Incremental Prognostic Value of Echocardiographic Strain and Its Association With Mortality in Cancer Patients

Isaac B. Rhea, MD, Sarada Uppuluri, MD, Stephen Sawada, MD, FACC, Bryan P. Schneider, MD, and Harvey Feigenbaum, MD, FACC, *Indianapolis, Indiana*

Background: Left ventricular global longitudinal systolic strain (GLS) has been shown to be superior to ejection fraction in detecting subclinical dysfunction in patients with cancer and predicting mortality in patients with cardiovascular disease. Cancer-related fatigue is common in the later stages of neoplastic malignancies and may be indicative of nonovert heart failure. The aim of this study was to determine whether reduced strain by echocardiography was associated with all-cause mortality in a cancer cohort.

Methods: In this retrospective study, 120 patients with cancer undergoing or scheduled to undergo chemotherapy and with normal ejection fractions (>50%) underwent assessments of GLS. GLS was derived by averaging all speckle-tracking strain segments of the left ventricle.

Results: Over an average follow-up period of 21.6 ± 13.9 months, 57 of 120 patients died. Univariate predictors of all-cause mortality ($P < .10$) were Eastern Cooperative Oncology Group performance status, male sex, hematologic malignancy, β-blocker use, and GLS. Multivariate analysis of all significant univariate variables showed that Eastern Cooperative Oncology Group performance status (hazard ratio, 2.12; 95% confidence interval, 1.54–2.92; $P < .001$), male sex (hazard ratio, 1.93; 95% confidence interval, 1.14–3.27; $P = .014$), and GLS (hazard ratio, 0.89; 95% confidence interval, 0.81–0.97; $P = .012$) were significantly and independently associated with mortality. Stepwise analysis of the multivariate associations showed an increase in the global χ^2 value after adding GLS ($P = .011$) to significant clinical variables.

Conclusions: Eastern Cooperative Oncology Group performance status, male sex, and GLS were significantly associated with all-cause mortality in patients with cancer with normal ejection fractions receiving chemotherapy. Adding GLS to significant clinical variables provided incremental prognostic information. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: Strain, Mortality, Neoplasia, Echocardiography, Speckle-tracking imaging, Prognosis

Left ventricular ejection fraction (EF) has long been considered the standard for assessing cardiac function in most cardiac disorders and in monitoring chemotherapy-induced cardiotoxicity. However, EF rarely declines to a measurable degree from some chemotherapy agents (i.e., anthracyclines) until irreversible damage has been done.[1] Strain echocardiography is an emerging technique that has been shown to be clinically useful because of its ability to detect myocardial dysfunction earlier and with greater sensitivity than EF or wall motion analysis. Left ventricular global longitudinal systolic strain (GLS) has been demonstrated to be a significant predictor of chemotherapy-induced cardiotoxicity in patients with preserved EFs.[2] It has also been demonstrated to be a predictor of multiple outcomes, including all-cause mortality in patient populations with a strong prevalence of cardiac disease.[3-7] This suggests that reduced strain is associated with death due to cardiac disease. However, strain echocardiography has not been investigated for its potential to predict death independently of underlying cardiac disease.

Because cancer-related fatigue (CRF) worsens as cancer progresses, it stands to reason that some factors responsible for CRF may correlate with mortality in patients with cancer.[8] Schünemann *et al.*[9] noted that CRF may be associated with subclinical cardiac dysfunction. Thus, we investigated whether mortality in patients with cancer without excess cardiac disease was associated with reduced cardiac function on strain echocardiography.

We compared the association of strain by speckle-tracking strain echocardiography with mortality against clinical performance status, which is a validated measure of determining prognosis across multiple cancer types.[10-13]

From the Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana (I.B.R., S.S., H.F.); the Division of Cardiology, Community Health Network, Indianapolis, Indiana (S.U.); and the Simon Cancer Center, Indiana University School of Medicine, Indianapolis, Indiana (B.P.S.).

Reprint requests: Isaac B. Rhea, MD, Krannert Institute of Cardiology, Indiana University, Medicine, 1800 N Capitol Avenue, Room E371, Indianapolis, IN 46202 (E-mail: isaac.b.rhea@gmail.com).

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Abbreviations

CRF = Cancer-related fatigue

ECOGPS = Eastern Cooperative Oncology Group performance status

EF = Ejection fraction

GLS = Left ventricular global longitudinal systolic strain

METHODS

Study Population

This study was approved by the Indiana University Institutional Review Board. We queried the echocardiography database (Fuji Synapse 4.0, Indianapolis, IN) for patients with cancer who underwent echocardiography with strain measurements in relation to chemotherapy or bone marrow transplantation. Per laboratory policy, if possible, strain was calculated at the time of echocardiography for all studies ordered either as standard cardiac monitoring for chemotherapy regimens or for workup in symptomatic patients with concern of chemotherapy-related cardiac toxicity. We identified 138 patients from 2009 to 2011 cared for at the Indiana University Simon Cancer Center who had both two-dimensional echocardiographic images and preexisting speckle-tracking polar plots calculated directly on the instrument consoles. We excluded patients with known systolic dysfunction (14 patients with EFs $< 50\%$ and one patient on inotropic therapy) and patients with overall poorly tracking strain studies ($n = 3$). The study population thus comprised 120 retrospectively identified patients with histories of recent or imminent chemotherapy, normal EFs, and previously acquired strain images (Figure 1). Nine patients underwent their studies before ever receiving chemotherapy for their active malignancies.

Clinical Data Methods

The clinical history was obtained via chart review in which the type of malignancy, age at time of last visit or death, sex, β-blocker use, Eastern Cooperative Oncology Group performance status (ECOGPS), and various comorbidities were documented from approximately the time the echocardiographic study was performed. Any past or imminent exposures to anthracyclines were recorded. ECOGPS and Karnofsky performance status are widely validated tools for measuring performance status and are often used to predict mortality for multiple cancer types.[11] ECOGPS was taken from oncology clinic and consult notes. See Table 1 for clinical descriptions of the different ECOGPS grades.

For cases in which only Karnofsky performance status was available, the value was converted to an ECOGPS grade as in equation 1. Four patients without distinct documentation of performance status had notes that heavily implied no functional limitations and were counted as an ECOGPS of 0.

$$\text{Rounddown}\left(5 - \frac{\text{KPS}}{20}\right) = \text{ECOGPS} \tag{1}$$

To determine if cancer was a likely cause of death, all patients who died were analyzed via chart review for the presence of advanced (i.e., potentially rapidly fatal) cancer and for any clinical indications of subsequent cardiotoxicity, defined as an absolute drop in EF of $>10\%$ to a level $<50\%$ at the time of the last echocardiographic study not readily explained by another acute process.

Echocardiographic Acquisition

Two-dimensional echocardiographic measurements were performed using a Vivid 7 or Vivid Q echograph (GE Medical Systems, Milwaukee, WI). The echocardiographic examinations were performed according to American Society of Echocardiography guidelines.[14] The images were recorded digitally and analyzed offline (Fuji Synapse 4.0).

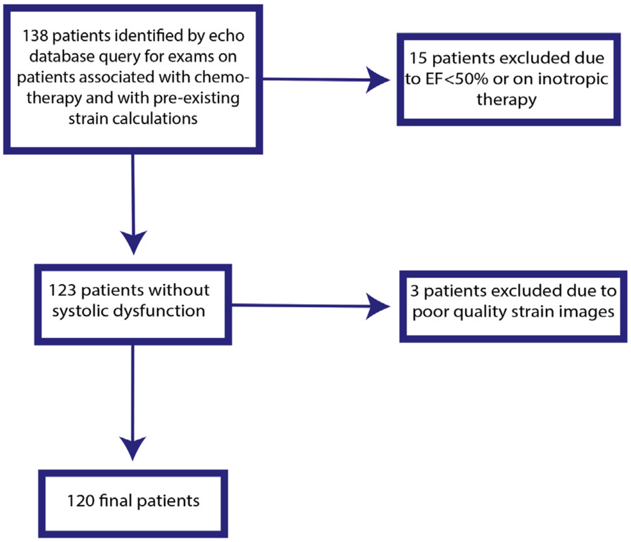

Figure 1 Flowchart detailing patient selection.

Strain Acquisition

The strain measurements were obtained by experienced sonographers using a Vivid 7 or Vivid Q echograph at the same time that the standard two-dimensional echocardiographic examinations were performed. To make the speckle-tracking strain calculations, apical four-, three-, and two-chamber views were stored in a cine loop format. Images were obtained between 50 and 70 frames/sec. The analysis was made at the conclusion of the examinations using a propriety software package on the instrument. The software used requires the operator to identify three points on each view (the two mitral annular attachments to the myocardium and also the apex). The software then automatically determines the strain measurements in the six segments of each view. The calculated peak strain values for the entire myocardium can then be displayed as a 17- or 18-segment polar plot, or "bull's-eye" diagram. The software calculates an average strain value for each view individually then a global average incorporating all three (Figure 2).

GLS measurements were taken directly from the polar plot screen without adjustment. Those echocardiograms in which polar plots could not be constructed and those with grossly poorly tracking data were not considered.

Reproducibility

Because our institution does not have the capability to retrospectively collect strain reproducibility data using the native GE software, we used data we had prospectively collected from a general cohort of patients who underwent echocardiography at roughly the same time as the study patients. Interobserver and intraobserver variability was measured using different cohorts of patients ($n = 36$ for both) with various pathologies and with EFs $> 50\%$. These studies had repeat strain analyses performed by the same sonographer or by a different sonographer for the purposes of determining reproducibility.

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