HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

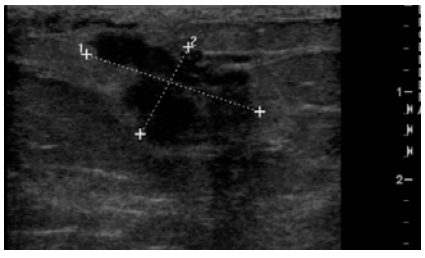
Potpourri: Cardio-Oncology Cases

Judy Hung, MD
Massachusetts General Hospital
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

No disclosures; Thank Michael Picard and Tomas Neilan for cases

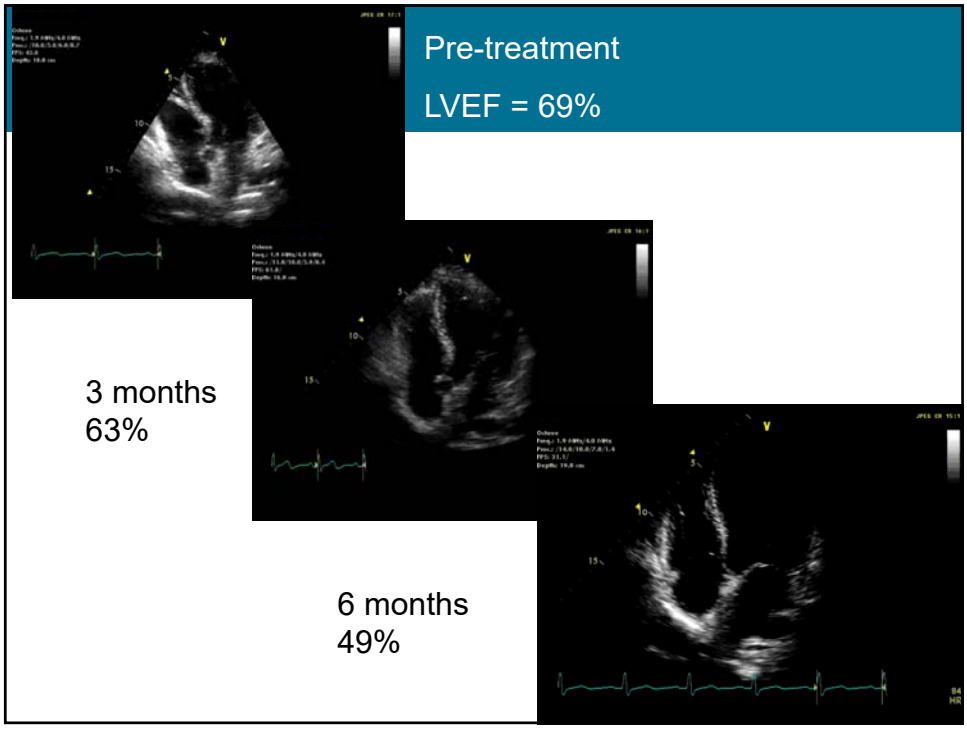
59 year old woman (sister diagnosed with breast cancer at age 39) self-examination detects lump in her left breast



Biopsy: ER- HER2+ poorly differentiated invasive carcinoma

Treatment: tumorectomy
adriamycin every 3 weeks x 4
paclitaxel+trastuzumab every week for 12 weeks
trastuzumab for 6 more months

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER



Cardiology consult for asymptomatic drop in LVEF

- Scheduled to start trastuzumab alone for 6 more months. What could you recommend ?
  - A. Delay start
  - B. Modify dose
  - C. Modify dosing interval
  - D. Add ACE inhibitor
  - E. Add beta blocker
  - F. Modify dose and add beta blocker
  - G. Modify dosing interval and add ACE inhibitor
  - H. Delay start and add beta blocker/ACE inhibitor

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Expert Consensus Statements for Cardio-Oncology

- Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging
  - JASE 2014;27:911-939
- Expert Consensus for Multi-modality Imaging Evaluation of Cardiovascular Complications of Radiotherapy in Adults: A Report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography
  - JASE 2013;26:1013-32
- SCAI Expert Consensus Statement: Evaluation, Management and Special Considerations of Cardio-Oncology Patients in the Cardiac Catheterization Laboratory.
  - Catheter Cardiovasc Interv 2016;87:E202-E223

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Cath lab issues in the cancer patient

- Some chemotherapies cause platelet activation / aggregation
- Thrombocytopenia associated with increased risk for thrombus formation – withholding aspirin from cancer patients with ACS associated with worse outcomes
- If PCI indicated:
  - POBA for cancer patients not candidates for DAPT and plt counts 10K-30K or if noncardiac procedure/surgery planned < 4 weeks
  - BMS with short term DAPT if plt cnt > 30K if other procedures/surgery/chemo can be postponed > 4 weeks
  - DES with longer term DAPT if plt cnt > 30K and and no immediate procedures/surgery/chemo

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Cancer Therapeutic-Related Cardiac Dysfunction - CTRCD

- Vary by chemotherapeutic agent
  - Irreversible,
  - reversible,
  - partially reversible
- Also occur with radiation therapy

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Definition of cardiotoxicity varies

LVEF decrease of >5% to LVEF< 55% + symptoms of HF

Asymptomatic decrease in LVEF > 10% to < 55%

Chemotherapeutic agent toxicity classification by mechanism of toxicity

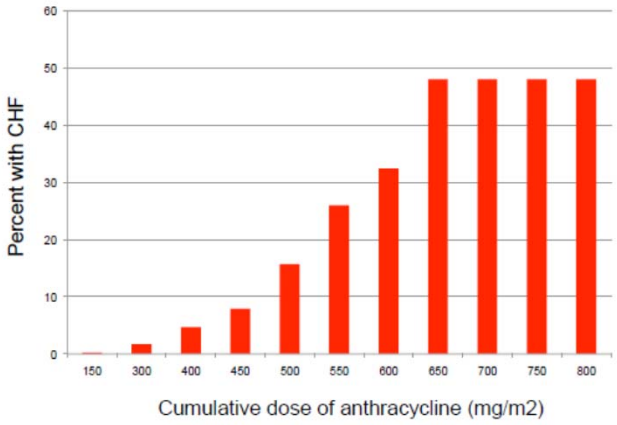
- Type I
  - Dose dependent
  - Irreversible (at cell level)
  - Early detection, prompt treatment may prevent progression
    - Later cardiac stress may exacerbate
    - Doxorubicin, epirubicin, idarubicin, mitoxantone
- Type II
  - Not dose dependent
  - Often reversible (does not cause apoptosis by itself)
    - Trastuzimab, lapatinib, pertuzimab, sorafenib, sunitinib, bevacizumab, bortezomib

LV dysfunction from chemotherapies

- Anthracyclines
  - Acute
    - Rare
      - » Repol and QT, conduction abnormalities; ACS; Myocarditis/pericarditis
  - Chronic (subacute onset / late onset)
    - Cumulative dose effect
    - Cardiomyocyte injury from oxidative stress
    - Ultrastructural effects
    - Late onset ? Triggered by 2nd insult
  - Irreversible cardiac effects ?

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Anthracycline cardiotoxicity: *dose dependence*



Swain et al. Cancer. 2003;97:2869-79

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Risk factors for anthracycline cardiotoxicity in the current era

Wang et al, Am J Cardiol 2015

- 5057 patients treated 2002-2012
  - 2.4 % had symptomatic HF or cardiac death
- Risk for MACE
  - Older age
  - Males with cardiac risk factors or cardiac therapies
  - Hematologic ca (rather than breast ca)
  - Baseline LVEF < 60%
  - LVEF decrease of 10
  - Enlarged LV at baseline

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Assessment of LV function for anthracycline patients
over 900,000 patients receive anthracyclines each year !

- Pre-chemo
- Prior to early doses
- Before every dose when cumulative dose > 400 mg/m^2 (?350, 240)
  - other toxic dose ranges for other agents
    - Epirubicin 720 mg/m^2
    - Cyclophosphamide 150 mg/kg
- Continue tx if LVEF ok
- Treat reduced LVEF and alter chemo
- ? Role of subclinical LV dysfunction

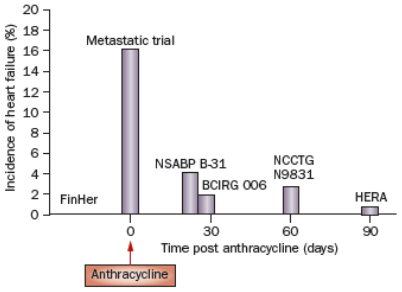
MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

LV dysfunction from therapies: Trastuzumab

- Antibody beneficial in patients that overexpress HER2 oncogene
- Binds to human epidermal growth factor receptor2 (HER2)
- Prevents HER2 interaction with HER4 receptor
  - Affects signaling involved in cardiomyocyte repair under stress
    - Such as oxidative stress in setting of anthracyclines
    - LV dysfunction in up to 1/3 + symptomatic CHF in 2-5% of pts treated with both tx
- Does not cause ultrastructural effects
- Effects not dose dependent and are reversible
  - Responsive to HF therapies

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Incidence of class III/IV HF as a function of time interval between AC and trastuzumab



Ewer et al, Nat. Rev. Cardiol.2010;7:564-575

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Goal: early detection of LV dysfunction

- Modify therapy
  - Dose reductions, dosing intervals, alternate therapies
- Interventions to slow progression of LV dysfunction or prevent late toxicity
  - Beta blockers, ACE inhibitors, ARBs

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Identifying high risk patients

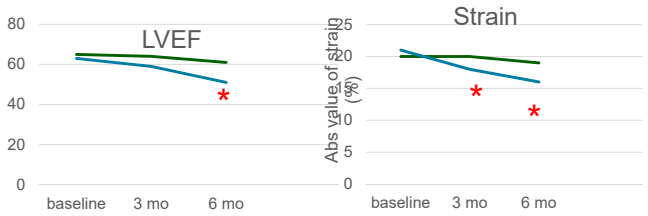
- Pre-treatment LVEF predictive of subsequent cardiotoxicity in breast cancer patients treated with anthracyclines or anthracyclines/trastuzumab
  - Tan-Chiu et al, J Clin Onc 2005;23:7811-9
    - 3 yr incidence of symptomatic HF function if LVEF
      - 12.5% with LVEF 50-54%
      - 3.8% with LVEF 55-64%
      - 0.9% with LVEF > 65%

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

- Subtle changes in LV systolic function may not be detected by echocardiographically quantified LVEF
  - Measurement variability / reproducibility
    - improved with LV contrast (2D), 3D echo
  - Image quality influenced by:
    - Post-mastectomy, post-radiation, breast expanders/implants
- Other options
  - Diastolic function - variable results
  - Tissue Doppler – s' shows promise (DiLisi et al, Anti-Cancer Drugs 2011)
    - Declines should raise concern for CTRCD

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Decreases in longitudinal strain at 3 months predictive of LV dysfunction at 6 months in breast ca pts receiving AC, Paclitaxel + Trastuzumab



32% of 81 pts had CREC defined cardiotox

No pre-treatment differences (including LVEF)

Reversible in 80% of those with cardiotoxicity

10% drop in peak longitudinal strain associated with cardiotoxicity
Hs-trop > 30 pg/ml at AC completion also associated wtih later cardiotoxicity

LVEF, diastolic function at AC completion not associated

91% neg PV when GLS stable or hs-trop < 30 pg/ml

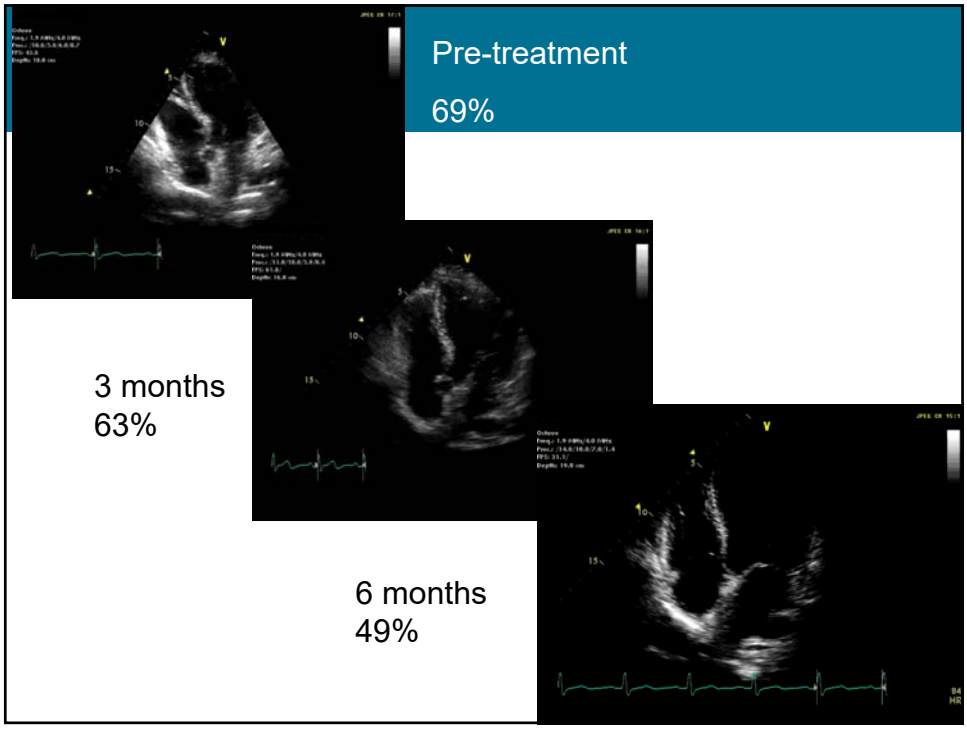
Sawaya et al, Am J Card 2011;107:1375-80; Sawaya et al, Circ CV Img 2012;5:596-603

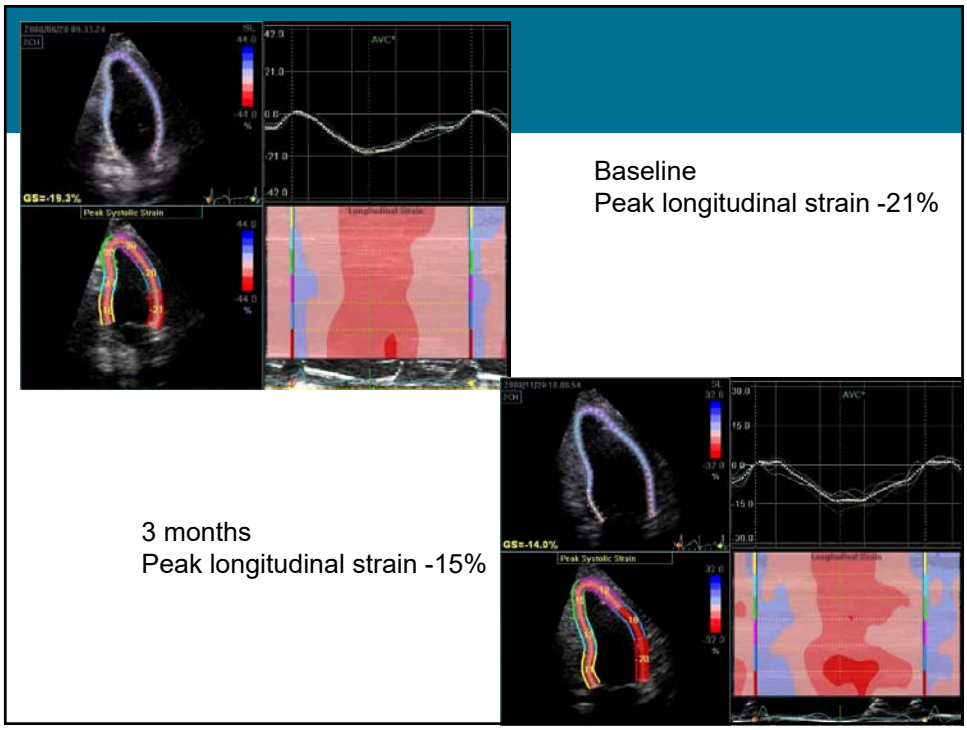
MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

	Sensitivity	Specificity	PPV	NPV
GLS <19%	74	73	53	87
usTnI >30 pg/mL	48	73	44	77
GLS <19% and usTnI >30 pg/mL	35	93	67	77
GLS <19% or usTnI >30 pg/mL	87	53	43	91

Sawaya et al. *Circ Cardiovasc Imaging*. 2012;5:596–603

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER


Pre-treatment
69%
3 months
63%
6 months
49%

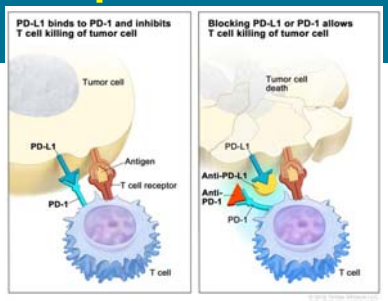

Baseline
Peak longitudinal strain -21%
3 months
Peak longitudinal strain -15%

Other agents

- Tyrosine kinase inhibitors
  - LV dysfunction and HF occur with some but not all
- Taxanes
  - Conduction abnormalities (most asymptomatic)
  - Exacerbate anthracycline HF
- Checkpoint inhibitors (programmed death receptor (PD-1) blocking Ab)
  - Myocarditis
- Anti T cell Ab, Chimeric antigen receptor T cells
  - Cytokine release syndrome

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Immune Checkpoint Inhibitors



www.cancer.gov

- T cells will attack cancer cells if they recognize them.
- Sometimes the T cells will not recognize cancer cells as “bad” as the cancer cells carry proteins that act like masks. One of these masks in PD-L1.
- PD-1 protein on T cells bind to PD-L1 and thinks they are healthy cells.
- Immune checkpoint inhibitors are drugs – often made of antibodies – that block PD-1 and PD-L1 and remove the blinders that prevented T cells from recognizing the cells as cancerous and leading an immune system assault on them.

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Checkpoint inhibitor cardiac abnormalities

- Variety of abnormalities
  - Chest pain, dyspnea, elevated troponin, ECG changes
- Fulminant myocarditis in 1.9% of 580 patients at MGH
  - Onset days to months from start of tx
  - Higher troponins (admission, peak and/or discharge) associated with worse outcomes

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

CTRD - Integrated approach - summary

- Limited scientific data
- Baseline cardiac assessment in all scheduled to get a potentially cardiotoxic agent
  - Hx, PhysEx, ECG, imaging
- If not possible in all, at least in those at high risk
  - Established CV ds, CV risk factors, age, expected hi dose type I, combination of type I + II
  - GLS, troponin desirable
- If LVEF or GLS below LLN or troponins elevated
  - Cardiol consult – discussion with onc to optimize benefit/risk of treatment plan
- Follow up based on agent

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Summary (continued)

- Type I agent
  - What defines high risk dose for anthracyclines ?
    - Cumulative dose 400 mg/sq m -> 5% HF risk but really a continuum
      - Earliest step up in risk occurs ~ 250 – 350 mg/sq m
        - » Pts w< 375 mg/sq m 26% LVEF < 50% at 6 mo
          - Drafts et al, JACC CV Img 2013;6:877-85
    - ASE Guidelines recommend evaluation before each dose exceeding 240 mg/sq m

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Summary (continued)

- Type II agents
  - Trastuzumab
    - Baseline echo then q 3 mo during tx
  - VEGF, VEGF receptor inhibitors
    - Baseline echo, 1 mo and q3 mo while on tx
  - Checkpoint inhibitors
    - Baseline ECG + Troponin, Troponin at each cycle
  - Other agents
    - f/u in those w/ known CV risk
- In all, treat HTN, CV risks, symptoms

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

The Oncology-Cardiology Tension

- How to position the cardiac work-up so as not to reduce effective cancer treatment
  - Pragmatic algorithms required
  - What is worse an LVEF of 40% or metastatic cancer ?
  - Willing to alter chemo if GLS abnl but LVEF nl ?

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

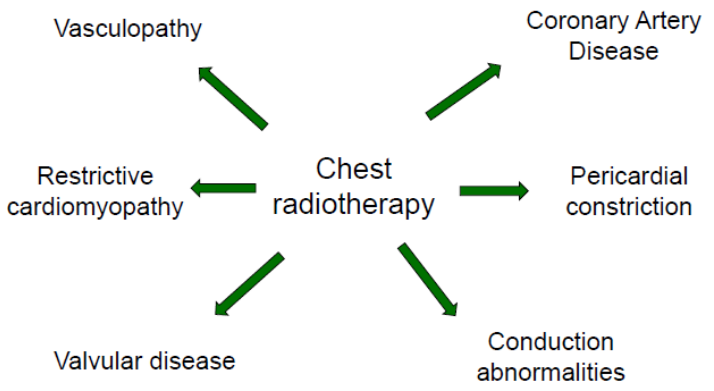
Radiation induced heart disease

JASE 2013;26:1013-1032

- Most common in lymphoma and breast ca
  - Valves – lymphoma
  - Coronary arteries – breast ca
- Less common with better cardiac shielding
    - Current prevalence unknown
- Cumulative dose effects
- Potentiated by adjuvant chemo

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Spectrum of radiation associated heart disease



MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Risk Factors

- Radiotherapy to the mediastinum
  - Hodgkin's Disease (Mantle Field Radiation)
  - Breast Cancers
  - Esophageal Cancers
- <40 y.o. when they received RT
- RT used with cardiotoxic chemotherapy
- Risk proportional to cumulative dose received

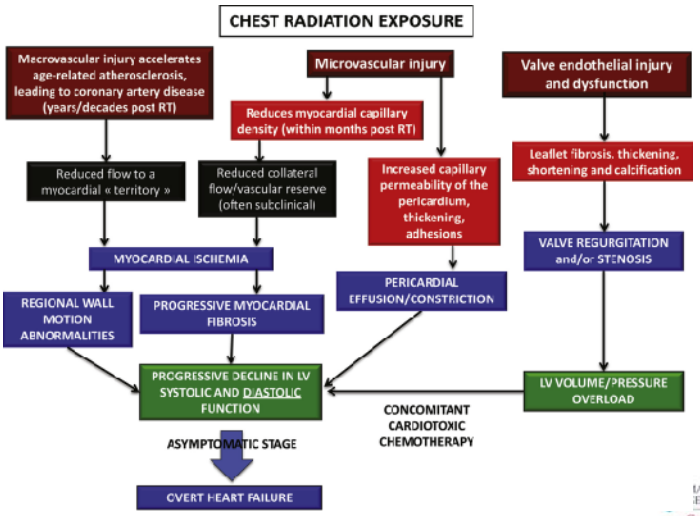
MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

RIHD Risk

- 1% after 10 years post radiation
- 5% at 15 years
- 6% at 20 years
- Valve disease >20 years after radiation exposure
  - Mild AR – 45%
  - Moderate AR – 15%
  - Mild MR – 48%
  - AS – 16%

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Pathophysiology of radiation induced heart ds
JASE 2013;26:1013-1032



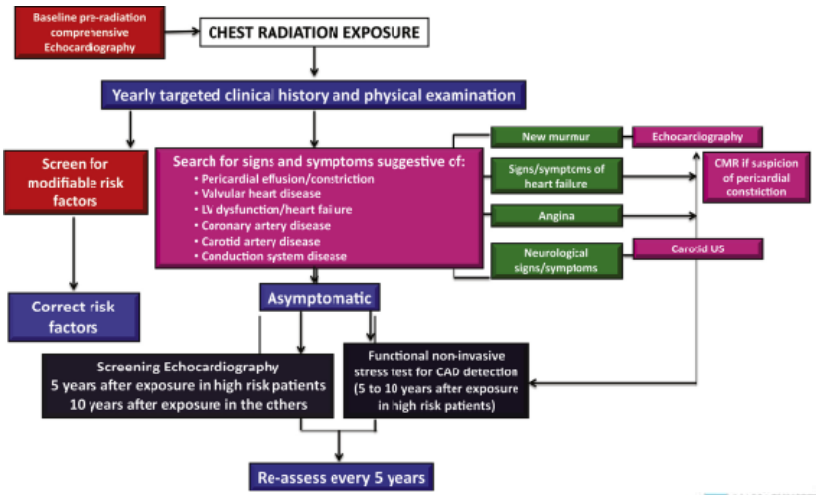
MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Role of echo

- LV systolic function
  - Global and regional (CAD)
- LV Diastolic function
  - Restrictive cardiomyopathy
- Pericardial disease
  - Pericarditis (acute)
  - Effuso-constrictive
  - Constriction (late)
- Valvular heart ds
  - Stenosis and regurgitation

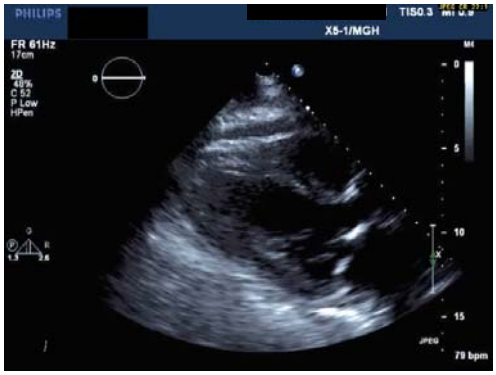
MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

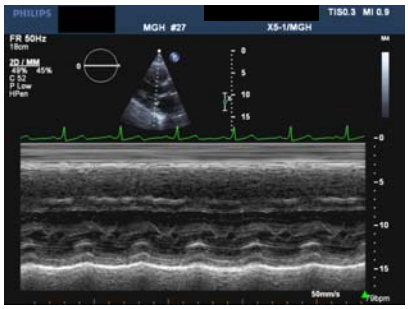
Cardiac follow up for patients receiving chest irradiation
JASE 2013;26:1013-1032



MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

68 yo M s/p mantle XRT for Hodgkins disease 43 years ago now s/p AVR for severe calcific AS

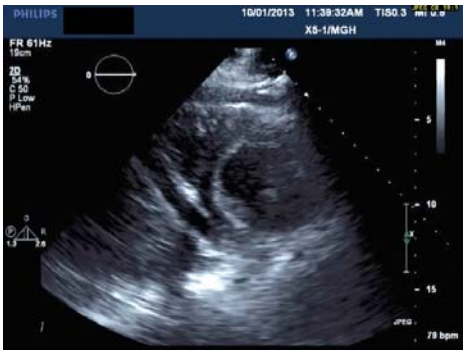


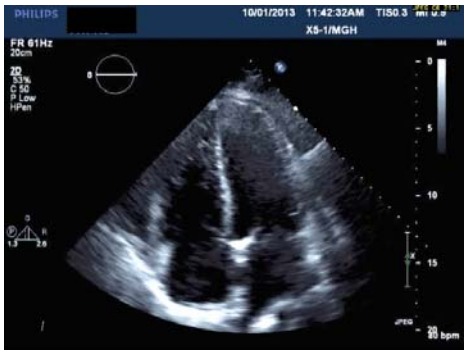


Pericardial effusion, Septal bounce, flattened posterior wall motion

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

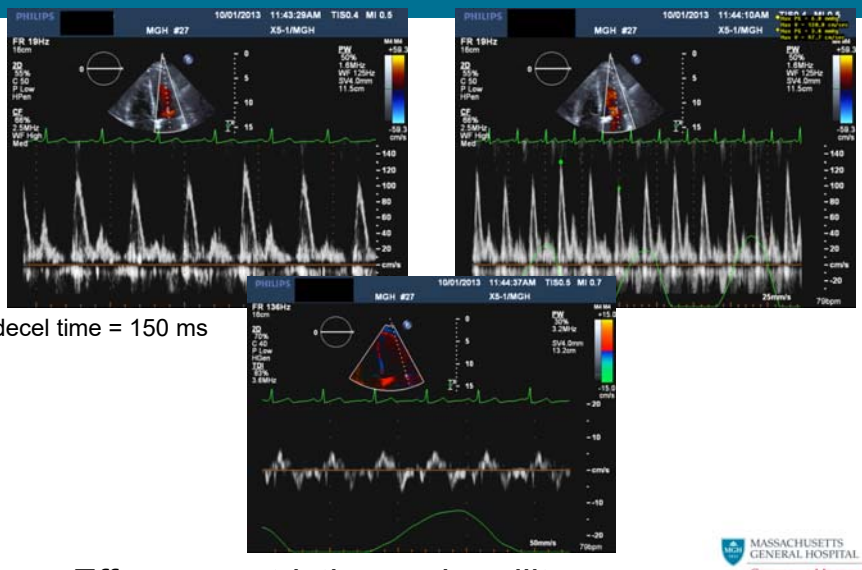
Pericardial effusion, septal bounce





MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Restrictive LV filling, respiratory variation, normal MV annular velocities

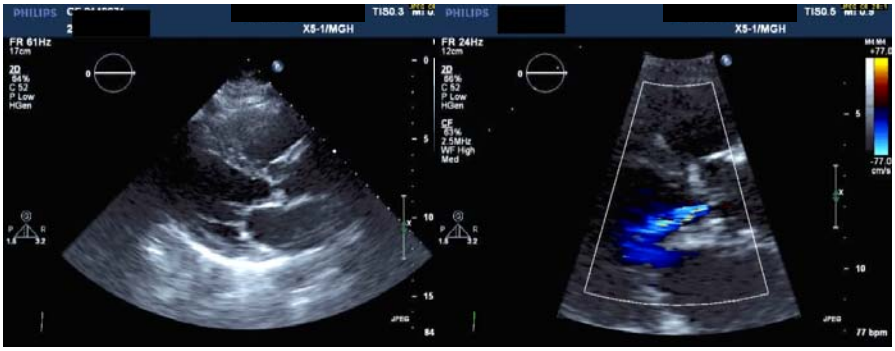


MV decel time = 150 ms

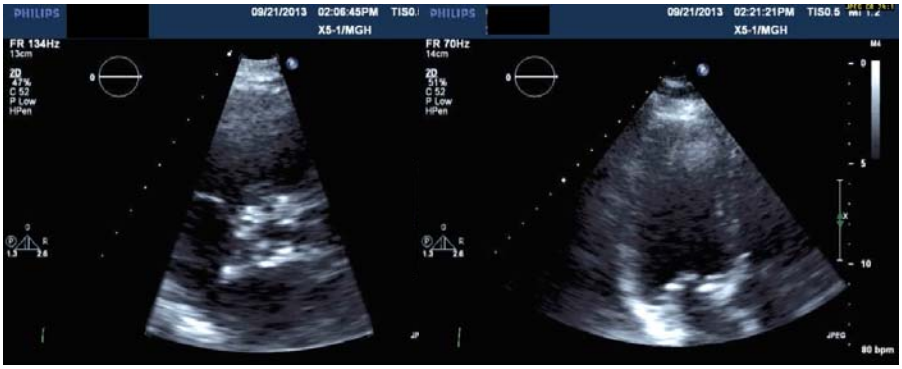
Effuso-constrictive pericardiits

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

52 yo F s/p mantle XRT for Hodgkins ds at age 16 with progressive calcification of valves



MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER



MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER