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. **© 2014 Elsevier Inc. All rights reserved.** **(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

Table 2
Echocardiographic comparison between patients with and without left ventricular (LV) systolic function recovery

Echocardiographic	EF Recovery		OR*	CI*	p Value
	Yes	No			
Ejection fraction at baseline	34 ± 8.5	33 ± 8.5	1.01	0.97−1.06	0.6
Left atrial volume index (mL/m^2)	27 ± 8.5	33 ± 10	0.93	0.88−0.97	0.001
LV end-diastolic volume (mm^3)	105 ± 34	114.5 ± 39	0.99	0.98−1.00	0.2
LV mass index (g/m^2)	100 ± 28	109 ± 36.5	0.99	0.98−1.00	0.1
LV hypertrophy					
No	35 (71)	30 (77)	1.0		
Mild to moderate	14 (29)	9 (23)	1.3	0.5−3.5	0.6
Pulmonary hypertension					
No	25 (45)	16 (35)	1.0		
Mild	32 (38)	13 (28)	1.0	0.4−2.6	0.2
Moderate-to-severe	10 (18)	17 (37)	0.4	0.1−1.1	

Data are presented as n (%) and mean ± SD.
OR = odds ratio.
* Per 1 unit increase of continuous variable.

Table 3
Multivariable logistic model for left ventricular (LV) recovery

Variable	OR*	CI*	p Value
Age (yrs)	0.95	0.92−0.99	0.01
Cardiotoxic chemotherapy	0.40	0.10−1.30	0.10
Ejection fraction at baseline	0.99	0.92−1.06	0.70
Left atrial volume index	0.94	0.88−0.99	0.04
BNP	0.97	0.94−0.99	0.04
LV end-diastolic dimension at baseline	1.00	0.98−1.01	0.60

OR = odds ratio.
* Per 1 unit increase of continuous variable.

a value ≥50%. We further subclassified recovery into 3 groups: (1) full recovery—defined as EF that increased ≥10% points and was ≥50% at the last echocardiogram; (2) partial recovery—defined as EF that increased by ≥10% points but remained <50%; and (3) no recovery—defined as <10% point increase in EF and EF <50%.

Clinical data were retrospectively collected from the time of diagnosis of LV systolic dysfunction, with special attention to New York Heart Association class and HF symptoms, presence of atrial fibrillation, hemodynamic shock (defined as low blood pressure requiring admission to intensive care unit and specific therapy for hypotension), history of any coronary artery disease, diabetes mellitus, hypertension, and tobacco use. Pulmonary hypertension was defined as mean pulmonary artery pressure >25 mm Hg at rest of >30 mm Hg at exercise. Cancer therapy at time of LV systolic dysfunction was also documented, with specific attention to use of chemotherapy agents and radiation therapy to the chest. Laboratory data were documented when obtained at the time of LV systolic dysfunction, specifically B-type natriuretic peptide (BNP) levels, serum troponin-I levels, and serum creatinine. Additionally, attempts at determination of etiology of HF were also investigated and documented.

HF therapy instituted at the time of LV systolic dysfunction was documented according to the major family of agents, that is ACEIs, β blockers, diuretics, aldosterone receptor antagonist, and so on. Patients were treated according to the published guidelines[16,17] to the extent that hemodynamic status and concomitant cancer therapies permitted. Follow-up was included retrospectively from the date of LV systolic dysfunction diagnosis until November 2011. Date and cause of death were obtained from the medical records. For those alive by November 2011, clinical status was documented.

Categorical variables are expressed as number and percent and continuous variables as mean (SD or median [interquartile range]) when the distribution was not normal. Comparisons between patients with and without recovery were done with the Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Potential predictors of recovery were those available at baseline. Univariable logistic regression analyses were performed to evaluate the association between a patient variable and a recovery. The association was expressed as odds ratio and its 95% confidence interval (CI). Variables with a p ≤0.2 in univariable analysis and some prespecified variables (baseline LVEF, LV end-diastolic dimension, and the use of cardiotoxic chemotherapy) were chosen for multivariable logistic regression analysis, where variables with a p <0.05 were considered independently associated with recovery. Survival was described with the Kaplan-Meier method, and differences between patients with and without recovery were tested with the log-rank test. To evaluate the discriminative ability of LAVI to differentiate between recovery and no recovery, we performed receiver-operating characteristic analysis and quantified the ability with the c-statistic. SAS 9.2 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses.

Results

Throughout 2009, of 7,648 consecutive patients with cancer who underwent echocardiographic evaluation, 366 (4.8%) had EF <50%. Of these, 104 patients had previously documented normal EF and at least 1 subsequent echocardiogram, meeting inclusion criteria. Baseline characteristics are listed in Table 1.

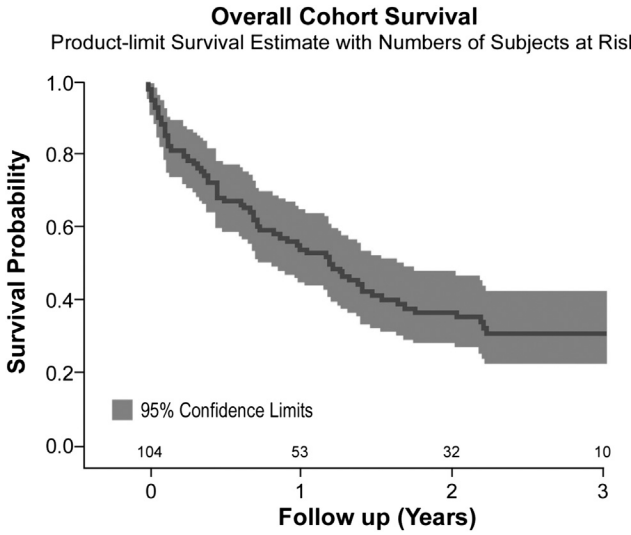

Figure 1. Overall cohort survival: product-limit 3-year survival estimate with number of subjects at risk.

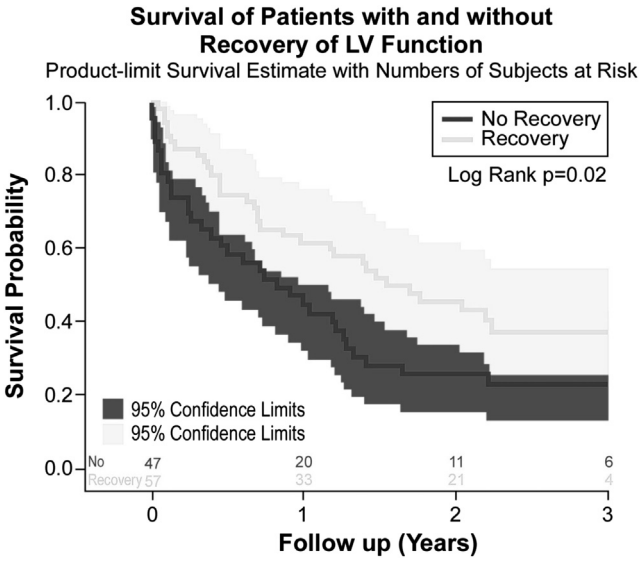

Figure 2. Survival of patients with and without the recovery of LV function: product-limit survival estimate with numbers of subjects at risk demonstrating favorable survival of patients who experience LV function recovery.

The most common malignancies were leukemia (30%), lymphoma (19%), genitourinary cancer (11%), breast (10%), lung (10%), sarcomas (6%), and others (17%). In this cohort, 32% and 68% of patients had stage III and IV cancer, respectively.

Cancer therapy consisted of anthracyclines, 48%; cyclophosphamide, 35%; vascular endothelial growth factor inhibitors, 26%; and trastuzumab, 7%. In this cohort, 25 patients (24%) received radiation therapy to the chest. Cardiotoxic therapy had been prescribed in 60 patients (58%).

The mean documented EF before chemotherapy initiation was 61% ± 9%. Regional wall motion abnormalities were described in 41 patients (40%). Information on diastolic function was available in 91 patients (88%) and was abnormal in 73 patients (80%), with 22 patients (30%) presenting with Grade 4 diastolic dysfunction. Echocardiographic parameters at presentation of LV systolic dysfunction of patients with and without recovery are listed in Table 2.

LV systolic dysfunction was thought to be chemotherapy induced in 53 patients (51%), other causes such as sepsis and arrhythmia in 36 patients (35%), and unknown in 15 patients (14%). Evaluation of coronary artery disease was carried out in 38 patients (35%), none of whom had severe enough coronary artery disease to account for their cardiomyopathy.

At the last echo, LV systolic dysfunction recovery had occurred in 57 patients (55%). The mean EF of those with recovery versus no recovery was 51% ± 0.8% and 31% ± 0.9% ($p < 0.0001$), respectively. In the recovery group, LVEF was >55% in 20 patients (35%), 50% to 54% in 13 patients (23%), 45% to 49% in 15 patients (26%), and 40% to 44% in 9 patients (16%).

Baseline characteristics of recovered versus not were similar (Table 1), except for LAVI that was significantly lower in those who recovered (26 ± 8 vs 33 ± 10 ml/m^2, $p = 0.0002$). HF treatment was administered to 102 patients (98%). Interestingly, there was a significantly higher use of spironolactone in those who did not recover compared with those who did (35% vs 7%, respectively, $p = 0.0004$). Finally, there was no difference in rates of recovery between those with exposure to cardiotoxic therapy and those with other etiologies of LV systolic dysfunction (61% vs 38.5%, respectively, odds ratio 1.4, 95% CI 0.64 to 3.06, $p = 0.39$).

When we analyzed recovery as return of LV function to EF ≥50%, 33 patients (32%) recovered and 71 patients (68%) did not. Further, when stratified into full (EF increase ≥10% points and EF ≥50%), partial (EF increase ≥10% points and EF <50%), and no recovery (EF increase <10% and points and EF <50%), there were 33 (32%), 24 (23%), and 47 (45%) patients, respectively.

We conducted uni- and multivariable analyses to determine baseline predictors of recovery. Results of the univariable analysis are listed in Tables 1 and 2. Multivariable analysis confirmed age, LAVI, and BNP as independent predictors of recovery (Table 3).

A receiver-operating characteristic analysis for LAVI showed an area under the curve of 0.69 (95% CI 0.55 to 0.79) suggesting a modest discriminatory power of LAVI for predicting recovery. Assuming that higher values of LAVI are associated with lower chances of recovery, a LAVI of 30 ml/m^2 was able to discriminate between recovery versus no recovery with a sensitivity of 70% and a specificity of 66%.

The mean follow-up was 1.94 ± 1.6 years; at last follow-up, 69 patients (66%) were dead. Survival of the entire cohort is shown in Figure 1. When stratified by the recovery of LV function, there was significant survival advantage in patients with LV function recovery (Figure 2). At 1, 2, and 3 years, differences in survival between patients with and without recovery were 15%, 20%, and 14% ($p = 0.02$, 95% CI 1% to 41%), respectively. Finally, when we stratified the groups as full recovery (EF increase ≥10% and points and EF ≥50%), partial recovery (EF increase ≥10% and points and EF <50%), and no recovery (EF increase <10% and points and EF <50%), there was a survival advantage to

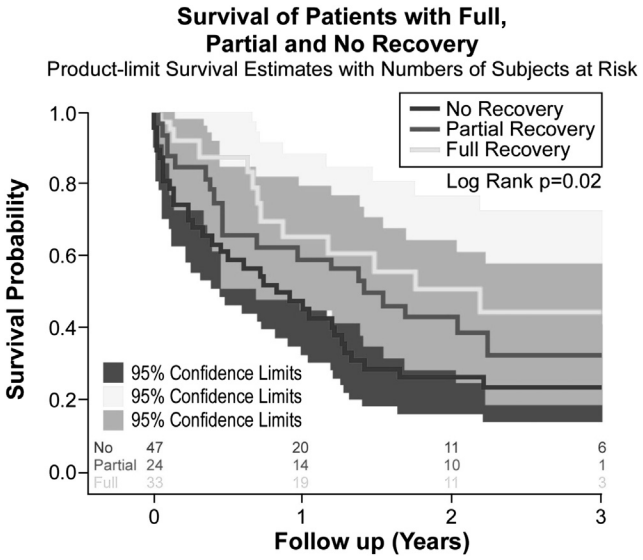

Figure 3. Survival of patients with full, partial, and no recovery of LV function: product-limit survival estimate with numbers at risk, demonstrating favorable survival of patients with full or partial recovery compared with those without recovery of LV function.

those with partial or full recovery compared with those without (Figure 3). Among the 69 patients who died by November 2011, 33 patients (48%) died of cancer progression, 29 patients (42%) died of treatment-related complications, 25 patients (24%) died of sepsis, 4 patients (4%) died of intracranial hemorrhage, 1 patient (1%) died of HF, and 6 patients (9%) unknown.

Discussion

We report herein the largest cohort of patients with cancer who developed LV systolic dysfunction during cancer therapy. We also illustrate the incidence and determinants of recovery from LV systolic dysfunction, and most importantly, its impact on survival. Our main finding is that recovery from LV systolic dysfunction in patients with advanced cancer occurs not infrequently and results in prolonged survival. An interesting finding is that LV systolic dysfunction occurred independently of cardiotoxic therapy in almost a third of patients and did not appear to significantly impact the likelihood of recovery. Importantly, we show that recovery can be predicted by a smaller LAVI, lower BNP, and younger age at presentation.

There are several interesting observations in our cohort that are perhaps distinctively different from previous reports as we approach the problem from the perspective of LV systolic dysfunction detection in a dedicated cancer hospital in which all patients have advanced cancer and are undergoing a wide range of cancer therapies. In this mixed population of patients with stages III and IV cancer, LV systolic dysfunction occurred in $<5\%$ of patients, perhaps in part because of insufficient testing with echocardiography. Most patients presented with asymptomatic LV systolic dysfunction, preserved LV end-diastolic volume, and only a minority with New York Heart Association class IV symptoms.

Importantly, almost half of the patients who developed LV systolic dysfunction had not received therapy considered significantly cardiotoxic, suggesting that half of the patients had other causes for developing LV systolic dysfunction. These patients more likely developed LV systolic dysfunction from acute illnesses, tachycardia, and myocarditis, whether inflammatory, cytokine induced, or viral induced. This finding underscores the need for appropriate etiologic investigation of LV systolic dysfunction and not to automatically assume that LV systolic dysfunction in patients with cancer is caused by chemotherapeutic agents (guilty by association).

Recovery from LV systolic dysfunction occurred in over half of the patients, independent of cardiotoxic drug use. This finding corroborates the notion that etiologically, LV systolic dysfunction in advanced patients with cancer most often resembles that of patients with myocarditis and acute cardiomyopathies,[7,18] where the incidence of myocardial recovery is high. Our rates of recovery are different previous studies that focused on patients who had received cardiotoxic chemotherapy agents (e.g., doxorubicin), where the assumption was that the agent was always responsible for the cardiomyopathy. Although that may be true in some cases, the finding that a subset of patients developed LV systolic dysfunction without receiving cardiotoxic therapy challenges this assumption.

Also, contrary to previous reports,[10] recovery did not appear to be determined by the usage of HF medications, perhaps because of the high percentages of β blocker and ACEIs in both groups. Interestingly, the use of aldosterone antagonists was inversely associated with LV systolic dysfunction recovery. Although the numbers are small, this finding may be explained by that only patients who did not initially respond to ACEIs and β blocker therapy were treated with these agents.

Importantly, we also show that younger age, lower BNP, and smaller LAVI independently predict recovery. A smaller LAVI at the time of LV systolic dysfunction presentation was a strong independent predictor of subsequent recovery among patients with cancer with LV systolic dysfunction. LAVI has been described as an important prognostic marker of cardiovascular disease,[19] but this is the first time it is linked to improvement of LV function in patients with LV systolic dysfunction. It is possible that a larger LAVI at presentation is an early marker for patients who have high filling pressures, who have rapidly progressive remodeling, and who will eventually progress to dilated LV, from which they are less likely to recover. The finding that lower BNP levels were also independently associated with recovery corroborates this hypothesis. Further supporting this argument is that, unlike previously described,[7] LV end-diastolic volume was not a determinant of LV recovery. The reason for this may be that the predominance of diastolic dysfunction from either cardiotoxicity or radiation therapy may have contributed to increased LAVI without LV dilatation. Finally, this may support the anecdotal observation that, unlike in other forms of cardiomyopathy, LV dilatation appears to be a less prominent feature in patients with chemotherapy-induced cardiomyopathy that progress to end-stage HF.[20]

Our patients had very poor survival, reflecting the adverse prognosis associated with stage III or IV cancer,[21] and that mortality was driven by cancer progression and treatment-related complications. Nevertheless, recovery of

LV function was associated with a 20% increase in 2-year survival. It appears, therefore, that despite the severity of their underlying disease, there is clearly an advantage to recovering LV function. It is possible that patients with better LV function were treated more aggressively, or without interruptions, resulting in prolonged progression free and overall survival. Taken together, our findings underscore the need for careful monitoring of LV function in patients with cancer, with early detection and aggressive treatment of LV systolic dysfunction.

Major limitations to this study are selection and referral biases, unavoidable because all patients were recruited from the echocardiography database and were a priori found to have an abnormal EF, presumably because a cardiac abnormality was suspected. Because the timing and doses of chemotherapy are not documented, a definitive temporal correlation with LV systolic dysfunction cannot be made, limiting the ability to establish causal relation in regard to LV systolic dysfunction etiology. Finally, although this is the largest series available for this type of patients, the numbers remain relatively low and therefore prone to type 2 error.

Disclosure

The authors have no conflicts of interest to disclose.

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