Survivorship: Managing Cardiac Toxicities

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Faculty Biography

Anecita Fadol, PhD, RN, FNP-BC, FAANP is Assistant Professor, Department of Nursing; Assistant Professor, Department of Cardiology at The University of Texas MD Anderson Cancer Center; and Adjunct Associate Professor at The University of Texas School of Nursing in Houston, Texas.

Dr. Fadol received her various nursing degrees in the Philippines and from The University of Texas School of Nursing. She received her PhD in Nursing from Texas Woman's University in Houston, Texas.

Dr. Fadol has won dozens of nursing awards, most recently the 2015 James and Suzanne Cyrus Award for Outstanding Clinical Research and the 2015 Excellence in Patient Education Award from the American Association of Heart Failure Nurses.

Dr. Fadol is the author or co-author of several journal articles, abstracts, and book chapters, as well as editor of the Cardiac Complications of Cancer Therapy, a book published by Oncology Nursing Society. She has also written several teaching manuals. Dr. Fadol serves as a reviewer or editor for numerous editorial boards, including the Journal of the Advanced Practitioner in Oncology and The American Academy of Nurse Practitioners. She is active in dozens of professional societies.

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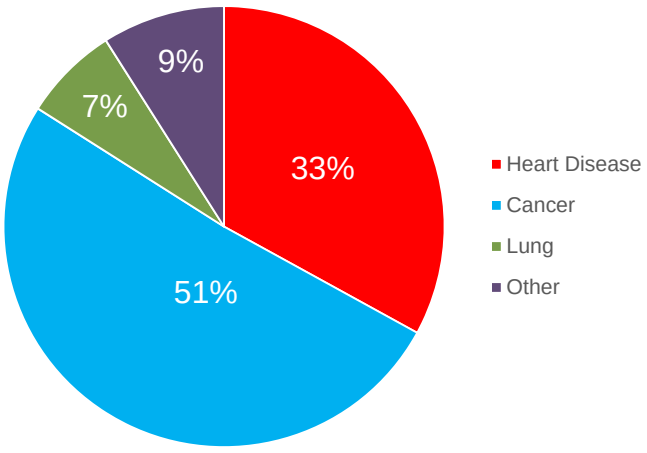
Background

- Approximately 14.5 million cancer survivors are alive in the US today and projected to increase to almost 19 million by 2024[1]
- 67% of adults diagnosed with cancer today will be alive in 5 years
- 75% of children diagnosed with cancer today will be alive in 10 years
- Heart disease is the second most common cause of death among cancer survivors
- Cancer treatments (chemotherapy and radiation therapy) can lead to short term and long-term cardiovascular complications

[1]American Cancer Society. Cancer Treatment and Survivorship Facts & Figures 2014-2015.ACS 2014
Vejpongsa & Yeh 2014, Journal of the American College of Cardiology. 64 (9). 938-945

Causes of Death in Cancer Survivors



NHANES survey. Presented in AACR March 2012

Cardiotoxicity Landscape

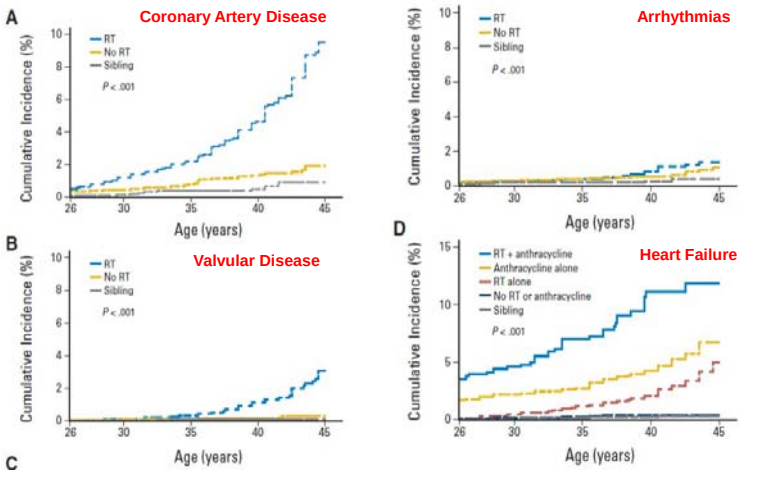
Radiation

- **Asymptomatic**
  - Pericarditis
  - Cardiomyopathy
  - Valvular
  - CAD
  - Arrhythmia/Conduction
  - Carotid
  - Autonomic
- **Symptoms**

Chemotherapy

- **Asymptomatic**
  - Cardiomyopathy
  - More Risk Factors
  - Arrhythmias/Conduction
  - Autonomic
- **Symptoms**

NCI CCSS: Age-Specific Cumulative Incidence of Four Major Cardiac Outcomes in 10,724 5-year Survivors Compared to 3159 Siblings



Armstrong et al. JCO 2013

Case # 1

- A 34-year old male with history of Ewing's sarcoma of the left femur when he was 9 years old was seen in clinic for complaints of exertional dyspnea and fatigue. Cancer treatments include doxorubicin (375 mg/m^2), cyclophosphamide(9600 mg), etoposide, and vincristine. LVEF ↓ 48% from baseline LVEF of 55% (Normal LVEF $\geq$55%).

Case # 2

- A 21-yr. old male with history of Hodgkin's lymphoma in the mediastinum was referred to cardiology for atrial fibrillation and ↓LVEF of 41%.
- Cancer treatment includes: ABVD x 6 cycles (dox. 300 mg/m2); ifosfamide10000 mg/m2; mitomycin 120 mg, and consolidative XRT. He also had an autologous stem cell transplant .

Case # 3

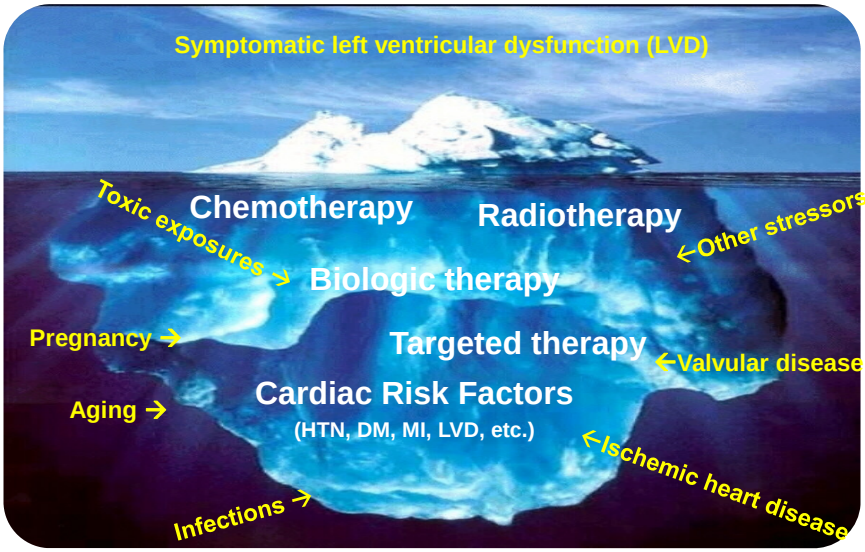
- A 63 year old female with history of breast cancer and medullary thyroid carcinoma was seen in clinic with complaints of fatigue and exertional dyspnea. Her chemotherapeutic regimen treatment for breast cancer 20 years ago included 6 cycles of anthracyclines (cumulative dose of 450mg/m^2) and radiation therapy(16 Gy). She recalls having been told at the time that the risk of anthracycline-induced cardiotoxicity was about 5%.

Cardiotoxicity

- National Cancer Institute (NCI)– "Toxicity that affects the heart." (www.cancer.gov/dictionary)
- Cardiac Review Committee (Trastuzumab Clinical Trials) defines chemotherapy-induced cardiomyopathy as one or more of the following:
  - CMP with a reduction in LVEF, either global or more severe in the septum
  - Symptoms associated with HF (S3 gallop, tachycardia)
  - Reduction in LVEF from baseline
    - Reduction in LVEF of ≥5% to <55% *with* accompanying S/S of HF
    - Reduction of LVEF in the range of ≥ 10% to < 55% *without* accompanying S/S of HF

Albini, et al. (2010). JNCI. 102(1). 14-25

Cardiotoxicity In Cancer Survivors



Objectives

- Identify the causes of cardiac toxicity in cancer survivors
- Describe how cardiomyopathy following anthracycline treatment can be prevented
- Discuss how nurses can encourage a healthy lifestyle in cancer survivors

Causes of Cardiomyopathy/Heart Failure in Cancer Survivors

- Ischemic etiology
- Non-ischemic etiology
  - Chemotherapy-induced
  - Cardiac amyloidosis
  - Myocarditis, Endocarditis
  - Hemochromatosis
  - Hypertension secondary to anti-VEGF
  - Mantle radiation to the chest

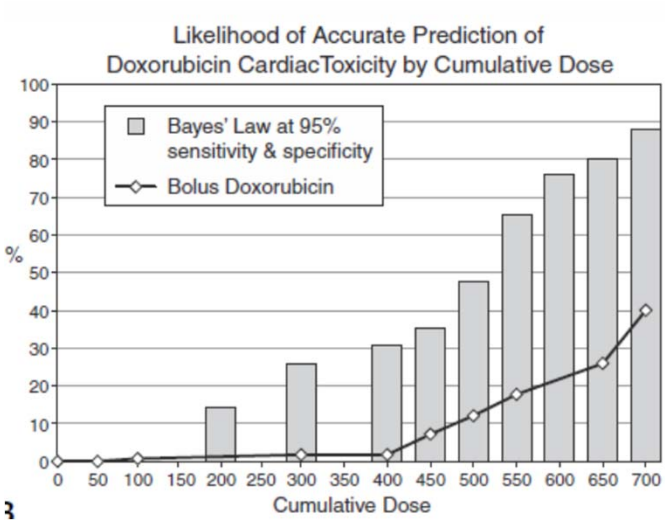
Chemotherapy-induced Cardiomyopathy (LVD)

LVD incidence	(%)
Anthracyclines	
• Doxorubicin	3-28
• Epirubicin	0.9-3.3
• Idarubicin	5-18
Alkylating agents	
• Cyclophosphamide	7-28
• Ifosfamide	17
Antimetabolites	
• Decitabine	5
Antimicrotubule agents	
• Docetaxel	2.3-8
• Ixabepilone	0.5
Monoclonal Antibody-based tyrosine kinase inhibitor	
• Adotrastuzumab emtansine	1.8
• Bevacizumab	1.7-3
• Pertuzumab	4.4-16
• Trastuzumab	*2-28*

LVD Incidence	(%)
Proteasome Inhibitor	
• Bortezomib	2-5
Small molecule tyrosine kinase inhibitors	
• Afatinib	
• Axitinib	2
• Carfilzomib	3
• Dabrafenib	8-9
• Dasatinib	2-4
• Imatinib mesylate	0.5-1.7
• Lapatinib	1.5-2.2
• Pazopanib	1
• Ponatinib	6-15
• Sorafenib	<1
• Sunitinib	2.7-11
• Trametanib	7-11
• Vandetanib	0.9
Miscellaneous	
• Tretinoin	3

Yeh & Bickford, JACC 2009, 53:2231-2247

Doxorubicin Cardiotoxicity



Ewer & Benjamin, Cancer and the Heart 2006

Anthracycline Agents: Relative Cardiotoxicity

Agent	Conversion Factor	5% Incidence Cardiotoxicity
Doxorubicin	1	450 mg / m^2
Daunorubicin	0.5	900 mg / m^2
Epirubicin	0.5	935 mg / m^2
Idarubicin	2	225 mg / m^2
Mitoxantrone	2.2	200 mg / m^2

Keefe, DL (2001). Seminars in Oncology.28(4).2-7

Risk Factors for Anthracycline-Induced Cardiomyopathy

Risk Factors	Description
Cumulative dose of chemotherapy	Higher incidence in cum. dose >300 mg/m2 of doxorubicin or >600 mg/m2 of epirubicin (1% to 5% up to 550 mg/m2, 30% at 600 mg/m^2 and 50% at 1gm/m^2 or higher)
Age at time of exposure	Extremes of age (<18 years or >65years) Development of toxicity even at lower cumulative dose
Concomitant administration of other cardiotoxic drugs	Combination chemotherapy (paclitaxel, traztuzumab, cyclophophamide, etoposide, melphalan, mitoxantrone)
Concurrent or prior chest irradiation	Radiation involving the left side of the chest
Pre-existing cardiovascular disease	Presence of CAD, HTN, and LVD
Longer duration of survival	Chronic cardiotoxicity may occur even after 30 years of treatment

Carver et.al. 2007; Swain ,Whaley & Ewer, 2003

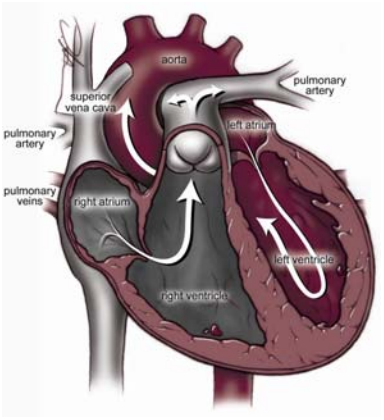
Types of Anthracycline Induced Cardiomyopathy

Type	Onset	Clinical Manifestation
Acute onset	Anytime from the initiation or within two weeks of therapy	ECG changes, arrhythmias (SVT), LVD, increased BNP, pericarditis, myocarditis, syndrome of acute fulminant HF, death
Early chronic progressive	Within one year of treatment	Subclinical decline in myocardial function or symptoms of clinical HF
Late onset chronic progressive	After 1 year to decades after therapy	Subclinical decline in myocardial function or symptoms of clinical HF

Bristow et. al, 1978; Pai & Nahata, 2000; Silber, et al. 2004

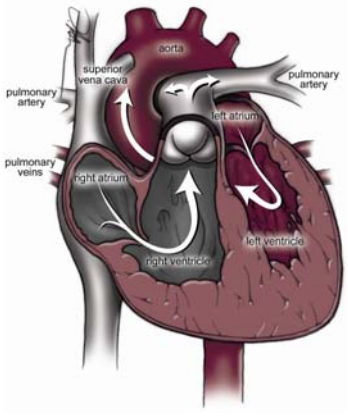
Types of Heart Failure
(based on LVEF)

Systolic Dysfunction (HFrEF)



EF < 50%

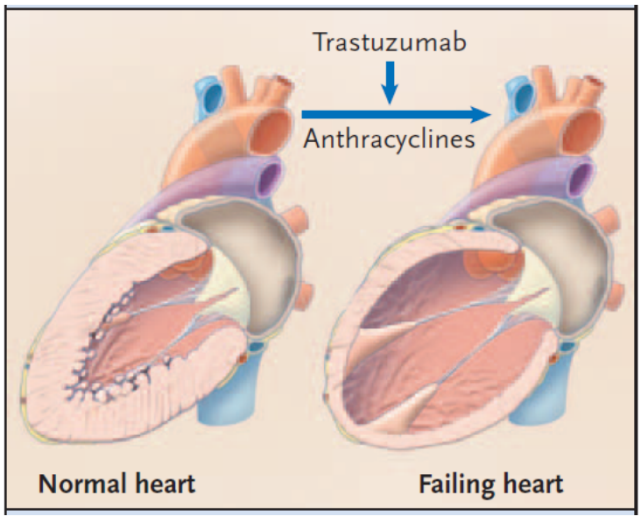
Diastolic dysfunction (HFpEF)



EF ≥ 50%

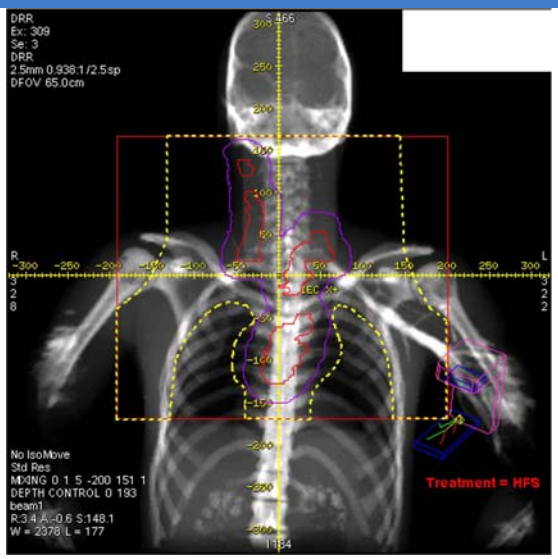
Fadol, A, et al. (2015) Heart Success: A Resource Guide for Individuals Living with Cancer and Heart Failure

Dilated Cardiomyopathy



Googleimages.com

Mantle Radiation to Chest



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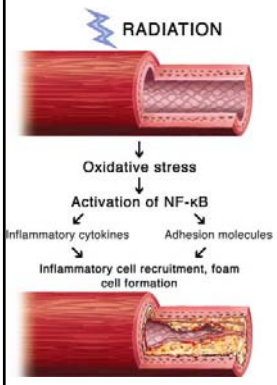
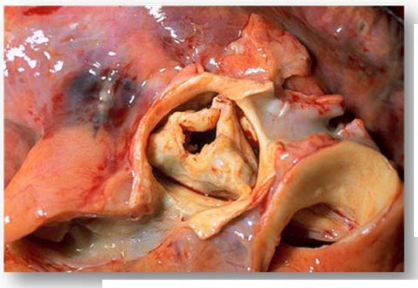
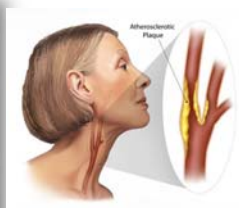
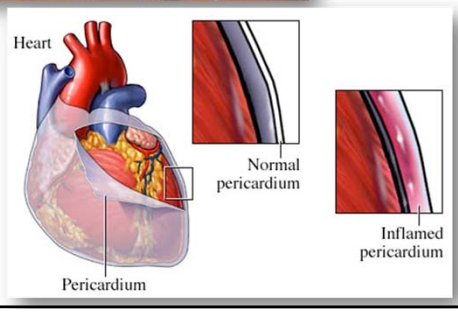
Radiation –Induced Cardiovascular Disease









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Major Coronary Event According to the Mean Radiation Dose to the Heart

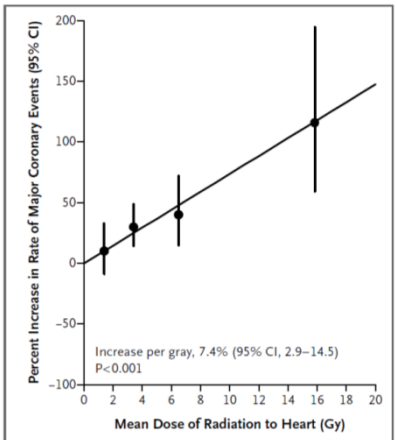


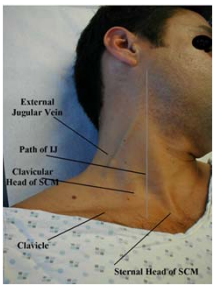
Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Darby et al. NEJM (2013). 368(11).987-998

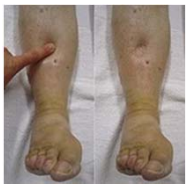
Monitoring for Signs and Symptoms of Heart Failure

Shortness of Breath

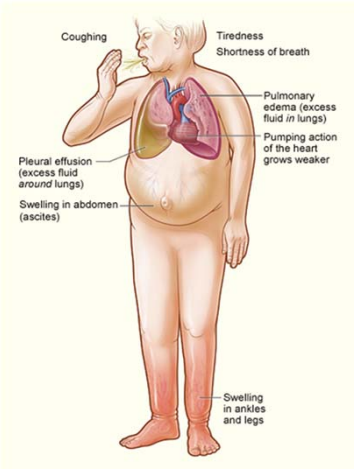
Paroxysmal Nocturnal Dyspnea



Jugular Venous Distention



Lower extremity edema



Googleimages.com

Objectives

- Identify the causes of cardiac toxicity in cancer survivors
- Describe how cardiomyopathy following anthracycline treatment can be prevented
- Discuss how nurses can encourage a healthy lifestyle in cancer survivors

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Survivorship

NCCN Guideline for Anthracycline-induced Cardiac Toxicity

For high risk survivors, the panel emphasizes the need for a thorough clinical screening for heart failure within one year after completion of anthracycline therapy.

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Survivorship: Anthracycline-Induced Cardiac Toxicity

INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- History and physical
  - Assess for signs and symptoms of heart failure
  - Assess patient's ability to perform routine and desired activities of daily living
  - Look for signs of volume overload
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known coronary artery disease [CAD], or baseline evidence of structural heart disease)
- Review other cardiovascular risk factors
  - Smoking
  - Alcoholism
  - Obesity
  - Family history of cardiomyopathy or other heart disease
- Review medications
- Review oncologic history
  - Review total cumulative dose of anthracycline
  - Other systemic therapy and/or chest radiation therapy

→

- Cardiovascular risk factor management
- Consider two-dimensional echocardiogram with doppler flow study for survivors with one or more cardiac risk factors within 1 year after completion of anthracycline therapy

SCARDIO-2

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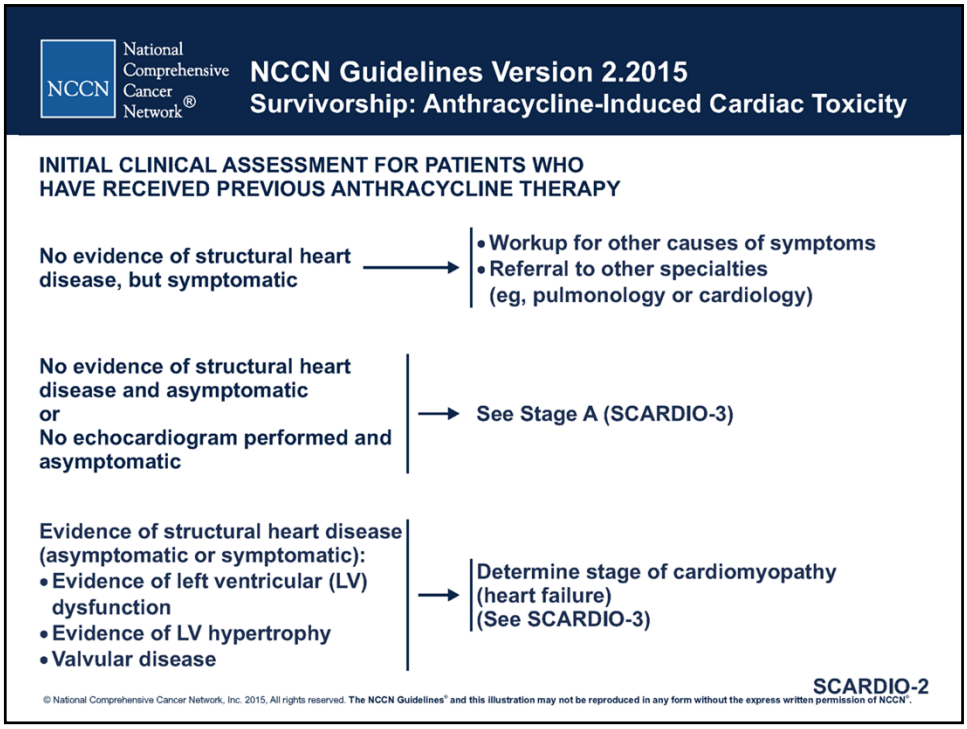
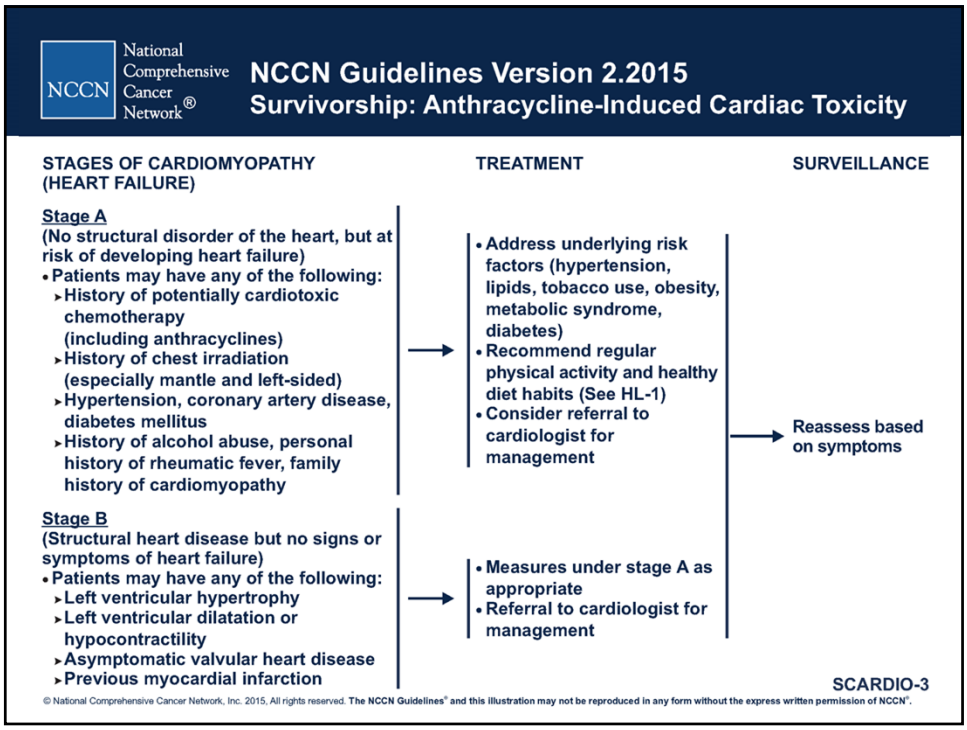
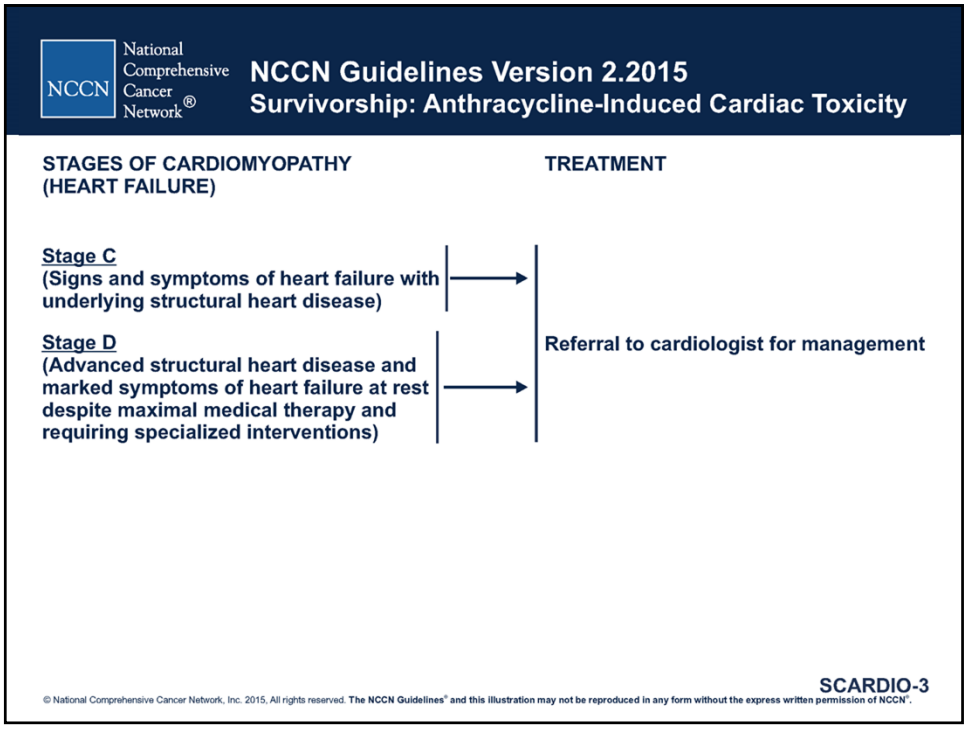






Stages of Cardiomyopathy (Heart Failure)

	Stage	Patient Description
A	High risk for developing heart failure (HF)	• Hypertension • CAD • Diabetes mellitus • Family history of cardiomyopathy • Cardiotoxic Chemotherapy
B	Asymptomatic HF	• Previous MI • LV systolic dysfunction • Asymptomatic valvular disease
C	Symptomatic HF	• Known structural heart disease • Shortness of breath and fatigue • Reduced exercise tolerance
D	Refractory end-stage HF	• Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Hunt SA et al. *J Am Coll Cardiol.* 2001;38:2101–2113.

General Guidelines for Cardiac Monitoring of Cancer Survivors

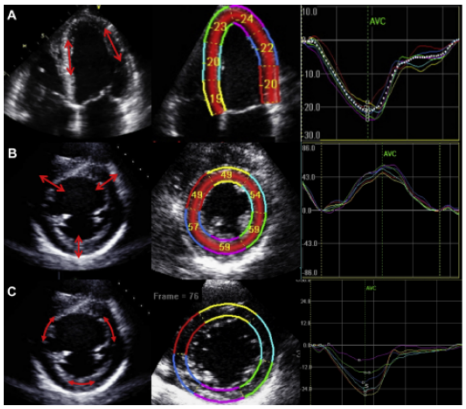
- Manage according to ACC/AHA Guidelines
- European Society of Medical Oncology Cardiology Oncology Clinical Practice Guidelines
  - All cancer patients treated with cardiotoxic chemotherapy considered at risk for HF
  - In patients with LVEF <40% standard HF treatment with ACE inhibitors and beta-blockers recommended
  - The earlier HF therapy is begun (within 2 months from the end of anthracycline therapy) the better the therapeutic response

Curigliano G. et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii155-66.

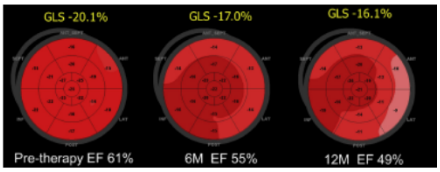
Current Practice for Monitoring Anthracycline-Induced Cardiomyopathy

- Baseline assessment of left ventricular function
  - Echocardiography
  - MUGA (multigated acquisition scan)
  - Myocardial perfusion stress test
- Cardiac biomarkers
  - Troponin T and troponin I
  - B type atrial natriuretic peptide
- Cardiac Imaging
  - Cardiac MRI
  - PET (Positron emission tomography) scan

Myocardial Strain Imaging by Echocardiography



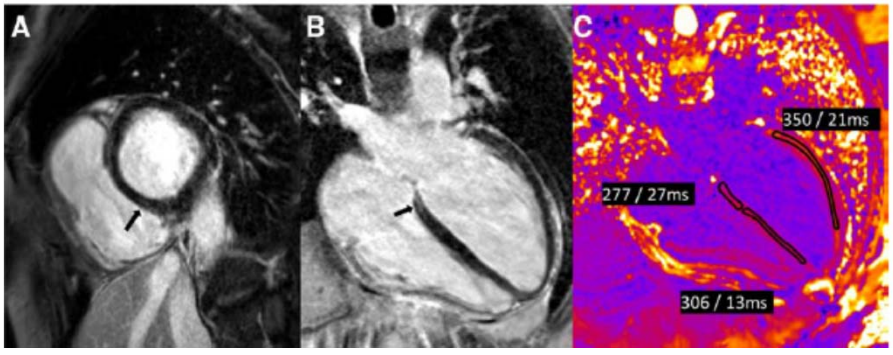
Speckle Tacking Echocardiography with Strain Measurement



Early strain changes to predict subsequent cardiotoxicity

Travendinarathan, P. et al. (2014).JACC 63(25). 2751-2768

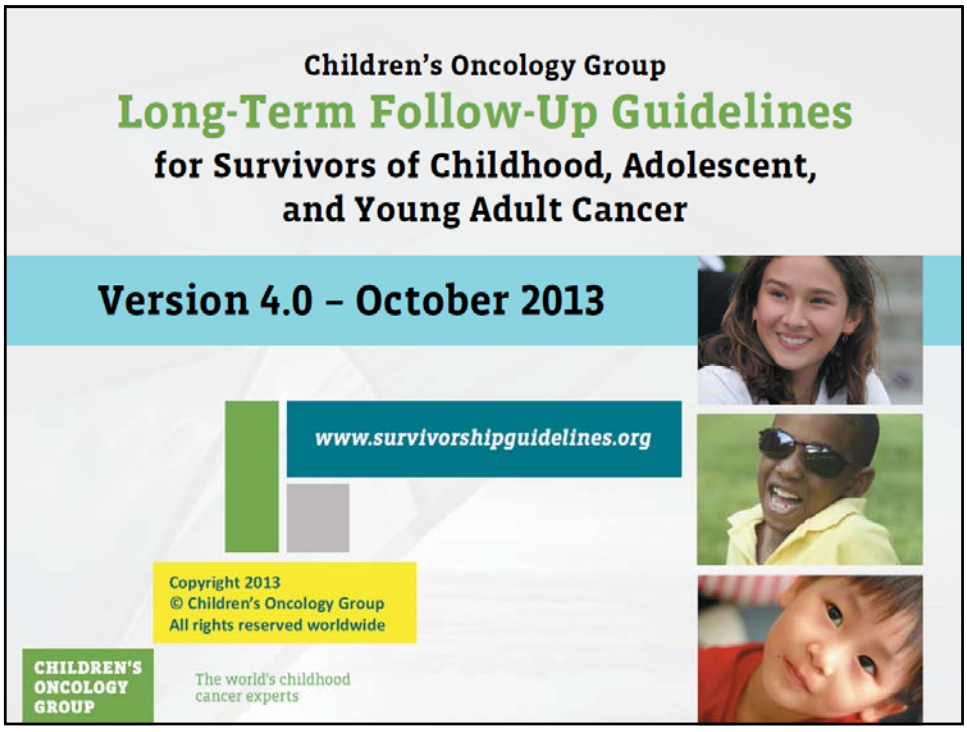
Cardiac MRI in the Assessment of Cardiac Toxicity



Thavendiranthan,P. et al. (2013). Circ Cardiovasc Imaging.1080-1091

Approaches to Reduce the Risk of Anthracycline Cardiotoxicity

- **Primary Prevention**
  - Limiting the cumulative dose
  - Altering the administration of anthracycline (Infusion instead of bolus)
  - Use of anthracycline analogues or liposomal formulations
  - Use of cardioprotectant concomitant with anthracycline administration (i.e. dexrazoxane)
- **Secondary Prevention**
  - Use of ACE-I and beta blockers
  - Risk-based screening
  - Screening for cardiac dysfunction
  - Lifestyle modification



COG Guidelines for Cardiac Screening

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM (or comparable cardiac imaging)			
Age at Treatment*	Radiation with Potential Impact to the Heart§	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	< 200 mg/m^2	Every 2 years
		≥ 200 mg/m^2	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m^2	Every 5 years
		≥100 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
≥5 years old	Yes	<300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
	No	<200 mg/m^2	Every 5 years
		≥200 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
Any age with decrease in serial function			Every year

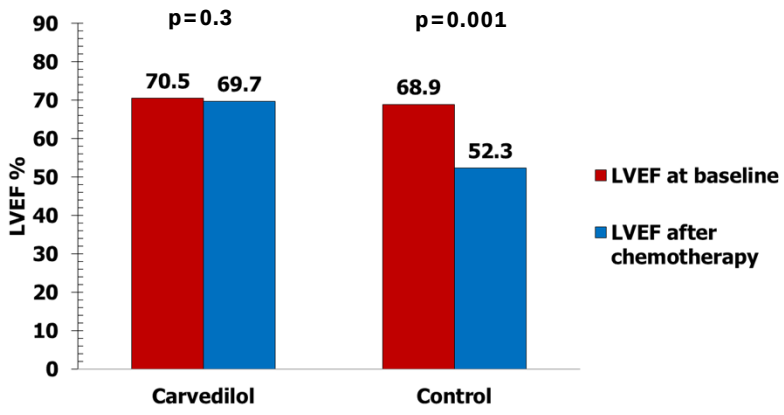
*Age at time of first cardiotoxic therapy (anthracycline or radiation [see Section 80], whichever was given first)
§See Section 80
†Based on doxorubicin isotoxic equivalent dose [see conversion factors on previous page, "Info Link (Dose Conversion)"]

Potential Cardioprotective Strategies to Prevent Cardiotoxicity

Class of Cancer Therapy	Potential Cardioprotective Therapies	Hypothesized Biologic Mechanism of Action
Anthracyclines	Dexrazoxane	Decreased ROS formation Reduced anthracycline-induced DNA damage (Top2 β)
	HMG-CoA reductase inhibitors	Reduce cell death and Top2 β-mediated DNA damage
	β blockers	Increased prosurvival signaling Mitigation of oxidative stress Enhanced lusitropy
	ACE inhibitors	Improved intracellular calcium handling Improved cardiomyocyte metabolism Improved mitochondrial function
	Exercise training	Decrease ROS formation Reduced pro-apoptotic signaling Improved calcium handling Improved myocardial energetics via augmented AMPK activity
	Bivalent neuregulin	Biased ErbB signaling

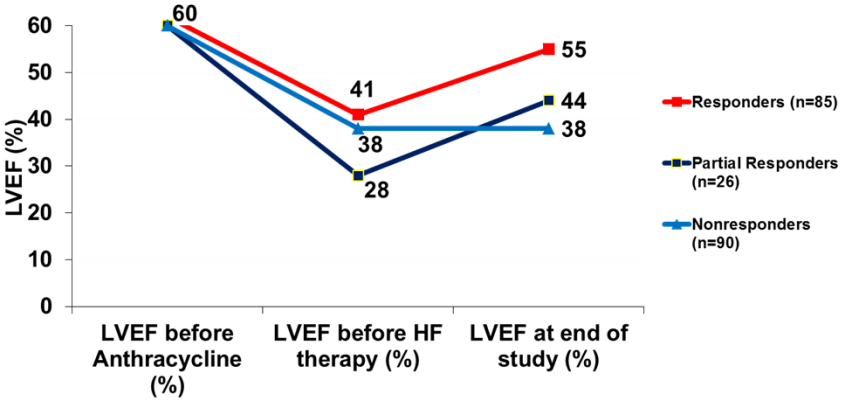
Hahn, et al. , 2014 JAHA, 1-14

Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy



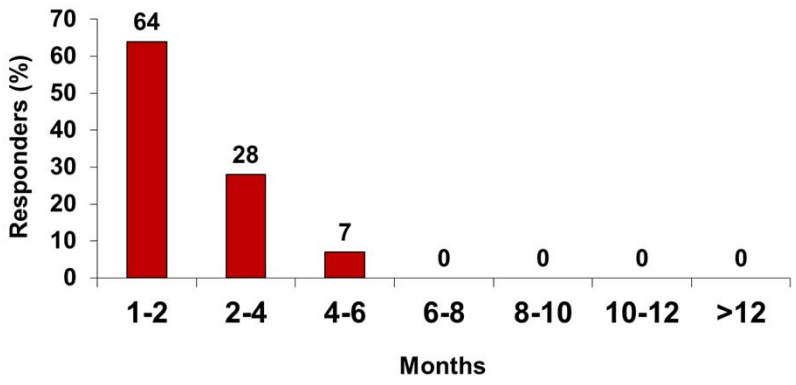
Kalay N et al. J Am Coll Cardiol. 2006; 48: 2258-62.

Anthracycline-Induced Cardiomyopathy Response to ACEI/BB



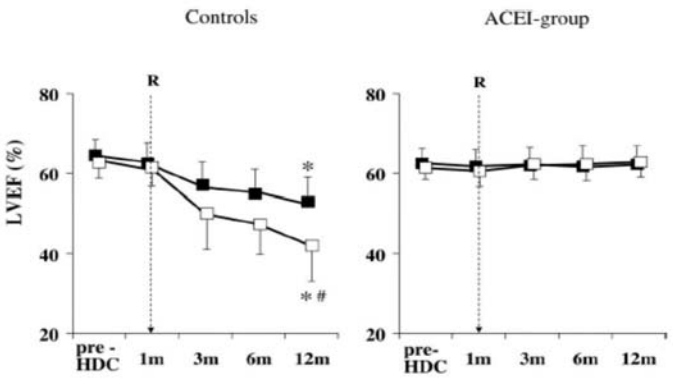
Cardinale, D. J Am Coll Cardiol, 2010; 55:213-220.

Percentage of Responders According to Time Elapsed from Anthracycline Administration and Start of HF Therapy



Cardinale, D. J Am Coll Cardiol, 2010; 55:213-220.

LVEF at baseline and during 12-month follow-up in control and the ACE-I groups in patients with or without persistent TnI increase



LVEF at baseline and during the 12-month follow-up in control subjects (left) and the ACEI group (right) in patients with (□) or without (■) persistent TnI increase. For treatment effect, *P*0.001; for effect of persistent TnI increase, *P*0.001; for interaction between treatment and persistent TnI increase, *P*0.001. R indicates randomization. **P*0.001 vs. baseline and randomization for all time points; #*P*0.001 vs. patients without persistent TnI increase.

Cardinale D et al. *Circulation*. 2006;114:2474-81

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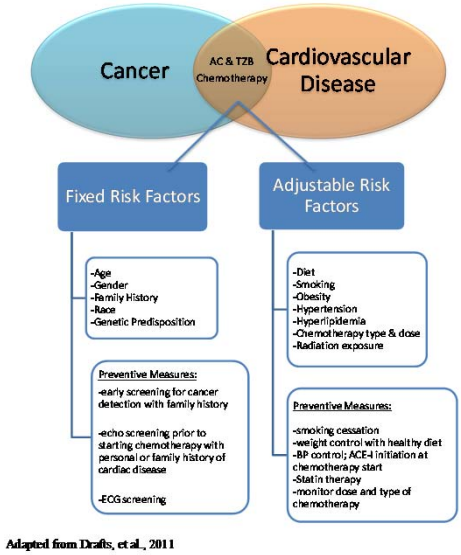
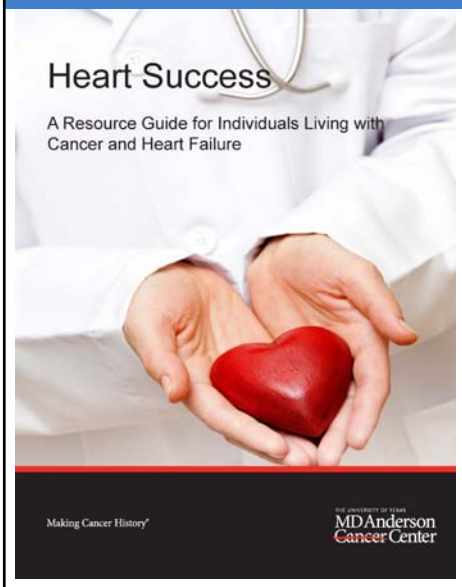
- Discuss how nurses can encourage a healthy lifestyle in cancer survivors

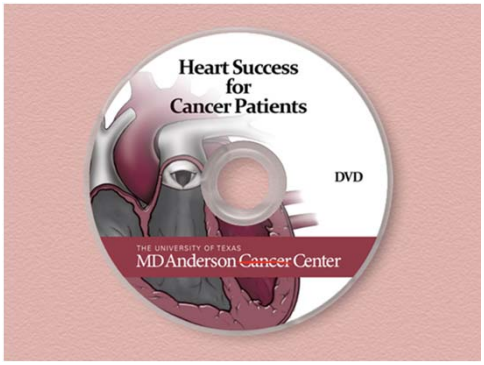
Overlap of Cardiovascular Disease and Cancer



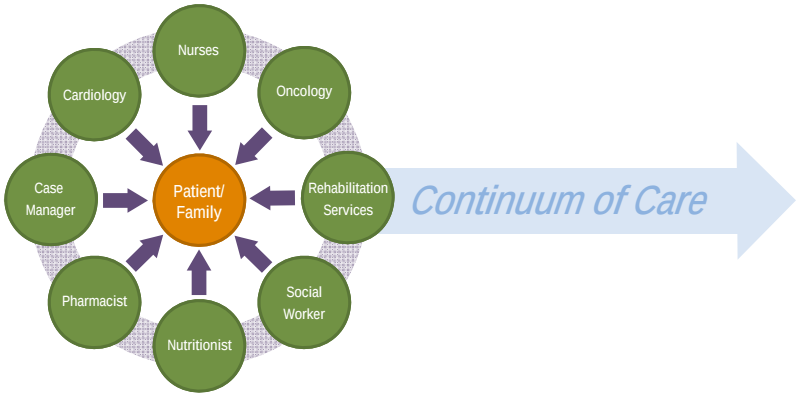
Adapted from Drafts, et al., 2011

Patient Education





Heart Success Program



Location	Emergency Center/Inpatient	Outpatient/Cardiomyopathy Clinic	Home/Hospice
Tools	Heart Failure Order Set	Heart 2 Heart Support Group	Home Care

Non-Pharmacologic Management of Hypertension

- Smoking cessation
- Weight reduction (BMI < 25 kg/m^2)
- Decreased mental stress
- Sodium restriction (<2.4 g of sodium per day)
- Alcohol restriction (Men $\leq$ 2 drinks/day; women $\leq$ 1 drink per day)
- Increased physical activity (30 minutes per day most days of the week)

McLaughlin AN and Policarpo G. Commun Oncol 2012;9:324-30

Lifestyle Modification

Lifestyle modification	Approximate reduction in SBP (mm Hg)
Weight reduction	5 – 20
Dietary approaches (i.e. DASH diet)	8 – 14
Sodium restriction	2 - 8
Exercise	4 – 9
Moderation of alcohol intake	2 – 4

McLaughlin AN and Policarpo G. Commun Oncol 2012;9:324-30

Sample Home BP Diary

Appendix 2 Home Blood Pressure Monitoring Diary and Instructions

Today's date _____

Patient Name_____ *(initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, 110/85).
2. Record the date, then record your blood pressure twice each day using a home blood pressure monitor:
   - each morning while you are resting or reading (not while you are active: dressing, making breakfast, etc.)
   - each evening at bedtime or while you are relaxing during the evening
3. If you take your blood pressure at other times of the day, please record the numbers and time under "Other readings".
4. Normal blood pressure is usually considered to be 120/80 mmHg. If your systolic pressure is greater than 150 or your diastolic blood pressure is greater than 90 twice in a row measured several hours, please contact your doctor's office at _____ for instructions.
5. Please bring this form to every clinic visit or appointment.

Date	AM readings	PM readings	Other readings (include time of day)	Date	AM readings	PM readings	Other readings (include time of day)
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	
	/	/			/	/	

Maitland ML et al. J Natl Cancer Inst 2010;102:596-604

Back to our case studies

Case # 1

- A 34-year old cancer survivor with history of Ewing's sarcoma of the left femur when he was 9 years old. Cancer treatments include doxorubicin (375 mg/m2), cyclophosphamide (9600 mg), etoposide, and vincristine. Presented to the clinic for exertional dyspnea. LVEF ↓ 48% (2012) from baseline LVEF 55% (1990).
- Treated with ACE-I and β blockers. LVEF recovered
- Most recent LVEF was 56% (2015)

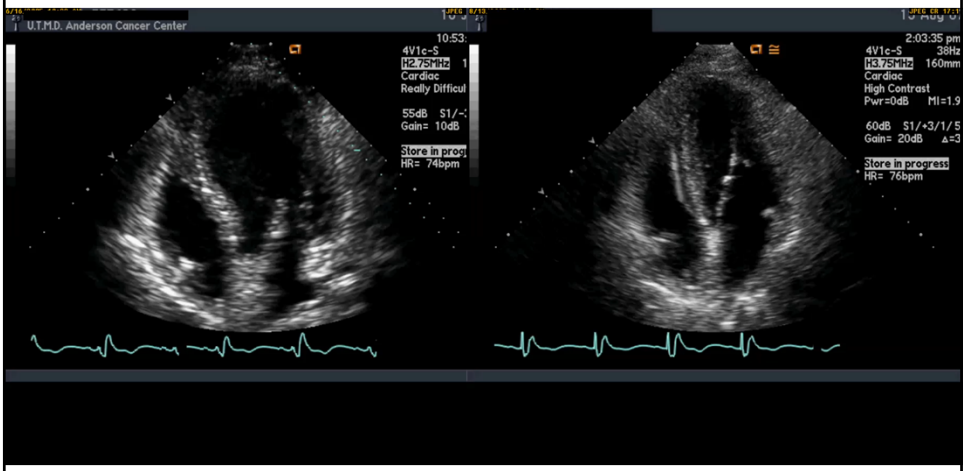
Case # 2

- A 21-yr. old male cancer survivor, diagnosed with Hodgkin's lymphoma in the mediastinum 12/2009. Cancer treatment includes: ABVD x 6 cycles (dox. 300 mg/m2; ifosfamide 10000 mg/m2; mitomycin 120 mg; consolidative XRT. 9/27/11- autologous stem cell transplant . Referred to cardiology in 2011 for atrial fibrillation and ↓LVEF of 41%.
- Was treated with β blockers & ACE-I with LVEF recovery.
- Most recent LVEF of 54% (2015).
- Exercise on a regular basis and observing a heart healthy diet
- Currently in Medical school

Case study # 3

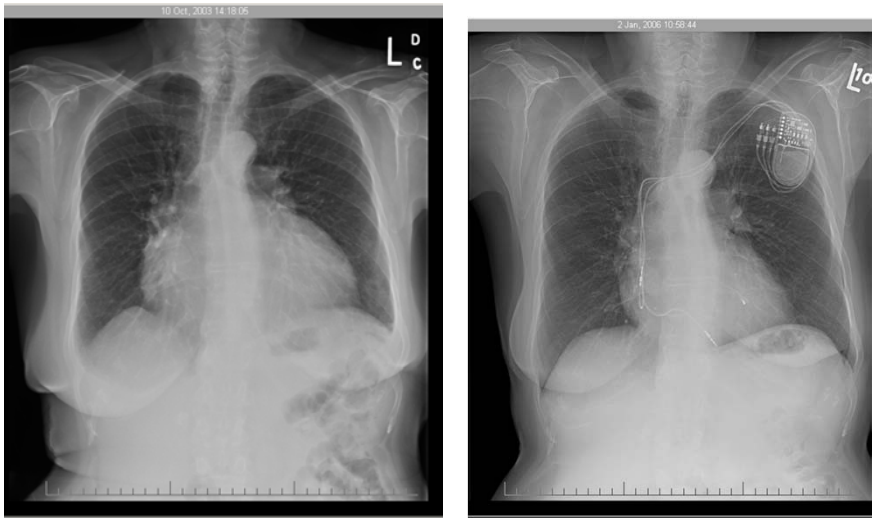
- A 63 year old female with history of breast cancer and medullary thyroid carcinoma is seen in clinic with complaints of fatigue and exertional dyspnea. Her chemotherapeutic regimen treatment for breast cancer 20 years ago includes 6 cycles of anthracyclines (cumulative dose of 450mg/m^2) and radiation therapy(16 Gy). She recalls having been told at the time that the risk of anthracycline-induced cardiotoxicity was about 5%.

Recovery of Heart Function



MD Anderson Echocardiography Lab

Heart Failure in Survivors: It Isn't a Death Sentence



MD Anderson Chest X-ray

Conclusion

- Early detection and management of chemotherapy-induced cardiotoxicity is essential to improve outcomes and quality of life in cancer survivors.
- Identify at risk patients and utilize preventive measures to prevent cardiovascular complications
- Utilize evidenced- based guidelines for monitoring and long-term follow up of cancer survivors
- Multidisciplinary approach to minimize and treat cardiotoxicity associated with cancer treatment
- Nurses has a critical role in patient education regarding cancer survivorship