ORIGINAL ARTICLE

Role of 3D Myocardial Strain Imaging in Detecting Chemotherapy Induced Cardiotoxicity in Lymphoma Patients

Ali M. Al Amin [a], Ahmed Al-Habbaa [a], Hesham A. Alabady [b], Ahmed S. A. Swailam [a,*]

[a] Department of Cardiology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt
[b] Department of Oncology and Nuclear Medicine, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: ***Three-dimensional (3D) echocardiography has proven to be the most consistent and reliable ultrasound method for assessing left ventricular (LV) volumes and ejection fraction (EF) over a 6-month follow-up in patients receiving chemotherapy for cancer. A key benefit of 3D speckle tracking echocardiography (3D STE) lies in its ability to evaluate the entire LV from a single volumetric dataset, significantly reducing analysis time compared to the more labor-intensive two-dimensional (2D) speckle tracking echocardiography (2D STE).***

Aim: ***To identify subclinical myocardial involvement induced by chemotherapy in patients with lymphoma using 3D speckle tracking echocardiography, and to compare its diagnostic performance with 2D speckle tracking both during treatment and throughout follow-up.***

Methods: ***This prospective observational study enrolled 72 consecutive patients diagnosed with lymphoma, in accordance with established oncology and hematology guidelines, between March 2023 and January 2025. Participants were referred from the Oncology Department at Al-Hussein Hospital and the Tanta Oncology Center. All patients underwent 2D GLS and comprehensive three-dimensional (3D) echocardiographic strain assessments at baseline, during chemotherapy, and six months post-treatment.***

Results: ***3D strain metrics, particularly 3D global longitudinal strain (3D GLS), have shown superior sensitivity and specificity over 2D GLS in detecting early subclinical LV dysfunction among patients with lymphoma.***

Conclusion: ***All parameters derived from 3D-STE exhibit greater sensitivity and specificity in identifying chemotherapy-induced cardiotoxicity among lymphoma patients. Compared to 2D GLS, 3D-STE enables earlier detection of cardiac dysfunction in this population.***

Keywords: 2D GLS ; 3DSTE; subclinical LV dysfunction; lymphoma

1. Introduction

In 2022, Egypt recorded a total of 10,545 lymphoma cases—including both non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL)—as reported by the World Health Organization (WHO) and the Global Cancer Observatory.[1,2]

In Egypt, Non-Hodgkin lymphoma (NHL) is the fourth most prevalent cancer overall, accounting for 5.9% of all cancer types across both sexes, and ranks as the fifth most common malignancy among males.[1,2]

R-CHOP—comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone—remains the standard first-line treatment regimen for managing non-Hodgkin lymphoma (NHL).[3,4,5] For Hodgkin lymphoma (HL), the standard therapeutic approach typically involves combined modality treatment, which includes chemotherapy—often incorporating antibody-drug conjugates—alongside radiotherapy. The conventional chemotherapy regimen used is ABVD, comprising doxorubicin, bleomycin, vinblastine, and dacarbazine.[6]

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* Corresponding author at: Cardiology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.
E-mail address: ahmdswylm09@gmail.com (A. S. A. Swailam).

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Starting from the 1990s, cancer-related death rates have consistently decreased, which has been accompanied by a continuous rise in the number of cancer survivors (CS). [7,8]

Cardiovascular diseases (CVDs) represent some of the most common adverse effects, raising increasing concern due to their potential contribution to early-onset morbidity.[9]

Transthoracic echo (TTE) is the imaging modality of choice for initial risk assessment, as it allows for quantitative evaluation of LV function. [10]

Contemporary criteria for diagnosing cancer therapy-related cardiac dysfunction (CTR-CD) primarily rely on a decline in LV ejection fraction (LVEF) and/or significant variations in 2D GLS. 3D echo is the modality of choice for accurately evaluating LVEF and cardiac chamber volumes.[11]

The benefits of 3D STE have been investigated in oncologic populations. Accordingly, the present study aimed to assess and compare the utility of 2D STE, 3D volumetric imaging, and 3D STE in detecting early LV dysfunction in lymphoma patients receiving chemotherapy.

2. Patients and methods

This prospective observational study enrolled 72 consecutive individuals diagnosed with lymphoma (according to oncology and hematology guidelines)[3,4,12,13], in the period between March 2023 and January 2025, who were referred from the oncology department at Al-Hussein University Hospital and Tanta Oncology Center.

The study was conducted at Al-Hussein echo lab, the Islamic Cardiology Centre of Al-Azhar University, and Tanta University.

Patients diagnosed with lymphoma > 18 years; referred and scheduled to receive chemotherapy according to oncology and hematology guidelines, with preserved 3D LVEF > 53% and sinus rhythm, were recruited in our study.

Patients who declined participation, those with suboptimal image quality, and individuals with a history of cardiomyopathy or heart failure (HF), history of radiotherapy or chemotherapy, Patients scheduled to receive radiotherapy, patients diagnosed with significant valvular or congenital heart diseases, and patients with significant arrhythmia, which could interfere with proper echocardiographic measurement, were excluded.

History was taken from all patients, including age, sex, weight, height, body surface area (BSA), HTN, and DM. The focused examination included vital data, as well as general and local cardiac examinations to assess gallop, audible murmur, or basal crepitus. A standard resting 12-lead ECG was recorded to identify the heart rate, rhythm, and corrected QT (QTc) using Fredericia criteria.[14]

Echocardiographic data were obtained using a Vivid E95 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway), equipped with both two-dimensional (M5S-D) and three-dimensional (4D) 3.5-MHz transducers, offline speckle-tracking analysis software, along with a specialized background processing workstation (EchoPAC BT 11.1.0, GE Medical Systems, Horten, Norway).

Complete 2D and 3D echos were done to all patients at baseline (before starting chemotherapy), after two cycles, four cycles, shortly after treatment completion, and 6 months after therapy. Two-dimensional conventional echocardiographic assessments—including M-mode and Doppler studies—were conducted following the American Society of Echocardiography's (ASE) recommended guidelines.[15,16] These evaluations encompassed measurements such as the aortic root, left atrial size, and left ventricular ejection fraction (LVEF) calculated via the modified Simpson's method. Diastolic function and strain analysis were interpreted using the ASE's 17-segment LV model.[15,17] 2D GLS values from all three imaging planes were consolidated and displayed using a standardized bull's-eye plot..

3D echo was performed using a 3D volumetric transducer to acquire high-quality images of the LV endocardial border from an apical four-chamber view in 4D mode. This enabled the calculation of LV volumes and EF, along with comprehensive 3D STE parameters, including 3D global longitudinal strain (GLS), global area strain (GAS), global radial strain (GRS), and global circumferential strain (GCS)

The studied patients were divided into two groups according to the development of cardiotoxicity (according to the definition of ESC Cardio-oncology guidelines 2022),[18,19] into group I, which consisted of 52 patients without cardiotoxicity, and group II, which consisted of 20 patients with cardiotoxicity.

The collected data were analyzed using statistical software tools, specifically SPSS version 27 (IBM Corp., Armonk, NY, USA) and MedCalc. Quantitative variables were expressed as mean values along with their corresponding standard deviations.

3. Results

There were no statistically significant differences between the study groups in terms of age or sex. (p-value = 0.931 & 0.56 respectively).

There was high statistically significant increase in BSA in group II patients (with cardiotoxicity (2.0 ± 0.1 m2) when compared with BSA in group I patients (without cardiotoxicity (1.8 ± 0.1 m2) as shown in table 1.

Table 1. demographics and BSA of the two groups.

		GROUP I (PATIENTS WITHOUT CARDIOTOXICITY) (N = 52)		GROUP II (PATIENTS WITH CARDIOTOXICITY) (N = 20)			P VALUE
AGE (YEARS)	Mean		44.7		45	t = -	0.931
	±SD		10.7		12.8	0.09	
SEX	Male	30	57.7%	10	50%	X^2	0.56
	Female	22	42.3%	10	50%	= 0.34	
BSA (M^2)	Mean		1.8		2.0	t = -	< 0.001
	±SD		0.1		0.1	6.34	

There was a highly statistically significant (p-value < 0.001) increased Doxorubicin dose in group II patients (665.4 ± 153.6 mg) when compared with Doxorubicin dose of group I patients (521.9 ± 103.1 mg).

Regarding 2D TTE and 2D GLS, the following table shows no statistically significant differences between two groups as regard LVEDV, LVESV, 2D EF at bassline and throughout treatment, but diastolic function and LA diameter shows statistically significant differences after treatment and continues till 6 months after, also 2D GLS shows statistically significant difference as early as 2 Cycles and continue throughout treatment till 6 months after therapy as shown in table 2.

Table 2. TTE among patients group at baseline, 4 cycles and 6 months after therapy.

PARAMETER	TIME POINT	GROUP I (NO CARDIOTOXICITY)	GROUP II (CARDIOTOXICITY)	P-VALUE
LA DIAMETER (CM)	Baseline	3.37 ± 0.37	3.34 ± 0.4	0.817
	4 cycles	3.4 ± 0.4	3.47 ± 0.35	0.563
	Shortly After treatment	3.42 ± 0.44	3.88 ± 0.32	< 0.001
	6 months post	3.44 ± 0.46	4.19± 0.34	<0.001
E/A RATIO MEAN ±SD	Baseline	1.08 ± 0.15	1.11 ± 0.14	0.464
	4 cycles	1.03 ± 0.16	1.04 ± 0.16	0.830
	Shortly After treatment	1 ± 0.15	0.89 ± 0.11	0.005
	6 months post	0.99± 0.15	0.77 ± 0.09	<0.001
E/E' RATIO MEAN ±SD	Baseline	6.69 ± 0.66	6.86 ± 0.52	0.562
	4 cycles	7.76 ± 0.48	7.75 ± 0.52	0.953
	Shortly After treatment	8.04 ± 0.46	8.92 ± 0.88	< 0.001
	6 months post	8.23± 0.45	10.72 ± 1.05	<0.001
LVEDV MEAN ±SD (ML)	Baseline	100.9 ± 15.9	103.7 ± 17.3	0.524
	4cycles	102.8 ± 15.7	106.2 ± 17.3	0.425
	6 months post	105.9 ± 15.2	111.1 ± 15.9	0.209
LVESV MEAN ±SD (ML)	Baseline	40 ± 8.7	40.6 ± 8.5	0.786
	4 cycles	40.9 ± 6.9	42.3 ± 8.4	0.464
	6 months post	45.3 ± 6.5	47.8 ± 6.3	0.136
2D EF MEAN ±SD (%)	Baseline	60.2 ± 4.4	59.8 ± 4.1	0.675
	4 cycles	60.1 ± 3.6	60.3 ± 4	0.906
	6 months post	56.4 ± 2.7	56.1 ± 2.9	0.623
2D GLS MEAN ±SD (%)	Baseline	-21.6 ± 1.1	-21.1 ± 1.6	0.218
	At 2 cycles	-21.3 ± 1.1	-20.4 ± 1.8	0.013
	At 4 cycles	-21 ± 1.1	-19.8 ± 2.1	0.002
	Shortly After treatment	-20.3 ± 1	-17.3 ± 1.3	< 0.001
	6 months post treatment	-19.9 ± 1	-16.5 ± 1.1	< 0.001

Receiver operating characteristic (ROC) curve analysis revealed that 2D GLS measured after two and four chemotherapy cycles could differentiate cardiotoxicity using cutoff values greater than –20 and –19, respectively, with varying sensitivity and specificity. After treatment 2D GLS demonstrated strong predictive capability for cardiotoxicity at a threshold of > –18.9 as shown in figure 1

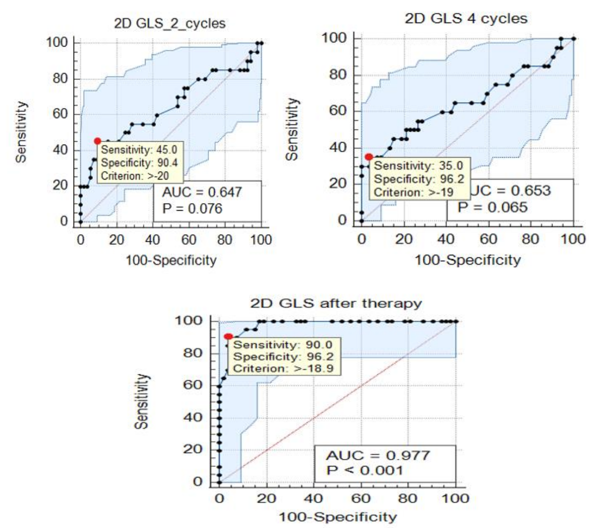

Figure 1. ROC curve for discrimination of cardiotoxicity as regards 2D GLS.

As regard 3D TTE and 3D STE: 3D LV volumes, there were no statistically significant difference (p-value > 0.05) of 3D LVEDV (baseline, 2 cycles, 4 cycles, shortly after therapy & 6 months after therapy) between two groups as regard cardio-toxicity. However, LVESD showed no statistically significant difference (p-value = 0.656) between baseline 3D LVESV of the two groups as regards cardiotoxicity that becomes statistically significant (p-value = 0.008) increased 3D LVESV at 2 cycles in group II patients when compared with 3D LVESV of group I patients at 2 cycles and continues to be Statistically significant at 4 cycles, shortly after treatment and 6 months after therapy in group II patients when compared with 3D LVESV of group I patients

As regards 3D EF, there was no statistically significant difference of baseline levels as regard cardiotoxicity. 3D EF became statistically significantly lower at 2 cycles in group II. The difference became high statistically significant at 4 cycles, shortly after therapy and 6 months after therapy.

As regard 3D strain 3D GLS , there was no statistically significant difference (p-value = 0.176) of baseline 3D GLS between two groups as regards cardiotoxicity.

With treatment there were high statistically significant (p-value < 0.001) decreased 3D GLS in group II patients when compared with 3D GLS of group I patients at 2 cycles, 4 cycles, after therapy and 6 months after therapy. The same results was found also in 3D GCS, GAS and GRS. as shown in table 3.

Table 3. comparison of 3D TTE and 3D STE among patient groups.

PARAMETER	TIME POINT	GROUP I (NO CARDIOTOXICITY)	GROUP II (CARDIOTOXICITY)	P-VALUE
3D LVEDV MEAN ±SD (ML)	Baseline	121.9 ± 19.3	130 ± 18.5	0.113
	At 2 cycles	121.4 ± 19.2	129.6 ± 18.8	0.106
	At 4 cycles	125.6 ± 19.3	133.4 ± 18.5	0.125
	Shortly after treatment	126.7 ± 19.4	134.3 ± 18.3	0.132
	6 months post	127.7 ± 19.4	136.4 ± 18	0.089
3D LVESV MEAN ±SD (ML)	Baseline	49 ± 10	50.1 ± 9.9	0.656
	At 2 cycles	49.2 ± 9.8	56.2 ± 9.9	0.008
	At 4 cycles	53.3 ± 10	60.5 ± 9.7	0.008
	Shortly after treatment	55.5 ± 9.4	64.1 ± 9	0.001
	6 months post	56.4 ± 9.2	67.5 ± 8.6	< 0.001
3D EF MEAN ±SD (%)	Baseline	59.5 ± 2.9	58.3 ± 3.2	0.138
	At 2 cycles	59.1 ± 3	56.4 ± 2.8	0.001
	At 4 cycles	57.3 ± 2.6	54.3 ± 2.7	< 0.001
	Shortly after treatment	55.8 ± 2.3	51.9 ± 2.2	< 0.001
	6 months post	55.4 ± 2.3	50 ± 1.7	< 0.001
3D GLS MEAN ±SD (%)	Baseline	-21.5 ± 0.9	-21.1 ± 1.2	0.176
	At 2 cycles	-20.8 ± 0.8	-18 ± 1.6	< 0.001
	At 4 cycles	-19.3 ± 1	-14.7 ± 1.2	< 0.001
	Shortly after treatment	-18.5 ± 0.9	-12.6 ± 1.1	< 0.001
	6 months post	-17.6 ± 0.9	-11.7 ± 1.3	< 0.001
3D GCS MEAN ±SD (%)	Baseline	-23.2 ± 1.2	-22.6 ± 1.13	0.093
	At 2 cycles	-22.3 ± 1.2	-20.1 ± 1.6	< 0.001
	At 4 cycles	-20.8 ± 1	-16.6 ± 1.2	< 0.001
	Shortly after treatment	-20.4 ± 0.8	-14.7 ± 0.9	< 0.001
	6 months post	-19.4 ± 1	-13.7 ± 1.4	< 0.001
3D GAS MEAN ±SD (%)	Baseline	-34 ± 2.5	-33 ± 2.6	0.154
	At 2 cycles	-33.3 ± 2.2	-30.1 ± 1.7	< 0.001
	At 4 cycles	-31.6 ± 2.07	-26.1 ± 0.9	< 0.001
	Shortly after treatment	-30.3 ± 1.6	-22.2 ± 1.3	< 0.001
	6 months post	-29.8 ± 1.8	-21.1 ± 1.1	< 0.001
3D GRS MEAN ±SD (%)	Baseline	56.8 ± 4.3	55.4 ± 2.8	0.187
	At 2 cycles	55.7 ± 3.5	50.7 ± 3.6	< 0.001
	At 4 cycles	53.7 ± 3.4	45.5 ± 3.3	< 0.001
	Shortly after treatment	51.5 ± 3.1	42.1 ± 3.2	< 0.001
	6 months post	50.5 ± 3.1	40.6 ± 3.6	< 0.001

Using ROC curve, it was shown that 3D GLS at 2 cycles can be used to discriminate cardiotoxicity at a cutoff level of >-20 as depicted in figure 2.

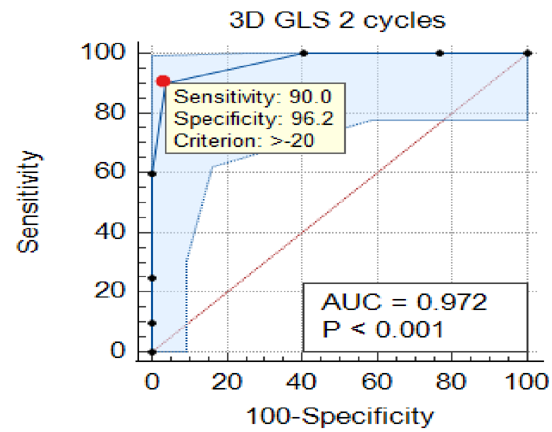

Figure 2. ROC curve for discrimination of cardiotoxicity as regards 3D GLS.

4. Discussion

Lymphoma is considered one of the most common tumors in adults in Egypt.[1]

Our study sought to identify subclinical myocardial involvement induced by chemotherapy in lymphoma patients through 3D speckle tracking echocardiography, and to compare its diagnostic performance with that of 2D speckle tracking both during treatment and throughout post-therapy follow-up.

In our study, there were 56 patients (77.8%) non-Hodgkin lymphoma, and 16 patients (22.2%) were Hodgkin lymphoma in the studied patients.

Thirteen patients of 56 with NHL developed cardiotoxicity, which represents 23% of the studied patients, while seven patients of 16 with HL developed cardiotoxicity, which represents 43%.

When we studied diastolic function (E/A ratio, E/e′ ratio) and LA diameter, we found that during all treatment cycles, there were no significant differences between study groups as regards all diastolic indexes. Shortly after therapy, there was a statistically significant (p-value < 0.001) increase in LA diameters and E/e′ ratio, and a statistically significant (p-value = 0.005) decrease in E/A ratio in group II patients when compared with the LA of group I patients. These differences persisted for 6 months after therapy.

This comes in agreement with Upshaw et al.[20] study, which represents the most extensive prospective study to date evaluating diastolic function in a cohort of 362 breast cancer patients treated with anthracyclines, trastuzumab, or sequential anthracycline–trastuzumab therapy. Over a median follow-up exceeding two years, patients exhibited significant reductions in E/A ratios and both lateral and septal e′ velocities, alongside notable increases in E/e′ values (p < 0.01).

Also, Rashid H. et al.,[21] assessed left ventricular diastolic function and cardiotoxic chemotherapy.

Their findings indicated a significant reduction in the E/A ratio at both three and six months post-treatment ($p = 0.0002$ and $p = 0.0001$, respectively), along with a notable increase in septal E/e′ at the same time points ($p = 0.01$ and $p = 0.0002$).

In our study, as regards 2D LV volumes and EF, there were no statistically significant differences (p-value > 0.05) of 2D LVEDV, 2D LVESV, and 2D EF (baseline, two cycles, four cycles, shortly after therapy, and 6 months after therapy) among the studied groups regarding cardiotoxicity.

These findings aligned with those previously reported by Upshaw et al. 20 and Song FY, et al.[22] regarding 2D LVEDV, 2D LVESV, and 2D EF, which showed no statistically significant differences.

As regards 2D GLS, we found a non-statistically significant difference in the baseline between the two groups. However, with treatment cycles, there were progressive decreases of 2D GLS with an increase in the mean % changes. There was a statistically significant decrease in 2D GLS at 2 and 4 cycles between the two groups. This became highly significant (p-value < 0.001) till 6 months after therapy.

These findings were partially consistent with the observations reported by Song FY et al.[22] who noted a significant reduction in 2D GLS following completion of chemotherapy ($p = 0.007$), whereas no statistically significant change was observed after four treatment cycles.

When we studied 3D LV volumes, no statistically significant difference (p-value > 0.05) of 3D LVEDV (baseline, two cycles, four cycles, shortly after therapy, 6 months after therapy) was detected between the two groups with regard to cardio-toxicity. However, LVESD showed a statistically significant increase at two cycles of treatment, causing a statistically significant difference between the two groups, which progressed with treatment cycles till reaching a high statistically significant level (p-value < 0.001) 6 months after therapy.

As regards 3D EF, no statistically significant difference (p-value = 0.138) was noted at baseline levels regarding cardiotoxicity. 3D EF became statistically significantly lower at two cycles in group II. The difference became statistically significant at four cycles, shortly after therapy, and 6 months after therapy (p-value of all < 0.001).

This was in agreement with Mihalcea D et al.[23] who studied 110 cases of NHL at the third cycle and after therapy and concluded that there were statistically significant differences regarding 3D LVEDV, LVESV, and 3D EF after treatment with P value=0.01, 0.01, and 0.0001, respectively, with an early significant difference of 3D EF at third cycle (P value= 0.003).

At baseline, the comparison of 3D strain parameters between the two groups revealed no statistically significant differences. However, there were high statistically significant (p-value of all < 0.001) decreased 3D strain (GLS, GCS, GAS and GRS) at two cycles, four cycles, shortly after treatment and 6 months after therapy in group II patients when compared with 3D strain (GLS, GCS, GAS and GRS) of group I patients with increase of the mean % changes.

Among all 3D strain parameters, the 3D GLS was the most impacted, showing a significant decrease as early as the second cycle (14.6%) and persisting up to 6 months after treatment (44.5%).

A comparison between 2D GLS and 3D strain parameters revealed statistically significant differences in all 3D strain measurements as early as the second cycle.

Specifically, when comparing 2D GLS to 3D GLS, at two cycles, the mean % change was 3.6% for 2D GLS vs 14.6% for 3D GLS; although statistically significant, it didn't meet the criteria for subclinical cardiotoxicity.

By four cycles, the mean % change had increased to 6.8% for 2D GLS and 30.1% for 3D GLS, indicating that 3D GLS can detect subclinical cardiotoxicity earlier than 2D GLS. This earlier detection advantage also applies to other 3D strain parameters compared to 2D GLS.

Regarding the diagnostic performance of 3D strain parameters in discrimination of cardiotoxicity: cut-off values for 3D GLS, GCS, GAS, and GRS at two cycles were >-20, >-22, >-32, and <52, respectively.

Three-dimensional strain parameters, including 3D GLS, the sensitivity, and specificity for early detection of cardiotoxicity, were compared to 2D GLS.

Specifically, at 2-cycle,3D GLS shows superior diagnostic accuracy, with higher sensitivity (90%) and specificity (96.2%) when compared to 2D GLS at the same cycle.

These findings were consistent with those reported by Song FY et al.[22] who observed that 3D LV GLS, GCS, and right ventricular GLS (RV GLS) significantly declined after four cycles of chemotherapy. In contrast, D GLS and LV GCS demonstrated marked reductions only at the conclusion of treatment. At a cutoff value of –20.4, 3D GLS showed a sensitivity of 81% and specificity of 66% in distinguishing post-therapy patients from their baseline measurements.

The performance of 3D stains were closely related to those detected by Mihalcea D et al.[23] who concluded that the sensitivity and specificity of 3D GLS was the higher one with decrease > 19% reaches (89% and 85% respectively), while

3D GAS decrease > 28% was the second one with sensitivity and specificity (88% and 83% respectively).

4. Conclusion

Compared to 2D GLS, all parameters derived from 3D-STE demonstrated superior sensitivity and specificity in the early identification of chemotherapy-induced cardiotoxicity in lymphoma patients. These findings support the utility of 3D-STE as a reliable, non-invasive, and effective tool for early cardiotoxicity detection.

Disclosure

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