Independent and Incremental Value of Deformation Indices for Prediction of Trastuzumab-Induced Cardiotoxicity

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Background: Assessment of left ventricular systolic function is necessary during trastuzumab-based chemotherapy because of potential cardiotoxicity. Deformation indices have been proposed as an adjunct to clinical risk factors and ejection fraction (EF), but the optimal parameter and optimal cutoffs are undefined. The aim of this study was to determine the best means of early detection of subsequent reduction of EF in patients with breast cancer treated with trastuzumab.

Methods: Eighty-one consecutive women (mean age, 50 ± 11 years) receiving trastuzumab were prospectively studied, 37 of whom received concurrent anthracyclines. Conventional echocardiographic indices (mitral annular systolic [s′] and diastolic [e′] velocities) and myocardial deformation indices (global longitudinal peak systolic strain [GLS], global longitudinal peak systolic strain rate [GLSR-S], and global longitudinal early diastolic strain rate [GLSR-E]) were measured at baseline and at 6 and 12 months. Cardiotoxicity was defined as a >10% decline as a percentage of baseline EF in 12 months.

Results: In the 24 patients (30%) who later developed cardiotoxicity, myocardial deformation indices decreased at 6 months (GLS, $P < .001$; GLSR-S, $P = .009$; GLSR-E, $P = .002$ vs baseline), but e′ was unchanged. The strongest predictor of cardiotoxicity was ΔGLS (area under the curve, 0.84); an 11% reduction (95% confidence interval, 8.3%–14.6%) was the optimal cutoff, with sensitivity of 65% and specificity of 94%. In sequential models, the clinical model ($\chi^2 = 10.2$) was improved by GLSR-S ($\chi^2 = 14.7$, $P = .03$) and even more so by GLSR-E ($\chi^2 = 18.0$, $P = .005$) or GLS ($\chi^2 = 21.3$, $P = .0008$). Discrimination improvement by adding GLS was confirmed by an integrated discrimination improvement of 18.6% (95% confidence interval, 8.6%–28.6%; $P = .0003$). A net 29% of the patients without events were reclassified into lower risk categories, and a net 48% of the patients with events were reclassified into higher risk categories, resulting in a total continuous net reclassification improvement (>0) of 0.77 (95% confidence interval, 0.33–1.22; $P = .036$).

Conclusions: GLS is an independent early predictor of later reductions in EF, incremental to usual predictors in patients at risk for trastuzumab-induced cardiotoxicity. (J Am Soc Echocardiogr 2013;26:493-8.)

Keywords: Strain, Strain rate, Cardiotoxicity, Trastuzumab, Breast cancer

Breast cancer is the most common malignancy in women all over the world[1] and has been the most common malignancy in American women for more than three decades.[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 type 2–positive breast cancers.[3-5] Because of its potential cardiotoxicity, trastuzumab treatment requires careful monitoring of left ventricular (LV) function during treatment.[6] Measurement of LV ejection fraction (EF) is the most common method of monitoring cardiac function during cancer treatment. Cardiotoxicity has been defined as a symptomatic EF reduction of 5% or an asymptomatic 10% reduction to an EF <55%.[7] However, EF is an imperfect parameter for the detection of cardiotoxicity because of its inherent variability: the 95% confidence intervals (CIs) for EF measurement exceed 0.10.[8] Moreover, EF fails to detect early subtle changes, and when reduced, it reflects a marker of advanced myocyte damage accompanied by a poor prognosis.[9,10] Deformation parameters such as strain and strain rate have been useful to detect subclinical myocardial dysfunction,[11-13] but the incremental value to traditional clinical variables and EF is unknown.

Thus, we sought (1) to elucidate the optimal parameter for early recognition of cardiotoxicity and (2) to ascertain whether deformation indices are incremental to clinical risk factors and baseline

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2013.02.008

Abbreviations

AUC = Area under the curve

CI = Confidence interval

EF = Ejection fraction

GLS = Global longitudinal peak systolic strain

GLSR-E = Global longitudinal early diastolic strain rate

GLSR-S = Global longitudinal peak systolic strain rate

LV = Left ventricular

NRI = Net reclassification improvement

EF for detecting further reductions of systolic function in patients with breast cancer treated with trastuzumab.

METHODS

Study Population

We enrolled 93 consecutive women receiving trastuzumab as part of their treatment for breast cancer at Cleveland Clinic (Cleveland, OH), and the University of Queensland (Brisbane, Australia). All patients underwent at least three echocardiographic studies (at baseline and at 6 and 12 months). Because β-blockers may have protective effect on chemotherapy-induced cardiomyopathy, 12 patients taking β-blockers were excluded from the analysis. The final population therefore comprised 81 patients (mean age, 50 $\pm$ 11 years).

The study was approved by the institutional review boards of both institutions, and written informed consent was gathered for studies obtained outside of usual medical care. The authors had full access to and take responsibility for the integrity of the data.

Standard Echocardiography

Patients underwent echocardiography at baseline (before the initiation of trastuzumab) and at 6 and 12 months of therapy. Echocardiography was performed using standard commercial echocardiographic systems (Vivid 7 and E9; GE Medical Systems, Milwaukee, WI). Sector size and depth were adjusted to achieve optimal visualization of all LV myocardium at the highest possible frame rate. Acquisition was obtained at end-expiration. Multiple consecutive cardiac cycles of the three standard apical views were acquired and stored digitally for subsequent analysis. EF was calculated using the biplane method of disks[14] and traced at least twice by an experienced single observer.[8] Cardiotoxicity was defined by an EF reduction of $\geq$10%.

Tissue Doppler–derived indices were measured using the apical four-chamber view. Peak systolic (s′) and early diastolic (e′) mitral annular velocities were calculated by averaging septal and lateral mitral annular velocities.

Measurement of Myocardial Strain and Strain Rate

Three apical views were used to obtain both global longitudinal peak systolic strain (GLS) and global longitudinal peak systolic strain rate (GLSR-S) and global longitudinal early diastolic strain rate (GLSR-E), using standard, commercially available software (EchoPAC PC version 11.0.0; GE Medical Systems).[15,16] The adequacy of tracking was verified manually, and the region of interest was readjusted to achieve optimal tracking. Percentage change (Δ) was calculated between baseline and 6 months. In addition to longitudinal deformation parameters, global circumferential peak systolic strain and global radial peak systolic strain were measured from the parasternal short-axis view at the midpapillary muscle level and used for the evaluation of longitudinal, radial, and circumferential strain.

Reproducibility

Intraobserver and interobserver variability were evaluated in 10 random subjects using intraclass correlation coefficients with their 95% CIs and coefficients of variation with the root-mean-square method.

Statistical Analysis

Continuous data are presented as mean $\pm$ SD and categorical data as percentages. Student's t tests and paired t tests were used to compare continuous variables as appropriate. Chi-square and Fisher's exact tests were applied to compare categorical variables. Receiver operating characteristic curve analyses with 1,000 bootstraps were performed to compare the prediction of significant 12-month reduction in EF and to determine the optimal cutoff values. The best cutoff value was defined as the point with the highest sum of sensitivity and specificity. Logistic regression analysis was used to determine predictors of significant decrease in EF. Variables were put into the model on the basis of previously reported risk factors (age, hypertension, diabetes mellitus, dyslipidemia, smoking, and baseline EF).[5,12,17] A series of nested models was constructed, starting with known clinical risk factors and followed successively by baseline EF, $\Delta e'$, $\Delta s'$, ΔGLS, and ΔGLSR-S. The incremental value was assessed using the likelihood ratio test using model χ^2. Because five comparisons were performed, P values $<.01$ were considered to show a significant increment in the nested models. Reclassification was evaluated using the integrated discrimination improvement and net reclassification improvement (NRI) methods described by Pencina *et al.*[18] The integrated discrimination improvement measured the change in the difference in the mean predicted probabilities of outcomes between subjects (with and without events) after adding GLS to the base model with known clinical risk factors and baseline EF. Because there is no established risk category for cardiotoxicity, category-free NRI (NRI > 0) is reported.[19] Statistical analyses were performed using SPSS version 20.0.0 (SPSS, Inc., Chicago, IL) and MedCalc version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium), and P values $<.05$ were considered statistically significant.

RESULTS

Patient Characteristics

Clinical characteristics are summarized in Table 1. Of the entire population, 37 patients (46%) received anthracycline sequentially with trastuzumab. Twenty-four women (30%) developed cardiotoxicity at 12 months. Baseline cardiac risk factors of both groups were similar. There were no differences in the staging of breast cancer, surgery, radiation, or the use of taxanes among the two groups. The maximal cumulative doses of anthracyclines (doxorubicin, 240 mg/m^2; epirubicin, 600 mg/m^2) were not exceeded in all patients and did not differ between the groups.

The intraobserver intraclass coefficients for GLS, GLSR-S, and GLSR-E, were 0.85 (95% CI, 0.54 to 0.96), 0.91 (95% CI, 0.70 to 0.98), and 0.90 (95% CI, 0.66 to 0.97), respectively. The corresponding interobserver intraclass coefficients were 0.71 (95% CI, 0.23 to 0.92), 0.85 (95% CI, 0.28 to 0.97), and 0.87 (95% CI, 0.56 to 0.97). Intraobserver and interobserver variability for EF were 0.74 (95% CI, 0.02 to 0.94) and 0.36 (95% CI, -1.42 to 0.84). Intraobserver and interobserver absolute (relative) differences of EF were 2 $\pm$ 2% (3 $\pm$ 4%) and 4 $\pm$ 4% (8 $\pm$ 5%).

Table 1 Patient characteristics

Variable	Whole (n = 81)	No cardiotoxicity (n = 57)	Cardiotoxicity (n = 24)	P
Age (y)	50 ± 11	51 ± 12	50 ± 11	.72
Heart rate at baseline echocardiography (beats/min)	75 ± 15	73 ± 14	80 ± 17	.11
Hypertension	17 (21%)	11 (20%)	6 (25%)	.78
Diabetes	6 (7%)	4 (7%)	2 (8%)	.80
Dyslipidemia	13 (16%)	11 (20%)	2 (8%)	.37
Smoking	12 (15%)	7 (11%)	5 (25%)	.52
Stage				.65
Early	37 (45%)	24 (43%)	13 (54%)	
Locally advanced	32 (40%)	24 (42%)	8 (33%)	
Metastatic	12 (15%)	9 (16%)	3 (13%)	
Surgery	72 (89%)	51 (89%)	21 (88%)	.89
Radiation	50 (62%)	37 (66%)	13 (54%)	.51
Anthracycline use	37 (46%)	26 (46%)	11 (46%)	.82
Doxorubicin	25 (31%)	16 (28%)	9 (38%)	
Epirubicin	12 (15%)	10 (17%)	2 (8%)	
Taxane use	74 (91%)	51 (89%)	23 (96%)	.62

Data are expressed as mean ± SD or as number (percentage).

Table 2 Results of echocardiographic variables measured at baseline and after the initiation of chemotherapy

	No cardiotoxicity			Cardiotoxicity		
Variable	Baseline	6 mo	12 mo	Baseline	6 mo	12 mo
EF (%)	62 ± 3.6	60 ± 3.7	60 ± 3.5	64 ± 4.6	58 ± 5.5	55 ± 5.3
GLS (%)	−20.0 ± 2.0	−19.7 ± 2.0	−19.5 ± 2.4	−20.7 ± 2.6	−18.3 ± 2.1	−18.3 ± 2.6
GLSR-S (/sec)	−1.05 ± 0.16	−1.05 ± 0.18	−0.97 ± 0.16	−1.17 ± 0.24	−1.00 ± 0.15	−0.97 ± 0.18
GLSR-E (/sec)	1.32 ± 0.31	1.35 ± 0.32	1.29 ± 0.33	1.36 ± 0.28	1.20 ± 0.27	1.13 ± 0.29
s′ (cm/sec)	8.0 ± 1.9	7.5 ± 2.0	6.8 ± 1.8	9.1 ± 2.1	7.2 ± 1.4	7.1 ± 1.6
e′ (cm/sec)	9.8 ± 3.5	9.6 ± 3.0	8.9 ± 3.3	10.0 ± 3.1	8.7 ± 2.6	8.9 ± 2.8
GCS (%)	−17.0 ± 4.0	−16.4 ± 3.0	−15.7 ± 3.4	−17.8 ± 3.9	−15.9 ± 3.5	−15.7 ± 4.3
GRS (%)	50.0 ± 17.1	47.2 ± 17.3	52.3 ± 17.7	50.9 ± 18.5	41.5 ± 14.9	45.7 ± 16.2

GCS, Global circumferential peak systolic strain; *GRS*, global radial peak systolic strain.
Data are expressed as mean ± SD.

Changes in Echocardiographic Parameters

A summary of serial echocardiographic parameters of both groups is shown in Table 2. Although Δe′ was not significantly different between the groups at 6 months, s′ (P = .04), ΔGLS (P < .001), ΔGLSR-S (P = .009), and ΔGLSR-E (P = .002) were significantly reduced in patients developing cardiotoxicity (Table 3).

Table 3 Percent changes in echocardiographic parameters in 6 months within the groups

	No cardiotoxicity	Cardiotoxicity	P
GLS	0.2 ± 8.6	11.4 ± 9.8	<.001
GLSR-S	−0.2 ± 16.8	12.8 ± 19.4	.009
GLSR-E	5.1 ± 21.2	−11.9 ± 14.5	.002
s′	−5.0 ± 18.9	−17.0 ± 23.9	.04
e′	3.5 ± 37.1	−10.0 ± 28.7	.09
GCS	−1.0 ± 29.7	9.3 ± 27.4	.18
GRS	8.3 ± 48.5	−10.0 ± 39.3	.11

GCS, Global circumferential peak systolic strain; *GRS*, global radial peak systolic strain.

Prediction of Subsequent Decrease in EF

Receiver operating characteristic curve analyses showed that Δs′, ΔGLS, ΔGLSR-S, and ΔGLSR-E at 6 months were all predictors of a >10% decrease in EF at 12 months. Change in e′ (P = .14) was not predictive. ΔGLS was the strongest predictor of EF reduction (area under the curve [AUC], 0.84; P < .001), with an optimal cut point of 11% reduction (95% CI, 8.3%–14.6%) having sensitivity of 65% and specificity of 94%. Similar findings were associated with ΔGLSR-E (AUC, 0.74; P = .001), for which a 3.6% reduction had sensitivity of 82% and specificity of 67% (P = .14 vs ΔGLS). Other myocardial markers were less effective: with ΔGLSR-S (AUC, 0.73; P = .005), a 6.4% reduction had sensitivity of 73% and specificity of 67% (P = .003 vs ΔGLS), and with Δs′ (AUC, 0.70; P = .032), a 3.5% reduction had sensitivity of 86% and specificity of 49% (P = .05 vs ΔGLS) (Figure 1). The absolute value (rather than Δ) of GLS at 6 months was also a significant predictor of subsequent decrease in EF, but its AUC of 0.67 (P = .015) was smaller than that

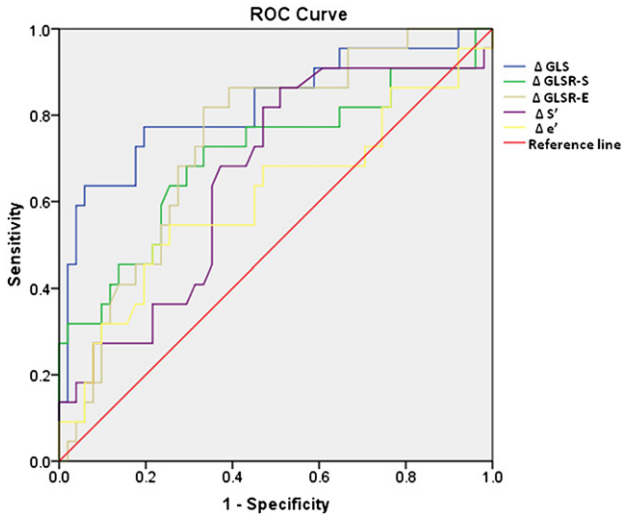

Figure 1 Receiver operating characteristic curves to predict subsequent decrease in EF. Discriminative abilities of the deformation parameters were evaluated to predict a >10% decrease in EF at 12 months.

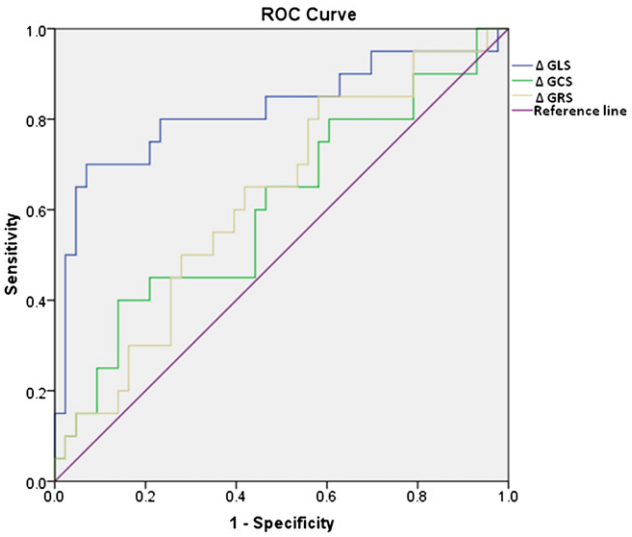

Figure 2 Receiver operating characteristic curves to predict subsequent decrease in EF. Discriminative abilities of the deformation parameters were evaluated to predict a >10% decrease in EF at 12 months. *GCS*, Global circumferential peak systolic strain; *GRS*, global radial peak systolic strain.

of ΔGLS ($P = .08$). The optimal cut point for this parameter (−21%) had sensitivity of 96% and specificity of 66%.

After adjusting for age, hypertension, diabetes mellitus, dyslipidemia, smoking, and baseline EF in a logistic regression analysis, ΔGLS (odds ratio per 0.01-point strain [i.e., 1%] change in GLS, 0.90; 95% CI, 0.84–0.97; $P = .004$) and ΔGLSR-E (odds ratio per 0.01-point strain rate [i.e., 1%] change in GLSR-E, 0.95; 95% CI, 0.92–0.99; $P = .01$) at 6 months were independently predictive of cardiotoxicity.

Among the three different components of LV strain, only GLS ($P < .001$), GLSR-S ($P = .009$), and GLSR-E ($P = .002$) were significantly reduced in the cardiotoxicity group at 6 months compared with the group without cardiotoxicity (Table 3), whereas global circumferential peak systolic strain ($P = .18$) and global radial peak systolic strain ($P = .11$) were not. In addition, changes in longitudinal indices were the best predictors of subsequent decrease in EF (GLS: AUC, 0.84, $P < .001$; global circumferential peak systolic strain: AUC, 0.61, $P = .015$ vs GLS; global radial peak systolic strain: AUC, 0.62, $P = .06$ vs GLS; Figure 2).

Incremental Value of Deformation Indices for Predicting Subsequent Reduction in EF

A model using only clinical variables (age, diabetes mellitus, hypertension, dyslipidemia, and smoking) and baseline EF gave an overall χ^2 value of 10.2 (Figure 3). The addition of either ΔGLSR-E ($\chi^2 = 18.5$, $P = .005$) or ΔGLS (χ^2 21.3, $P = .0008$) improved the power of prediction of cardiotoxicity of the model. Although the C-statistic of the model with only clinical risk scores and baseline EF was 0.74 ($P = .12$), it was improved by adding ΔGLS (C-statistic = 0.80, $P = .003$). Adding GLS reclassified a net 29% of the patients without events into lower risk categories and a net 48% of the patients with events into higher risk categories, resulting in a total continuous NRI (NRI > 0) of 0.77 (95% CI, 0.33–1.22; $P = .036$) and integrated discrimination improvement of 18.6% (95% CI, 8.6–28.6; $P = .0003$).

In a subgroup analysis of patients without either angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, ΔGLS was still the strongest predictor of EF reduction (AUC, 0.80; $P < .001$), and the addition of either ΔGLSR-S ($P = .030$) or ΔGLS ($P = .0008$) improved the power of prediction of cardiotoxicity of the model.

DISCUSSION

The results of this study show that deformation parameters can provide added value to clinical parameters and baseline EF in the prognostication of subsequent reductions of EF in patients undergoing treatment with potentially cardiotoxic agents. In addition, this study shows that longitudinal strain is the most sensitive and robust predictor of early toxicity and subsequent EF decrease during trastuzumab therapy, compared with circumferential or radial strain. This study builds on the previous work by our and other groups in showing that GLS is the optimal marker, that it provides incremental information to that provided by other methods (especially EF), and that it identifies optimal cut points for change.

Cardiotoxicity

Cardiovascular toxicity is one of the most devastating complications of cancer treatment. Heart failure in the setting of anthracycline therapy has a 2-year mortality rate of up to 60%, representing a 3.5-fold greater hazard compared with patients with idiopathic dilated cardiomyopathy.[20] With the availability of cures for many cancers, cardiovascular complications have become the main threat to patients surviving cancer.[21] As a result, earlier and more sensitive methods of identifying patients at risk for future LV dysfunction are of paramount importance, because these patients may benefit from modulation of their cancer therapies and/or intervention with cardioprotective regimens. A crucial goal should be to avoid "the cured cancer patient of today…becoming the heart failure patient of tomorrow."[22]

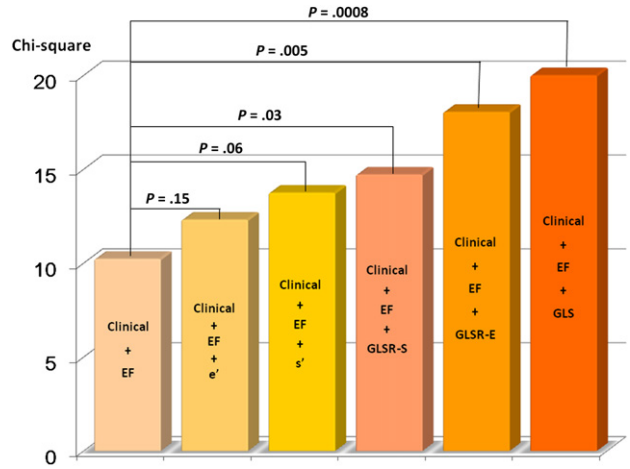

Figure 3 Incremental predictive value of Δe′, Δs′, ΔGLS, ΔGLSR-S, and ΔGLSR-E by nested logistic regression models, presented as global χ^2 values. The addition of ΔGLS, ΔGLSR-S, or ΔGLSR-E resulted in significant incremental improvement in the predictive value on the risk factors (age, hypertension, diabetes mellitus, dyslipidemia, smoking, and baseline EF).

Traditionally, EF has been the parameter used to adjudicate cardiotoxicity. Unfortunately, this is an imperfect marker for the detection of cardiotoxicity, not only because of load dependence and inherent variability[8] but because it fails to detect early subtle changes in LV function.[9,10]

Strain as a Marker of Cardiotoxicity

Myocardial deformation indices have been shown to identify subclinical dysfunction in a variety of diseases. The results of this study confirm previous studies of longitudinal deformation parameters that showed reduction in strain[12,13,23] or strain rate[11] to be the best predictors of subsequent cardiotoxicity. During trastuzumab treatment, all three components of deformation parameters decreased at 6 months, although only longitudinal parameters fell significantly. This suggests not only that longitudinal parameters are more sensitive than the others but also that there is no compensatory increase in circumferential and radial direction. These findings are concordant with the observation that longitudinal LV mechanics are the most vulnerable and most sensitive to the presence of myocardial disease.[24]

In contrast, the usefulness of tissue Doppler–derived s′ is still controversial, with previous studies showing contradictory results.[12,13] One study[13] showed that tissue velocity imaging detected preclinical changes (reduced s′), but the other study[12] showed no difference in s′ between control and anthracycline plus trastuzumab, whereas anthracycline plus trastuzumab had higher s′ (9.7 ± 1.2 cm/sec) than anthracycline alone (8.7 ± 1.3 cm/sec). Similarly, ΔGLSR-E had significant prognostic value, but Δe′ did not, although diastolic parameters are usually very sensitive to early changes in cardiac function in the majority of cardiac diseases.[25-27] This study showed there was no further incremental value of adding either e′ or s′ to the clinical and EF model. These may reflect the intrinsic limitation of angle dependency of tissue velocity imaging, by which speckle strain is unaffected.

The major clinical risk factors for trastuzumab-induced cardiotoxicity are low EF at baseline, preexisting hypertension, advanced age, diabetes mellitus, and smoking.[5,12,17] The present study demonstrates that the use of longitudinal deformation parameters provides additional information to these clinical parameters and baseline EF. After adjusting for these clinical parameters, GLS and GLSR-E were found to be independent predictors of cardiotoxicity in patients treated with trastuzumab. Because GLS is a robust parameter, we would recommend its use for risk stratification and decision making regarding the initiation of cardioprotective therapy.

Study Limitations

The most important limitations of this study were the exclusion of biomarkers. The importance of biomarkers for the detection of preclinical cardiac dysfunction is still controversial in trastuzumab-induced cardiotoxicity,[13,23,28] because cardiac dysfunction appears to arise from impairment of contractility rather than loss of myocytes, and there is no associated release of troponin. This is in contrast with anthracycline-induced cardiomyopathy.[22]

The use of EF change as the marker of cardiotoxicity is subject to the measurement variability of this surrogate end point but is inherent in trying to define a subclinical process. Awaiting the development of heart failure symptoms would imply the detection of a more advanced disease than we need to identify.

Finally, the application of threshold values, derived through receiver operating characteristic curve analysis, to the same patients provides an optimistic evaluation of sensitivity and specificity values. We presented the likely range of the designated cutoffs by application of bootstrapping. The limited number of patients is inherent in the selection process for this study: only about 20% of breast cancers are human epidermal growth factor receptor type 2 positive,[29] and LV dysfunction occurs in 20% to 30% of them.[30] Prospective validation of these cutoff values in a separate study on a multicenter basis will be important. In addition, multiple comparisons in relatively small numbers of patients may lower confidence, and further evaluation in larger numbers of patients will be important.

Clinical Application

GLS may be used as an independent and incremental early predictor of later reduction in EF in patients at risk for trastuzumab-induced cardiotoxicity. In patients with baseline strain measurements, the 95% CIs suggest that reductions of strain of <8% appear not to be meaningful, and those >15% are very likely to be abnormal. In patients without baseline strain measurements, a proposed cutoff of −19%[31] conforms to the CIs around the optimal cutoff of −20.5% in this study, but the AUC for absolute strain values is less, and change in strain appears to be preferable.

ACKNOWLEDGMENTS

We gratefully acknowledge the sonographers at Cleveland Clinic and at Princess Alexandra Hospital, as well as Danielle M. Brennan and Petr Otahal for statistical advice.

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