ORIGINAL INVESTIGATION

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Prediction of trastuzumab-induced cardiotoxicity in breast cancer patients receiving anthracycline-based chemotherapy

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Abstract

Background Adjuvant trastuzumab improved overall survival and reduced the risk for disease recurrence in women with breast cancers, because of its potential cardiotoxicity, careful monitoring of left ventricular (LV) function during treatment is required.

Methods This study investigates, whether myocardial strain imaging and level of N-terminal pro-brain natriuretic peptide (NT-pro BNP) could predict subsequent reduction in LVEF in breast cancer patients received adjuvant trastuzumab. 61 women with pathologically proven breast cancer HER-2 positive received AC (Doxorubicin–Cyclophosphamide) for 4 cycles, followed by paclitaxel with Trastuzumab were enrolled. Clinical, conventional echocardiographic parameters, myocardial strain imaging [global longitudinal peak systolic strain (GLS), radial and circumferential systolic strain] and level of NT pro-BNP were measured at baseline, after 3, 6, 9 and 12 months of trastuzumab therapy.

Results Of 61 patients, 18 patients (29.5%) developed trastuzumab-induced cardiomyopathy (CM) at 6 and 9 months of therapy (LVEF declines ≥ 10%), GLS and radial strain significantly decreased in CM group at 3 months of trastuzumab treatment, the value of GLS at 3 months was the strongest predictors of cardiotoxicity its area under the curve (AUC 0.98) with an optimal cut-off for GLS (− 18%) having 92.5% sensitivity and 83% specificity. NT-pro BNP levels were not predictive of later trastuzumab-induced cardiac dysfunction.

Conclusion Myocardial strain imaging has been able to predict pre-clinical changes in LV systolic function and GLS is an independent early predictor of subsequent reduction in EF in breast cancer patients treated with trastuzumab.

Keywords Breast cancer · Trastuzumab · Cardiotoxicity · Myocardial strain

Introduction

Breast cancer is the most common malignancy in women all over the world, for more than three decades [1, 2]. The addition of adjuvant trastuzumab has substantially improved overall survival and reduced the risk for disease recurrence in women with human epidermal growth factor receptor (HER) type-2 positive breast cancers. [3, 4] Because of its potential cardiotoxicity, trastuzumab treatment requires careful monitoring of left ventricular (LV) function during treatment [5, 6].

The measurement of LV ejection fraction (EF) is the most common method of monitoring cardiac systolic function during cancer treatment. Cardiotoxicity has been defined as reduction of EF ≥ 5 to < 55% with symptoms of heart failure or an asymptomatic ≥ 10% reduction to an EF to < 55%. However, EF is an imperfect parameter for the detection of cardiotoxicity because of its inherent variability [7] and also EF fails to detect early subtle changes, and when reduced, it reflects a marker of advanced myocyte damage accompanied by a poor prognosis [8–10]. Myocardial strain imaging measured by Speckle-tracking echocardiography (STE) is a sophisticated technique that provides direct quantitative evaluation of myocardial motion and deformation independently of angle and ventricular geometry which could detect early myocardial dysfunction [11].

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Natriuretic peptides, released from ventricular myocardium during hemodynamic stress, are widely used in the early detection of heart failure and shown to be sensitive markers of left ventricular dysfunction and powerful markers of morbidity and mortality in heart failure. However, the ability of N-terminal pro-B-type natriuretic peptide (NT-proBNP) to predict early left ventricular dysfunction in the setting of trastuzumab-induced cardiotoxicity remains unconfirmed [12].

This study was done to assess, whether myocardial strain imaging and biomarker of cardiac wall stress (NT-pro BNP) obtained early in the course of the treatment of breast cancer patients could predict subsequent reduction of LVEF occurring during the full course of the treatment.

Patients and methods

From December 2014 to December 2016, sixty-one female patients with pathologically proven breast cancer HER-2 positive attended to the Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital were included.

Patients fulfilled the following criteria: age between 30 and 60 years HER-2 positive (defined as immunohistochemical overexpression "$3 \pm$" or evidence of gene amplification by fluorescence in situ hybridization) breast cancer, performance status (PS) of ≤ 2 according to Eastern Cooperative Oncology Group (ECOG) scale, (WBC count $\geq 3.5 \times 10^9$/L, absolute neutrophil count of $\geq 1.5 \times 10^9$L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥ 10 gm/dL), adequate renal function (creatinine clearance ≥ 60 mL/min) and average liver enzymes and serum bilirubin. Patients suffering from secondary malignancy or concurrent serious, uncontrolled medical illness (e.g., immune-compromised patients, serious infection, severe peripheral neuropathy, and clinically significant cardiac illness) were excluded from this study. No prior therapy for metastatic disease was allowed.

Design of the study

This study is a prospective single-arm, phase II single institution study. Protocol approval by the Ethics Committee in the Faculty of Medicine, Tanta University, with a signed informed consent from all included patients consent before the initiation of any treatment.

Treatment plan and dose medication

Patients received AC (Doxorubicin 60 mg/m^2–Cyclophosphamide 600 mg/m^2) IV day 1, cycle every 21 days for 4 cycles, followed by Paclitaxel 80 mg/m^2 weekly for 12 weeks with Trastuzumab 4 mg/kg IV with the first dose of Paclitaxel, followed by Trastuzumab 2 mg/kg 4 weekly

to complete 1 year of Trastuzumab treatment. Treatment was infused on an inpatient basis. Adequate CBC, tests of liver and renal functions were insured every month. In case of disease progression or major toxicities therapy was discontinued.

Patient assessment for early cardiac dysfunction

Echocardiography

Patients were evaluated before chemotherapy, before initiation of trastuzumab treatment (3 weeks after the last anthracyclines cycle), and every 3 months subsequently till the end of trastuzumab therapy (12 months induration), total study duration over 15 months.

At each visit patients were asked for symptoms of heart failure, clinically examined, transthoracic echocardiography were performed and plasma level of NT-proBNP were measured.

Patients who had LVEF < 50% at baseline were excluded. Primary end point was the occurrence of trastuzumab-mediated cardiomyopathy defined as at least decline in LVEF 10% up to below 55% associated with or without signs and symptoms of heart failure.

Serial TTE was performed at cardiology department, Tanta University using vivid 9. General electronics (GE) with 3.5–5 (MHz) passed array transducers. LVEF was calculated from the apical four and two chamber views using a modified Simpson biplane method.

Measurement of myocardial strain

Peak systolic strain was measured using speckle tracking technique, for peak longitudinal strain measurement 2D imaging were recorded from apical four, two and three chamber views, endocardial and epicardial borders were tracing, Off line measurement of the 2D strain were obtained, speckle tracking was performed using the semi-automatic AFI algorithm (Automated Function Imaging, Version 112, GE Healthcare, Horten, Norway) that analyses myocardial motion by adequate tracking frame-to-frame speckle changes in 2D images. The peak systolic strain values were measured as the peak values on the curves during ejection phase for each of the LV 18 segments [13].

The peak global longitudinal strain (GLS) was calculated by averaging all the measured segmental values of the different left ventricular walls (lateral, septal, inferior, posterior, anterior, and anteroseptal), Global radial and circumferential peak systolic strain was performed using (Echo Pac, version 112, GE) calculated by averaging the peak systolic strain values in all 6 segments of the parasternal short-axis view at mid papillary muscles level.

Laboratory assay of NT-proBNP levels by ELISA

Blood Collection and Laboratory Assay: Specimens—blood samples were obtained before chemotherapy, before initiation of trastuzumab treatment (3 weeks after the last anthracyclines cycle), and every 3 months subsequently till the end of trastuzumab therapy.

Whole blood was collected by standard venipuncture in VACUETTE® Blood Collection Tubes (Greiner Bio-One, Austria) containing clot activator/Sep and serum separator tube (SST). Serum samples for determination of NT-pro BNP were aliquoted and stored frozen at −20 °C to avoid loss of human NT-pro BNP.

NT-proBNP levels were measured by Human NT-proBNP, ELISA Kit Catalog No: E0485 h (EIAab Science Co.Ltd). Briefly, the methodology is based on the competitive binding enzyme immunoassay. The micro titer plate provided has been pre-coated with an antibody specific to NT-proBNP, during the reaction, the sample or standard competes with a fixed amount of biotin-labeled that are present on a pre-coated Monoclonal antibody specific to NT-proBNP. By the prepared wash the excess conjugate and unbound sample or standard are washed from the plate. Next, to each microplate well Avid in conjugated to Horseradish Peroxidase (HRP) is added to these wells and incubated. Then a TMB substrate solution is added to each well. The reaction is terminated by the addition of a sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of the samples is then determined by comparing the O.D. of the samples to the standard curve.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent samples t test of significance was used when comparing between two means. Chi-square (X^2) test of significance was used to compare proportions between two qualitative parameters. Pearson's correlation coefficient (r) test was used for correlating data. Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of parameter and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.

Results

Patient characteristics

Sixty-one cancer breast female patients were recruited in the study from December 2014 to December 2016 with pathologically proven cancer breast HER2 positive. Most of our patients were > 50 years old with percentage 55.7%, the mean age were 47.4 ± 9.1 years.

Forty (65.6%) patients presented with early stage, 5 (8.2%) patients were smokers, 22 (36.1%) were hypertensive while 7 (11.4%) were diabetics. Thirty-nine (63.9%) patients were presented with right cancer breast, while 22 (36.1%) presented with left sided cancer breast. All the patients underwent surgery, either MRM (modified radical mastectomy) or conservative surgery. Fifty-five (90.2%) patients received radiation therapy. As regard the chemotherapy received all the patients received adjuvant DC followed with Trastuzumab.

Eighteen (29.5%) of our patients developed cardiotoxicity which was discovered on the regular follow up. Baseline risk factors for cardiotoxicity of both groups were similar with non-significant p value (Table 1).

Echocardiographic parameters results

Changes in LVEF

Total 61 patients, 18 patients developed cardiomyopathy (CM), and trastuzumab induced CM defined a declines ≥ 10% in left ventricular EF baseline in asymptomatic patients.

The mean baseline of LVEF was 62.8 ± 2.1 and 62.1 ± 2.9% for those with and without CM the difference

Table 1 The cardiotoxicity according to patients characteristics

Patient characteristics	Cardiotoxicity (18)		No cardiotoxicity (43)		p value
	N	%	N	%	
Age					
< 50	7	38.9	20	46.5	0.472
> 50	11	61.1	23	53.5	
Stage					
Early	9	50	31	72.1	0.098
Locally advanced	9	50	12	27.9	
Smoking	3	16.7	2	4.7	0.119
Hypertensive	9	50	13	30.2	0.143
Diabetics	3	16.7	4	9.3	0.410
Dyslipidemia	6	33.3	9	20.9	0.305
Site					
Right breast	10	55.6	29	67.4	0.378
Left breast	8	44.4	14	32.6	
Surgery	18	100	43	100	–
Radiation	16	88.9	39	90.7	0.829
Chemotherapy					
Doxorubicin	18	100	43	100	–
Taxane use	18	100	43	100	–

in LVEF was non-significant, in women who developed CM, the decrease in LVEF most frequently within 6 month of the treatment with trastuzumab (12 patients), less commonly (6 patients) within 9 month of therapy. The mean LVEF decline from (62.8 ± 2.1 to $45 \pm 3.7\%$) within 6 month, then progressive decline to $40.3 \pm 2.1\%$ at 9 months, there was a significant difference in LVEF between normal patients and those with CM (61.6 ± 3.1 and $45.7 \pm 3.7\%$), respectively ($p = 0.001$) (Table 2).

The declines in LVEF and development of the signs and symptoms of heart failure necessitating discontinuation of trastuzumab and initiation of heart failure therapy with beta blockers and angiotensin converting enzyme inhibitors.

The LVEF began to recover in most of the patients at 12 months ($40.3 \pm 2.7\%$ at 9 months to $48.2 \pm 2.1\%$ at 12 months).

The cut-off value for LVEF to diagnosis of trastuzumab-related cardiomyopathy was 53% in this study.

Five patients developed symptomatic heart failure during the course of therapy, 2 patients at 6 months and 3 patients at 9 months of trastuzumab therapy. Cardiotoxicity was found in all symptomatic patients, peak GLS was $\leq -18\%$ in all symptomatic patients after 3 months of therapy.

Effect of trastuzumab on myocardial strain

The peak GLS was decrease from $-20.07 \pm 1.04\%$ at baseline to $-18.8 \pm 0.8\%$ at 3 months of therapy in the CM group and continued to decrease up to 9 months, peak GLS was significantly reduced in CM group at 3 months compared with the group without cardiomyopathy ($p = 0.001$) (Table 2, Figs. 1, 2).

Similarly the peak radial and circumferential strain decreased early at 3 months of treatment in CM group and continued to declines up to 9 months, The peak radial and circumferential strain were significantly reduced in CM group at 3 months compared with the group without cardiotoxicity ($p = 0.001$ for radial and $p = 0.031$ for circumferential strain) (Table 2, Fig. 3).

Predictive value of myocardial strain in the development of cardiomyopathy

Receiver operating characteristic (ROC) curve analyses for GLS showed that the value of GLS at 3 months was a predictor of $\geq 10\%$ reduction in EF at 6 and 9 months of trastuzumab therapy, its area under the curve (AUC 0.98) with an optimal cut-off for GLS (-18%) having 92.5% sensitivity and 83% specificity. The positive predictive value, negative predictive value and accuracy of GLS were 95%, 80% and 90%, respectively. Similarly, the ROC curve analyses for peak radial strain and peak circumferential systolic strain showed that the values of these parameters at 3 months predict the reduction in EF at subsequent months (AUC 0.84) for peak radial strain with optimal cut-off (35%) giving 85% sensitivity and 61% specificity, and for circumferential strain (AUC 0.65) with optimal cut-off (-17.5%) having a sensitivity of 65% and specificity of 54%. The changes in GLS were the strongest predictors of subsequent decrease in the EF (Table 3, Fig. 4).

The intra-observer and inter-observer variability for GLS were 0.91 and 0.85 with coefficient of variation 4.3 and 5.2%, respectively.

Predictive value of NT-pro BNP levels

At baseline the level of NT-pro BNP within the normal range for all patients, at follow-up the NT-pro BNP levels did not change significantly between the patients with and without trastuzumab-induced cardiomyopathy. The elevated NT-pro BNP levels were not predictive of later trastuzumab-induced cardiac dysfunction (Table 4).

Table 2 Echocardiographic parameters of patients with and without trastuzumab-mediated cardiomyopathy measured at baseline and at follow-up

Parameter		Cardiomyopathy	Normal	p value
LVEF (%)	Baseline	62.82 ± 2.19	62.19 ± 2.95	0.423
	3 months	59.65 ± 2.76	61.02 ± 2.89	0.098
	6 months	45.76 ± 3.72	61.67 ± 3.11	0.001*
	9 months	40.35 ± 2.76	60.95 ± 2.52	0.001*
	12 months	48.24 ± 2.11	60.84 ± 2.22	0.001*
2D speckle tracking				
GLS (%)	Baseline	-20.07 ± 1.04	-20.44 ± 1.44	0.329
	3 months	-16.89 ± 0.80	-20.12 ± 1.35	0.001*
	6 months	-14.74 ± 1.05	-19.63 ± 1.25	0.001*
	9 months	-12.29 ± 1.38	-19.48 ± 1.00	0.001*
	12 months	-15.68 ± 1.52	-17.77 ± 8.42	0.303
GRS (%)	Baseline	40.28 ± 7.14	42.19 ± 6.27	0.302
	3 months	31.92 ± 8.38	43.48 ± 6.92	0.001*
	6 months	24.17 ± 8.73	43.28 ± 7.71	0.001*
	9 months	22.22 ± 7.39	42.67 ± 7.71	0.001*
	12 months	26.50 ± 8.54	42.91 ± 7.47	0.001*
GCS (%)	Baseline	-18.34 ± 2.35	-18.17 ± 2.06	0.783
	3 months	-16.21 ± 2.36	-17.45 ± 1.79	0.031*
	6 months	-15.33 ± 2.31	-17.10 ± 1.75	0.001*
	9 months	-14.95 ± 2.31	-17.13 ± 1.75	0.001*
	12 months	-15.59 ± 2.58	-16.58 ± 1.99	0.117

LVEF left ventricular ejection fraction, *GLS* global longitudinal peak systolic strain, *GRS* global radial peak systolic strain, *GCS* global circumferential peak systolic strain
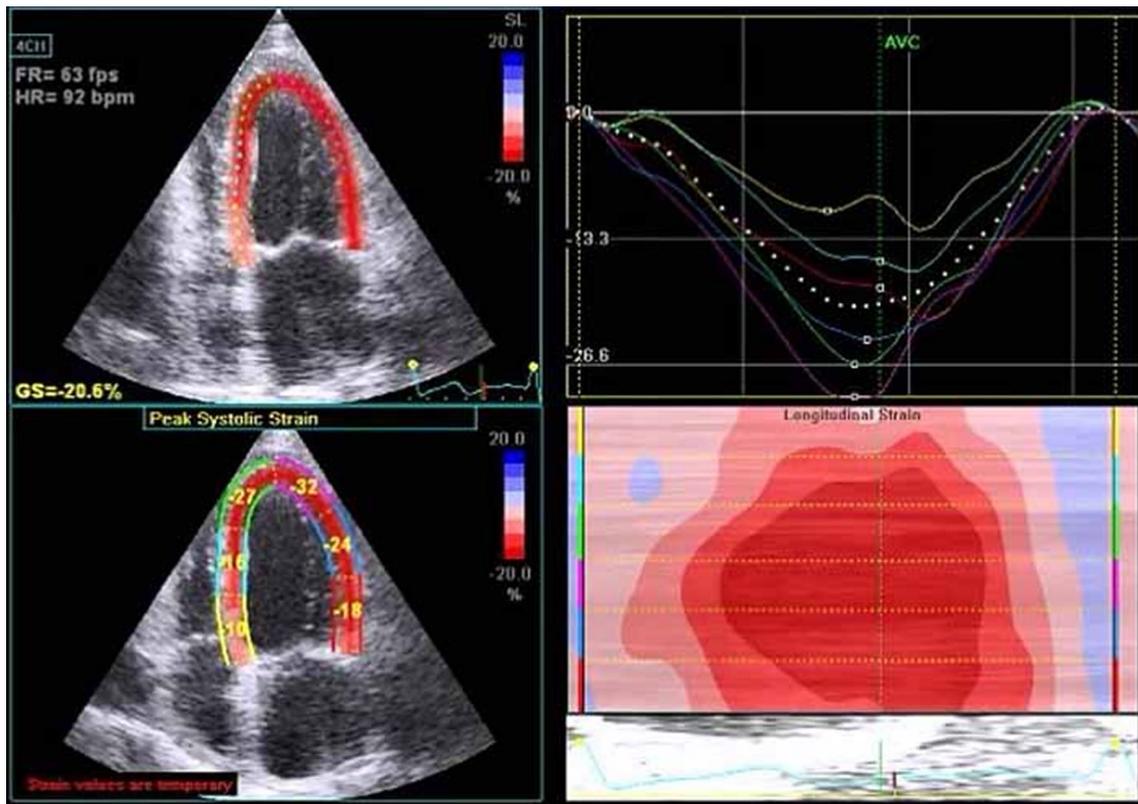
*Significant

Fig. 1 Global longitudinal peak systolic strain in patient without trastuzumab-related cardiomyopathy

Fig. 2 Global longitudinal peak systolic strain in patient developed trastuzumab-mediated cardiomyopathy

Discussion

Trastuzumab had therapeutic benefits in reducing breast cancer disease recurrence, but cardiotoxicity is one of the most devastating complication, especially when used in combination of anthracycline. Heart failure in anthracycline therapy has 2-year mortality rate up to 60% [14]. Cardiotoxicity have become the main threat to patients surviving cancer [15] therefore, early methods for identifying patients at risk for future LV dysfunction are important, because these patients may benefit from modulation
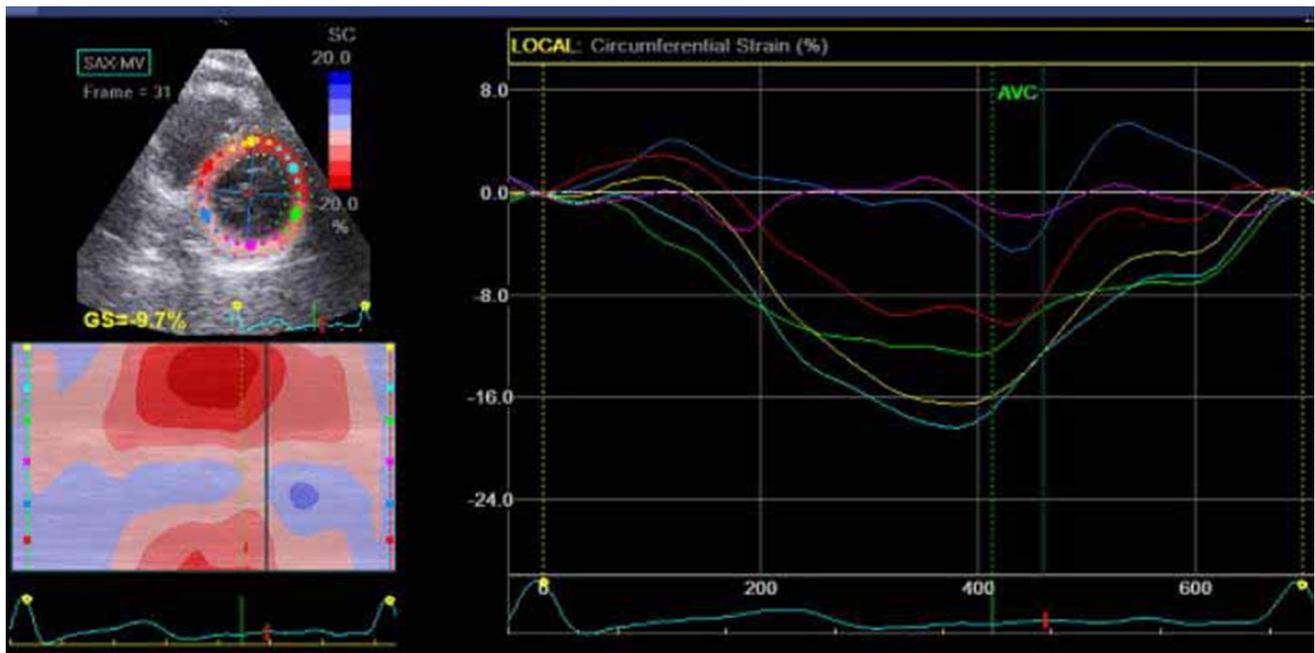
Fig. 3 Global circumferential peak systolic strain in patient developed trastuzumab-related cardiomyopathy

Table 3 Cutoff value for global longitudinal, radial and circumferential peak systolic strain to predict subsequent decrease in EF

Parameters	Cutoff	AUC	Sensitivity	Specificity	Accuracy
GLS (%)	− 18	0.98	92.5	83	90
GRS (%)	35	0.84	85	61	77
GCS (%)	− 17.5	0.65	65	54	57

Table 4 Serial NT-pro BNP levels of patient with and without cardiomyopathy

Biomarker		Cardiomyopathy	Normal	p value
NT-proBNP	Baseline	14.24 ± 0.93	13.93 ± 1.65	0.469
	3 months	14.97 ± 1.57	14.32 ± 1.68	0.489
	6 months	15.06 ± 1.86	14.61 ± 1.66	0.284
	9 months	15.97 ± 1.60	15.10 ± 2.44	0.120
	12 months	17.36 ± 1.81	16.91 ± 1.61	0.673

NT-proBNP N-terminal pro-B-type natriuretic peptide normal levels up to 20 ng/ml
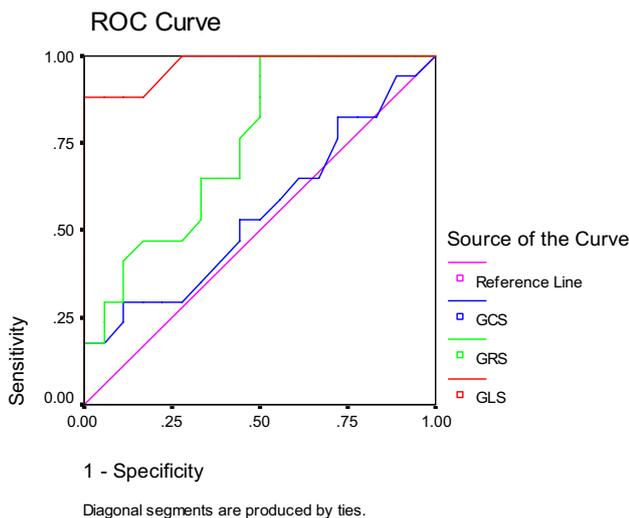

Fig. 4 Receiver operating characteristic curve (ROC) for global longitudinal, radial and circumferential peak systolic strain to predict subsequent decrease in EF

of their cancer therapies and starting cardio protective regimens.

This study provides insight into the use of non-invasive imaging and cardiac biomarkers for early detection of trastuzumab-induced cardiomyopathy. However, the use of EF changes as a marker of cardiotoxicity is subjected to the measurement variability, also failed in the detection of early LV dysfunction, awaiting for the development of heart failure symptoms imply the detection of more advanced disease.

In our study, we found the classic risk factors (hypertensions, diabetes mellitus, age, and smoking) and NT-pro BNP levels are not predictors of trastuzumab cardiotoxicity. The age of the patients was not an important predictive risk factor, this result was not matching to the results of North American prospective randomized clinical studies [16, 17]. On the other hand, there are also studies that could

not confirm its predictive value, among them the HERA study [18]. A lot of studies could not either prove the impact of patients' age in predicting cardiac dysfunction among patients receiving trastuzumab adjuvant treatment [19, 20].

Hypertension was not a risk factor in patients in our study, and this was confirmed in several studies [17, 21]. There are also studies that could not demonstrate its predictive role [22, 23].

Smoking and diabetes were not risk factors in our study this was in accordance with Petrowiski et al. [24] which was also not risk factors in their study.

Our study did not demonstrate any significant difference in the levels of NT-pro BNP during 1 year of trastuzumab treatment in the majority of patients, it could not identify patients at risk for trastuzumab cardiotoxicity.

Many studies aimed to demonstrate the utility of NT-pro BNP level in predicting trastuzumab cardiotoxicity were disappointing [25–27], the results of this study confirm the results of Matos et al. [28] to assess clinical, echocardiographic parameters and level of NT-pro BNP in breast cancer patients receiving adjuvant therapy with trastuzumab at baseline after 4, 8 and 12 months of therapy, found that level of NT-pro BNP was within normal range and was not useful to predict early trastuzumab-related cardiac dysfunction.

Myocardial deformation imaging could identify subclinical dysfunction in a variety of disease, previous studies have evaluated the utility of myocardial deformation parameters in pre-clinical detection of trastuzumab inducing cardiomyopathy [29, 30]. Our results showed that systolic strain parameters allow for early detection of pre-clinical cardiomyopathy before conventional echocardiography parameters (LVEF) in breast cancer patients receiving trastuzumab therapy.

At 3 months after initiation of trastuzumab therapy, strain parameter reduced significantly in patients who developed cardiotoxicity, although LVEF showed no difference between both group, the reduction in both global longitudinal and radial strain predict subsequent cardiotoxicity. These results confirm the results of the previous studies [30, 31], Fallah-Red et al. [32] evaluated 42 breast cancer patients who received trastuzumab in the adjuvant setting, 10 patients developed CM, peak GLS and radial strain decreased as early as 3 months in the trastuzumab-mediated cardiomyopathy group, concluded that both TVI and strain imaging were able to detect pre-clinical systolic dysfunction, before conventional changes in LVEF in patients receiving trastuzumab in the adjuvant setting.

In this study, the longitudinal strain fell significantly at 3 months of therapy and was the more sensitive parameters for early detection of subsequent cardiomyopathy, these finding was concordant with the study of Negishi et al. [33] who study (the incremental value of deformation indices for prediction of trastuzumab—induced cardiotoxicity) in 81 women receiving trastuzumab, concluded that: GLS is an independent early predictor of later reduction in EF in patients at risk for trastuzumab induced cardiotoxicity.

The major risk factors for trastuzumab induced cardiomyopathy are low LVEF at baseline, the presence of cardiovascular risk factors (hypertension, diabetes mellitus, advanced age and smoking) [33] this study demonstrates the use of GLS with these parameters could provide additional information for subsequent reduction in LVEF and after adjusting these clinical parameters, GLS could be an independent predictor of cardiotoxicity in patients treated with trastuzumab.

Conclusion

Myocardial strain imaging is able to predict pre-clinical changes in LV systolic function and GLS is an independent early predictor of subsequent reduction in EF in breast cancer patients treated with trastuzumab.

Study limitation

- The application of absolute strain values derived through ROC curve analysis, to the same patients provides evaluation of sensitivity and specificity values.
- Limited number of breast cancer patients in this study and cardiomyopathy occurs in 29% of them, prospective validation of these cutoff values in a separate multicenter study on large number of patients will be important.

Compliance with ethical standards

Conflict of interest Wafaa S. El-Sherbeny, Nesreen M. Sabry and Radwa M. Sharbay declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethics Committee in the Faculty of Medicine, Tanta University and with Helsinki Declaration of 1964 and later revision.

Informed consent Informed consent was obtained from all patients included in the study.

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