Kettering Cancer Center

on the Kettering Medical Center campus

Opening January 2017

Cardiovascular - Oncology

PRESENTED BY:

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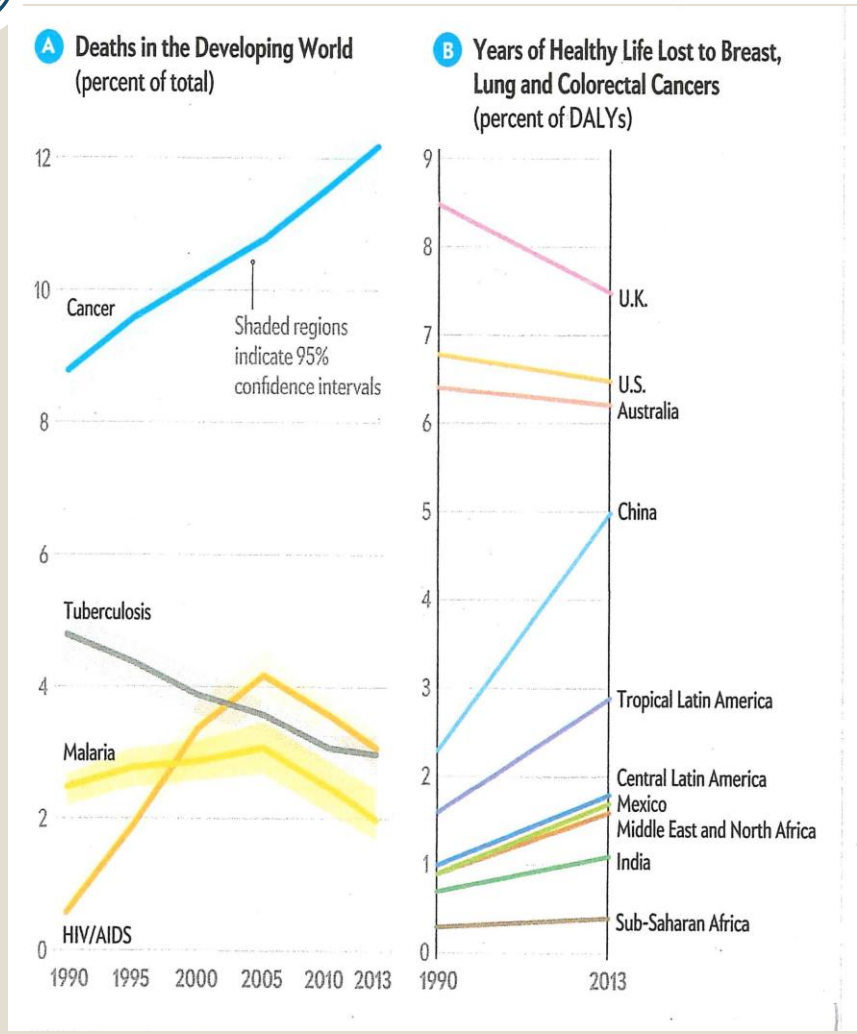
- Staff Cardiologist
- Southwest Cardiology/KPN
- No Financial Disclosures

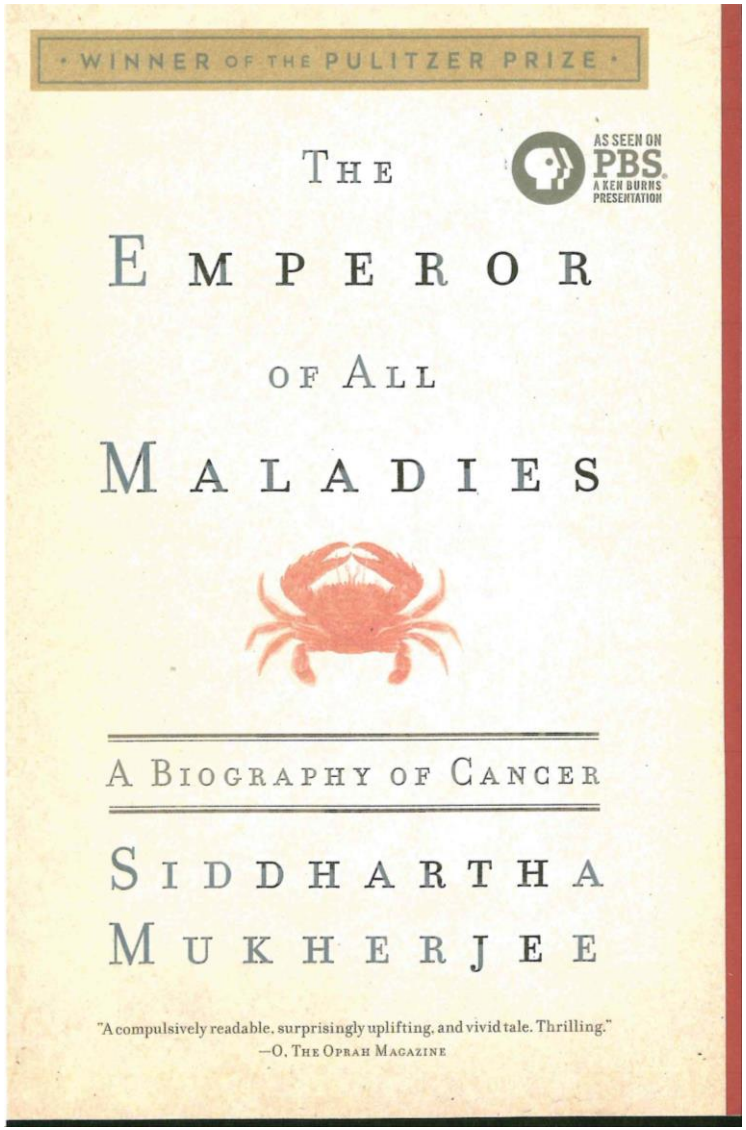
Background

- Mid 1970's Anthracycline caused decrease in LV ejection fraction
- Most toxicity in first year post Rx
- Toxicity from Anthracycline may not be evident for years or decades after exposure
  - As high as 8% of patients
  - May appear 10-20 years later

Scientific American August 2016

- Cancer approx. 13% of total deaths in the world
- In 2013, Breast, Lung, Colorectal Cancer accounted for 6-8 years of lost healthy life in US, UK, Australia
- Cancer-curse of the developing world




• WINNER OF THE PULITZER PRIZE •
AS SEEN ON PBS A KEN BURNS PRESENTATION
THE EMPEROR OF ALL MALADIES
A BIOGRAPHY OF CANCER
SIDDHARTHA MUKHERJEE
"A compulsively readable, surprisingly uplifting, and vivid tale. Thrilling."
—O, THE OPRAH MAGAZINE

Currently, there are more than-

- 14 million cancer survivors in the United States
- By 2020, 20 million survivors are expected
- Cancer drugs not only kill cancer cells, but also cause collateral damage to healthy cells

Incidence of cardiovascular disease in the cancer patient is higher than in the general population

Prevalence of Cardiovascular Diseases by Type of Malignancy

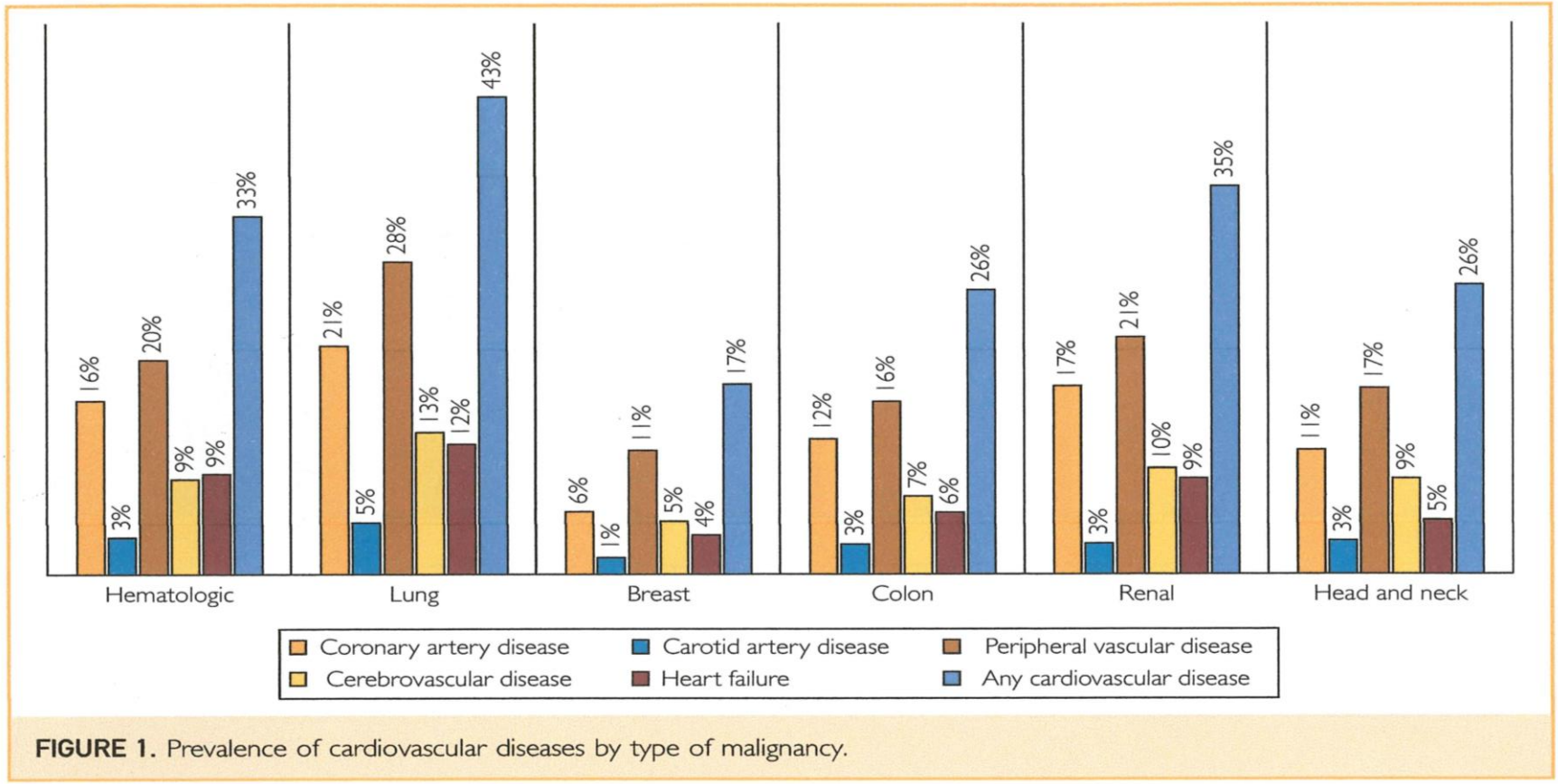


FIGURE 1. Prevalence of cardiovascular diseases by type of malignancy.

Management Strategies by Type of Malignancy

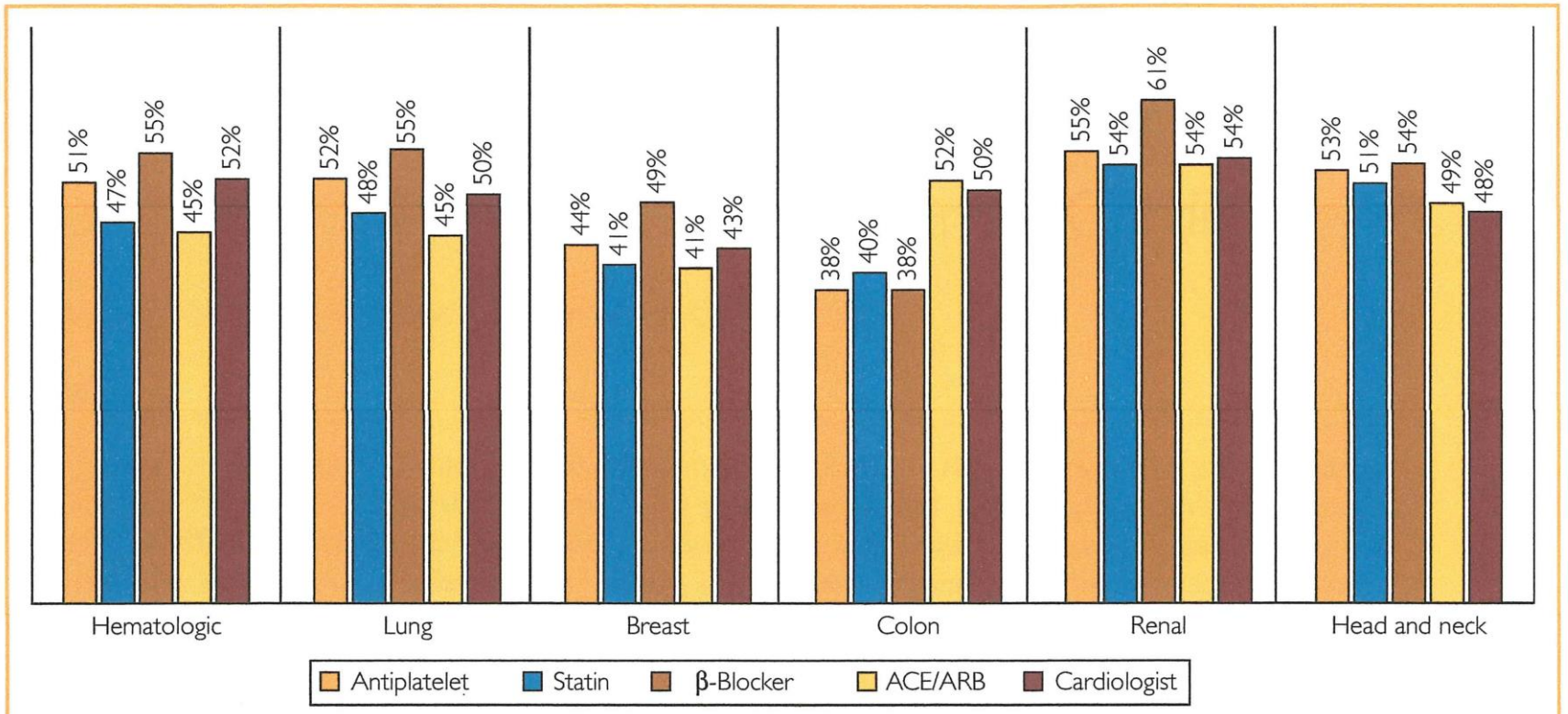


FIGURE 2. Management strategies in patients with cardiovascular disease by type of malignancy. ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Evaluation and Management of Patients with Heart Disease and Cancer: Cardiovascular -Oncology

Joerg Herrmann, MD; Amir Lerman, MD; Nicole P. Sandhu, MD, PhD; Hector R. Villarraga, MD; Sharon L. Mulvagh, MD; and Manish Kohli, MD

Abstract

The care for patients with cancer has advanced greatly over the past decades. A combination of earlier cancer diagnosis and greater use of traditional and new systemic treatments has decreased cancer-related mortality. Effective cancer therapies, however, can result in short- and long-term comorbidities that can decrease the net clinical gain by affecting quality of life and survival. In particular, cardiovascular complications of cancer treatments can have a profound effect of the health of patients with cancer and are more common among those with recognized or unrecognized underlying cardiovascular diseases. A new discipline termed ***cardiovascular-oncology*** has thus evolved to address the cardiovascular needs of patients with cancer and optimize their care in a multidisciplinary approach.

 ■ Mayo Clin Proc. 2014:89(9):1287-1306

Cardiovascular - Oncology

- Integration of care to optimize the best outcome for the cancer patient
  - Concept is not new
  - **Goal** – Maximize survival of cancer patient, minimize adverse cardiac effect of therapy, and enhance Quality of Life.

Cardiovascular-Oncology – Why?

- Address Cardiovascular needs of the cancer patient
- Collaborative effort of multiple disciplines
  - Cardiology ⟷ Oncology
  - Radiation oncology
  - Pharmacologist
  - Imaging specialists
    - Ultrasound, MR, PET, Nuclear
  - Nursing
  - Dieticians
  - Social Workers
  - Physiatrists
  - Spiritual
  - Alternative Therapies

Team Approach

- Cancer and its therapy results in fatigue and frequently shortness of breath (for many reasons)
- In this setting, there is a clear need to know if there is preexisting heart disease
- Post cancer therapy - there is need for long term continued observation and care

It is important to recognize that all chemotherapy agents may have potential cardiotoxic effects.

Heart Failure	Severity
Anthracyclines	+++
Cyclophosphamide	++
Mitomycin	++
HER2 antagonists	+++
Alemtuzumab	+
VEGF inhibitors	+
Paclitaxel*	+
Docetaxel*	+
Carfilzomib	+
Ischemia	
Fluorouracil	++
Cisplatin	++
Capecitabine	+
Interleukin-2	+
Paclitaxel	+
Androgen Deprivation Therapy	++
Hypertension	
VEGF inhibitors	+++
Cisplatin	+++
Interferon-alpha	++
Pulmonary Hypertension	
Dasatinib	+
Bradycardia	
Paclitaxel	++
Thalidomide	+
Arterial Thrombotic Events	
Bevacizumab	+
Nilotinib	++
Ponatinib	++

QT Prolongation	Severity
Arsenic Trioxide	++++
Vorinostat	+
Dasatinib	+
Lapatinib	+
Nilotinib	+
Atrial Fibrillation	
Anthracyclines	+
Cisplatin	++
Melphalan	++
Interleukin-2	+++
Ibrutinib	+++
Thromboembolism	
VEGF inhibitors	++
Erlotinib	++
Thalidomide	+++
Lenalidomide	+++
Tamoxifen	+
Cisplatin	++
Vorinostat	+
Edema	
Imatinib	+++
Thalidomide	++
Bortezomib	++
Carfilzomib	++
Pericardial Effusion	
Dasatinib	+

Table 1

Cardiotoxicity Associated With Various Cancer Therapy Agents

Severity is denoted by + signs.

*In conjunction with anthracyclines.

HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor.

Modified from Yeh ET, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation 2004;109:3122-31.

ASE Definition

- CTRCD – Cancer Therapeutics-Related Cardiac Dysfunction
  - Decrease in $LVEF_X$ >10% to value <53%
- Reversibility
  - Reversible to within 5% of baseline
  - Partially reversible
    - Improve by >10% points but remaining >5% points below baseline
- Irreversible
  - Improved by <10% points and remaining >5% points below baseline

Cardiotoxicity – National Cancer Institute

- Chemo/Radiation may have adverse effects on heart and/or vascular system
- Cancer patients are surviving longer-important to recognize late cardiotoxicity
  - Direct effect on Cardiac Myocytes → CHF
  - Indirect effects
    - Hypertension/systemic/pulmonary effects
    - Arterial/venous vascular effects
      - Coronary artery disease
      - Thromboembolism
    - Arrhythmias-conduction abnormalities
    - Valvular disease
    - Pericardial disease

Cardiotoxicity – National Cancer Institute *Con't*

- May cause changes in drug metabolism
  - Calcium channel blockers may increase intracellular levels of cardiotoxic therapy
    - e.g. Verapamil, Diltiazem

Another Definition for Cardiotoxicity

Cardiovascular Toxicity

Any disorder (abnormality) of heart or circulatory system that occur during or after anti cancer therapy.

Pharmacological Reports - 67 (2015) 1098-1102

Collateral Damage of Cancer Therapy

- Cardiac
- Vascular
- INCREASED RISK OF DEVELOPING NEW CANCER

Cardiotoxicity in Real World

Unfortunately-

- Potential cardiotoxicity effects not recognized until released into the “real world of chemotherapy”

- Cancer trials exclude cardiac patients

Cardiovascular - Oncology – Goals

- Recognize cancer patient at increase risk to develop cardiac toxicity
- Prevent adverse effects
  - Early recognition
  - Careful monitoring
  - Provide protective medication
  - Manage, minimize toxicity
- **ENHANCE QUALITY OF LIFE**
- **CANCER PATIENT SHOULD NOT BECOME HEART FAILURE PATIENT**

Common Access Point – Cancer Center

Clinically

- Heart failure symptoms/not always obvious:
- Signs of Heart Failure
  - Tachycardia
  - Edema
  - S_3 Gallop

Once the ejection fraction is reduced, there already is advanced disease

Characteristics of Type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-Blockers, ACE inhibitors	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2-4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effects of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

Type 1 - Cardiotoxicity

- Anthracyclines (doxorubicin, epirubicin)
  - DNA Fragmentation
  - Release O_2 Free Radicals
- Dose Dependent
  - >550 mg/m² – 25% risk
  - Risk factors for toxicity-age, history of heart disease, female gender, radiation therapy, other chemo agents, decrease ejection fraction <50%
- Risk increased if given with Herceptin (trastuzumab)

Type 1 – Cardiotoxicity *Con't*

- Anthracyclines
  - Effective anticancer therapy discovered 50 years ago (Dr. Paul Ehrlich "Chemotherapy")
  - Still play important role in current therapies
    - Risk for CHF up to 400mgm/m^2 $\longrightarrow$ 5%

Type II - Cardiotoxicity

- Trastuzumab (Herceptin)
  - R_x: HER-2 Positive Metastatic Breast Cancer
  - Inhibits HER-2 Receptor
  - Severe heart failure up to 4%
  - Symptomatic heart failure up to 5%
  - Asymptomatic decrease cardiac function 14%

  - Usually reversible
  - May tolerate reintroduction after recovery

Those who fail to recover = previously exposed to Anthracycline
Recovery (6-12 months)?

Other HER2 Antagonists

- Lapatinib (Tykerb)
- Pertuzumab (Perjeta)
- T-DMI (Kadcyla)
- ? May have less cardiotoxicity

Cardiac Ischemia

- Coronary Vascular Endothelial Dysfunction
- Coronary Vasospasm (etoposide)
- Vaso occlusive complication (vinblastine)
- Atherogenic effects of Chemo

Arrhythmia

- Direct toxicity
- Metabolic changes
  - Interleukin 2 (Proleukin)
    - Increase vascular permeability
    - Volume depletion
  - Repolarization abnormality (arsenic-increase QT 40%)
  - Change in hepatic metabolism
  - Drug – Drug interaction (imatinib)

Pericarditis

- Inflammation / myopericarditis
  - Cyclophosphamide, cytarabine, bleomycin

Thrombo Embolic Complications

- Hypercoagulable state and vascular injury
  - Thalidomide
- ASA?
- CANCER PATIENTS “CLOT **AND** BLEED”!

Radiation Therapy

- Improves outcomes in a variety of malignancies
- May have serious side effects
- “Recent” changes in radiation therapy have decreased changes secondary to radiation

Radiation Therapy

- Late effects usually second to third decade Affects 10-30% by 10 years post therapy
- Children as young as 12
  - Sudden death secondary to left main stenosis post therapy

Radiation Therapy

- Valvular fibrotic change
- Endothelial damage → CAD
- Myocardial fibrosis systolic / diastolic dysfunction
- Pericarditis / Constrictive
- Additive effect with chemo

Radiation Therapy - Pathophysiology

- Inflammation, DNA Disruption, Endothelial Dysfunction, Fibrosis, Small Vessel Occlusion
- Synergistic effect with Chemo

Radiation Effects on the Heart/Vessels

- CAD / Vascular
- Valvular (Mitral & Aortic)
- Myocardial Disease
  - Cardiomyopathy
    - Systolic
    - HFPEF
- Pericardial
- Conduction System Disease

CAD - Radiation Effects

- Ostial Stenosis
  - Left main
  - RCA
  - LAD
- Vascular → Carotid, subclavian internal mammary!
- Valvular
  - Aortic / Mitral
  - Regurgitation early (Retraction)
  - Stenosis, calcification (Late)
    - 25% → Ca^{++} Aortic – Mitral Curtain

Pericardial

- Acute (weeks)
- Chronic
  - 5-10 years - constrictive, effusive constrictive
- Conduction System
  - RBBB LBBB
    - Pacemaker
  - Ventricular ectopy
  - Autonomic Dysfunction
    - ? Denervation
    - Persistent tachycardia

Post Radiotherapy Evaluation

- Not Clear
- Baseline Stress Echo at 5 years?
  - Or after age of 30
- Now pregnant
  - Assess during 2nd trimester
- Annual EKG
  - Conduction Disease
  - Athletic Screening
  - ? MR, ? Ca Score
- Caroid ultrasound/cerebro vascular disease
- Exam/Bruit?

Who Should Be Evaluated?

- Team Approach
  - Evaluation of previously treated patients
  - Pre-cancer therapy
  - Ongoing evaluation during therapy
  - Post therapy – F/U – Decades
  - To include specialized therapies for complications beyond CHF, (i.e. arrhythmias, end stage disease)
  - Metastatic, invasive disease
  - Preop surgical cancer patient?
  - (inpatient consultation)

Guidelines-Don't Exist

- Consensus Statements
  - ASE
  - European Society of Cardiology
  - Cancer Society
  - SCAI
- Nuclear Medical Society
- No guidelines for monitoring more than 70 agents currently available
- No guidelines for long term surveillance post cancer treatment

Evaluation to Include

- Detailed clinical cardiovascular evaluation ("Risk Score")
- EKG, Chest X-ray
- Baseline Echo, Serial Echo, EFX (Preferably 3D), 2D (Biplane Simpsons) contrast, wall motion score index
- Strain – Detect Subclinical LV systolic dysfunction

Cardiac Ultrasound

- Preferably 3D if available
- Important to calculate $LVEF_X$
- Consecutive studies, preferably same:
  - Lab
  - Personnel
  - Vendor

Diastolic parameters are currently not recommended in predicting LV dysfunction (they are not good predictors of future systolic dysfunction)

Plana
European Assoc. Cardiovascular Imaging-2014

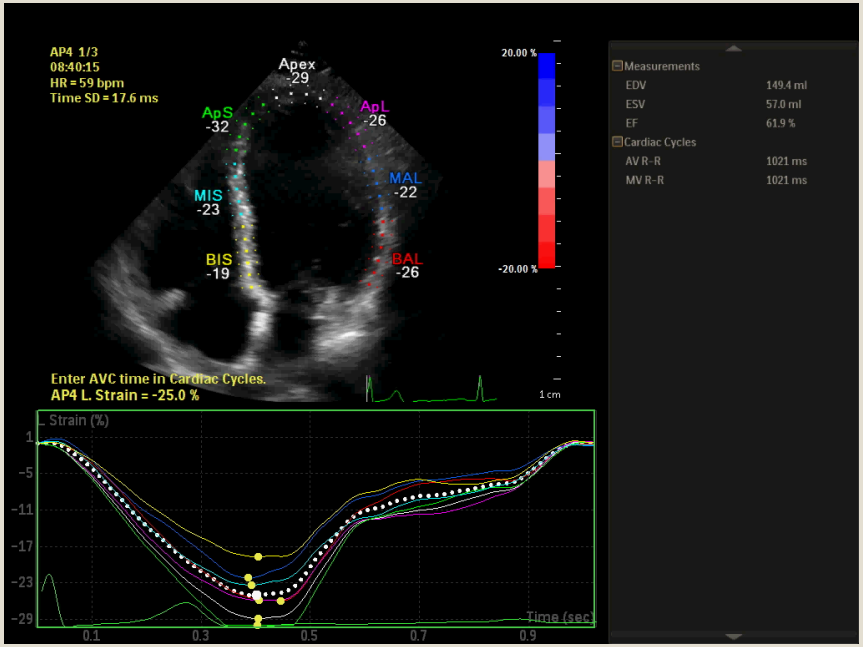
Myocardial deformation is best for early detection of cardiotoxicity

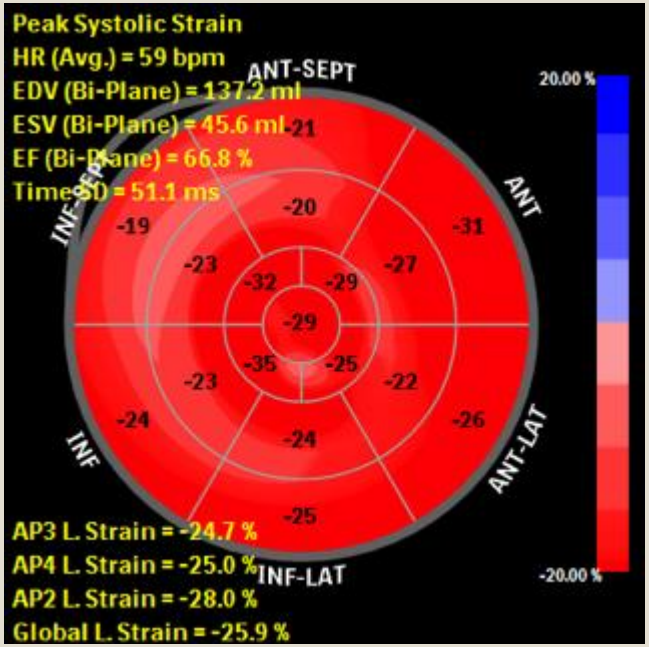
Thavendiranathan
JACC -2014

Myocardial Deformation (Strain)

- Robust method to measure myocardial function
- Strain=dimension less index reflecting deformation of myocardium during one cycle length
  - It is measured as a percentage of its initial length
  - Prognosticates decrease in $LVEF_X$

LV Strain


AP4 1/3
08:40:15
HR = 59 bpm
Time SD = 17.6 ms
Apex
-29
ApS
-32
ApL
-26
MIS
-23
MAL
-22
BIS
-19
BAL
-26
20.00 %
-20.00 %
Measurements
EDV 149.4 ml
ESV 57.0 ml
EF 61.9 %
Cardiac Cycles
AV R-R 1021 ms
MV R-R 1021 ms
Enter AVC time in Cardiac Cycles.
AP4 L. Strain = -25.0 %
1 cm
L Strain (%)
Time (sec)


Peak Systolic Strain
HR (Avg.) = 59 bpm
EDV (Bi-Plane) = 137.2 ml
ESV (Bi-Plane) = 45.6 ml
EF (Bi-Plane) = 66.8 %
Time SD = 51.1 ms
ANT-SEPT
ANT
ANT-LAT
INF-LAT
INF
INF-SEPT
20.00 %
-20.00 %
AP3 L. Strain = -24.7 %
AP4 L. Strain = -25.0 %
AP2 L. Strain = -28.0 %
Global L. Strain = -25.9 %

Risk Assessment

Medication-related risk	Patient-related risk factors
High (risk score 4):	Cardiomyopathy or heart failure
Anthracyclines, Cyclophosphamide, Ifosfamide, Clofarabine, Herceptin	CAD or equivalent (incl. PAD)
Intermediate (risk score 2):	HTN
Docetaxel, Pertuzumab, Sunitinib, Sorafinib	Diabetes mellitus
Low (risk score 1)	Prior or concurrent anthracycline
Bevacizumab, Dasatinib, Imatinib, Lapatinib	Prior or concurrent chest radiation
Rare (risk score 0)	Age <15 or >65 years
For example, Etoposide, Tituximab, Thalidomide	Female gender

Overall risk by Cardiotoxicity Risk Score (CRS)

(Risk categories by drug-related risk score *plus* number of patient-related risk factors:
CRS>6: very high, 5-6: high, 3-4: intermediate, 1-2: low, 0: very low)

Monitoring Recommendations

- **Very high cardiotoxicity risk:** TTE with strain before every (other) cycle, end, 3-6 months and 1 year, optional ECG, cTn with TTE during chemotherapy
- **High Cardiotoxicity risk:** TTE with strain every 3 cycles, end, 3-6 months and 1 year after chemotherapy, optional ECG, cTn with TTE during chemotherapy
- **Intermediate cardiotoxicity risk:** TTE with strain, mid-term, end and 3-6 months after chemotherapy, optional ECG, cTn mid-term of chemotherapy
- **Low cardiotoxicity risk:** Optional TTE with strain and/or ECG, cTn at the end of chemotherapy
- **Very low cardiotoxicity risk:** None
  - Mayo Clinic
    - ?? Over test

Management Recommendations

- **Very high cardiotoxicity risk:** Initiate ACE-I/ARB, Carvedilol, and statins, starting at lowest dose and start chemotherapy 1 week prior to initiation to allow steady state, up-titrate as tolerated
- **High cardiotoxicity risk:** Initiate ACE-I/ARB, Carvedilol, and/or statins
- **Intermediate cardiotoxicity risk:** Discuss risk and benefit of medications
- **Low cardiotoxicity risk:** None, monitoring only
- **Very low cardiotoxicity risk:** None, monitoring only

Most Commonly Used Chemotherapeutic Agents with Cardiotoxicity Potential

Chemotherapeutic class and agents	Cardiomyopathy incidence	Other types of cardiovascular toxicity
Anthracyclines-Doxorubicin	3% - 26%	Myopericarditis, cardiac arrhythmias, ECG abnormalities
Epirubicin	0.9%-3.3%	Cardiac arrhythmias, ECG abnormalities
Idarubicin	5%-18%	ECG abnormalities
Mitoxantrone	0.2%-30%	Cardiac arrhythmias, ECG abnormalities, myocardial ischemia, hypertension
Alkylating agents-Cyclophosphamide (high dose)	7%-28%	Peri-/myocarditis, cardiac tamponade, arrhythmias
Ifofamide	17%	Arrhythmias, cardiac arrest, myocardial hemorrhage, myocardial infarction
Busulfan	Rare	Endomyocardial fibrosis, pericardial effusion and tamponade, ECG changes, chest pain, hyper-/hypotension, thrombosis, arrhythmias
Mitomycin	10%	
5-Fluorouracil	2%-20%	Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes including ventricular ectopy, hypotension
Capecitabine	2%-7%	Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes, thrombosis
Cytarabine	Undefined	Pericarditis, chest pain (including angina)
Platinum agents Cisplatin	Rare	Arterial vasospasm, cardiac/cerebral/mesenteric/limb ischemia, hypo-/hypertension, arrhythmias
Antimicrotubule agents - Viscristine	25%	Hyper-/hypotension, myocardial ischemia and infarction, arrhythmias

Monoclonal anti-body based tyrosine kinase inhibitors

Chemotherapeutic class and agents	Cardiomyopathy incidence	Other types of cardiovascular toxicity
Bevacizumab	1.7%-3%	Hypertension, arterial and venous thromboembolism
Trastuzumab	2%-28%	Hyper-/hypotension, arrhythmia, vascular thrombosis
Pertuzumab	3%-7%	Hypo-hypertension, arrhythmia
Alemtuzumab	Rare	
Small-molecule tyrosine kinase inhibitors-Dasatinib	2%-4%	Pericardial effusion, hypertension, arrhythmia, QT interval prolongation
Imatinib mesylate	0.5%-1.7%	Pericardial effusion, and tamponade, anasarca, arrhythmias, hypertension, Raynaud disease
Lapatinib	1.5%-2.2%	QTc interval prolongation, myocardial ischemia (Prinzmetal angina)
Sunitinib	3%-15%	Hypertension, arterial and venous thrombosis, arrhythmias, aortic dissection, QTc prolongation
Sorafenib	4%-28%	Hypertension, thrombosis, coronary vasospasm, myocardial ischemia/infarction
Pazopanib	7%-13%	Hypertension, thrombosis, myocardial ischemia/infarction, bradycardia, QTc interval prolongation
Proteasome inhibitor-Bortezomib	2%-5%	Ischemia, bradycardia
Miscellaneous All-trans-retnoic acid	6%	Hypotension, pericardial effusion
Pentostatin	3%-10%	Myocardial ischemia and infarction, acute arrhythmias
Interferon alpha-2b	25%	Hypotension, myocardial ischemia and infarction, ECG changes, sudden cardiac death
Afibercept	1%-6.8%	Hypertension, myocardial ischemia/infarction stroke

Strain Studies

- Sensitive measure of change in myocardial mechanics
  - Detect subclinical LV systolic dysfunction
- Some variation Men and Women
- Normal
  - Men 20.7 ± 2
  - Women 22.1 ± 1.8
- Tend to decrease with age
- Inter-vendor and software variability

Strain Studies – *Cont.*

- Abnormal
  - Reduction <8% - not significant
  - Reduction >15% clinically likely to be significant
- Limitations of Strain
  - Quality of image
  - Loading conditions
  - Lack of long term clinical trials
  - ? reproducibility
  - Vendor, software specific

Additional Studies May Include

- Evaluate valvular disease - TTE
- TEE may be necessary
- Pericardial evaluation
  - MR
  - CT
- Vascular disease
  - US carotids
  - ABIs

Stress Echocardiography

- Evaluate subclinical LV dysfunction
- Evaluate contractile reserve (patient with known CTRCD)
  - Dobutamine stress
- Treatments causing ischemia
  - Fluorouracil, Bevacizumab, Sorafenib, Sunitinib

Biomarkers

- Early identification and monitoring of CTRCD
- Troponin
  - Sensitive for myocardial injury
  - May identify early injury in patients receiving newer targeted R_x (Anti-VEGF, tyrosine kinase inhibitors)
  - Normalization with β Blocker, ASA , ACE, may allow rechallenge with drug
  - ? When to draw, how often, normal cut off

Biomarkers - *Cont.*

- BNP (Brain Natriuretic Peptide)
  - Reflect elevated filling pressures
  - Not consistent in identifying CTRCD?

Kinase Inhibition

- Monoclonal Antibody
- Small molecule kinase inhibitors
- VEGF inhibitors (signal pathways)
- TKIs with anti VEGF activity

Monoclonal Antibody

- Trastuzumab
  - Targets HER2 receptor
  - Symptomatic CHF 2-4%
  - Asymptomatic dysfunction 3-19%
  - 1/3 may have persistent cardiac dysfunction

VEGF Signaling Pathway Inhibitor

- Bevacizumab
- Sunitinib
- Sorafenib
- Ponatinib

- Increase BP 25-60% of patients
- Increase thrombotic vascular events
  - 10% risk of asymptomatic cardiac dysfunction
  - High incidence of thrombotic microangiopathy on renal biopsy (similar changes in preclampsia)

Small Molecule Inhibitors

- Imatinib
- Dasatinib (develop pulmonary hypertension)
- Nilotinib
- Ponatinib
  - Cardiac events, CNS, PAD (increased risk with associated cardiac risk factors)
- Ibrutinib
  - 3% incidence Atrial Fib

Immune Modulating Drugs

- Thalidomide, Lenalidomide
  - Risk arterial (MI, CVA) events

Proteasome Inhibitor

- Carfilzomib
  - CHF, Venous Thromboembolic Disease, Hypertension

Check Point Inhibitor

- Autoimmune myocarditis reported

Cardiovascular Effects of Targeted Cancer Therapies

New England Journal of Medicine October 13, 2016 pg. 1465

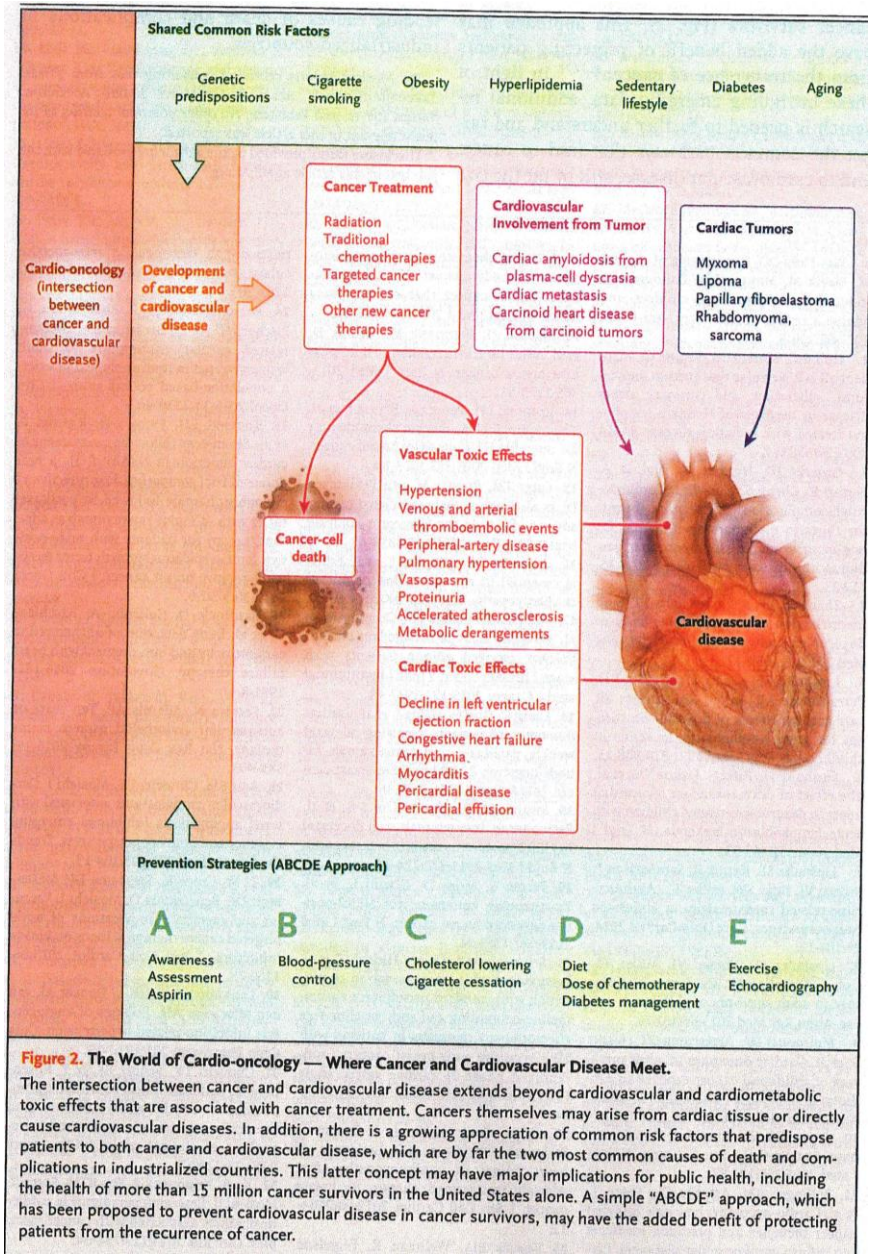


Figure 2. The World of Cardio-oncology — Where Cancer and Cardiovascular Disease Meet.

The intersection between cancer and cardiovascular disease extends beyond cardiovascular and cardiometabolic toxic effects that are associated with cancer treatment. Cancers themselves may arise from cardiac tissue or directly cause cardiovascular diseases. In addition, there is a growing appreciation of common risk factors that predispose patients to both cancer and cardiovascular disease, which are by far the two most common causes of death and complications in industrialized countries. This latter concept may have major implications for public health, including the health of more than 15 million cancer survivors in the United States alone. A simple "ABCDE" approach, which has been proposed to prevent cardiovascular disease in cancer survivors, may have the added benefit of protecting patients from the recurrence of cancer.

ABCDE Approach (Prevention)

- A
  - Awareness
  - Assessment
  - Aspirin
- B
  - Blood Pressure Control
- C
  - Cholesterol lowering
  - Cigarette Cessation
- D
  - Diet
  - Chemo Dose
  - Diabetic Control
- E
  - Exercise
  - Echo Surveillance

Moslehi, NEJM Oct 2016

Stanford Protocol for Monitoring Targeted R_x

Baseline Assessment
LVEF BNP
BP Control

BP at every clinic visit
– home monitoring

SBP > 140
SBP > 90

Start Therapy

Repeat at 1 month and every
3 months on treatment

10% Fall in LVEF Increase BNP or
100% Increase over baseline

Screen for HF
Symptoms

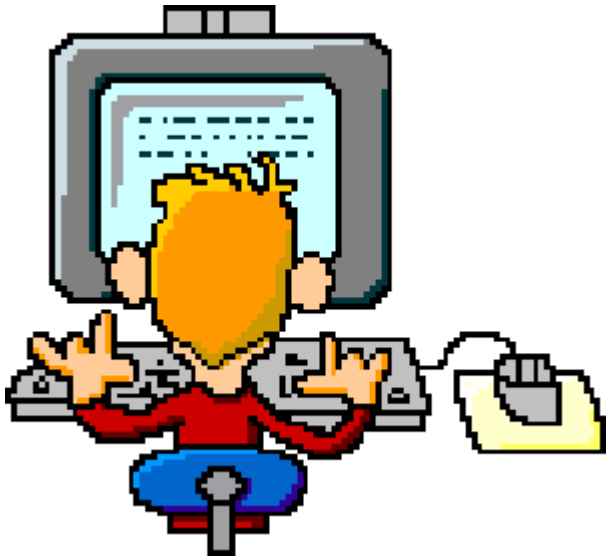
Symptoms

CHF Clinic

Case Slide

- Case

Best Monitoring Approach Requires Further Research



Other Monitoring Modalities

- MUGA (Traditional, 1970's - evaluate anthracycline toxicity)
  - Reproducible, serial testing
  - Disadvantage
    - Radiation exposure
  - No information re: Atrial size, valvular or pericardial disease
  - Maybe complementary to Echo

Other Monitoring Modalities

- CMR
  - Reference standard for LV, RV volume and function
  - Gold standard for myocardial viability
  - Detects decrease LV mass
  - Good correlation with Echo
  - Detect cardiac metastasis or invasion

If discontinuation of chemo therapy is being considered, and there is question of technical quality of Echo, then MR should be performed.

Earliest change maybe tissue edema.

Pyrophosphate Scan

- Annexin also shown to identify apoptosis on nuclear imaging – very early change
- Further study pending out of Canada

Posterboard Vancouver 10/2016

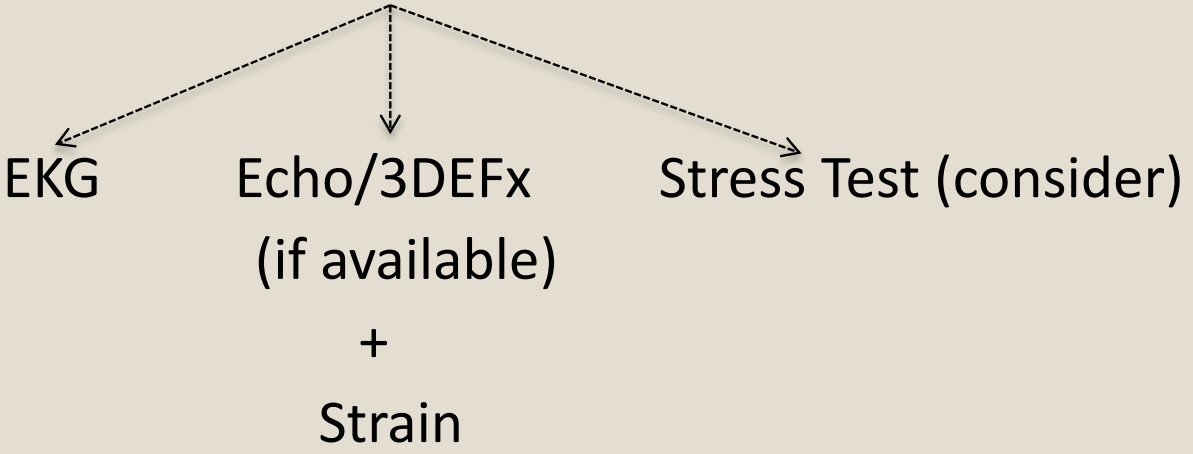
What should we do with our current knowledge base?

- Multidisciplinary approach requiring close collaboration between oncology and cardiology
- Baseline Assessment –
  - Every Patient? IDEAL
  - Risk score
  - Receiving Type 1 dose > 350mg/m^2 or combo Type I and II

Evaluation

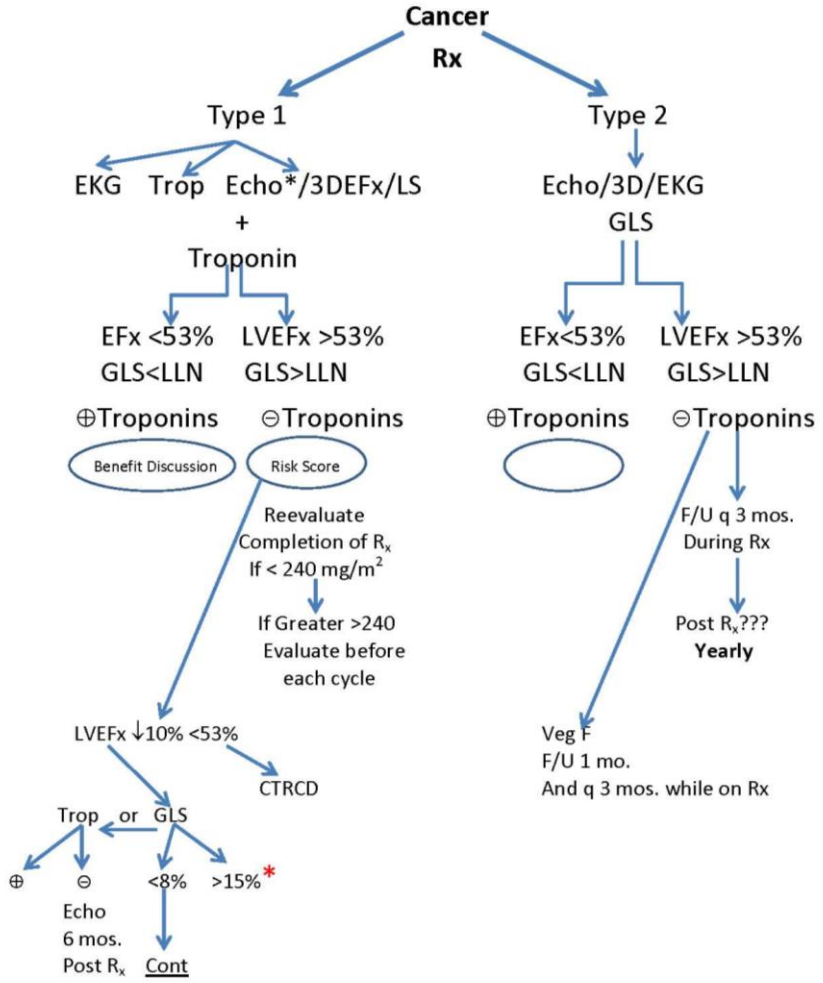
- Prior exposure to chemotherapy/radiation
  - Identify cancer
  - Identify agent
  - Radiation chemo R_x | How Much/Cancer Site

***HISTORY and CARDIOVASCULAR EXAM**



  - R_x Risk Factors
  - Surveillance

Pre Therapy

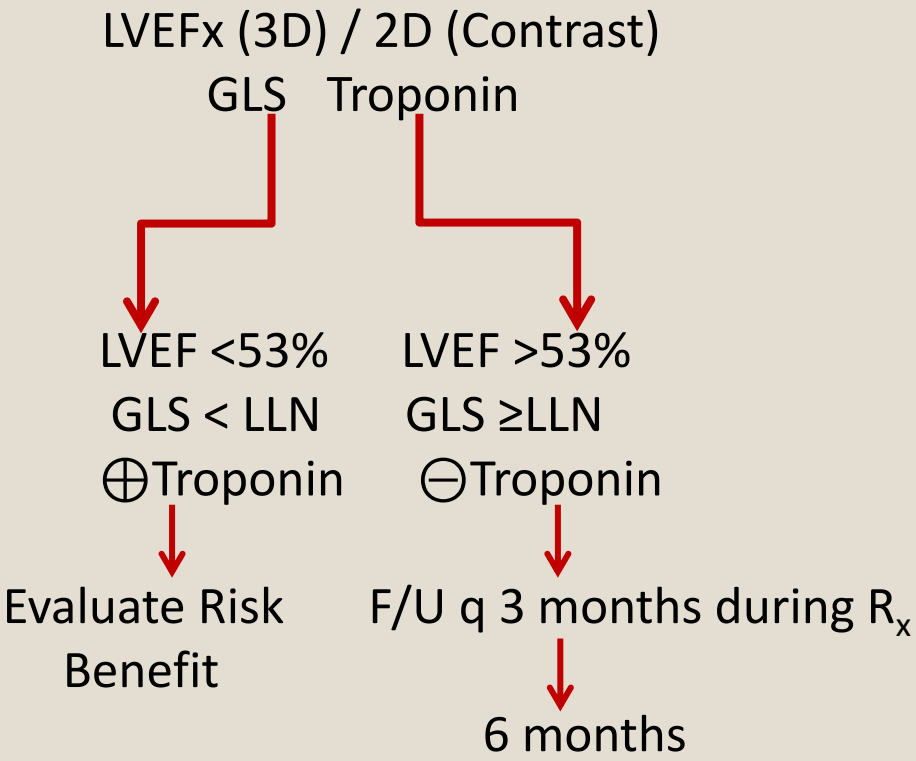


*If suboptimal Echo → CMR
LLN – Define <-18%
3D / or 2D – Biplane Simpsons /Contrast

*Confirm CMR after each cycle

Type 2 Following Type 1

Baseline



Treatment Available

- ACE
- ARB
- β Blocker (carvedilol preferred)
- ASA?
- Statin
  - Aldosterone
  - Dexrazoxane
- Stem Cell?
  - Anthracycline Cardiomyopathy
- LVAD?
- Transplant?

- Ongoing multiple studies
  - MANTICORE, PRADA, SUCCOUR, ELEVATE

Follow Up Essential

- How long?
- Frequency?
- How long Cardioprotection?
  - ? 12 months if normalized

- But – Late Cardiotoxicity May Be Decades

Primary Prevention – Small Study Size

- Relative risk reduction for LV dysfunction
  - β Blockers – 37-84%
  - ACE Inhibition (ARB) – 71-96%
  - Statin – 23-87%
  - Dexrazoxane – 55-73%

Eut J Cancer
2013:49 2900-9

Cardio-Oncology Services UK-2016

- Lack of consensus on management
- 13% of UK centers with Cardio-Oncology clinics
- Wide variation in practice among centers
- Looked at Anthracycline, Trastuzumab, and Radiotherapy possible toxicity
- Cardio-Oncology clinics performed more intensive monitoring

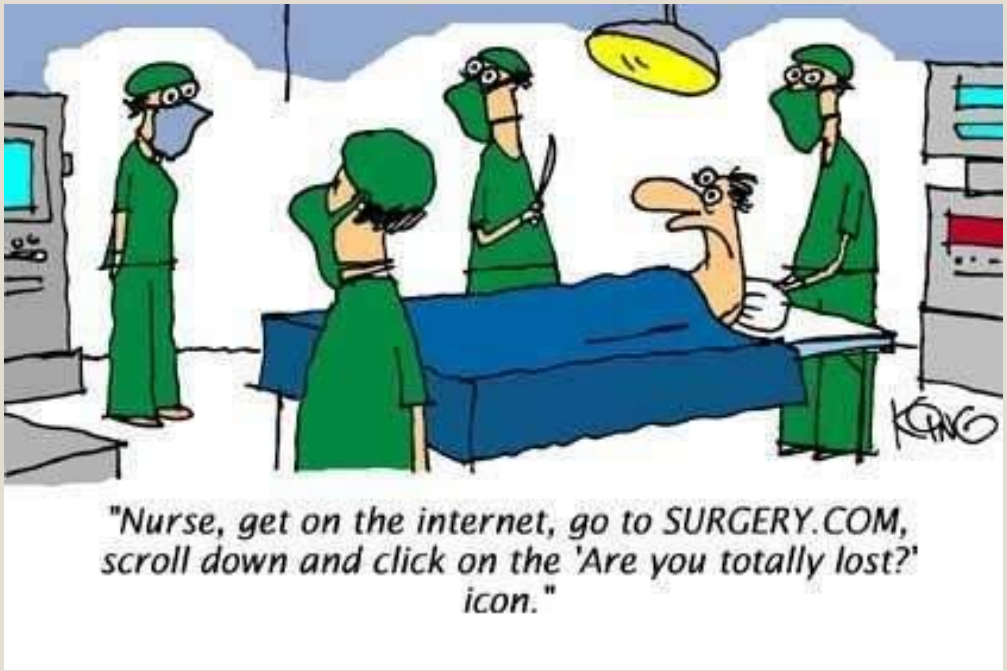
- Need:
  - Organization of Cardio-Oncology Services
  - Protocols/Guidelines for toxicity
  - Measure patient outcomes

JACC 2016 Vol 67 Issue 12

Should we develop a curriculum for cardiovascular oncology?

Fellowship Training – what's out there

- 7 Fellows in US / Canada - 2014
- No accreditation
- No internal funding
- No recognized structure to follow



Goals of the Curriculum

- Convey a knowledge base. Stimulate research.
- Integrate into mainstream cardiology and oncology training programs
- Reshape the mindset about traditional roles of cardiologists and oncologists .
- Graduates expand best practices outside the cloistered "cardio oncology centers", improve practice, lessen disparities in practice.

Richard M. Steingart MD
Chief, Cardiology Service
Memorial Sloan-Kettering Cancer Center

Level 1 (Internal Medicine Residents)

- Basic knowledge of cancer agents and their potential to cause cardiac damage
- Imaging strategies – basic knowledge on cardiac imaging in oncology patients
- Basic understanding of treatment strategies for cancer patients experiencing cardiac toxicities

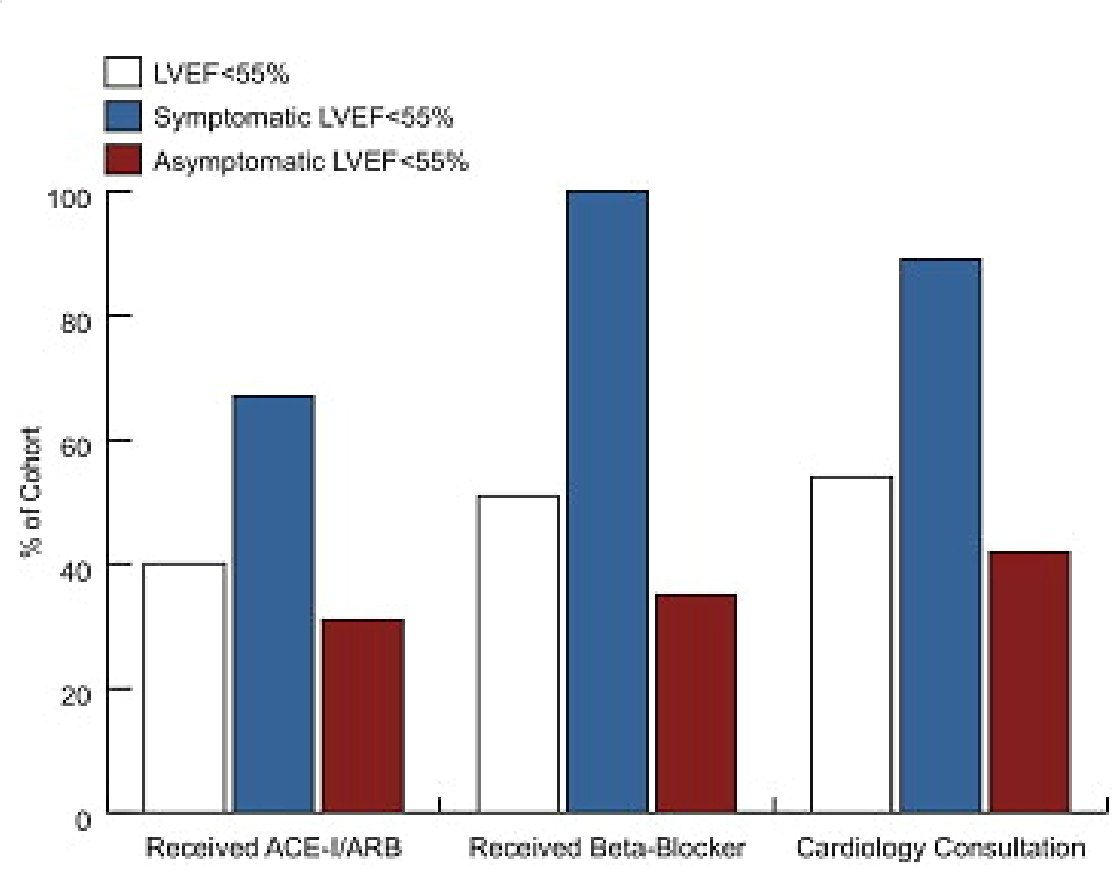
Level 2 (Medical/Cardiology Resident)

- For residents who wish to broaden their exposure to cardiac oncology patients
- More detailed assessment of patients
- Intermediate knowledge base
- More exposure to advanced cardiac imaging eg. advanced echocardiography (strain/3D)
- Understanding of the role of biomarkers in early detection of cardiac toxicity

Level 3 (Cardiac Oncology Fellow)

- 12-24 months of dedicated fellowship training
- Advanced knowledge of cancer agents and potential toxicities
- Broad exposure to in - and out-patients
- Training in biomarkers, advanced imaging
- Actively involved in research

Why do we need cardiac oncologists?



Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies : Are Clinicians Responding Optimally?

Yoon , Telli , Kao , Matsuda , Carlson , Witteles

Journal of the American College of Cardiology, Volume 56, Issue 20, 2010, 1644 - 1650

What is Needed!

- Network / Collaboration
  - Facilitate networking: ICOS
  - Create working groups
  - Publicize Cardio-Oncology: websites, social media
  - Facilitate Research Collaborations: invite participation – group efforts
- Clinical
  - Centralize existing resources, create guidelines
  - Create a learning pathway
- Training
  - Develop a Fellowship program
  - Standardized Curriculum

Cancer and Cardiology – Survivors

- Where is the problem?
  - More cancer survivors
  - More heart damage
- More attention
  - Major cancer institutes

Need to foster cooperation between Cardiology and Oncology

Going Forward

- Absolute Necessity
  - Oncology leader
  - Cardiology leader
- Goal
  - Better Oncology care
  - Better Cardiology care
- End Result
  - Improved Quality of Life for cancer patient

International Registry

OCTOBER 2015
ICOS SUMMIT / NASHVILLE

International Registry

October 2015 (Susan Dent)
ICOS Summit / Nashville

A Work In Progress

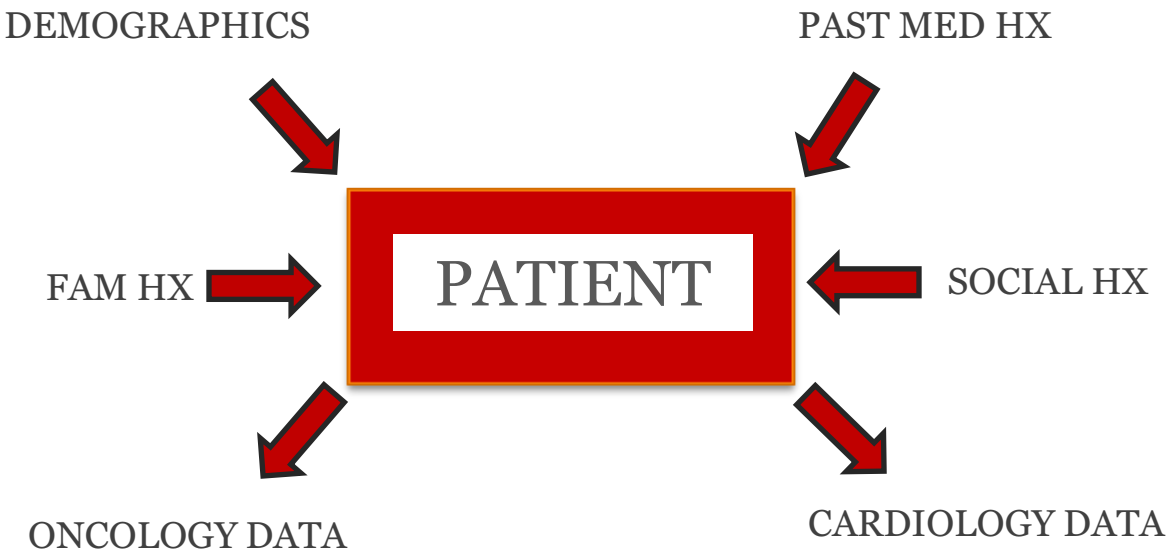
Vanderbilt
University of Pennsylvania
University Hospital
(La Paz, Madrid)
Vancouver General Hospital

Collecting 400 Data Elements

Clinical Database

International Registry

October 2015 (Susan Dent)
ICOS Summit / Nashville



- Clinical
- Pathology
- Lab
- Interventions
- Treatment
- Protocol

Retrospective Data _____ Prospective Data

International Registry

October 2015 (Susan Dent)
ICOS Summit / Nashville

INTERNATIONAL REGISTRY

OUTCOME

Develop Mathematical Models to **Predict** Cardio Toxicity

Develop **Surveillance** Strategies for Cancer Survivors

Take Home Messages

- Development of Cardio Oncology (Cardiovascular Oncology)
- Close Cooperation with
  - Medical Oncology Services
- Develop Q/A Committee
- Collaboration with
  - Major Centers – (Outreach Programs)
  - Sloan Kettering
  - Vanderbilt
  - Ottawa Medical Center

Take Home Messages (Cont'd)

- Combined Conference
  - With Major Center
  - Ex. Video Conference
- Community Involvement
  - Private Practice (Family Physician, Cardiology)
- Program Participation with
  - Rheumatology
  - Neurology
  - Nephrology
  - ?

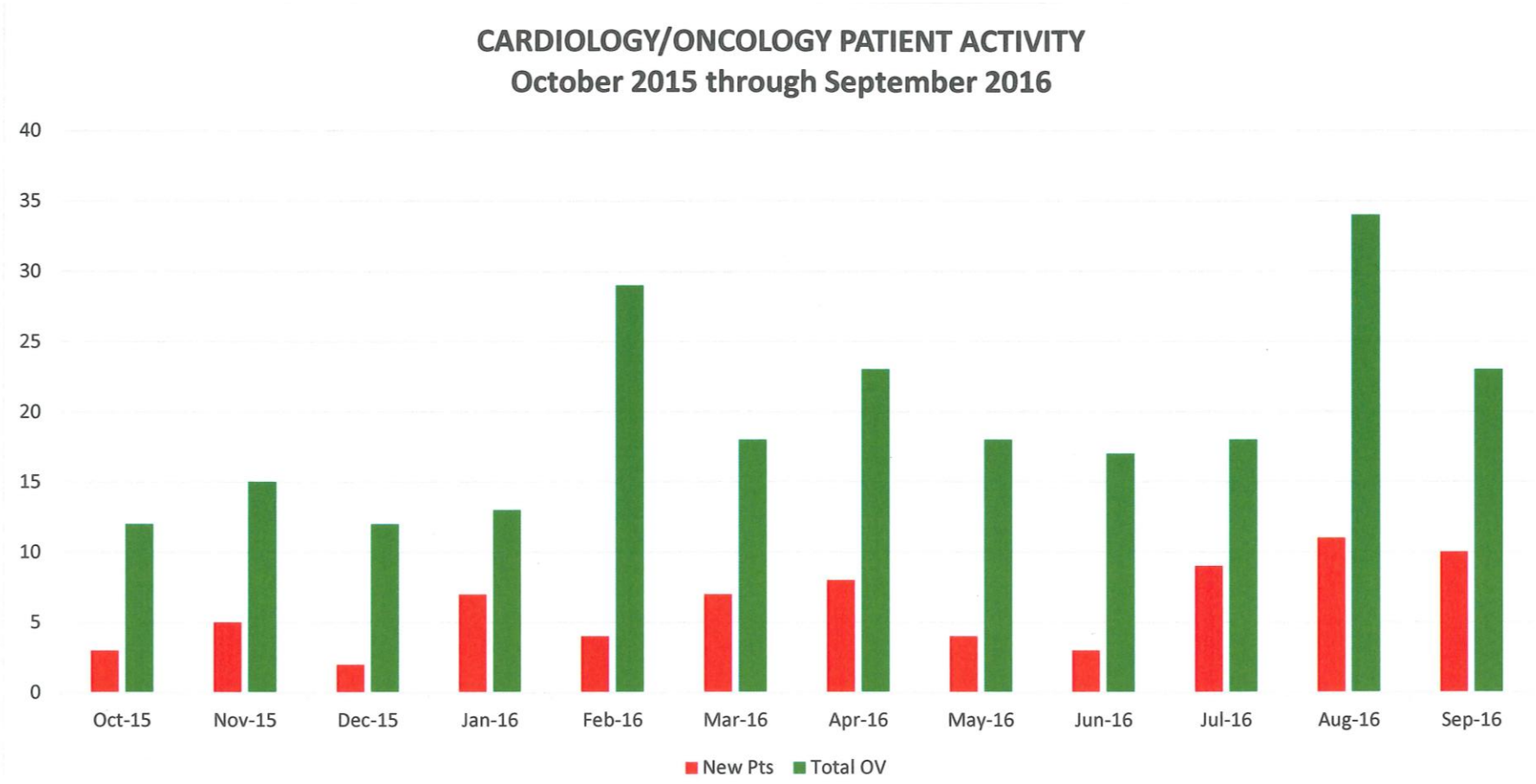
Take Home Messages (Cont'd)

- Image Evolution
  - ECHO Lab
  - MRI
  - PET
  - Nuclear Medicine
- Research Protocols (Pharmaceutical Support)
- Integration / Education
  - Medical Education

Take Home Messages (Cont'd)

- Development of Cardiovascular - Oncology Fellowship Program
- Expertise Requiring
  - Device Therapy / EP
  - Arrhythmia Management
  - PAD Management
  - Advanced CHF Program

Together we can make a difference in management of cancer patient and reduce the risk of developing heart failure.


CARDIOLOGY/ONCOLOGY PATIENT ACTIVITY
October 2015 through September 2016
40
35
30
25
20
15
10
5
0
Oct-15
Nov-15
Dec-15
Jan-16
Feb-16
Mar-16
Apr-16
May-16
Jun-16
Jul-16
Aug-16
Sep-16
New Pts
Total OV

In Conclusion

- We don't know what we don't know
- HOW can we make a difference?
  - **NOT** can we make a difference
- Final Question:
  - How important is a given medication for a patient?
  - Don't abandon the patient-
    - **Figure it out!**
- **Are you going to close your eyes OR are you going to look?**

Innovation

- We are in the innovation zone as described by Toby Cosgrove, MD in *The Cleveland Clinic Way*
- There needs to be collaboration across disciplines (multiple)
- We need new perspectives on old problems

I hope this has been a "pep talk" to encourage some of you to get involved in this fast changing field of **Cardiovascular Oncology**

The Future

- Restating words of Valentine Fuster, MD

  JACC, March 17, 2015 Editor

  - "Let us not…. fall into inertia… by acting as if our motor engine for curiosity and motivation is turned off."
- "What we know is a drop, what we don't know is an ocean" – Isaac Newton
- This is a fascinating field of which we know little.

Cancer survivor of today should not become the heart failure patient of tomorrow

-Mayo Clinic

The 17th Annual Benjamin Schuster, MD Colloquium

PRESENTED BY THE KETTERING CARDIOVASCULAR INSTITUTE

Cardiovascular Oncology– Avoiding a Broken Heart

Wednesday, February 22, 2017

The Benjamin and Marian Schuster Performing Arts Center
Dayton, OH

KETTERING Health Network.

$25 Registration fee (includes lunch)
3.5 CME ($50 fee for physicians)

To register and for more details visit:
ketteringhealth.org/2017Colloquium

SPEAKERS

Daniel Lenihan, MD, FACC
President, International CardiOncology Society - North America
Professor of Medicine
Director, Clinical Research Program, Vanderbilt Heart and Vascular Institute
Nashville, TN

Susan Dent, MD, FRCPC
President, Canadian Cardiac Oncology Network
Medical Oncologist, the Ottawa Hospital Cancer Center
Ottawa ON, Canada

John Groarke, MD, MSc, MPH
Cardiovascular medicine specialist at Brigham and Women's Hospital
Cardio-oncologist at Dana Farber Cancer Institute
Instructor of Medicine at Harvard Medical School
Boston, MA

Register Today @ *ketteringhealth.org/2017colloquium*

Questions?