Echocardiography and cancer therapeutics-related cardiac dysfunction

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Abstract

Cancer therapeutics-related cardiac dysfunction (CTRCD) has become a leading cause of morbidity and mortality for cancer survivors, with the mortality rate for patients with CTRCD reportedly being as high as 60% by 2 years after treatment. Although early detection of subclinical left ventricular (LV) dysfunction is essential for delaying progression to heart failure (HF) in patients with a history of using cardiotoxins, assessment of such dysfunction can be challenging. CTRCD may present initially as asymptomatic LV dysfunction and ultimately as symptomatic HF, which can occur even decades after the discontinuation of the treatment. Once CTRCD has developed, the mortality rate is very high because CTRCD is believed to be refractory to conventional pharmacological therapy and to be associated with a poor prognosis. Thus, there has been a growing interest in early detection of CTRCD by means of global longitudinal strain (GLS) assessed by two-dimensional speckle-tracking echocardiography, because it is a more sensitive and robust parameter for detecting subclinical LV dysfunction than other conventional LV functional parameters such as LV ejection fraction. This article reviews the utility of GLS for early detection of cardiotoxicity in patients during and after cancer chemotherapy, and future perspectives for the management of such patients.

Key words: Echocardiography, Cancer therapeutics-related cardiac dysfunction, Global longitudinal strain

Introduction

Since the first account of anthracycline-induced heart failure (HF) in the 1960s, a number of alternative cancer therapies have been linked to left ventricular (LV) dysfunction, including HER-2 antagonists, anti-angiogenic agents, proteasome inhibitors, and radiation therapy, alone or in combination. Multiple studies have shown that the cardiovascular effect of cancer regimens has a significant impact on the short- and long-term outcomes for cancer patients, with cardiovascular events being the leading cause of morbidity and mortality competing with the underlying cancer [1]. Currently, LV dysfunction caused by cancer chemotherapy is known as cancer therapeutics-related cardiac dysfunction (CTRCD) which has become a leading cause of morbidity and mortality for cancer survivors [2, 3], with the mortality rate for patients with CTRCD reportedly being as high as 60% by 2 years after treatment [4]. Patients without HF symptoms or LV structural abnormalities, but with a history of using cardiotoxins such as doxorubicin (Type I CTRCD) and trastuzumab (Type II CTRCD), are included in Stage A HF [5] because of the irreversible LV myocardial changes due to anticancer drugs, such as myocyte loss, interstitial fibrosis leading to diminished LV contractility, reduced LV wall thickness, and progressive LV dilation. Although early detection of subclinical LV dysfunction is essential for delaying progression to HF in patients with a history of using cardiotoxins, the assessment of such dysfunction can be challenging. While echocardiography plays a pivotal role in the quantification and early detection of LV structural findings, it has been reported that speckle-tracking echocardiographic parameters are also useful for the detection of early LV structural abnormalities. In particular, global longitudinal strain (GLS) assessed by two-dimensional speckle-tracking echocardiography has recently been reported to be a

sensitive marker for early subtle abnormalities in LV myocardial performance (Figure 1), helpful for prediction of outcomes for various cardiac diseases, and superior to conventional echocardiographic indices such as LV ejection fraction (LVEF), mitral inflow E and mitral e' annular velocities ratio (E/e') [6-10]. In addition, there has been a growing interest in early detection of CTRCD by means of GLS, because it is a more sensitive and robust parameter for detecting subclinical LV dysfunction than other conventional LV functional parameters such as LVEF [11-17]. The use of GLS to help detect subclinical LV dysfunction is also endorsed by the 2014 expert consensus for multimodality imaging issued by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) as well as by the American Society of Clinical Oncology (ASCO) guidelines [14, 18].

This article reviews the utility of strain imaging, especially GLS, for early detection of cardiotoxicity in patients during and after cancer chemotherapy, and discusses future perspectives for the management of such patients.

Clinical condition of CTRCD

Advances in cancer treatment have resulted in significant improvement in cancer-specific survival. With prolonged survival, cancer survivors are increasingly subject to late cardiovascular disease related to cancer therapies compounded by the development or progression of age-related cardiovascular risk factors. Consequently, a higher incidence of cardiovascular disease has been observed among subgroups of cancer survivors [19, 20], potentially attenuating the survival gains from advances in oncological treatment. The overarching concept of CTRCD comprises heterogeneous effects that different categories of cancer therapies can exert on the cardiovascular

system, from apoptosis and necrosis of myocardial cells to microvascular and macrovascular effects such as ischemia and promotion of inflammation and fibrosis [21-23]. The revolution in personalized cancer therapeutics, often targeting molecular pathways with essential roles in cardiomyocyte or vascular homeostasis, has greatly increased interest in cardiovascular injury while providing unprecedented insights into cardiovascular biology. Historically, several definitions of CTRCD have been proposed, but the ASE and EACVI consensus statement published in 2014 defined CTRCD as a decline in LVEF of >10% to an absolute value of <53% [14]. This definition largely agrees with recommendation for trastuzumab by the Food and Drug Administration (FDA), with the exception of the updated low-normal LVEF limit of 53%, which was based on the revised standards for echocardiographic chamber quantification [14]. The definition of CTRCD from trastuzumab and anthracycline trials cannot be simply extrapolated to guide evaluation of the cardiovascular toxicity of other cancer therapies, which could be acting through different mechanisms, be administered for different pathological processes or as part of a particular multimodality oncology regimen.

Importance of early detection of CTRCD

CTRCD may present initially as asymptomatic LV dysfunction and ultimately as symptomatic HF, which can occur even decades after the discontinuation of the treatment. Once CTRCD has developed, the mortality rate is really high because CTRCD is believed to be refractory to conventional pharmacological therapy and to be associated with a poor prognosis (Figure 2) [24-26]. On the other hand, Cardinale et al reported that promptly initiation of cardioprotective drugs such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers allows for complete

recovery of LVEF and positively impacts cardiac outcomes for patients with Type I CTRCD. They also showed that complete LVEF recovery was not observed in patients more than 6 months after initiation of cardioprotective drugs. Therefore, early recognition of CTRCD provides an opportunity to mitigate cardiac injury and risk of developing late cardiac events. Echocardiography serves as the basis for the detection and surveillance of CTRCD in patients during and after cancer therapy. LVEF is the most common echocardiographic parameter for LV systolic function, and the usefulness of LVEF for CTRCD detection has been previously reported. However, LVEF is an inaccurate parameter of CTRCD because it is insensitive to early changes in cardiac function during a potentially cardiotoxic treatment. Moreover, it is not an accurate predictor for HF patients who receive anthracycline therapy due to the fact that the heart has ample reserves so that LVEF does not start to deteriorate until the later stages of the disease [25, 27, 28]. Interest has thus been growing in the possibility of measuring a more sensitive and robust non-invasive simple parameter for LV function. In the early stages of the disease or in the case of subclinical LV dysfunction, strain imaging can be of highly effective for diagnostic evaluation and ~~to~~ determination of prognosis. In this respect, the ability of GLS to contribute to the prediction of both subclinical LV dysfunction and cardiovascular outcome for a number of cardiac disorders may be superior to that of LVEF [7, 9]. In fact, some recent investigators have used GLS for the identification of early LV dysfunction after chemotherapy [11-13, 16, 29-35]. Furthermore, the systematic review of 1,504 patients during or after cancer chemotherapy showed that early changes in GLS appear to be the best measure for predicting cardiotoxicity [13]. Specifically, a 10% to 15% early reduction in GLS during

chemotherapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or HF.

GLS reflects LV longitudinal myocardial systolic function, and usually can be assessed by means of two-dimensional speckle-tracking, which is a post-processing computer algorithm that uses routine grayscale digital images [7]. Although several manufacturers have devised a variety of speckle-tracking echocardiographic approaches, the basic approach is similar. Speckle-tracking derived strain information is not dependent on the Doppler angle of incidence, which makes it possible to analyze longitudinal strain. According to the ASE guidelines, GLS is determined as the averaged peak longitudinal strain of 18 LV segments from the three standard apical views, and is often expressed as an absolute value (Fig. 2) [36]. GLS is currently considered ~~as~~ a useful parameter for assessing subclinical LV dysfunction or predicting cardiovascular outcomes for various types of cardiac disease and even for Stage A HF [37] or a general population [6, 38, 39]. Furthermore, the European Society of Cardiology (ESC) position paper currently recommends GLS as a diagnostic tool for the detection of CTRCD. The LV wall is not homogenous and is composed of three layers of fibers, with the endocardial layer often the first to be affected by various diseases. Because this layer is mainly responsible for long-axis contraction which can be assessed as GLS, a reduction in its longitudinal function has been found to be an early and accurate indicator of LV dysfunction with high susceptibility to CTRCD as well as ischemia, fibrosis, and hypertrophy [12-14, 40-43]. Much earlier, Milei et al. used anthracycline-treated rabbits to provide pathological evidence that anthracycline cardiotoxicity generated progressive vacuolization of the myocardial fibers, leading to severe myocytolysis in the LV sub-endocardium and the interventricular septum [42].

Miyoshi et al also reported that global area strain detected by means of three-dimensional speckle-tracking imaging, which can quantify the ratio of endocardial area change when it is coupled with the factors of both endocardial longitudinal and circumferential strain obtained from all LV segments, was the only parameter independently associated with the cumulative anthracycline dose in 55 patients with preserved LVEF after receiving anthracycline chemotherapy [44].

Current clinical implications of GLS for cancer therapy

Interest is currently high in the assessment of GLS during and after chemotherapy in cancer patients who are scheduled to undergo chemotherapy for early detection of subclinical LV dysfunction as a potential means for better management of cancer patients with preserved baseline LVEF (Table 1). Negishi et al demonstrated that a relative decrease of 11% in GLS between baseline and 6 months after treatment with trastuzumab was the strongest predictor of cardiotoxicity with sensitivity of 65%, specificity of 94%, and area under the curve of 0.84 in 81 patients with breast cancer[12]. In another study by this group [11], 159 patients who were initially treated with anthracyclines, trastuzumab or both, were divided into two groups using a cutoff value of a decrease in GLS of 11% 6 months after chemotherapy, and patients whose GLS had decreased by ≥11% were followed up for another 6 months after the initiation of β-blockers. LVEF in patients treated with β-blockers improved after 6 months, but not in patients not treated with β-blockers. As mentioned earlier, the systematic review of the Journal of the American College of Cardiology showed that a 10% to 15% early reduction in GLS during chemotherapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or HF [13]. In addition, the

ASE/EACVI consensus statement used the results of published studies to define a relative percentage decrease in GLS of >15% from baseline as clinically meaningful evidence of subclinical LV dysfunction [14].

Some investigators have reported that baseline (pre-chemotherapy) GLS is useful for predicting CTRCD or adverse cardiovascular events in cancer patients with preserved LVEF without overt HF (Table 2) [45, 46]. Mousavi et al showed that baseline GLS can help predict the occurrence of major adverse cardiac events in various types of cancer patients treated with anthracyclines and with a baseline LVEF of 50-59% [45]. They also showed that GLS≤ 16% was associated with a 4.7-fold increase in major adverse cardiac events compared with GLS>16%. Hatazawa et al recently reported that during a long-term follow-up, baseline GLS was identified as the only independent predictor of Type I CTRCD for patients with malignant lymphoma, and that baseline GLS≤19% was associated with the development of Type I CTRCD and hospitalization for HF [46].

In addition to cumulative dose, hypertension, atrial fibrillation, LV hypertrophy, LV diastolic dysfunction, renal disease, older age, and female gender are considered some of the risk factors for the development of Type I CTRCD in cancer patients without cardiac disease [47-49], and all of them are comorbidities significantly associated with LV longitudinal myocardial dysfunction (i.e. low GLS) but preserved LVEF. In fact, patients with malignant lymphoma and preserved baseline LVEF who underwent anthracycline chemotherapy but with abnormal GLS are more likely than those with normal GLS to have LV hypertrophy, atrial fibrillation, and higher E/e' [46]. Thus, watchful observation during and after chemotherapy or after early preventive strategies with established cardioprotective medications but before chemotherapy, may

be advisable for cancer patients with preserved LVEF who have the aforementioned comorbidities and low baseline GLS.

Future perspectives for the role of GLS for patients who are scheduled to undergo chemotherapy

Prospects for GLS for the early detection of subclinical LV dysfunction appear to be promising in terms of predicting the development of CTRCD and delaying progression to HF for patients with preserved LVEF who are scheduled to undergo chemotherapy. The findings reported in this review article indicate~~s~~ that LV longitudinal myocardial dysfunction identified in terms of low GLS can first be detected in patients with preserved baseline LVEF who are scheduled to undergo chemotherapy. This suggests the importance of GLS assessment for detecting. Silent abnormalities such as subclinical LV dysfunction may lead over time to symptomatic LV dysfunction, but such progression may be positively affected by early treatment. Thus, GLS-guided management of patients with preserved baseline LVEF who are scheduled to undergo chemotherapy may result in prevention of future development of CTRCD and symptomatic HF (Fig. 3).

Issues regarding clinical implications that need to be resolved

Measurement of GLS has certain limitations, the primary cause being variations occurring during post-processing. The most important limitation is that different vendors have reported significantly different measurements of GLS [50, 51]. However, this issue has been minimized since Strain Standardization Taskforce intervention [52]. Furthermore, the difference among vendors in GLS measurements is

at most equivalent to or even smaller than that in LVEF measurements [51], and the reproducibility of GLS measurements was found to be as good as, and in many cases superior to, that of conventional echocardiographic measurements [51].

Ideally, all patients who are scheduled to undergo chemotherapy should undergo echocardiography, which should be repeated on a periodic basis during and after chemotherapy. Since the number of echocardiographic examinations is anticipated to increase, close cooperation between echocardiography laboratory staff, oncologists and cardiologists may be required for better management of such patients.

Conclusion

GLS-guided management for patients with preserved baseline LVEF who are scheduled to undergo chemotherapy may be able to assist in early prediction of the development of CTRCD, and prevent progression to later HF. In addition, it can offer new insights into the management of such patients.

Figure Legends

Figure 1: Example of the assessment of left ventricular (LV) longitudinal systolic myocardial function, known as global longitudinal strain (GLS), by means of two-dimensional speckle-tracking imaging, showing color-coded speckle-tracking images and corresponding longitudinal time-strain curves. GLS is determined as the averaged peak longitudinal strain of 18 segments from the three standard apical views. LV longitudinal strain can be also assessed as a polar plot.

Figure 2: An example case of a patient with abnormally low baseline GLS of 15.1%, with CTRCD occurring 6 months after chemotherapy. In addition, left ventricular function did not improve by administration of cardioprotective drugs such as angiotensin-converting enzyme inhibitor and β-blocker.
GLS= global longitudinal strain, CTRCD= Cancer therapeutics-related cardiac dysfunction, LVEDV=left ventricular end-diastolic volume, LVESV=left ventricular end-systolic volume, LVEF=left ventricular ejection fraction

Figure 3: Algorithm for GLS-guided management of patients with preserved baseline LVEF who are scheduled to undergo chemotherapy

Ethical statements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

Conflict of Interest

The author declares that there is no conflict of interest.

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Table 1
Implications of changes in GLS during chemotherapy for predicting CTRCD

Authors (Ref)	Published Year	Treatment	Cutoff value of GLS	Main Findings
Negishi et al (11)	2014	Anthracycline and/or trastuzumab	Reduction in GLS of 11% by 7 months after chemotherapy	β-blocker effective during 6-month follow-up for patients with ≥11% decrease in GLS by 7 months after chemotherapy
Negishi et al (12)	2013	Trastuzumab	Reduction in GLS of 11% by 6 months after chemotherapy	Reduction in GLS of 11% by 6 months after chemotherapy strongly associated with subsequent decrease in LVEF during 12-months follow-up
Thavendiranathan et al (13)	2014	Various	Early reduction in GLS of 10-15% after chemotherapy	10% to 15% early reduction in GLS during chemotherapy most useful parameter for prediction of cardiotoxicity based on a systematic review
Kang et al. (15)	2014	Anthracycline	Reduction in GLS of 15.9% from baseline by the third cycle of chemotherapy	>15.9% decrease in GLS from baseline to the third cycle of chemotherapy predictive of CTRCD
El-Sherbeny et al. (16)	2019	Anthracycline and trastuzumab	GLS of 18% ~~at~~ 3 months after chemotherapy	GLS of 18% by 3 months after chemotherapy predictive of CTRCD with 92.5% sensitivity and 83% specificity
Mornos et al. (31)	2013	Anthracycline	Reduction in GLS of 2.77% (absolute) and 13% (relative) by 6 weeks after chemotherapy	Reduction in GLS of 2.77% (absolute) and 13% (relative) by 6 weeks after chemotherapy associated with the development of CTRCD
Narayan et al. (32)	2017	Anthracycline and/or trastuzumab	N/A	Changes in GLS associated with decline in LVEF by 1-year follow-up, and LV recovery by 3-year follow-up

Charbonnel et al (33)	2017	Anthracycline	GLS of 17.45% after a cumulative dose of 150 mg/m^2	GLS of 17.45% after a cumulative dose of 150 mg/m^2 appears to be the strongest predictor of subsequent LVEF reduction at 1-year follow-up
Yu et al. (34)	2016	Paclitaxel, trastuzumab, and pertuzumab	N/A	Absence of significant changes in GLS was not associated with the development of CTRCD
Fei et al (35)	2016	Anthracycline and trastuzumab	N/A	GLS at the completion of chemotherapy was associated with the development of CTRCD, and GLS at the time of CTRCD diagnosis with subsequent recovery of LVEF.
Sawaya et al. (41)	2012	Anthracycline and/or trastuzumab	GLS of 19% at the completion of chemotherapy	GLS <19% at the completion of chemotherapy is predictive of CTRCD and the subsequent development of HF
Sawaya et al. (43)	2011	Anthracycline and/or trastuzumab	Reduction in GLS of 10% by 3 months after chemotherapy	Reduction in GLS of 10% by 3 months after chemotherapy is independent predictors of the development of CTRCD by 6 months

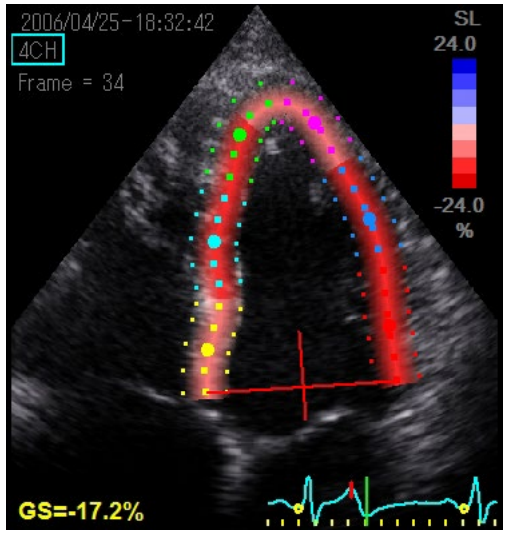
GLS=global longitudinal strain, CTRCD=cancer therapeutics-related cardiac dysfunction, LVH left ventricular hypertrophy, DM diabetes mellitus, LV left ventricular, E/e' mitral inflow E and mitral e' annular velocities ratio, BMI body mass index, LVEF left ventricular ejection fraction,

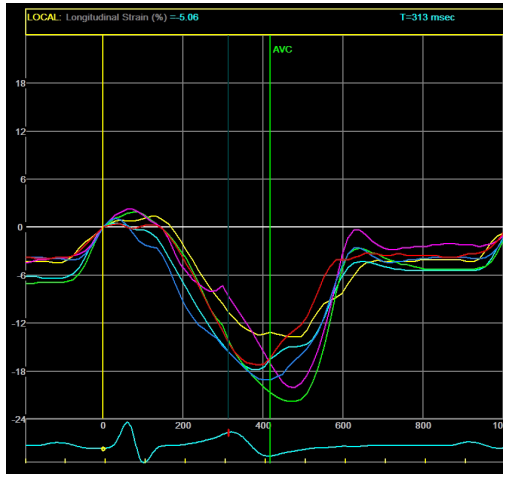
Table 2
Role of baseline GLS for predicting CTRCD

Authors (Ref)	Published Year	Treatment	Cutoff value of GLS	Main Findings
Rhea et al. (40)	2015	Various	N/A	GLS independently associated with mortality and an incremental prognostic value
Mousavi et al. (45)	2015	Anthracycline	16%	Baseline GLS≤ 16% associated with a 4.7-fold increase in major adverse cardiac events compared with baseline GLS>16% in various types of cancer patients treated with anthracyclines with a baseline LVEF of 50-59%
Hatazawa et al (46)	2018	Anthracycline	19%	Baseline GLS independent predictor of Type I CTRCD for patients with malignant lymphoma, and baseline GLS≤19% associated with unfavorable outcome during long-term follow-up

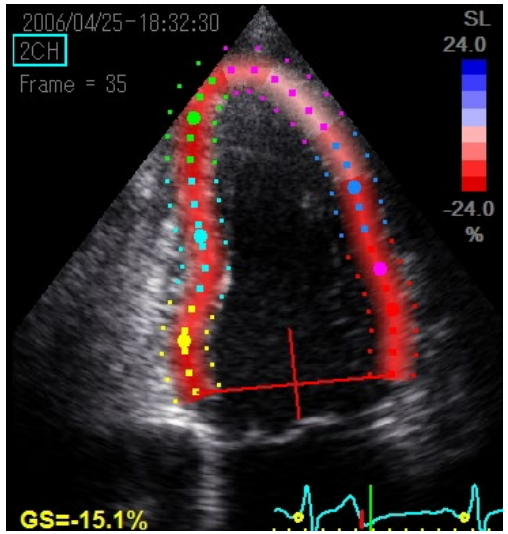
Abbreviations as in Table 1

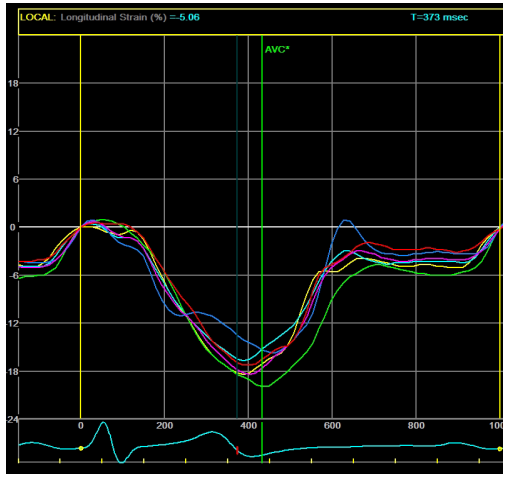
Apical 4-chamber view



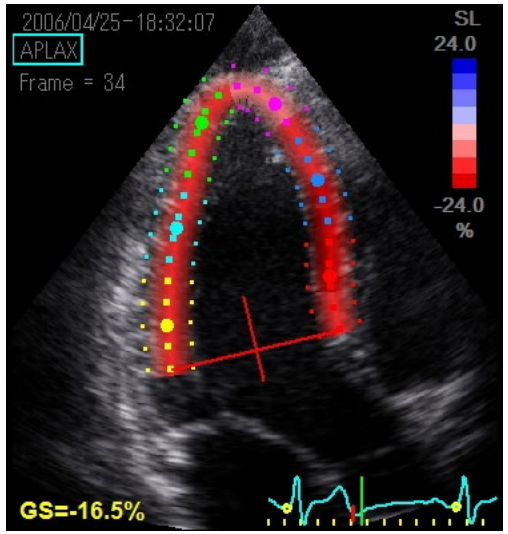


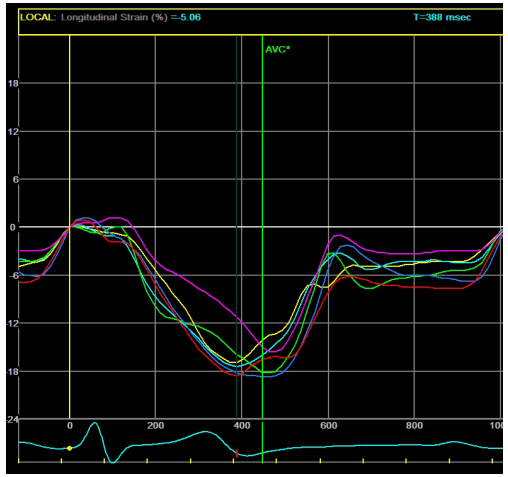
Apical 2-chamber view



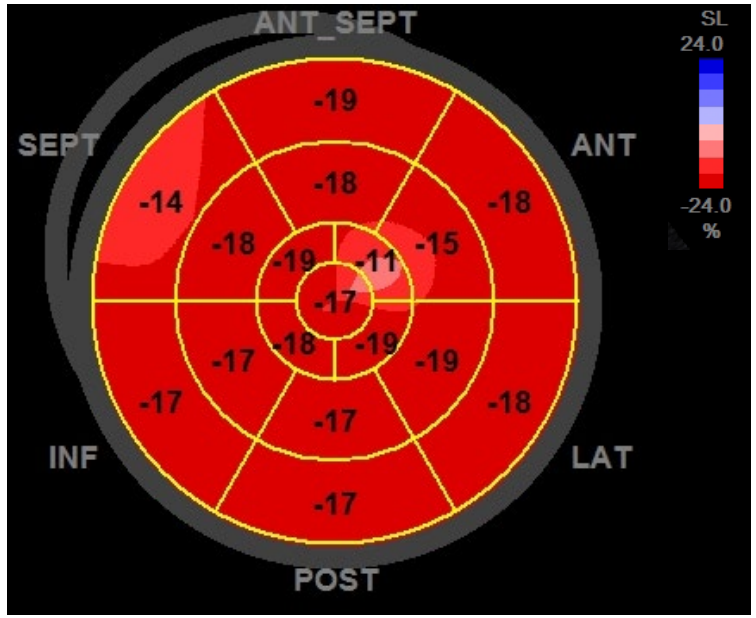


Apical long-axis view



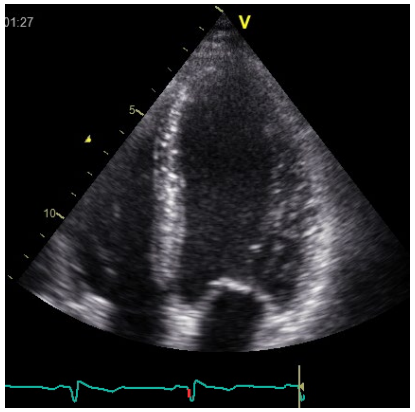


Polar plot of LV longitudinal strain

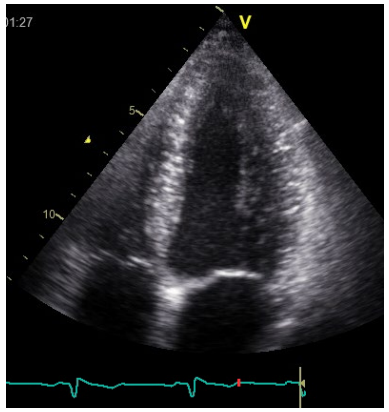


Baseline

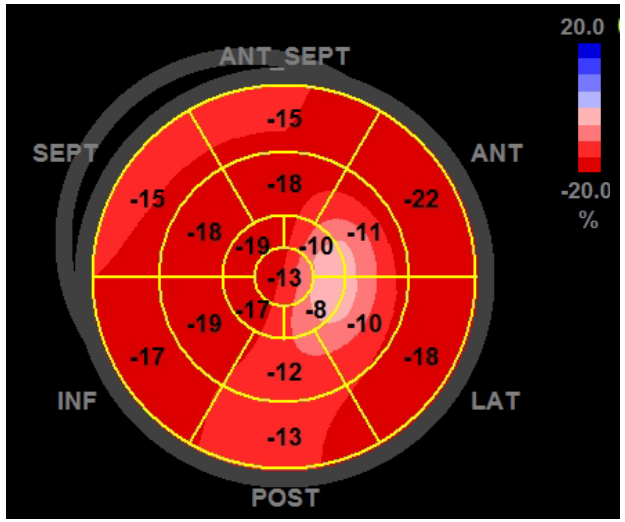
End-diastole



End-systole



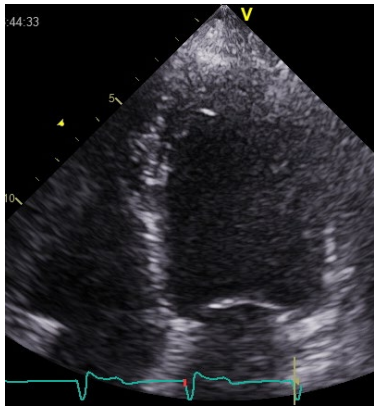
LVEDV: 72mL
LVESV: 28mL
LVEF: 61%



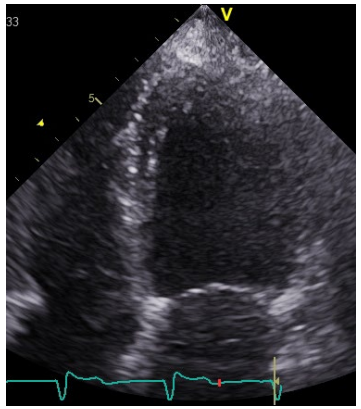
GLS: 15.0%

6 months after chemotherapy

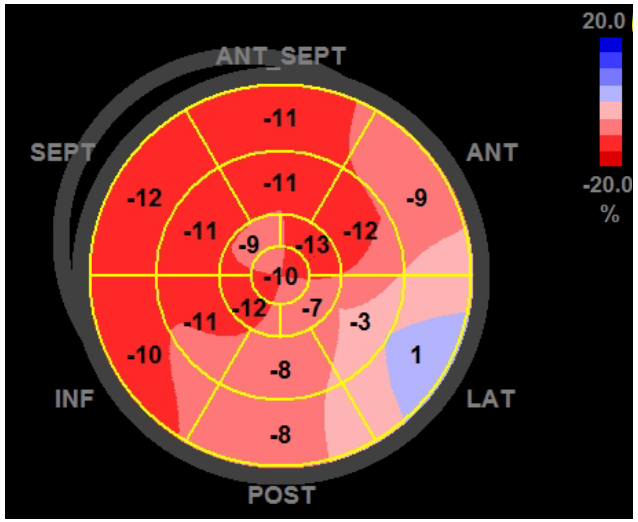
End-diastole



End-systole



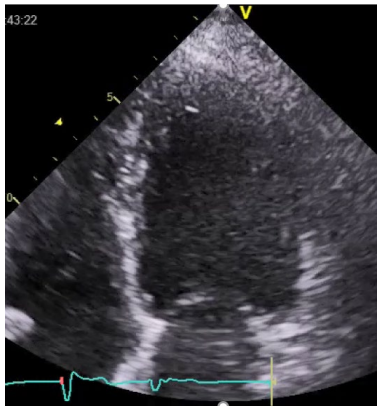
LVEDV: 147mL
LVESV: 103mL
LVEF: 30%



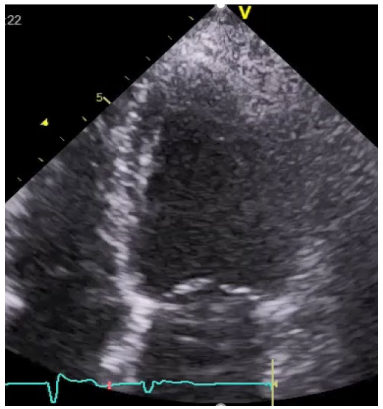
GLS: 9.0%

12 months after chemotherapy
(6 months after receiving cardioprotective therapy)

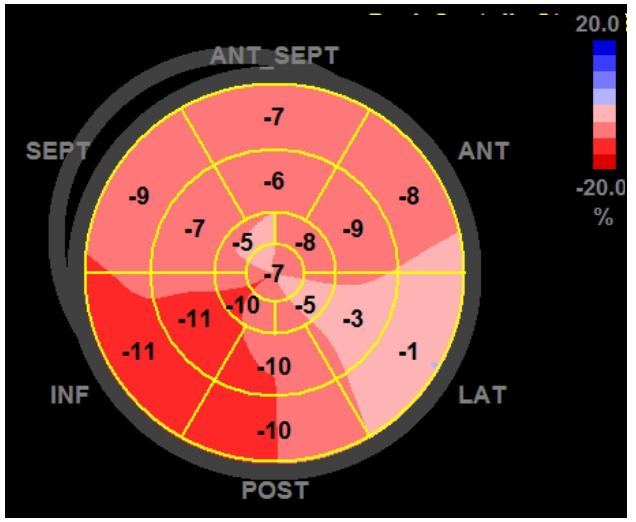
End-diastole



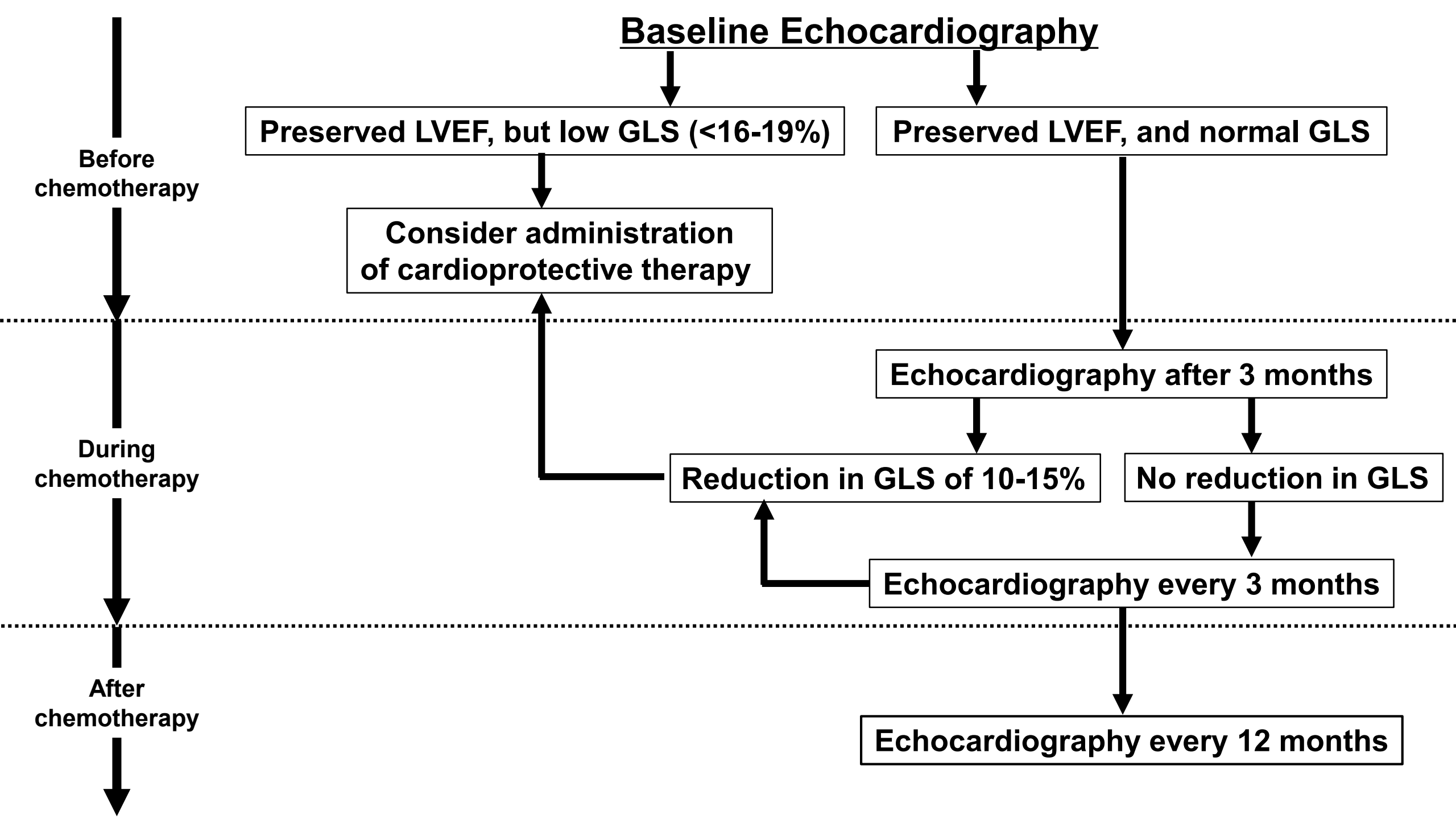
End-systole



LVEDV: 152mL
LVESV: 108mL
LVEF: 29%



GLS: 7.1%


Baseline Echocardiography
Preserved LVEF, but low GLS (<16-19%)
Preserved LVEF, and normal GLS
Before chemotherapy
Consider administration of cardioprotective therapy
Echocardiography after 3 months
During chemotherapy
Reduction in GLS of 10-15%
No reduction in GLS
Echocardiography every 3 months
After chemotherapy
Echocardiography every 12 months