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Echocardiography

Prevalence of Abnormal Echocardiographic Findings in Cancer Patients: A Retrospective Evaluation of Echocardiography for Identifying Cardiac Abnormalities in Cancer Patients

Iyad N. Daher, M.D.,* Christopher Kim, M.D.,† Ramy R. Saleh, B.S.,‡ Juan Carlos Plana, M.D.,§ Syed Wamique Yusuf, M.D.,* and Jose Banchs, M.D.*

*Cardiology Department, University of Texas MD Anderson Cancer Center, Houston, Texas; †Cardiology Department, University of Texas Health Sciences, Houston, Texas; ‡American University of Beirut Medical Center, Beirut, Lebanon; and §Section of Cardiovascular Imaging, Cleveland Clinic Foundation, Cleveland, Ohio

Background: Transthoracic echocardiography (TTE) is commonly used to assess cardiac morphology and function in cancer patients. The nature, distribution, and prevalence of significant echocardiographic abnormalities are unknown. We hypothesized that TTEs performed for cancer or cancer treatment indications, have a high prevalence of significant abnormalities (SA), including a large proportion of findings that may be overlooked by other imaging modalities. Methods: All TTE studies performed in a tertiary cancer center over a six-month period, from January to June 2007, were reviewed. The TTEs were divided into studies performed for a cardiovascular indication (CV) and those done for a cancer-related indication (CA). Reports were classified as normal, mildly abnormal, and significantly abnormal (SA) based on findings. Abnormal findings' distributions were compared between indication groups. Results: Three thousand nine hundred and twenty-four TTEs were performed and divided into either group CV (61.2%) or group CA (38.7%). The most common indication in the CV group was valvular diseases (29.9%). In the CA group, the majority of TTE were requested for evaluation during or after chemotherapy or radiation (94.7%). Around 41.9% of studies in group CV were classified as SA whereas 19.9% ($P < 0.001$) in the CA group were classified as such. The relative distributions of individual SA findings were compared between the indication groups and were not statistically different. Conclusions: One in five patients who had TTE studies for CA were found to have SA, and 81.5% of these may not have been found with other modalities. The TTE allows safe diagnosis of a wide range of abnormal findings that may be overlooked if alternative but less versatile modalities are used. (Echocardiography 2011;28:1061-1067)

Key words: echocardiography, cancer

The prevalence of cardiovascular (CV) disease in the cancer population may be higher than in the general population because of shared risk factors, age, and the impact of cancer therapy on CV function. In addition, as many patients survive with cancer for years, they are faced with treatment-related late CV effects, and more established CV diseases. As of January 2007, it is estimated that there are 11.7 million cancer survivors[1], representing approximately 4% of the population. More than 6 million of these cancer survivors are older than 65 years, and many of the potential CV complications are known to develop late (defined as >2 years following treatment completion).

Certain cancer patient subgroups have been found to have an inherently higher risk of CV disease, regardless of cancer treatment. This is thought to be due to shared risk factors, such as smoking, age, obesity, and physical inactivity. Recent estimates suggest that physical inactivity confers a population-attributable risk of breast cancer among white women of 2–15%,[2] in addition to its association with CV disease. Another study attributes a 34% and 63% increased breast cancer risk in overweight and obese patients, respectively.[3] Identification and intervention in these patients at high risk for CV complications may reduce a major cause of mortality.[4]

In some instances, the course of subclinical CV disease may also be shorter in cancer patients.

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Address for correspondence and reprint requests: Jose Banchs, M.D., 1400 Herman P. Pressler, Room 11.5030, Houston, TX 77030-3722. Fax: 713-745-1942; E-mail: jbanchs@mdanderson.org

For example, it has been demonstrated that among patients treated with radiation therapy for Hodgkin's lymphoma (HL), there are statistically higher than expected rates of valve surgery and coronary revascularization procedures starting as early as 5 years and up to 20 years after treatment.[5] CV disease is the second leading cause of death in HL survivors, after second malignancies.[6,7] Overall risk of CV disease in long-term HL survivors is estimated to be three to five times age-adjusted general population rates.[8] Radiation therapy, a mainstay of HL therapy, has been linked to increased age-adjusted rates of CV mortality in survivors with an estimated 13 per 10,000 person-year additional cardiac deaths,[9] and similar findings have been seen in the breast cancer population.[10]

A recent study of chemotherapy use and cardiotoxicity in women with breast cancer found that patients with heart disease before breast cancer diagnosis were more than twice as likely to experience heart disease during follow-up.[11] Women who received chemotherapy had a 20–55% increase in the incidence of CV disease; furthermore, the combination of radiation therapy and chemotherapy was associated with a 33% risk of heart disease.[11] Particular caution has been recommended with patients undergoing therapies that have potential cardiotoxic effects, such as anthracycline chemotherapy or antiangiogenic factors[12,13] or late CV effects, such as radiation to mediastinal structures.[12,14] The growing cancer patient segment of the population, therefore, presents unique CV screening and follow-up needs.

Echocardiography has emerged as a test of choice for the serial evaluation of cardiac disease in cancer patients, whether before treatment or during therapy.[15,16] It provides the comprehensive assessment of important parameters in cancer patients, including the evaluation of left ventricular (LV) systolic and diastolic function, pericardial disease, and detailed evaluation of valvular heart disease.[17] In addition, Doppler techniques can be used to complement hemodynamic assessment and to quantify valvular disease or pulmonary hypertension.[17] Additional techniques, such as 3D imaging and strain analysis show promise in the evaluation of cardiac masses[18] and early chemotherapy-induced cardiomyopathy,[19] respectively.

We hypothesized that transthoracic echocardiograms (TTEs), performed for cancer or cancer treatment indications, have a high prevalence of significant abnormalities (SA), including a large proportion of findings that may be overlooked by other imaging modalities. To test our hypothesis, we retrospectively reviewed the results of TTEs performed in our tertiary cancer center during a six-month period. We determined the nature, distribution, and prevalence of SA and compared the results based on whether the TTEs were performed for cancer-related or CV indications.

Methods:

Selection of Studies:

All TTEs performed in a tertiary cancer center (The University of Texas MD Anderson Cancer Center [MDACC], Houston, TX, USA), over a consecutive 6-month period, (January–June 2007) were initially selected for our retrospective evaluation. *International Statistical Classification of Diseases and Related Health Problems*, 9th edition[20] (ICD-9) codes for which the tests were ordered, related claims were retrieved, and the numbers of studies per specific indication code, over the 6-month period, were computed.

Grouping of Study Indications:

Echocardiograms were further divided into two groups, based on their clinical indications. Studies in the CV group included TTE requested for cardiac disease (i.e., suspected structural or functional cardiac disease, known cardiac diagnosis or symptom) whereas those in the CA group included indications based on cancer or its therapies (such as screening before or during treatment and individual cancer diagnoses).

Classification of Study Findings:

Echocardiogram reports from our study group were then individually reviewed and classified according to their findings into normal (N), mildly abnormal (MA), and significantly abnormal (SA). An SA was defined as a finding that would require further evaluation and/or therapy, including consultation with a cardiologist or additional cardiac imaging, regardless of whether such evaluation or therapy was pursued. An MA was defined as a finding outside the normal range, but not requiring added investigation or treatment. This classification was reached using a modified Delphi method: an initial draft was independently reviewed by five expert cardiologists (physicians with special training in echocardiography or more than 5 years of clinical academic practice including echocardiogram interpretation). Individual feedback was integrated and a new draft was generated. After a second round of feedback, the final classification system was unanimously approved (Table I).

Normal studies (N) were defined as reports where no abnormal findings (SA or MA) were present. The presence of an MA or SA finding assigned the study to the respective category. When a study had both SA and MA findings, it was

TABLE I

Echocardiographic Findings Classification

Individual Echocardiographic Findings	Overall Result Classification		
	Normal (All are Needed):	Mildly Abnormal (Presence of Any):	Significantly Abnormal (Presence of Any):
Chamber size and function	All measured parameters within normal limits	Mild chamber dilation Mild LV/RV hypertrophy LVEF between 40% and 50% Impaired/reduced relaxation (grade I) Mildly reduced RV function Mildly increased RVSP (30–40 mmHg) or mild pulmonary hypertension	Moderate or severe chamber dilation Moderate or severe LV/RV hypertrophy LV aneurysm LVEF $<$ 40% or EF drop $\geq$10% Any RWMA Pseudonormalization or restrictive filling pattern (grade II–IV) Any LVOT gradient (with or without SAM) Moderately or severely reduced RV function Moderately/severely increased RVSP ($>$40 mmHg) or moderate/severe pulmonary hypertension
Valve morphology and function	No or trace valve regurgitation only	Mild valve regurgitation and/or stenosis Any degree of valve sclerosis without stenosis Thickened valve without prolapse Prosthetic valve with normal function and normal or mildly elevated gradients	Moderate or severe valve regurgitation and/or stenosis Definite valve prolapse, ruptured chordae or flail leaflet Prosthetic valve with abnormal function/motion and/or moderately/severely elevated gradients Evidence of vegetations
Pericardium	No effusion or thickening	Minimal or small pericardial effusion	Moderate or large pericardial effusion, with or without tamponade Pericardial thickening
Miscellaneous	Normal variants (such as prominent crista terminalis, eustachian valve or Chiari network)	Mild great vessel dilation Lipomatous interatrial septum Aneurysmal interatrial septum	Any cardiac mass or thrombi Extracardiac masses adjoining/invading heart or great vessels Any congenital heart disease

EF = ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; RV = right ventricle; RVSP = estimated right ventricular systolic pressure; RWMA = regional wall motion abnormality; SAM = systolic anterior motion. Miscellaneous findings noted, but not used for classification, included presence of pleural effusions, catheters/pacemakers, and liver masses/cysts. Mild to moderate rating counted as moderate.

classified overall as SA. For all SA-classified studies, individual SA findings were collected.

Statistical Analysis:
Descriptive statistical analysis was performed for individual indication codes and for groups CV and CA. The proportion of reports in each category (N, MA, and SA) was computed for each group and compared using chi-square analysis. The relative distribution of SA findings (there could be more than one SA finding per SA-classified study) was compared using chi-square when all assumptions were met and Fisher's exact test, otherwise. A P-value less than 0.05 was defined as significant. Statistical analysis was performed using NCSS® 2000 software (NCSS, Kaysville, UT, USA).

Results:
A total of 3,924 TTE were performed from January 1, 2007 to June 30, 2007 at MDACC. Of these, 3,280 studies were initial studies (84%), and 644 were repeat exams. Based on the ICD-9 codes, TTE were divided into either group CV (CV indications), and included 2,405 out of 3,924 (61.2%), or into group CA (cancer-based indications), and included 1,519 out of 3,924 (38.7%), as shown in Table II.

TABLE II

Grouping of Studies by Indications

Study Indication Group % of Total Studies (N)	ICD-9 Code/Category	% of Studies (N)
Cardiac indications (group CV) 61.3 (2,405)	Valvular disease*	28.9 (696)
	Cardiomyopathy/heart failure	15.2 (366)
	Arrhythmia†/abnormal ECG	15.9 (363)
	Respiratory symptoms or disease	12.7 (305)
	Coronary artery disease	9.9 (239)
	Pericardial disease	8.1 (195)
	Right heart dysfunction/pulmonary hypertension	2.6 (62)
	Hypertension	2.1 (50)
	Syncope/dizziness	1.9 (47)
	Cerebrovascular disease	1.1 (27)
	Miscellaneous CV	2.3 (55)
Cancer indications (group CA) 38.7 (1,519)	Meds/screen	94.7 (1, 438)
	Radiation	1.2 (18)
	Amyloid	1.2 (18)
	Cardiac mass	1.2 (17)
	Miscellaneous CA	1.8 (28)

CV = cardiovascular; NEC = not elsewhere classified; NOS = not otherwise specified. Numbers expressed in percentage of the 4,594 studies with an ICD-9 code representing more than 1% of total studies performed. Total may be slightly different from 100% due to number rounding.
*Includes tricuspid valve disease (code 397) with 2.9%, mitral valve disorder (code 424) with 12.5%, aortic valve disorder (code 424.1) with 5.9% and tricuspid valve disorder (code 424.2) with 9.3%.
†Includes atrial fibrillation (code 427.31) with 3.5% and paroxysmal atrial tachycardia (427) with 4.4%.

The most common indication in the CV group was valvular diseases (29.9%) followed by cardiomyopathy and heart failure (15.2%), and abnormal ECG and arrhythmias, (15.1%) as seen in Table II. Coronary artery diseases only represented 9.9% of all echocardiograms requested for CV reasons. In the CA group, the vast majority of TTE were requested for evaluation during or after chemotherapy or radiation (94.7%).

The TTE findings were subsequently classified as previously discussed in Table I. In the CV group, 41.9% of studies were classified as SA; in the CA group, 19.9% ($P < 0.001$) of studies were classified as such (Table III). For each type of SA finding, a significantly higher number was detected in the CV group than in the CA group; however, the CA group had a surprising number of SA findings (Table IV). The relative distributions of individual SA findings were comparable (Figs. 1 and 2).

Discussion:

As expected, the CV group had a high proportion of SA findings (41.9%). However, the prevalence of such findings in the CA group was surprisingly high, with 1 of 5 studies showing an SA. Furthermore, 81.5% of the SA findings in the CA group might have been missed in screening with modalities other than TTE. About one-third of the studies were performed for indications related to cancer treatment (CA group), rather than known heart disease. In other settings, rates as high as 32% for important new findings and 22% for unexpected findings have been reported in a smaller study of 288 TTEs.[21]

In addition, the relative distributions of abnormal findings were identical between the two groups. Of the SA findings, more than one-third were valvular dysfunction, one-fifth to one-third LV systolic dysfunction, and about 11–17% showed significant LV diastolic dysfunction. Furthermore, approximately 8–14% showed a cardiac mass or thrombus and another 5–10% had a moderate-to-large pericardial effusion or pericardial thickening. Right heart dysfunction or pulmonary hypertension was noted in 19–32% of studies.

The heterogeneity of SA findings underscores the utility of echocardiograms in the cancer population. Multiple gated acquisition (MUGA) scans have been used to evaluate LV systolic function with the chief advantages being reproducibility and low interrater variability.[22] In our center, up to half the patients receiving anthracycline-containing chemotherapy are evaluated by MUGA instead of TTE. The MUGA, however, involves the use of radioactive isotopes and exposes patients to radiation, a significant concern if repeated interval imaging is required. On the other hand, not only do TTEs perform similarly for the evaluation of LV ejection fraction,[23] they also provide additional qualitative

TABLE III

Echocardiogram Findings Classification by Indication Groups

Echocardiogram Classification	Study Indication Group		P-Value for Difference (chi-square)
	CV (n = 2,405)	CA (n = 1,519)	
Normal % (n)	18.3 (441)	38.8 (590)	<0.0001 (284.4)
Mildly abnormal % (n)	39.8 (957)	41.3 (627)	
Significantly abnormal % (n)	41.9 (1,007)	19.9 (302)	

CV = cardiovascular indication for transthoracic echocardiogram; CA = indication related to cancer or its treatment, in absence of known cardiovascular indication.

and quantitative information, and are more convenient and available for serial evaluation.[24] Recently, cardiac magnetic resonance imaging (CMR) has emerged as a powerful diagnostic modality capable of providing a comprehensive diagnosis. Although CMR may be as useful as TTE in some patients at selected centers, its availability remains limited and its cost is high; it may also not be as seamlessly integrated in the flow of care as TTE.

In our study population, if MUGA scans had solely been used in place of a TTE to screen patients with no known prior cardiac disease (group CA), potentially 81.5% of the SA findings could have been missed, as they were not related to LV systolic dysfunction. In the cancer population, such findings may directly affect disease staging, treatment, and in many cases, outcomes.

Chemotherapy-induced cardiomyopathy is a well-documented complication of several cancer treatments.[12] Assessment of LV systolic function is helpful in selecting initial treatment and in deciding whether it needs to be stopped due to developing cardiomyopathy. In fact, for many patients with cancer, a "normal" TTE is not an end; rather it is the beginning of their cancer treatment. Furthermore, our experience with anthracycline cardiotoxicity has shown that early detection and treatment of cardiotoxicity could significantly reduce the development of clinical manifestations. The LV diastolic dysfunction is important as well, as it may precede LV systolic dysfunction as the earliest sign of cardiomyopathy.[24]

Serial echocardiographic monitoring for early detection of cancer treatment-related toxicity has been recommended by various authors[12,25] and endorsed as an appropriate testing indication;[16] this is particularly relevant as cancer patients as a group display well-known difficulties with accurate noncancer symptom reporting.[26–29] Specifically, prospective studies of LV dysfunction during chemotherapy have found asymptomatic cardiomyopathy in 10–50% of patients receiving anthracycline-based therapy,[30] and similar high rates were seen with trastuzumab,[31] another well-known cardiotoxic chemotherapy agent.[4] It is noteworthy that only 10% of TTEs in our study were performed because of cardiac symptoms.

Our specific patient subset has specific CV diagnostic and screening needs, for which TTEs are ideally suited. In our practice, we have used follow-up intervals for TTE of 4–8 weeks during cardiotoxic chemotherapy or mediastinal radiation, and yearly thereafter, with nuances for higher risk patients or therapies.

TABLE IV

Significant Echocardiographic Abnormalities by Study Indication Group

Significant Findings*	Study Indication Group		P-Value (chi-square)
	CV	CA	
Valvular dysfunction	44.6% (449)	34.1% (103)	0.001
Chamber or vessel size	32.2% (324)	23.8% (72)	0.006
Right heart dysfunction or pulmonary hypertension	31.7% (319)	18.9% (57)	<0.001
LV systolic dysfunction	30.6% (308)	19.5% (59)	<0.001
LV diastolic dysfunction	10.9% (110)	17.2% (52)	0.004
Pericardial thickening or effusion	10.3% (104)	5.0% (15)	0.004
Intracardiac mass or thrombus	8.0% (81)	13.9% (42)	0.002
Congenital heart disease	0.6% (6)	2.6% (8)	0.006†

CA = TTE performed for cancer or cancer treatment; CV = TTE performed for cardiovascular disease or symptoms.
*Individual studies may have more than one significant finding.
†Given empty cell, chi-square could not be used, Fisher's exact test is used instead.

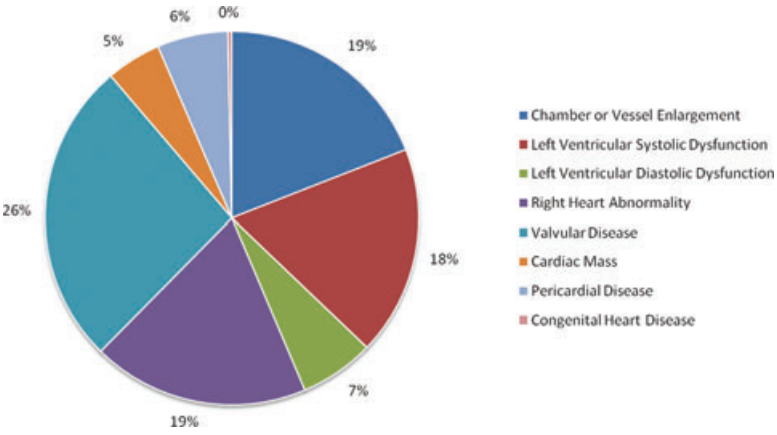

Figure 1. Relative distribution of significantly abnormal echocardiographic findings in the cardiovascular indication group.

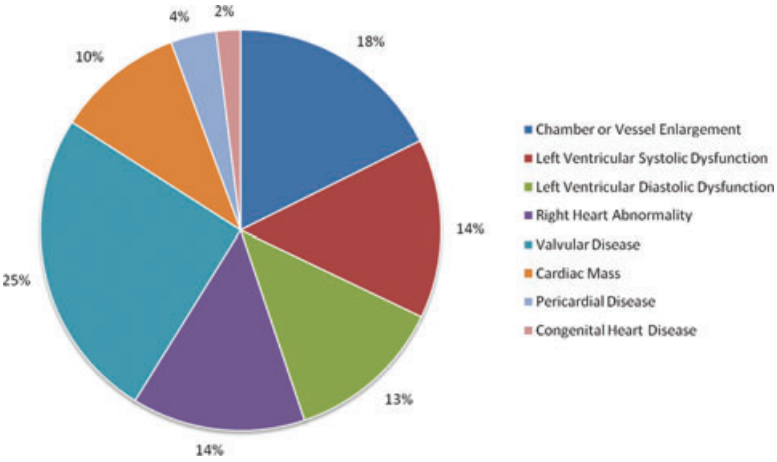

Figure 2. Relative distribution of significantly abnormal echocardiographic findings in the cancer indication group.

Our study included patients from a single tertiary cancer center, and our specific findings may not extrapolate to the general patient population. However, we feel that our echocardiogram report classification system could prove useful in other settings. Although ICD-9 codes may not always be specific to assess the ordering clinician's intention and the patient's clinical status, it is the best such data source. It is worth noting that in our center, these codes are entered only by the ordering clinicians, and not by clerical staff. The focus of our study did not include clinical outcomes beyond test results. We hope that this study will serve as the basis of a future prospective trial, assessing downstream clinical outcomes and comparing imaging modalities directly. To our knowledge, however, it is the largest study describing echocardiographic findings in a cancer population, and as such provides a unique perspective.

Transthoracic echocardiography is an essential modality for evaluation of cardiac structure and function in cancer patients. It allows clinicians to safely diagnose a wide range of abnormal findings, including in patients with no known preexisting heart disease. Many important findings demonstrated by echocardiography may be overlooked if alternative but less versatile modalities are used.

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