cardiac or myocardial involvement by lymphoma on baseline PET/CT, other available imaging examinations, or clinical records; (3) prior mediastinal radiation therapy or exposure to cardiotoxic cytotoxic drugs; (4) poorly controlled diabetes mellitus or fasting blood glucose levels > 150 mg/dL before PET scanning, to minimize physiological interference with myocardial glucose uptake; (5) non-diagnostic image quality due to motion artifacts or truncated field-of-view; or (6) history of receiving chronic beta-blocker therapy at the time of the PET/CT scan. The Institutional Review Board of 108 Military Central Hospital approved the study protocol, and the requirement for informed consent was waived due to the study's retrospective nature.

Chemotherapy Regimen, Clinical Data Collection, and Cardiac Assessment

All patients received standard first-line anthracycline-based chemotherapy regimens appropriate to their lymphoma subtype (e.g., R-CHOP or CHOP for non-Hodgkin lymphoma and ABVD for Hodgkin lymphoma), in accordance with institutional protocols and international clinical guidelines [11, 12]. The cumulative anthracycline dose was calculated for each patient using doxorubicin-equivalent doses. Demographic data, clinical characteristics, cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking status), laboratory findings, and oncologic staging were extracted from electronic medical records.

Cardiac function was assessed by TTE at baseline and during follow-up. All examinations were performed by two board-certified cardiologists who were masked to PET-derived metabolic data and independently adjudicated the cardiac outcomes. Standard measurements included LVEF, LV end-diastolic and end-systolic diameters, left atrial diameter (LAD), and diastolic function indices, in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [7]. LVEF was calculated using the biplane Simpson's method.

In the present cohort, CTRCD was operationally defined as a clinically significant reduction in LVEF on follow-up echocardiography, in accordance with the LVEF-based component of the 2022 ESC cardio-oncology guidelines.[13]. GLS and cardiac biomarkers, including BNP/NT-proBNP and troponin, were not systematically available in all patients because of the retrospective design and were therefore not used as mandatory diagnostic criteria.

FDG PET/CT Acquisition Protocol

All patients underwent FDG PET/CT scanning using a Discovery 710 PET/CT system (GE Healthcare, USA). PET/CT examinations were performed according to routine oncologic imaging protocols rather than dedicated cardiac metabolic imaging protocols. Patients were instructed to fast for at least 4–6 hours before tracer injection, and blood glucose levels were checked before FDG administration. No high-fat/low-carbohydrate diet, prolonged fasting, heparin administration, glucose loading, or insulin-based myocardial metabolic preparation was used. FDG was administered intravenously at a dose of 3.7–5.55 MBq/kg. Whole-body images from skull base to mid-thigh were acquired approximately 60 minutes after injection. A non-contrast CT scan was performed for attenuation correction and anatomical localization [5, 14, 15]. Baseline and post-treatment scans were acquired under comparable preparation and imaging conditions to reduce technical variability as much as possible [3]. Therefore, myocardial FDG uptake in this study should be interpreted within the context of routine oncologic PET/CT rather than dedicated myocardial viability or inflammatory imaging.

PET/CT Image Analysis

PET/CT image analysis was performed using a volume-of-interest (VOI)–based semi-automated segmentation method implemented in the PET VCAR software package (GE Healthcare, Milwaukee, WI, USA). The analysis was conducted by an experienced nuclear medicine physician (H.S., with > 5 years of experience in FDG PET interpretation) who was blinded to the patients' clinical data and echocardiographic outcomes.

Briefly, a three-dimensional VOI encompassing the entire LV myocardium was automatically generated based on standardized anatomical landmarks (Fig. 1). The VOI was subsequently reviewed and corrected to exclude the cardiac blood pool, adjacent extracardiac structures, and potential spillover activity from surrounding tissues, thereby ensuring accurate delineation of myocardial FDG uptake.

Visual analysis of myocardial FDG uptake patterns

The pattern of LV FDG uptake was visually classified into four categories based on the established criteria: (1) no uptake, defined as myocardial uptake comparable to or lower than that of the cardiac blood pool; (2) diffuse uptake, characterized by relatively homogeneous FDG distribution throughout the LV myocardium without focal or disproportionately increased activity; (3) focal uptake, in which localized myocardial regions demonstrated increased tracer accumulation, while the remaining myocardium showed uptake similar to or lower than the blood pool; and (4) Focal uptake on a diffuse uptake background, defined by focal areas of increased uptake superimposed on a background of diffusely increased myocardial activity [5]. Because scans were acquired under routine fasting without myocardial suppression protocols, diffuse LV uptake was expected in a substantial proportion of patients and was therefore evaluated as part of the real-world uptake spectrum rather than being excluded a priori.

Quantitative analysis

From the final adjusted LV VOI, uptake was measured as standardized uptake value (SUV). The quantitative parameters including maximum SUV (SUVmax), mean SUV (SUVmean), peak SUV (SUVpeak), metabolic volume of target LV myocardium (MTV), and total lesion glycolysis (TLG) were extracted. SUVpeak was defined as the average SUV within a small, fixed-size region of interest (approximately 1 cm³) centered on the area of highest uptake, as implemented in the PET VCAR software. MTV was defined as the metabolically active myocardial volume within the LV myocardium. Segmentation was performed using a semi-automated iterative adaptive threshold-based algorithm implemented in PET VCAR, in which the threshold was automatically determined according to lesion-to-background contrast. Voxels with SUV values equal to or greater than the calculated threshold were included in the VOI and used to determine MTV. TLG was calculated as SUVmean multiplied by MTV [14]. Additionally, SUVmax of epicardial adipose tissue was measured.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), as appropriate, and categorical variables as frequencies and percentages. Comparisons between CTRCD and non-CTRCD groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables and the chi-square test for categorical variables, according to data distribution and variable type. Logistic regression analyses were performed to identify independent predictors of cardiotoxicity. Variables with $p < 0.05$ in univariable analysis were entered into multivariable models. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff values, and the area under the curve (AUC) was calculated. All statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA) and Medcalc version 20 (MedCalc Software Ltd., Ostend, Belgium). A two-sided p value < 0.05 was considered statistically significant.

Results

Clinical and Echocardiographic Characteristics

A total of 68 patients were included in the final analysis, including 47 patients without cardiotoxicity and 21 patients with cardiotoxicity. The patient characteristics are summarized in Table 1. The distributions of age, lymphoma subtype, and disease stage were comparable between the two groups (all $p = \text{n.s.}$). The CTRCD group was characterized by a significantly higher proportion of male patients compared to the non-cardiotoxicity cohort ($p = 0.046$). Baseline laboratory parameters, including lactate dehydrogenase (LDH), albumin, white blood cell (WBC) count, and neutrophil-to-lymphocyte ratio (NLR), did not differ significantly between groups. Similarly, the baseline echocardiographic indices including LAD, LV diastolic diameter (LVDD), interventricular septum (IVS) thickness, LV posterior wall (LVPW), and LVEF showed no statistically significant differences (all $p = \text{n.s.}$). After treatment, most clinical and echocardiographic parameters remained comparable between the two groups. However, IVS thickness

was significantly higher in the cardiotoxicity group than in the no cardiotoxicity group ($p = 0.047$). In addition, a small but statistically significant difference in LVPW thickness was observed ($p = 0.042$). LVEF measured at this early post-treatment assessment tended to be lower in the cardiotoxicity group but did not reach statistical significance ($p = 0.067$).

Table 1
Comparison of clinical and echocardiographic parameters between patients with and without cardiotoxicity.

Factor		No Cardiotoxicity	Cardiotoxicity	p
Gender	Male (n,%)	11 (23.4)	10 (47.6)	0.046*
	Female (n,%)	36 (76.6)	11 (52.4)	
Age (years), median (range)		52 (18–86)	58 (35–83)	0.176
Stage	I/II	22 (46.8)	9 (42.9)	0.76
	III/IV	25 (53.2)	12 (51.7)	
Lymphoma	Hodgkin	4 (8.5)	1 (4.8)	0.58
	Non – Hodgkin	43 (91.5)	20 (95.2)	
Before treatment	LDH (U/L)	210 (138–1310)	240 (107–1161)	0.396
	Albumin (g/L)	39.7 (4.2–47.2)	40 (26.4–49)	0.745
	WBC (x10 ⁹ /L)	7.98 (3.82–24.7)	7.69 (1.75–14.68)	0.343
	NLR	3.16 (0.33–17.63)	2.74 (0.68–21.74)	0.963
	LAD (mm)	30 (24–44)	29 (26–60)	0.165
	LVDD (mm)	45.53 ± 3.59	44.48 ± 2.75	0.32
	IVS (mm)	10 (7–16)	10 (8–12)	0.332
	LVPW(mm)	9 (7–15)	9 (8–12)	0.852
	LVEF (%)	66.15 ± 4.74	67.95 ± 4.74	0.95
After treatment	LDH (U/L)	248 (2.54–769)	220 (137–458)	0.113
	Albumin (g/L)	42.7 (25.7–50)	41.2 (31.5–46.7)	0.453
	WBC (x10 ⁹ /L)	5.89 (0.63–17.41)	5.62 (2.23–16.14)	0.494
	NLR	2.72 (0.04–22.25)	2.75 (0.52–12.73)	0.377
	LAD (mm)	30 (25–47)	30 (27–58)	0.551
	LVDD (mm)	45 (40–59)	45 (41–52)	0.408
	IVS (mm)	9 (8–13)	10 (8–13)	0.047*
	LVPW(mm)	9 (1–13)	9 (7–11)	0.042*

*: significant difference, LDH: lactate dehydrogenase; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; LAD: left atrial diameter; LVDD: left ventricular diastolic diameter; IVS: interventricular septum; LVPW: left ventricular posterior wall; LVEF: left ventricular ejection fraction

Factor	No Cardiotoxicity	Cardiotoxicity	p
LVEF (%)	68 (38–79)	64 (50–70)	0.067
*: significant difference, LDH: lactate dehydrogenase; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; LAD: left atrial diameter; LVDD: left ventricular diastolic diameter; IVS: interventricular septum; LVPW: left ventricular posterior wall; LVEF: left ventricular ejection fraction			

Baseline FDG PET/CT Findings

Baseline PET/CT parameters of the LV did not differ significantly between patients with and without subsequent cardiotoxicity (Table 2, all $p = n.s.$), although overall SUV were lower in the cardiotoxicity group (SUVmax: 3.46 vs. 5.7; SUVmean: 2.32 vs. 3.39; SUVpeak: 2.92 vs 4.25). MTV, TLG, and epicardial adipose tissue SUVmax also showed no significant differences. Qualitative analysis of baseline myocardial FDG uptake patterns showed no significant association with subsequent cardiotoxicity (Table 3). The proportions of cardiotoxicity were similar between patients with no uptake and diffuse uptake patterns before treatment. Although the focal/diffuse pattern showed a numerically higher proportion of subsequent cardiotoxicity, this difference was not statistically significant.

Table 2
LV PET/CT parameters before chemotherapy in patients with and without subsequent cardiotoxicity

SUVmax	Cardiotoxicity	No Cardiotoxicity	p
	3.46 (2.41–5.40)	5.7 (2.73–9.82)	0.24
SUVmean	2.32 (1.75–4.18)	3.39 (2.23–5.11)	0.26
SUVpeak	2.92 (2.06–5.42)	4.25 (2.23–7.9)	0.36
MTV	24.82 (0–111)	44.99 (0–114)	0.86
TLG	62.28 (0–272.22)	137.6 (0–594.3)	0.68
SUVmax epicardial adipose tissue	2 (1.33–2.41)	1.7 (1.3–2.87)	0.96
<i>Data are presented as median (interquartile range, IQR).</i>			

Table 3
Relationship between FDG uptake patterns in the LV prior to chemotherapy with subsequent cardiotoxicity

No uptake	Cardiotoxicity	No Cardiotoxicity	p
	7 (29.2%)	17 (70.8%)	0.82
Diffuse	10 (29.4%)	24 (70.6%)	0.79
Focal	0 (0%)	1 (100%)	0.51
Focal/diffuse	4 (44.4%)	5 (55.6%)	0.34

Post-treatment FDG PET/CT Findings

After chemotherapy, several PET/CT parameters of the LV demonstrated significant differences between patients with and without cardiotoxicity (Table 4). Following chemotherapy, SUVmax was significantly elevated in patients who developed cardiotoxicity compared to those who did not (9.13 vs. 6.34, $p = 0.04$). Similarly, volumetric metabolic parameters, including MTV and TLG, demonstrated a marked increase in the cardiotoxicity group ($p = 0.017$ and $p = 0.03$, respectively). By contrast, SUVmean and SUVmax of epicardial adipose tissue did not show statistically significant differences (all $p = \text{n.s.}$).

Table 4
LV PET/CT parameters after chemotherapy in patients with and without subsequent cardiotoxicity

SUVmax	Cardiotoxicity	No Cardiotoxicity	p
	9.13 (5.3–14.25)	6.34 (2.9–11.1)	0.04*
SUVmean	4.7 (3.44–7.27)	3.73 (2.39–5.31)	0.135
SUVpeak	7.29 (4.42–10.73)	5.1 (2.4–8.65)	0.07
MTV	106 (59.14–155)	63.23 (0–124)	0.017*
TLG	488.59 (204.9–910.65)	243.1 (0–618.1)	0.03*
SUVmax epicardial adipose tissue	2.49 (1.96–3.4)	1.97 (1.7–2.6)	0.67
<i>Data are presented as median (interquartile range, IQR).</i>			

Qualitative analysis of myocardial FDG uptake patterns further highlighted important associations (Table 5). None of the patients with post-treatment no myocardial FDG uptake developed cardiotoxicity, and all patients in the no uptake category belonged to the non-cardiotoxicity group (0% vs. 100%, $p = 0.003$). A focal/diffuse uptake pattern was more frequent in cardiotoxicity group compared with no cardiotoxicity group (63.6% vs. 36.4%, $p = 0.01$). In contrast, diffuse uptake alone did not differ significantly between groups.

Table 5
Relationship between PET/CT parameters and FDG uptake patterns in the LV after chemotherapy with subsequent cardiotoxicity

No uptake	Cardiotoxicity	No Cardiotoxicity	p
	0 (0%)	15 (100%)	0.003*
Diffuse	14 (33.3%)	28 (66.7%)	0.58
Focal	0	0	-
Focal/diffuse	7 (63.6%)	4 (36.4%)	0.01*
*: Significant difference			

Images of a representative case are shown in Fig. 2.

ROC Curve and Logistic Regression Analyses for Predicting Cardiotoxicity

In ROC curve analysis, SUVmax, MTV, and TLG demonstrated significant discriminatory ability (Fig. 3). The optimal cutoff value for SUVmax was 8.49, yielding a sensitivity of 61.9% and specificity of 65.9% (AUC = 0.659, $p = 0.029$). For MTV, a threshold of 66.9 provided higher sensitivity (71.4%) but moderate specificity (55.3%), with an AUC of 0.681 ($p = 0.006$). TLG showed the strongest predictive performance, with a cut-off of 187.8 resulting in sensitivity of 76.2% and specificity of 46.8% (AUC = 0.665, $p = 0.016$). These results indicate that elevated post-treatment SUVmax, MTV, and TLG are significantly associated with the risk of developing cardiotoxicity, although their predictive accuracy is moderate.

In univariate logistic regression analysis (Table 6), patients with post-treatment SUVmax ≥ 8.49 showed a nearly threefold increased risk of cardiotoxicity compared to those with SUVmax < 8.49 (OR = 2.87, 95% CI: 0.99–8.3, $p = 0.05$). Similarly, elevated MTV (≥ 66.9) and TLG (≥ 187.8) were associated with higher odds ratios of cardiotoxicity, although these did not reach statistical significance (OR = 2.84, $p = 0.064$; OR = 2.56, $p = 0.11$, respectively). Notably, patients with a focal/ diffuse myocardial uptake exhibited a significantly higher risk of cardiotoxicity, with an odds ratio of 5.38 (95% CI: 1.37–21.12, $p = 0.016$). Significant variables in the univariate analysis were entered into the multivariate model to identify independent predictors. In multivariate analysis, both post-treatment SUVmax and focal/diffuse myocardial uptake pattern emerged as independent predictors of cardiotoxicity. Patients with SUVmax ≥ 8.49 had a significantly higher risk of developing cardiotoxicity (OR = 6.97, 95% CI: 1.39–34.94, $p = 0.018$). Notably, the focal/diffuse myocardial uptake pattern emerged as a robust independent predictor, carrying a substantial risk of cardiotoxicity (OR = 16.63, 95% CI: 2.42–114.45, $p = 0.004$).

Table 6
Univariate regression analysis and multivariate regression analysis of prognostic factors for cardiotoxicity after chemotherapy

Factor	Univariate OR (95% CI)		Multivariate OR (95% CI)	
	OR (95% CI)	p	OR (95% CI)	p
SUVmax (< 8.49 vs ≥ 8.49)	2.87 (0.99–8.3)	0.05*	6.97 (1.39–34.94)	0.018*
MTV (< 66.9 vs ≥ 66.9)	2.84 (0.94–8.59)	0.064	N/A	N/A
TLG (< 187.8 vs ≥ 187.8)	2.56 (0.81–8.22)	0.11	N/A	N/A
Focal/diffuse uptake	5.38 (1.37–21.12)	0.016*	16.63 (2.42–114.45)	0.004*
*: significant difference				

Discussion

In this retrospective observational study, increased post-treatment myocardial FDG uptake was associated with CTRCD in lymphoma patients treated with anthracycline-based chemotherapy. Specifically, post-treatment SUVmax ≥ 8.49 (OR = 6.97, p = 0.018) and a focal/diffuse uptake pattern (OR = 16.63, p = 0.004) remained independently associated with CTRCD in multivariate analysis. However, the discriminatory performance of PET-derived parameters was moderate, and these findings should be interpreted cautiously. Conversely, no patient with absent post-treatment myocardial FDG uptake developed CTRCD in this cohort. However, this observation should be interpreted cautiously and requires external validation before being used for clinical risk stratification.

A key methodological consideration is that myocardial FDG uptake is strongly influenced by substrate availability and patient preparation. In dedicated cardiac protocols, preparation is tailored to the clinical question: myocardial viability imaging promotes glucose utilization, whereas inflammatory or infection imaging attempts to suppress physiological myocardial uptake. In contrast, the present study used routine oncologic PET/CT protocols, in which myocardial uptake was not specifically controlled. Therefore, increased or absent myocardial FDG uptake may partly reflect physiological metabolic variability rather than treatment-related myocardial injury alone.

Recent studies have suggested that increased myocardial FDG uptake, incidentally detected on whole body oncologic scans, may serve as an early marker of cardiotoxicity [3, 5, 12, 13]. Evidence indicates that this increased uptake correlates with subsequent declines in LVEF or echocardiographic abnormalities [2, 13]. Since these scans are conducted in a fasting state, they may capture early, incidental metabolic signatures of myocardial stress or "metabolic remodeling" before clinical dysfunction emerges. Current literature presents a metabolic paradox: while some studies report increased FDG uptake as a sign of acute stress, others find decreased uptake indicating late-stage myocardial exhaustion. There is a critical lack of data standardizing post-treatment quantitative thresholds (SUVmax, MTV, TLG) to resolve these contradictions [3, 5, 13, 14]. In addition to baseline

metabolic characteristics, evaluating temporal changes in myocardial FDG uptake between pre-treatment and post-treatment PET/CT scans may provide additional insight into chemotherapy-related myocardial injury. Anthracycline-induced cardiotoxicity is a progressive process that involves early metabolic remodeling before the development of structural abnormalities or measurable decline in left ventricular ejection fraction. Therefore, dynamic alterations in PET-derived quantitative parameters, such as SUVmax, MTV, and TLG, may better reflect early myocardial responses to chemotherapy than single time-point measurements. Assessing these metabolic changes using routinely acquired oncologic PET/CT scans may thus provide an additional opportunity for early identification of patients at increased risk of cardiotoxicity without requiring dedicated cardiac imaging.

Our findings align with emerging evidence suggesting that FDG PET/CT captures metabolic shifts specifically the "metabolic switch" from fatty acid oxidation to glucose utilization that precede mechanical dysfunction. While our results mirror studies reporting increased uptake post-anthracycline therapy, other studies contrast with reports of decreased uptake in late-stage injury. Lin et al. reported that SUVmax and SUVmean of the LV increased significantly after anthracycline-based chemotherapy, and that abnormal uptake patterns correlated with both impaired ejection fraction and increased incidence of cardiovascular toxicity [5]. Palomino-Fernández et al. demonstrated that reduced homogeneity of myocardial FDG uptake, derived from radiomic features, was predictive of cancer therapy related cardiac dysfunction [16]. This discrepancy likely reflects the temporal phase of injury. Our post-treatment imaging captured an acute phase dominated by metabolic stress and inflammatory responses. In contrast, studies showing decreased uptake may have imaged patients during a phase of irreversible cellular exhaustion and loss of viable myocardium. The current literature has not yet established a standardized or clinically applicable myocardial FDG PET profile for anthracycline-related cardiotoxicity. Differences in patient preparation, fasting duration, myocardial suppression protocols, timing of post-treatment imaging, PET-derived parameters, and CTRCD definitions may contribute to inconsistent findings across studies. Therefore, the present findings should be interpreted as exploratory and hypothesis-generating rather than as evidence of a validated PET-based cardiotoxicity phenotype.

The substantial risk associated with the focal/diffuse pattern (OR 16.63) underscores that metabolic heterogeneity, rather than global SUV elevation, is the most sensitive indicator of subclinical damage. This suggests that anthracyclines induce localized "hotspots" of severe metabolic strain. From a clinical standpoint, identifying these high-risk signatures allows for early diagnostic triage; patients with these markers warrant intensive monitoring, while those with no uptake may avoid unnecessary cardiac interventions [17]. Several factors may explain these differences. The timing of imaging is critical, as studies that performed PET/CT at intermediate treatment stages may have captured a point when myocardial injury was already advanced, leading to reduced FDG uptake due to impaired glycolytic activity [16]. In contrast, our post-treatment imaging likely reflected a phase dominated by metabolic stress and inflammatory responses, resulting in higher FDG uptake. Differences in patient selection and baseline characteristics also play a role, since some studies excluded individuals with pre-existing cardiovascular risk factors while others included broader populations, leading to variability in susceptibility and metabolic response [5, 16, 18]. Methodological variations further contribute, with

some investigators relying on SUVmean, others on radiomic heterogeneity indices, and others on qualitative uptake patterns, whereas our combined approach using both quantitative thresholds (SUVmax, MTV, TLG) and qualitative pattern analysis provided a more integrated assessment. Finally, biological mechanisms must be considered, as increased uptake is likely to reflect inflammation, oxidative stress, and compensatory glucose utilization during early or subclinical phases of injury, while decreased uptake may correspond to late-stage, irreversible damage characterized by loss of viable myocardium [3, 5, 16, 17]. Taken together, these considerations suggest that increased and decreased myocardial FDG uptake are not necessarily contradictory but may instead represent different temporal phases of chemotherapy-induced injury.

The primary strength of this study lies in its integration of quantitative thresholds and qualitative uptake patterns within a real-world oncologic imaging framework. However, several limitations should be acknowledged. First, the retrospective, single-center design and modest sample size may limit the generalizability of our findings. Second, although patients with clinically or radiologically suspected myocardial involvement by lymphoma were excluded, cardiac involvement was not systematically assessed using dedicated cardiac MRI or histopathology because of the retrospective design. Therefore, occult myocardial involvement cannot be completely excluded. Third, PET/CT scans were performed using routine oncologic protocols without dedicated myocardial metabolic preparation. Because myocardial FDG uptake is influenced by fasting duration, dietary status, glucose metabolism, and insulin state, physiological myocardial glucose utilization may have contributed to the observed uptake patterns. Accordingly, our findings should be considered exploratory and hypothesis-generating, and should not be directly extrapolated to dedicated cardiac FDG PET protocols or used as a validated clinical decision tool without prospective validation. Because of the limited sample size and the small number of patients in some uptake-pattern categories, we could not perform stable sensitivity analyses after excluding diffuse or focal/diffuse uptake patterns. This limits our ability to fully distinguish physiological diffuse myocardial FDG uptake from treatment-related metabolic changes. Fourth, the lack of systematic cardiac MRI, systematic coronary evaluation, GLS, regional strain analysis, and biomarker validation means that cardiotoxicity was defined primarily by clinical and echocardiographic criteria. Therefore, we could not assess whether focal myocardial FDG uptake corresponded spatially to regional abnormalities in myocardial deformation. Although patients with documented coronary artery disease were excluded, occult coronary artery disease could not be fully excluded and may have influenced focal or focal-on-diffuse myocardial FDG uptake patterns, particularly given the higher proportion of male patients in the CTRCD group. Fifth, although post-treatment PET/CT was generally performed within 3–6 weeks after the last chemotherapy cycle and follow-up echocardiography at least 6 months after completion of chemotherapy, imaging intervals were based on routine clinical practice rather than a prospectively predefined imaging schedule. Finally, while SUVmax, MTV, and TLG showed significant associations with CTRCD, their moderate discriminatory performance suggests that PET-derived parameters should be interpreted cautiously and ideally integrated with established cardiac biomarkers and echocardiographic parameters in future prospective studies. The SUVmax cutoff of 8.49 was derived from ROC analysis within this retrospective cohort and should therefore be regarded as

exploratory and cohort-specific. Given the moderate AUC and the absence of standardized myocardial metabolic preparation, this threshold should not be interpreted as a validated clinical discriminator. External validation in prospective cohorts using standardized imaging protocols is required before any SUVmax threshold can be applied clinically.

Conclusion

This retrospective observational study suggests that increased post-treatment myocardial FDG uptake, particularly elevated SUVmax and focal/diffuse uptake pattern, is associated with CTRCD in lymphoma patients treated with anthracycline-based chemotherapy. Absence of post-treatment myocardial FDG uptake was observed only in patients without CTRCD in this cohort. However, the discriminatory performance of PET-derived parameters was moderate, and the findings should be interpreted as hypothesis-generating rather than as evidence supporting immediate clinical implementation. Prospective studies using standardized myocardial metabolic preparation, predefined imaging timepoints, and comprehensive cardiac assessment are needed before PET-derived myocardial parameters can be incorporated into routine cardio-oncology surveillance.

Abbreviations

AUC – Area under the curve	LVEF – Left ventricular ejection fraction
BNP – B-type natriuretic peptide	MBq – Megabecquerel
NT-proBNP – N-terminal pro-B-type natriuretic peptide	MTV – Metabolic volume (of LV myocardium)
CTRCD – Cancer therapy-related cardiac dysfunction	MUGA – Multigated radionuclide angiography
CT – Computed tomography	NLR – Neutrophil-to-lymphocyte ratio
FDG – Fluorodeoxyglucose	CI – Confidence interval
GLS – Global longitudinal strain	OR – Odds ratio
IVS – Interventricular septum	PET – Positron emission tomography
LAD – Left atrial diameter	ROC – Receiver operating characteristic
LDH – Lactate dehydrogenase	ROI – Region of interest
LLN – Lower limit of normal	SD – Standard deviation
LV – Left ventricle / left ventricular	SUV – Standardized uptake value
LVDD – Left ventricular diastolic diameter	SUVmean – Mean standardized uptake value
SUVmax – Maximum standardized uptake value	TLG – Total lesion glycolysis (of LV myocardium)
TTE – Transthoracic echocardiography	VOI – Volume of interest

Declarations

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Conflict of interests: Mai Huy Thong, Mai Hong Son, Tran Ba Khoa and Jin Chun Paeng declare that they have no conflict of interest.

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Figures

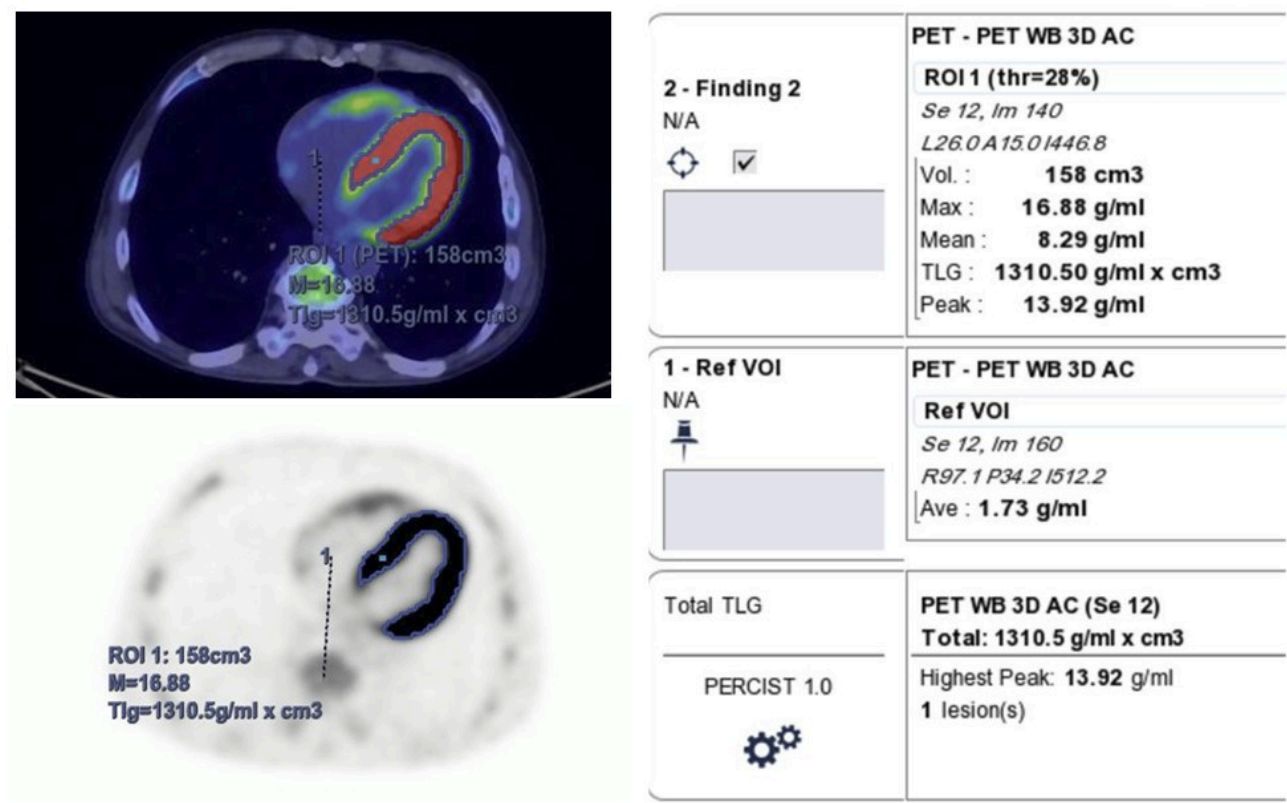


Figure 1

Semi-automated segmentation of the left ventricular (LV) myocardium on FDG PET/CT using PET VCAR software. A three-dimensional VOI encompassing the LV myocardium was generated using an adaptive threshold-based algorithm. Quantitative metabolic parameters including SUVmax, SUVmean, metabolic volume (MTV), and total lesion glycolysis (TLG) were extracted

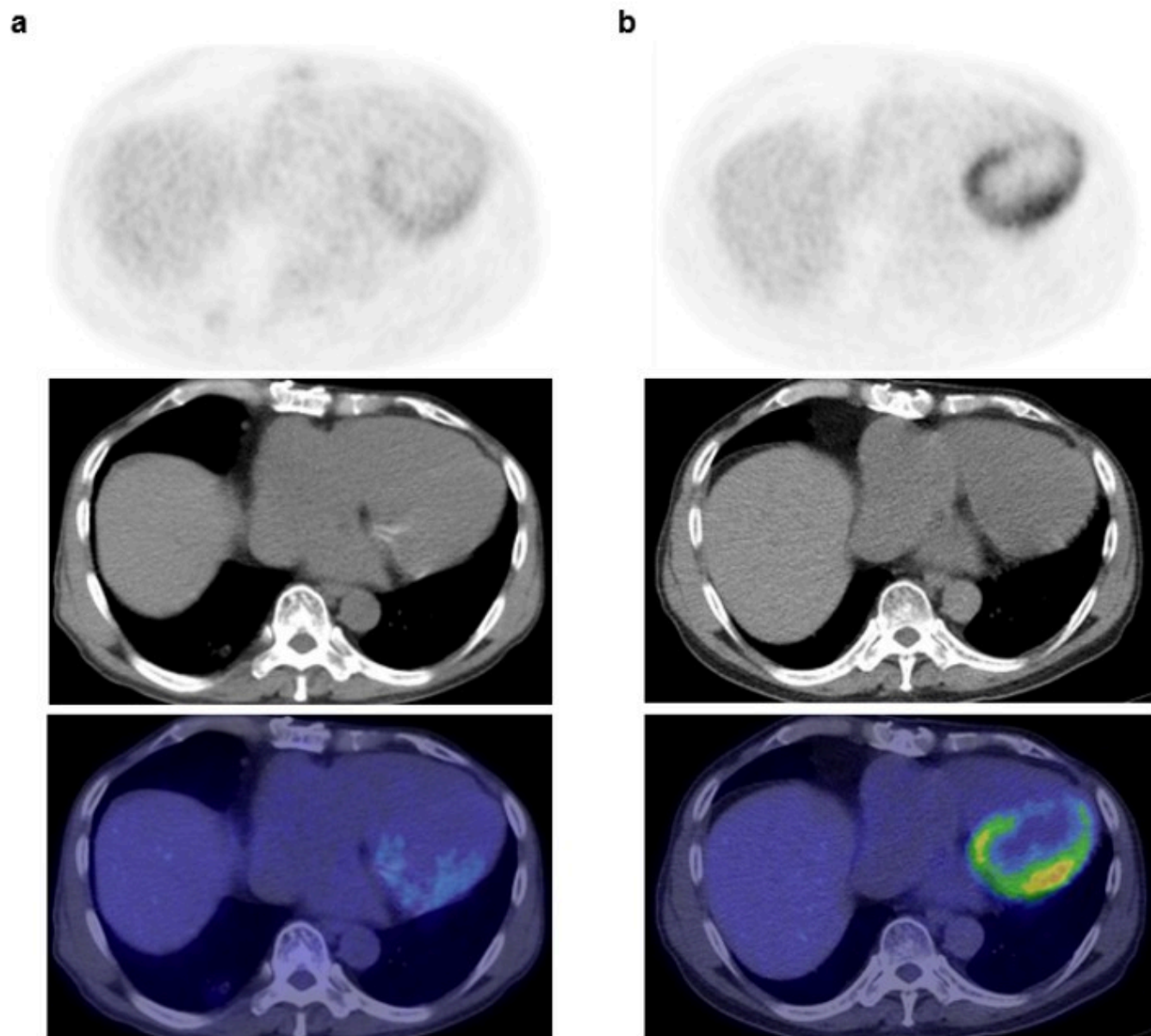


Figure 2

A representative FDG PET/CT in a 66-year-old man with stage IV lymphoma. A. Pre-treatment FDG PET/CT shows mild physiological FDG uptake in the LV myocardium. B. Post-chemotherapy FDG PET/CT (after six cycles) demonstrates markedly increased focal/diffuse FDG uptake in the LV wall. Follow-up echocardiography subsequently demonstrated LV systolic dysfunction consistent with chemotherapy-related cardiotoxicity.

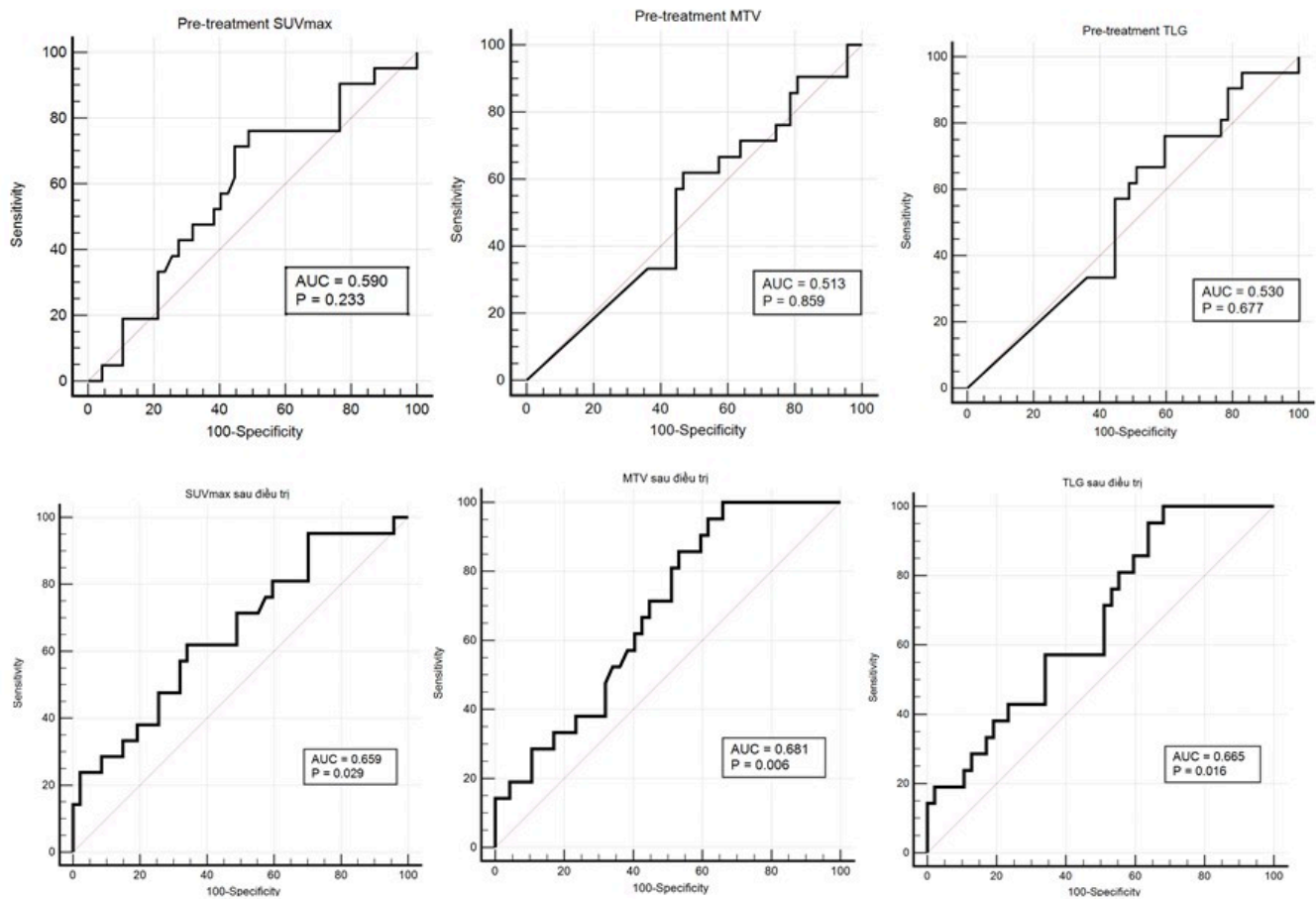


Figure 3

ROC curves and AUC of FDG PET/CT metabolic parameters for predicting cardiotoxicity