# Incidence, Predictors, and Impact on Survival of Left Ventricular Systolic Dysfunction and Recovery in Advanced Cancer Patients

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**Although left ventricular (LV) dysfunction occurs not uncommonly in the course of cancer therapy, little is known about its natural history and prognostic impact on patients. To investigate the incidence, predictors, and impact on survival of LV systolic dysfunction and recovery during cancer therapy, we conducted a retrospective cohort observational study over 1 year at the University of Texas MD Anderson Cancer Center. We enrolled patients with a decrease in ejection fraction by echocardiography to <50% while undergoing cancer therapy from January 2009 to December 2009. We collected and analyzed their chart data. Of 7,648 patients with echocardiograms in 2009, 366 (4.8%) had ejection fraction <50% and 104 met study criteria. LV systolic dysfunction was associated with cardiotoxic therapy in 53 patients (51%). Recovery occurred in 57 patients (55%) and was independently predicted by younger age, smaller left atrial volume index, and lower B-type natriuretic peptide. At last follow-up, 69 patients (66%) were dead, and 35 (34%) were alive. There was a 20% advantage in 2-year survival among patients with LV systolic recovery compared with those without (95% confidence interval 4% to 41%, p = 0.02). In this retrospective study, LV systolic dysfunction recovery occurred in over half of the patients, appeared independent of cardiotoxic etiology, and associated with a 20% survival benefit at 2 years. Multivariable predictors of recovery are younger age, a small left atrial volume index, and lower B-type natriuretic peptide.**  **(Am J Cardiol 2014;113:1893−1898)**

In the noncancer population, myocardial recovery has been frequently observed in select cardiomyopathies, such as tachyarrhythmia induced,[1] endocrine,[2] nutritional,[3] viral,[4] catecholamine induced,[5] and in patients with heart failure (HF) treated with mechanical circulatory support.[6] Multiple predictors of myocardial recovery have been identified in noncancer patients with new onset left ventricular (LV) systolic dysfunction, such as LV end-diastolic volume, baseline LV ejection fraction (EF), and systolic blood pressure.[7] In contrast, LV systolic dysfunction in patients with cancer has mostly been studied from the prism of direct cytotoxic effects of cardiotoxic chemotherapy and thus, recovery has been shown to occur less often.[8,9]

Published data suggest that angiotensin-converting enzyme inhibitors (ACEIs) and β blocker therapy and earlier intervention are associated with better chances of LV function recovery,[10] although large-scale validation studies are lacking. The impact on survival of patients who recover from LV systolic dysfunction during cancer therapy has also not been fully studied. Herein, we sought to investigate the incidence, predictors, and impact on survival of recovery from LV systolic dysfunction in patients with cancer during cancer therapy.

## Methods

With Institutional Review Board approval, we retrospectively queried the MD Anderson echocardiography laboratory database and identified sequential patients with echocardiograms performed during the year of 2009 whose EFs were <50%. We then excluded those without previous documentation of EF >50% before initiation of cancer therapy or subsequent follow-up echocardiograms. The date of LV systolic dysfunction diagnosis was defined as that of the first abnormal echocardiogram in our system, subsequent to any imaging modality or documented office note recording a normal EF, which in many cases occurred before 2009. Patients in the cohort were in- or outpatients, age ≥18 years with advanced cancer actively receiving cancer therapy. Patients were considered to have received cardiotoxic therapy if they had been treated with agents known to be associated with a >5% risk of LV dysfunction at currently employed doses (anthracyclines and trastuzumab).[11]

All echocardiograms were reviewed by 2 independent investigators blinded to the sequence and dates of the echocardiograms, who re-measured all parameters according to the published guidelines of the American Society of

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Table 1
Univariable analysis: comparison of clinical characteristics between patients with and without recovery

| Variable | Recovery (n = 57) | No Recovery (n = 47) | Univariable OR for Recovery (95% CI)* | p Value |
|---|---|---|---|---|
| Age (yrs) | 52 (±16) | 58 (±16) | 0.9 (0.9−1.0) | 0.05 |
| Men | 26 (46) | 19 (40) | 1.2 (0.6−2.7) | 0.6 |
| Malignancy | | | | |
| Leukemia/lymphoma | 30 (53) | 21 (45) | 1.4 (0.6−3.0) | 0.4 |
| Other | 27 (47) | 26 (55) | 1 | |
| NYHA class | | | | |
| 0 | 22 (39) | 11 (23) | 1 | 0.4 |
| I | 17 (30) | 16 (34) | 0.5 (0.2−1.4) | 0.4 |
| II | 10 (17) | 10 (21) | 0.5 (0.2−1.6) | |
| III−IV | 8 (14) | 10 (21) | 0.4 (0.1−1.3) | |
| Atrial fibrillation | 18 (32) | 14 (30) | 1.1 (0.5−2.5) | 0.8 |
| Atrial flutter | | | | |
| Current or past | 17 (30) | 12 (26) | 1.2 (0.5−2.9) | 0.7 |
| Unknown | 1 (2) | 2 (4) | — | |
| Sepsis | 18 (32) | 8 (17) | 2.2 (0.9−5.8) | 0.1 |
| Smoker | 17 (30) | 20 (43) | 0.6 (0.3−1.3) | 0.2 |
| Coronary artery disease | 12 (21) | 17 (36) | 0.5 (0.2−1.1) | 0.1 |
| Diabetes mellitus | 6 (11) | 9 (19) | 0.5 (0.2−1.5) | 0.2 |
| Hypertension | 26 (46) | 22 (47) | 1.0 (0.4−2.1) | 0.9 |
| Cardiotoxic chemotherapy | 42 (74) | 39 (83) | 0.6 (0.2−1.5) | 0.3 |
| Anthracyclines | 30 (53) | 23 (49) | 1.2 (0.5−2.5) | 0.7 |
| Trastuzumab | 5 (9) | 2 (4) | 2.2 (0.4−12) | 0.4 |
| Cyclophosphamide | 18 (32) | 18 (38) | 0.7 (0.3−1.7) | 0.5 |
| Chest radiation | 15 (26) | 10 (21) | 1.3 (0.5−3.3) | 0.6 |
| Pulmonary embolism | 11 (20) | 10 (21) | 0.9 (0.3−2.4) | 0.8 |
| Diastolic HF | | | | |
| Grade 1 | 15 (26) | 13 (28) | 1 | |
| Grade 2 | 7 (12) | 9 (19) | 0.7 (0.2−2.3) | 0.9 |
| Grade 3 | 6 (11) | 7 (15) | 0.7 (0.2−2.7) | |
| Grade 4 | 17 (30) | 14 (30) | 1 (0.3−2.9) | |
| HF diagnosis | | | | |
| Chemo-induced | 30 (53) | 23 (49) | 1.2 (0.5−2.7) | 0.9 |
| Other cause | 19 (33) | 17 (36) | 1 | |
| Unknown | 8 (14) | 7 (15) | — | |
| HF at follow-up† | 19 (33) | 31 (66) | 0.3 (0.1−0.6) | 0.001 |
| BNP (pg/ml) | 577 (176−1,653) | 1,332 (307−2,817) | 0.9 (0.9−0.9)‡ | 0.04 |
| Troponin I (ng/dl) | 0.13 (0.03−0.51) | 0.12 (0.04−0.4) | 1.0 (0.9−1.0)§ | 0.8 |
| Creatinine (mg/dl) | 0.8 (0.6−1.1) | 0.9 (0.7−1.2) | 0.6 (0.3−1.4) | 0.3 |
| β blocker | 49 (86) | 38 (81) | 1.5 (0.5−4.1) | 0.5 |
| ACEI/ARB | 34 (60) | 33 (70) | 0.6 (0.3−1.4) | 0.3 |
| Spironolactone | 4 (7) | 16 (34) | 0.1 (0.05−0.5) | 0.001 |
| Statins | 18 (32) | 18 (38) | 0.7 (0.3−1.7) | 0.5 |

Data are presented as n (%), mean ± SD, and median (IQR).
ARB = angiotensin receptor blocker; IQR = interquartile range; NYHA = New York Heart Association; OR = odds ratio.
* Per 1 unit increase of continuous variable.
† Not considered for multivariable analysis as it was measured after baseline.
‡ Per 100 units increase.
§ Per 0.1 unit increase.

Echocardiography.[12−14] We measured LVEF using the biplane method of disks (modified Simpson's). We included those with EF confirmed as <50% and with previous EF >50% by ≥5 percentage points. All subsequent echocardiograms were similarly measured. Any discordance between the readers was resolved by consensus. Recovery was based on the last echocardiogram.

Echocardiographic 2-dimensional parameters including LVEF, left atrial volume index (LAVI), LV hypertrophy, LV end-diastolic dimension and volume, LV mass and LV mass index, and the presence of valvular heart disease were measured according to the published recommendations[14] and documented. Valvular heart disease was subclassified into mild, moderate, or severe whether regurgitant or stenotic lesions were present. Diastolic function was assessed using Doppler and tissue Doppler techniques as published by the American Society of Echocardiography[15] and classified as grade 1 (normal), 2 (impaired relaxation), 3 (pseudonormal), and 4 (restrictive).

LV systolic dysfunction recovery was defined as an increase in EF of ≥10% points from the lowest documented EF and absent if EF did not increase by ≥10% points. We also separately analyzed recovery defined as EF that returned to