Global longitudinal strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients by three dimensional speckle tracking echocardiography

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Abstract

Ninety-four women with breast cancer who received epirubicin (360 mg/m2) underwent three-dimensional (3D) speckle tracking echocardiography (STE) at baseline, after the completion of two cycles and four cycles of the regimen respectively were enrolled in the study. 3D STE assessment included left ventricular ejection fraction (LVEF), global area strain (GAS), global longitudinal strain (GLS), global circumferential strain (GCS) and global radial strain (GRS). Meanwhile, serum high-sensitive troponin I (hs-cTnI) and N-terminal portion pro-natriuretic peptide type B (NT-proBNP) were measured. Cancer therapy-related cardiac dysfunction (CTRCD) was defined as reduction of 3D LVEF $>$ 10% to a value $<$ 54%. CTRCD occurred in 9 (9.6%) patients during anthracycline treatment. The changes in 3D LVEF was not significant after chemotherapy. Values of 3D GLS and 3D GAS showed a significant deterioration during anthracycline treatment ($p < 0.001$ and $p = 0.001$, respectively) in all patients. Compared to non-CTRCD patients, the CTRCD patients had significantly reduction in 3D GLS (-15.5±3.2% vs -17.0±2.7%, $p<0.001$) and 3D GAS (-31.0±3.9% vs -32.3±3.3%, $p<0.001$) at the end of anthracycline chemotherapy. The optimal cutoff value with -15.5% of 3D GLS had a good discrimination for predicting CTRCD, with 87.5% sensitivity and 74.6% specificity. Spearman correlation analysis showed a moderate negative correlation between 3D GLS and anthracycline doses ($r = - 0.54$, $p < 0.001$). 3D GLS could potentially improve the ability for detecting early, subclinical anthracycline-related cardiotoxicity in breast cancer patients.

Introduction

Anthracycline -related cardiotoxicity in cancer patients may lead to premature morbidity and death, which maybe have a significant impact on the prognosis of patients[1]. Although cancer therapy-related cardiac dysfunction (CTRCD) has aroused increasing attention in recent years, which is the ideal screening tool remains unresolved. Risk assessment of CTRCD included clinical history, examination, cardiac biomarkers and measurement of cardiac function[2]. Left ventricle ejection fraction (LVEF) is the primary parameter to detect cardiac dysfunction in the clinical setting [3, 4]. Although a valid measure, LVEF has some limits, such as geometrical assumptions, load dependency, and observer variability[5]. Besides, LVEF declines may occur at late stage, after irreversible cardiac injury[6, 7]. As an alternative, myocardial deformation imaging, especially global longitudinal strain (GLS), is a promising technique to identify left ventricular dysfunction[8, 9]. Multiple prior studies have demonstrated potential utility for 3D STE in the diagnosis and prediction of CTRCD [10-12]. The main advantage of 3D STE corresponds to the ability of evaluating the whole left ventricle movement of speckles from an entire scan volume and effectively reducing the time of analysis in comparison with two-dimensional (2D) STE[13]. 3D STE also has a higher reproducibility of measurements

and allows for tracking out-of-plane motion of speckles[14]. However, the advantages of 3D STE remains to be proven in breast cancer patients.

The current study sought to evaluate the usefulness of 3D STE in predicting early myocardial damage in breast cancer patients undergoing anthracycline chemotherapy.

Methods

Study design

We consecutively enrolled 100 eligible female breast cancer patients receiving anthracyclines chemotherapy into this single-center prospective study from January 2016 to July 2019. The study was approved by the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University Ethics Board. All participants signed an informed consent before their enrollment. The study complied with the Helsinki Declaration.

Exclusion criteria included previous myocardial infarction and ascertained coronary artery disease, arterial hypertension, cardiomyopathy, arrhythmias, more than mild valvular stenosis or regurgitation, prosthetic valves or pacemakers, congenital heart disease, LVEF$<$ 50% before chemotherapy, diabetes mellitus and chronic kidney disease. All patients received a 4-cycle EC (epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2) chemotherapy regimen, with an inter-cycle interval of 21 days. Demographic data, the administered cumulative anthracycline dose, echocardiographic parameters and cardiac biomarkers were documented. Two-dimensional echocardiography, 3D-STE, serum high-sensitive cardiac troponins troponin I (hs-cTnI) and N-terminal portion pro-natriuretic peptide type B (NT-proBNP) were routinely performed during the following 3 stages: at baseline, the middle of chemotherapy (epirubicin cumulative dosages of 180 mg/m^2) and the end of chemotherapy (epirubicin cumulative dosages of 360 mg/m^2).

Echocardiographic data acquisition

All subjects underwent standard transthoracic echocardiography by a GE Vivid E9 ultrasound machine (GE Healthcare, Horten, Norway) equipped with M5S (1.7-3.3 MHz). Real-time 3D echocardiographic imaging was acquired in the same ultrasound machine by the 4V-D probe (1-5 MHz). Conventional 2D, M-mode, Doppler measurements were performed according to the recommendations of the American Society of Echocardiography guidelines[4]. Four consecutive beats data during a single breath hold were acquired for analysis. The LVEF were manually calculated from LV end-diastolic volume (EDV) and end-systolic volume (ESV) according to the biplane Simpson's method in the 2D mode. Volume parameters were standardized by body surface area (BSA). Three-dimensional images were taken for all subjects and data analysis was performed with EchoPAC BT12 workstation (GE Healthcare). The software automatically and simultaneously depicted the endocardial and epicardial borders through the entire cardiac cycle in three different vectors with manual delineation of the mitral valve edges and apex, and rejection of segments of poor imaging quality. 3D volume and 3D strain were automatically calculated. The global area strain (GAS), GLS, global circumferential strain (GCS) and global radial strain (GRS) were calculated by averaging of 17 regional segments values from the LV myocardial wall. Rejected segments were excluded from the calculation of global strain values. Global strain values were not calculated if more than three segments were rejected. All strain measurements were performed by two experienced echocardiographer who was blinded to subject characteristics.

A randomly selected cohort of 10 patients was analyzed to evaluate intra-observer and inter-observer variabilities for 3D strain measurements and 3D LVEF. Intra-observer and inter-observer variability of 3D STE data were calculated as intraclass correlation coefficients (ICCs). The inter-observer ICCs for 3D GAS, 3D GLS, 3D GCS, 3D GRS, and 3D LVEF were0.81, 0.86, 0.84, 0.83 and 0.85, respectively. Similarly, intra-observer measurement showed ICCs of 0.86 for 3D GAS ,0.88 for 3D GLS, 0.83 for 3D GCS, 0.85 for 3D GRS and 0.82 for 3D LVEF, indicating satisfactory reproducibility of 3D STE.

An reduction of 3D LVEF $>$ 10% to a value $<$ 54% associated with or without signs and symptoms of heart failure was considered to be CTRCD[2].

Cardiac biomarkers assays

Concentrations of hs-cTnI and NT-proBNP were measured on an Elecsys 2010 analyzer (Roche Diagnostics Corporation, Indianapolis, IN, USA) using a commercially available electrochemiluminescence immunoassay.

The 99th percentile reference limit of hs-cTnI is 10 pg/ml. NT-proBNP >125 pg/ml was considered elevated. Blood samples corresponding to the baseline and follow-up timepoints were included for analysis. Biomarker assessment were routinely performed within 24 hours after epirubicin cumulative dosages of 180 mg/m^2 and 360 mg/m^2 during follow-up time.

Statistical analysis

Continuous variables were summarized as mean and standard deviation or median and interquartile range (IQR), whereas categorical measures were summarized as percentage and frequencies.

Differences across all timepoints were compared using one-way ANOVA for continuous variables (Mann-Whitney U test for variables with non-normal distribution). Comparisons between CTRCD group and non-CTRCD group were performed by independent samples t-test. The correlation between 3D STE parameters and the cumulative doses of epirubicin was calculated by Spearman's test, while the correlation between 3D STE parameters and cardiac biomarkers was calculated by Pearson's test. Receiver operating curve (ROC) analysis was performed to determine the capability of 3D strain values for predicting CTRCD using area under the curve (AUC). The optimum cutoff value for discriminating CTRCD was determined using the maximum sensitivity and specificity. All statistical tests were 2-sided and statistical significance was set at $p < 0.05$. Analyses were performed using the SPSS Version 20.0 software package (SPSS 20.0, Chicago, IL, USA).

Results Baseline characteristics

After excluding six patients (one for uncontrolled hypertension, three for poor acoustic windows and two for inadequate image quality), a total of 94 patients successfully completed chemotherapy. None had an episode of atrial fibrillation or clinical cardiac dysfunction through the follow-up. Baseline characteristics of the study are shown in Table 1.

CTRCD occurred in 9 of the 94 patients (9.6%) during follow-up. No patients had cardiac symptoms at the baseline and through the chemotherapy cycle.

Standard echocardiography

The standard echocardiographic parameters before and during chemotherapy are showed in Table 2. There were no significant differences in LVEDVI, LVESVI, LVEF, LVAVI through the chemotherapy (all $p> 0.05$). The E/A ratio, E velocity deceleration time (DT) and E/ e' ratio also showed no significant differences during anthracycline treatment. The 2D GLS showed a significant deterioration at the end of chemotherapy ($p< 0.05$).

3D STE parameters

Table 3 displays the 3D STE analysis. After two cycles of chemotherapy (epirubicin cumulative dosages of 180 mg/m^2), no significant differences were observed in 3D STE parameters (all $p > 0.05$). Values of 3D GLS and 3D GAS showed a significant deterioration during anthracycline treatment ($p < 0.001$ and $p = 0.001$, respectively). Values of 3D GCS and 3D GRS showed no significant variation during the chemotherapy (both $p > 0.05$). Compared with the baseline, there were no significant differences in 3D LVEDVI, 3D LVESVI and 3D LVEF at the end of chemotherapy (all $p > 0.05$).

Cardiac biomarkers

At the end of chemotherapy, the hs-cTnI concentrations rose from 1.4 (0.7, 2.8) to 6.7 (4.6, 8.9) pg/ml ($p = 0.042$). However, the median value of NT-proBNP concentrations showed no significant difference during the chemotherapy ($p > 0.05$). Pearson's correlation analysis showed that hs-cTnI concentrations were significantly negatively correlated with 3D GLS at the end of chemotherapy ($r = -0.36$, $p = 0.031$) while no obviously correlated with 3D GAS ($p > 0.05$). Neither the correlation of NT-proBNP concentrations and

3D GLS, or NT-proBNP concentrations and 3D GAS were founded at the end of chemotherapy (both $p > 0.05$).

Relationship of 3D global strain and cancer therapeutics-related cardiac dysfunction

At baseline, there were no significant differences of LVEF or STE parameters between patients with and without CTRCD. At middle of chemotherapy, only 3D GLS (-17.6 ± 2.5% vs -18.3 ± 2.3%, p=0.015) was significantly reduced in patients with CTRCD. At the end of chemotherapy, all 3D volumetric and STE parameters were reduced in CTRCD patients compared with baseline, whereas no significant difference was observed in non-CTRCD patients (Table 4). Further analysis demonstrated that, the CTRCD group had significantly greater LVEDVI (62.0 ± 5.8 vs 58.8 ± 6.0, p = 0.037), LVESVI (24.3 ± 3.4 vs 21.2 ± 3.8, p = 0.023) and the lower LVEF (59.0 ± 5.3% vs 63.9 ± 6.1%, p = 0.011) compared to non-CTRCD group. Both 3D GLS (-15.5 ± 3.2% vs -17.0 ± 2.7%, p<0.001) and 3D GAS (-31.0 ± 3.9% vs -32.3 ± 3.3%, p < 0.001) were significantly reduced in patients who developed CTRCD. On the other hand, 3D GCS (-17.8 ± 3.0% vs -18.9 ± 2.7%, p = 0.038) and 3D GRS (38.7 ± 4.1% vs 40.1 ± 3.8%, p = 0.043) were marginally but significantly reduced after chemotherapy.

Receiver operating characteristic analysis showed that 3D GLS had a good discrimination for predicting CTRCD, with an AUC of 0.86, 87.5% sensitivity and 74.6% specificity at the end of chemotherapy (Figure 1). The optimal cut-off value for 3D GLS was -15.5%. The AUC for 3D GAS was 0.75. The optimal cut-off of 3D GAS for the discriminating patients with cardiotoxicity was -31.5% with a sensitivity of 75.0% and a specificity of 57.7 % (Table 5).

Association between anthracycline doses and 3D global strain

The association between 3D GLS and the cumulative dose of anthracycline was calculated by Spearman's test (r = - 0.54, p < 0.001) (Figure 2). Correlation coefficients for other strain parameters and cumulative dose of anthracycline: 3D GAS (r = - 0.26, p = 0.019), 3D GCS (r = - 0.16, p = 0.157) and 3D GRS (r = - 0.09, p = 0.430).

Discussion

In the study, we demonstrated that the diagnostic value of 3D STE parameters in early detection of LV systolic function deterioration in breast cancer patients undergoing anthracycline chemotherapy. Furthermore, 3D GLS was a better early predictor of CTRCD than other 3D STE parameters (GAS, GCS, and GRS). There was a moderate negative relation between 3D GLS and cumulative anthracycline dose.

Anthracyclines are widely used in treatments for breast cancer, but can induce cardiotoxicity, which is the main cause of cardiovascular morbidity in cancer survivors[15, 16]. There is still no consensus on the exact mechanism of anthracycline-induced cardiotoxicity. Oxidative stress hypothesis is the most commonly accepted pathophysiological mechanism. The generation of excess reactive oxygen species (ROS) and lipid peroxidation in cardiomyocytes cell membrane lead to apoptosis and myofilament degradation[17, 18]. Cardiac imaging and biomarkers were the main strategies for screening and detection of anthracycline cardiotoxicity. Echocardiography is the most widely used imaging modality for evaluating cardiac function in cancer patients receiving anthracycline treatment. And LVEF is the primary accepted parameter for detecting and monitoring anthracycline cardiotoxicity. However, LVEF cannot to detect early changes in cardiac function, before irreversible myocardial injuries [19, 20]. Cardinale et al [21] reported that the incidence of anthracycline-associated cardiotoxicity was 9%, and 98% of cases occurred within the first year and were asymptomatic. The early detection of anthracycline cardiotoxicity is of great importance in cancer patients, in order to initiate timely cardioprotective treatment and possibly prevent further deterioration of heart function. Up to date, the optimal methodology for early detecting subclinical CTRCD remains unclear. Recently, 2D STE has potential utility for detecting early impairment of cardiac systolic function before LVEF decreases[8, 19]. It is noteworthy that the main limitation of 2D STE is out-of-plane motion tracking of speckles that lead to increased noise and reduced accuracy[14]. Since cardiac motion is three dimensional and anthracycline-associated myocardial injuries is not limited to particular segments, 3D STE may be a

powerful tool for early detecting anthracycline cardiotoxicity in oncologic patients.

The optimal 3D STE parameter for early detection of anthracycline cardiotoxicity is still controversial. In a longitudinal cohort study of 143 patients with breast cancer, who received anthracyclines with or without trastuzumab, GCS and GLS were associated with LVEF declines during anthracycline treatment[11]. In the study of Chen et al[22],they found that GAS had greater value in predicting subclinical cardiotoxicity associated with anthracyclines. Although the previous studies showed inconsistent results, GLS was the best measure in early detection of anthracycline-related cardiotoxicity[2, 23, 24]. In our study, CTRCD occurred in 9 (9.6%) patients at the end of anthracycline chemotherapy. The 3D GLS deteriorated significantly at the end of anthracycline chemotherapy when compared to baseline (-18.7±2.2% vs. -16.4±2.9%, p<0.001). Deterioration in 3D global strain parameters before an abnormal LVEF was evident in numerous studies[20, 25, 26]. In the current study, 3D GLS and 3D GAS decreased significantly at the end of anthracycline chemotherapy, while no pronounced changes were observed in 3D LVEF. Deterioration of 3D GLS and 3D GAS showed correlation with CTRCD. At middle of chemotherapy, 3D GLS (-17.6 ± 2.5% vs -18.3 ± 2.3%, p=0.015) was the only parameter significantly reduced in patients with CTRCD. ROC analysis revealed that 3D GLS had the highest predictive accuracy in CTRCD with AUC 0.86. The optimal cutoff value for 3D GLS to predicting CTRCD was -15.5%, yielding a sensitivity of 87.5% and a specificity of 74.6%. The mechanism of GLS with the ability to detect subclinical LV dysfunction after anthracyclines chemotherapy may due to myocardium motion. The endocardial layer is often the first to be affected by various diseases, besides, the longitudinal movement of the endocardial myocardium has a pivotal role in LV systolic function[26].

As a new measurement parameter, GAS that integrates endocardial longitudinal and circumferential strain, might be useful for early detection of subclinical LV dysfunction related to anthracycline[22, 27]. The current results demonstrated 3D GAS was associated with CTRCD also supported the involvement of circumferential mechanics to global systolic function. Recent research demonstrated the potential superiority of GCS and GAS compared with other echocardiographic parameters for early detection of anthracycline cardiotoxicity; however, these patients received a greater cumulative anthracycline dose, combined with traztuzumab or radiotherapy[20]. Besides, there was longer follow-up time in patients after anthracycline chemotherapy[11].

The hs-cTnI is likely the most sensitive and specific marker of myocardial necrosis induced by anthracycline chemotherapy[28, 29]. The present study showed the hs-cTnI concentrations significantly rose from 1.4 to 6.7 ng/ml at the end of chemotherapy (p = 0.042). Although the hs-cTnI concentrations had associated with 3D GLS, it did not predict cardiotoxicity. The challenge currently is hs-cTnI does not reflect the damage extent of heart function as well as lack of definite cardioprotective strategy [30]. In this study, NT-proBNP concentrations did not change and did not predict cardiotoxicity after chemotherapy. NT-proBNP may be useful, but its role in detecting cardiotoxicity is not established in chemotherapy[2].

Cardiotoxicity of anthracyclines is always dose-dependent, that is, the incidence of myocardial injury has relation to the cumulative dose of the drug. In a long-term breast cancer survivors research[3], GLS declined in a linear fashion with increasing cumulative anthracycline dose. The effect of anthracycline dose on myocardial deformation using 3D STE was evaluated in the present study. Consistent with previous studies, there was a moderate negative relation between 3D GLS and cumulative anthracycline dose (r = - 0.54, p < 0.001). 3D GAS was also found to have correlation with the cumulative dose of anthracycline (r = - 0.26, p =0.019), while either GCS or GRS.

The present study had some limitations. First, its small size and short follow-up duration, which had obvious reflections on the absence of clinical events and low rate of reduction in LVEF. Nevertheless, this cohort showed that 3D strain parameters predicted the subsequent diagnosis of CTRCD. Long-term surveillance should be considered for those who developed overt heart failure. Another limitation of the study is that comprehensive researches are needed to establish the utility of 3D measures in cardio-oncology population undergoing chemotherapy, although 3D STE may be feasible in a cohort of breast cancer patients in this study. Finally, intervendor variability in 3D strain is well-documented and the reference values for 3D strain are not yet fully established. The results of this study are not likely to be interchangeable among software vendors.

Conclusions

Subclinical LV systolic dysfunction was present in anthracycline-chemotherapy patients in spite of preserved left ventricular ejection fraction. Due to its ability to predict CTRCD, 3D GLS could potentially detecting early, subclinical anthracycline-related cardiotoxicity in breast cancer patients. Ongoing and future studies remain to be performed to understand the mechanisms of early 3D GLS deterioration after anthracycline chemotherapy.

Conflicts of Interest The authors declare that they have no conflict of interest.

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Table 1 Clinical characteristics at baseline

Variable	Mean ± SD	Range
Age (years)	49.8±9.2	32-68
Body mass index (kg/m^2)	24.3±3.6	20.6-31.6
Body surface area(m^2)	1.6±0.1	1.5-1.7
Systolic blood pressure (mmHg)	114.5 ± 10.5	90-140
Diastolic blood pressure (mmHg)	72.2 ± 6.7	50-90
Heart rate (bpm)	71.9 ± 8.6	56-104

Table 2 Standard Echocardiographicparameters at baseline, middle of the chemotherapy, and the end of chemotherapy

Variables	Baseline	Middle chemotherapy	End chemotherapy	p
LVEDVI (ml/m^2)	54.1±5.6	55.6±5.7	60.2±6.0	0.390
LVESVI (ml/m^2)	18.8±3.0	19.5±3.4	23.6±3.7	0.103
LVEF (%)	65.2±4.8	64.9±5.1	60.8±5.0	0.161
LAVI (ml/m^2)	24.3±4.9	24.8±5.0	27.4±5.2	0.463
E/A ratio	1.2±0.3	1.1±0.3	1.1±0.4	0.508
E velocity DT (ms)	200.7±45.2	196.2±48.6	192.9±52.4	0.214
E/ e' ratio	8.0±2.4	7.8±2.3	7.7±2.2	0.182
GLS	-21.3±2.5	-19.5±2.3	-17.8±2.0$^{*\#}$	0.000

LVEDVI, left ventricle end-diastolic volume index; LVESVI, left ventricle end-systolic volume index; LVEF, left ventricle ejection fraction; LAVI, left atrium volume index; E/A, peak early (E) and late (A) wave velocity of mitral annulus ;DT, deceleration time; GLS, global longitudinal strain.

* p< .05 for comparison with baseline; $^{\#}$p< .05 for comparison with middle chemotherapy.

Table 3 Real-time three dimensional echocardiographic parameters at baseline, during the chemotherapy, and the end of chemotherapy

Variables	Baseline	Middle chemotherapy	End chemotherapy	p
LVEDVI (mL/m^2)	53.1±5.2	54.3±5.5	59.6±5.8	0.586
LVESVI (mL/m^2)	17.8±2.9	18.8±3.2	22.0±3.4	0.092
LVEF (%)	66.5±4.6	65.3±5.2	62.1±5.7	0.084
GAS (%)	-34.4±2.6	-33.7±2.8	-31.8±3.4$^{*\#}$	0.001
GLS (%)	-18.7±2.2	-18.1±2.3	-16.4±2.9$^{*\#}$	<0.001
GCS (%)	-19.3±2.5	-19.0±2.6	-18.6±2.8	0.305

Variables	Baseline	Middle chemotherapy	End chemotherapy	p
GRS (%)	40.7±3.5	40.5±3.7	39.7±3.9	0.376

LVEDVI, left ventricle end-diastolic volume index; LVESVI, left ventricle end-systolic volume index; LVEF, left ventricle ejection fraction; GAS, global area strain; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain.

* p< .05 for comparison with baseline; #p< .05 for comparison with middle chemotherapy.

Table 4Comparison of three dimensional echocardiographic parameters in patients with and without CTRCD.

Variables		CTRCD (n=9)	non-CTRCD (n=85)	p
LVEDVI (mL/m^2)				
	Baseline Middle chemotherapy End chemotherapy	53.1±5.1 55.4±5.5 62.0±5.8*	53.1±5.2 54.0±5.7 58.8±6.0	0.560 0.363 0.037
LVESVI (mL/m^2)	Baseline Middle chemotherapy End chemotherapy	17.9±3.0 19.3±3.2 24.3±3.4*	17.7±2.9 18.6±3.4 21.2±3.8	0.859 0.464 0.023
LVEF (%)	Baseline Middle chemotherapy End chemotherapy	66.2±4.1 65.2±5.0 59.0±5.3*	66.7±4.6 65.6±5.5 63.9±6.1	0.358 0.274 0.011
GAS (%)	Baseline Middle chemotherapy End chemotherapy	-34.3±2.7 -33.2±3.0 -31.0±3.9*#	-34.4±2.6 -34.0±2.8 -32.3±3.3	0.650 0.196 <0.001
GLS (%)	Baseline Middle chemotherapy End chemotherapy	-18.5±2.3 -17.6±2.5 -15.4±3.2*#	-18.8±2.2 -18.3±2.3 -17.0±2.7	0.702 0.015 <0.001
GCS (%)	Baseline Middle chemotherapy End chemotherapy	-19.3±2.5 -18.5±2.8 -17.8±3.0*	-19.2±2.5 -19.2±2.6 -18.9±2.7	0.649 0.308 0.038
GRS (%)	Baseline Middle chemotherapy End chemotherapy	40.5±3.4 40.0±3.7 38.7±4.1*	40.8±3.5 40.6±3.6 40.1±3.8	0.872 0.545 0.043

LVEDVI, left ventricle end-diastolic volume index; LVESVI, left ventricle end-systolic volume index; LVEF, left ventricle ejection fraction; GAS, global area strain; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain.

* p< .05 for comparison with baseline; #p< .05 for comparison with middle chemotherapy.

Table 5 ROC curve analyses of 3D STE parameters

Variables	Area under the curve	95% CI	Cutoff value (%)	Sensitivity	Specificity
3D GLS	0.86	0.83-0.91	-15.5	87.5	74.6
3D GAS	0.75	0.71-0.80	-31.5	75.0	57.7

Variables	Area under the curve	95% CI	Cutoff value (%)	Sensitivity	Specificity
3D GCS	0.66	0.61-0.72	-18.5	67.2	53.0
3D GRS	0.58	0.52-0.66	39.5	60.5	52.6

ROC, receiver operating characteristic; CI, confidence interval; GLS, global longitudinal strain; GAS, global area strain; GCS, global circumferential strain; GRS, global radial strain.