Expert Consensus for MMI Evaluation of Adult Patients During and After Cancer Rx

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Disclosures
No Real or Potential Conflict of Interests for this Talk
“CTRCD”

Cancer Therapy Related Cardiac Dysfunction

Outline

Cancer and the Cardiovascular Specialist
- Radiation therapy effects
- Chemotherapeutics (and the CTRCD definition)

Complementary role of Multimodality Imaging
- Review of ASE / ESE Guidelines (#10 key points)
- Specific focus on Echo (3D, Speckle-tracking)

Case Example (impact of GLS)
Two most common Deadly Diseases

Nearly ~1 million pts / yr receive anthracycline Rx (a ~5% risk = 50,000)

AHA Heart Statistics. Circulation

QUESTION

Myocardial damage after anthracycline administration occurs when?

A. Within the first few hours of the initial dose
B. After 250 g/m2
C. Between 250-400 g/m2
D. After >400 g/m2
E. Highly variable & occasionally not at all
**ANSWER**

*Myocardial damage* after anthracycline administration occurs when?

A. *Within the first few hours of the initial dose*
B. After 250 g/m²
C. Between 250-400 g/m²
D. After >400 g/m²
E. Highly variable & occasionally not at all

**CHEMOTHERAPY** history

- Myocardial damage is **immediate** after anthracycline Rx but **significant cardiac reserve** limits detection (EF)
- 1960’s: life-saving chemotherapy causes cardiac toxicity
- Oncologists learned to **limit doses** to avoid this
- 1970’s: serial EMB best Se/Sp
- **Natural improvement** in drugs (**less doses**) and imaging (**MUGA / Echo**) made risk/benefit EMB **unfavorable**
- Thus, **cardiac damage** may not be seen with routine testing or may require **years** after Rx (childhood survivors)
Balancing Act of Goals

MUGA / RNA

10 unit fall in LVEF or <50%

15% of high risk pts developed CHF within 1Y after Rx

75 ........ 1095 mg/M2 → CHF +

30 ........ 880 mg/M2 → CHF -

Total cumulative dose of Doxo causing CHF was not very different from doses that did not
KEY POINT #1 - definition

Highly effective chemo may cause CTRCD:

1. Type I CTRCD (e.g. anthracyclines)
   - Dose dependent, cell apoptosis, irreversible
   - Early detection & prompt Rx may prevent HF

2. Type II CTRCD (e.g. trastuzumab)
   - Not dose dependent, no apoptosis, ~reversible

DEFINITION: CTRCD

Universal LVEF Threshold

- Confirmed drop in LVEF >10 points to <53%
  - Need to confirm with REPEAT “cardiac imaging” 2-3 wks after initial study showing the fall in LVEF

- Symptomatic vs Asymptomatic CTRCD

- Reversible (to within 5% baseline)

- Partial (improved >10%; not to within 5% baseline)

- Irreversible (remains within 10% nadir)
KEY POINT #2 – LV systole

- Echocardiography: **method of choice** for the evaluation **before, during, and after** cancer therapy
- Accurate calculation of LVEF should be done with the **best method** in your echo lab (3DE recommended)
- If 2DE, modified biplane Simpson’s is recommended
- LVEF should be combined with **WMSI calculation**
- If no STE (GLS), **MAPSE** (M-mode) and/or **DTI (s’)** of the mitral annulus is recommended

*LVEF* by 2DE often **fails to detect small changes** in LV contractility
Reduced Ejection Fraction = extensive LV damage

*3DE

LV Systolic Function

*GLS via 2D Strain / STE
KEY POINT #3 - Valves

- Valves should be carefully evaluated
- Patients with *baseline (or changing) valve findings during chemo* require careful re-evaluation with serial echo during and after the course of Rx

PATIENT CASE

40F with multiple cycles of chemoRx and BMT
KEY POINT #4 - pericardium

- Pericardial disease: consider metastasis or effect from chemo and/or radiotherapy
- Pericardial effusion should be quantified / graded
- Echo / Doppler signs of tamponade should be investigated, particularly in malignant effusions
- CMR: useful to evaluate 1\textdegree
cardiac tumors w/wo compromise of the pericardium; if ‘constriction’ dx remains uncertain after echocardiography

65F; Breast Ca; p-eff found on CT; SBP ~100

Ms Jones

Ms Smith
What about Ms. Williams?

KEY POINT #5 – 3DE

- **3D echo** is the preferred technique for serial LVEF to detect CTRCD
- Advantages include better accuracy (detecting LVEF below LLN), reproducibility, and lower temporal variability compared with 2DE
- Costs, availability, reliance on image quality, and training currently limits wide application of 3DE
3D ECHOCARDIOGRAPHY

- Biplane Simpson similar to 3D if normal LV shape
  - In pts with LVEF <50% by CMR:
    - 3DE: sensitivity = 53%; False (-) rate 47%
    - 2DE: sensitivity = 25%; False (-) rate 75%

- 2D vs 3D serial evaluation of Chemo pts
  - Reproducibility 3DE 4.9% (vs 2DE 10%)
  - Lowest inter- & intra-variability and Highest test-retest


Hot off the Presses... Lorenzini JASE 2017

LVEF variability by 3DE: confounding factor for CTRCD dx
- Different software should not be interchanged
- GLS: offers predictive value for subsequent cardiotoxicity
KEY POINT #6 - contrast

- UCA is useful for endocardial dropout
- Recommended when two contiguous LV segments are not well visualized on apical images
- Contrast agents are not recommended with 3DE in the serial follow-up of patients with cancer

Contrast

Impacts LV WT and LVd
**KEY POINT #7 – Stress echo**

- **Stress echo** may help evaluate pts with IM / high pretest prob for CAD receiving Rx that cause ischemia (*fluorouracil, bevacizumab, sorafenib, sunitinib*)

- Stress echo may help determine *contractile reserve* of patients with CTRCD
KEY POINT #8 - Strain

- Strain should be measured with 2D STE > DTI
- GLS preferred to detect subclinical LV dysfunction
- Measures during chemo should be directly side-by-side compared with baseline value
  - Relative % reduction GLS <8% not meaningful (-20.0 > -8.4)
  - Relative % >15% very likely to be abnormal (-20.0 > -17.0)
  - No baseline exam, < -19% predicts later CTRCD
- For STE, use the same US machine

SPECKLE TRACKING

- There are > 20 peer-reviewed reports on deformation indices in detection of subclinical cardiotoxicity in pts treated for cancer
- Decrease in myocardial systolic function is rapid (within 2 hours of first dose) – 10-20%
  - This precedes reduced LVEF; or may occur without low LVEF
  - No preference to subendo, midmyo, or subepi (consistent with biopsy data of diffuse apoptosis)

SPECKLE TRACKING

GLS <16%

- Meta-Analysis: 24 articles
  - Normal GLS -15.9% to -22.1% (mean -19.7%)
  - There were NO normal patients with GLS <15.9%

*It is now recommended to give preference for GLS when a discrepancy exists between LVEF*

Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. JASE 2013;26:185-191

PATIENT CASE - EF

40F with multiple cycles of chemoRx

- 55% February
- 55% ~SOA April
- 50% SOA May
- 25% CHF August
PATIENT CASE - GLS

40F with multiple cycles of chemoRx

-19% February
-16% ~SOA April
-13% SOA May
-8% CHF August

PATIENT CASE

40F with multiple cycles of chemoRx

55% 55% 50% LVEF

-19 -16 -13 -8
Feb April May August

25%
Hot off the presses...

Following chemotherapy for BMT:
Myocardial deformation analysis detects subclinical bi-V dys - 1 month after BMT, mainly subendocardial layer - 3 months, subepicardial layer and LV twist are impaired

Suggests progressive subclinical cardiac dysfunction that precedes small reductions in LVEF

Abn GLS at 1 month predicts low LVEF at follow-up

http://dx.doi.org/10.1016/j.echo.2017.07.010

KEY POINT #9 - Troponin

- Elevated troponin may be a sensitive measure for early detection of CTRCD
- Natriuretic peptides, a marker of elevated filling pressures, are less consistent markers of early CTRCD
**TROPONIN** cardiac biomarkers

- Troponin: gold standard for **myocardial injury**
  - Predicts development of LV dysfunction after chemo
- N = 703; TnI each cycle (b/l, 12, 24, 36, 72hrs; 1mo)
- **106/111 adverse CV events** in TnI elevation groups
  - 37% early (<72hrs) and 84% late (1month)
  - PPV 84%; NPV 99% (**identifies low risk pts**)

Note: “persistent” worse than “transient” TnI increase values

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**KEY POINT #10 - MUGA**

- LVEF by MUGA is **highly reproducible**
- Main **limitations** are radiation, lack of ability to report on **pericardium, valves, and RV**
RADIATION THERAPY

- Radiation exposure to the thorax (Hodgkins, L>R breast)
  - Effective; used in >50% of cancer patients
    - High doses, younger age, coexistent CV risks
- Creating a growing population of CV dz
  - Pericardium
  - Coronaries
  - Vasculopathy
  - VHD
  - Cardiomyopathy
  - Conduction diseases


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52M; 18 yrs post XRT
CONCLUSIONS

- Multi-specialty cooperation
- Oncologists make final call with Cardiology input
- XRT results in ~20 year delayed Ca++ presentations
- Definition of CTRCD is now defined
  - LVEF fall 10%, <53%, repeat imaging within 3 wks
- 3D Full Volume = guideline recommended
- Global Longitudinal Strain = guideline recommended

THANK YOU

South Rim, Grand Canyon
Photo: Vince Sorrell
**EXTRA MATERIAL**

**HIGH RISK PATIENTS**

- **Who should be screened by cardiology?**
  - **QUESTION?** All pts versus high risk population?
  - Risk: age >65, HBP, DM, CAD, low / low normal EF, early decline, pt planning high dose (>350) or combined Rx
    - Consider cardio-protective therapies

- **Should TnI be considered another guide?**

- **N = 413; Type I Rx; N = 114 (24%) with TnI +**
  - Randomized to ACEi Rx (<1 mo after Rx) versus no Rx
  - LV size, LVEF, events **(2% vs 52%)** were improved

*Cardinale D, et al. Circulation 2006;114:2474-2481*
INTEGRATED APPROACH

- Integrated approach combines modern imaging with biomarkers for optimal subclinical detection and early preventive Rx
  - Used in “series”: reduction in frequency of imaging
  - Used in “parallel”: strategy for enhanced surveillance
- GLS < -19% or TnI + 93% specific for CTRCD
  - Versus 73% either parameter alone
  - Sensitivity 87% compared to 48% or 74% individually

PUTTING IT ALL TOGETHER

- Close corroboration between Onco, Card, and IM
- Baseline evaluation in all preferred; high risk in min
- This should include ECHO
  - Echo should include 3D and GLS / GCS; RWMA; contrast?
  - If images suboptimal (or borderline), perform CMR
- LVEF <50% or GLS <16% or TnI + … CARD CONSULT
  - Strongly consider cardioprotective Rx

Systemic Effects of Anti-VEGF Therapy

Table #1. Characteristics of Type I and II Chemotherapy-Related Cardiac Dysfunction

<table>
<thead>
<tr>
<th>Characteristic agent</th>
<th>Type I myocardial damage</th>
<th>Type II myocardial damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical course and typical response to anti-remodeling therapy (BB, ACE-1)</td>
<td>May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress</td>
<td>High likelihood of recovery (to or near baseline cardiac status) in 2-4 months after interruption (reversible)</td>
</tr>
<tr>
<td>Dose effects</td>
<td>Cumulative, dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td>Effect of re-challenge</td>
<td>High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death</td>
<td>Increasing evidence for the relative safety of re-challenge (additional data needed)</td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)</td>
<td>No apparent ultrastructural abnormalities (though not thoroughly studied)</td>
</tr>
</tbody>
</table>

Abbreviation: CRCD, chemotherapy-related cardiac dysfunction.

Lung cancer (bevacizumab)
- Inhibition of tumor growth, tumor cavitation

Hepatocellular carcinoma (sorafenib)
- Tumor necrosis

Renal cell carcinoma (sunitinib)
- Tumor shrinkage, tumor cell necrosis

Colorectal cancer (bevacizumab)
- Deceleration of tumor growth, efficient chemotherapy delivery

Normal Tissues
(VEGF constitutively expressed)

- Hypertensive remodeling
- Microvascular rarefaction
- Cardiomyopathy (sunitinib and sorafenib)

Microcirculation: 1. normal arteriole, 2. functional rarefaction (endothelial dysfunction, vasoconstriction), 3. anatomic rarefaction

- Thrombotic microangiopathy
- Glomerulopathy / glomerulonephritis
- Proteinuria
- Hypertensive nephropathy
Appendix #1. Recommended Cardio-Oncology Echo Protocol

Standard Transthoracic Echo
- In accordance with ASE/EAE guidelines and ICAEL

2D Strain Imaging Acquisition
- Apical 4, 2, 3 chamber views
  - Acquire at least 3 cardiac cycles
  - Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
  - FPS between 40 – 60 or at least 46% of HR
- Aortic VTI (aortic ejection time)

2D Strain Imaging Analysis
- Quantify segmental and global strain (GLS)
- Display the segmental strain curves from apical views in a quad format
- Display the global strain in a bull’s eyes plot

2D Strain Imaging Pitfalls
- Ectopy
  - Breathing Translation

3D Imaging Acquisition
- Apical 4 chamber full volume to assess LV volumes and EF calculations
- Single and multibeats optimizing spatial and temporal resolution

Reporting
- 2D Biplane Simpson’s method/3D EF
- GLS

RADIATION THERAPY

X-ray induced DNA breaks = apoptosis

Radiation-Induced Cardiovascular Injury
Risk factors
- Higher radiation doses
- Minimal or no cardiac protection techniques at time of irradiation
- Cardiac volume exposed to irradiation
- Young age at irradiation
- Increasing interval from time of radiation
- Pre-existing cardiovascular risk factors

Acute Cardiac Injury
(less common)
- Acute pericarditis
- Myocarditis

Late Cardiac Injury
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Coronary artery disease
- Valvular disease
- Conduction disturbances

Medium or Large Vessel Vasculopathy
- Thoracic aortic calcification (porcelain aorta)
- Carotid/axillary/subclavian artery stenosis

Groarke JD, et al. CV complications of radiation therapy… Eur Heart J. 2013
Thoracic: suspect cardiac injury
- CAD: Sx-guided (ACS – invasive / non-ACS – functional)
  - Asymptomatic: CCTA, CACS (or functional) 5yrs post XRT
  - Pericardium: Sx-guided only (TTE +/- CMR or CCT)
  - VHD: Routine TTE 10yrs post-XRT (sooner if Sx)
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- VHD: Routine TTE 10yrs post-XRT (sooner if Sx)

Head and Neck: suspect arterial disease
- CVA Sx or carotid bruit: Carotid US +/- MRA/CTA
- No Sx but PAD and/or RF’s AND 10yrs post: US +/- MR/CT

ALL: CT chest PRIOR to CT surgery (guide surgical risk: mediastinal fibrosis, porcelain Ao)

CTRCD Guidelines

- EMB used for Dx 1970’s (replaced by serial LVEF)
  - Variable: LVEF measures / onset of dysfunction / cardiac reserve
- Diagnosis: >10% fall in LVEF to <53% on 2 serial echo’s
  - Subcategorized as Reversible, Partially reversible, Irreversible
- Type of Injury: Type I vs Type II CTRCD
  - Randomized to ACEi Rx (<1 mo after Rx) versus no Rx
  - LV size, LVEF, events (2% vs 52%) were improved
ECHO Modalities

- **LVEF using biplane Simpson or 3DE**
  - Use contrast as needed (? 2 segments apical views)
- **Include WMSI** since subtle WMA commonly missed on routine 2DE
- **3DE: better accuracy for LVEF <50%**
  - Better reproducibility / lower variability vs 2DE
  - Do not combine with contrast (basal drop out limits use)

Subclinical LVD

- Imaging:
  - LVEF 50-54%: increased cardiac event rates
  - Despite DDfx preceding LVd, evidence DOES NOT support DDfx indices for prediction of CTRCD
  - STRAIN (myo deformation): STE preferred > DTI
  - GLS best predictor of early CTRCD (compared serially)
    - <8% reduction is NOT considered clinically meaningful
DEFORMATION IMAGING

- N=81; breast cancer; Type I and II agents
- Follow up: 15 months; quarterly echo’s
- Post-Rx GLS predicted 100% heart failure (all <=-19%)
  - Also predicted LVEF <55% or decrease >10% at f/u
  - Unknown if this persists longer
- GLS was predictive, but GCS and radial strain wasn’t
  - Radial strain – not sensitive enough (fractional thickening)
  - GCS is a compensatory mechanism for impaired GLS

Cardiac monitoring in patient receiving type 1 regimen

- CHF
  - Confirmed drop of 10 points to LVEF < 50% (*)
  - GLS < 16%

- Asymptomatic drop of 10 points to LVEF 50 – 54% **
  - Relative drop GLS >15% as compared to baseline
    - + troponin

- LVEF > 55%
  - GLS > 19%
  - Relative drop of GLS of <8% as compared to baseline
    - - Troponins

- Cancer treatment at discretion of clinician
- Cardiology consultation

No evidence of sub-clinical LV dysfunction

* Consider confirmation with other modality 3D / MRI / MUGA.

Initiation of trastuzumab

Baseline evaluation of systolic function
LVEF: 3D (preferred) / 2D (consider contrast)
GLS, Troponin I

LVEF < 50%*
- Cancer treatment at discretion of clinician
- Cardiology consultation
- Follow up with LVEF/GLS before each trastuzumab treatment, or troponin after, then at 6 months of follow up.

LVEF 50-54%
- Follow up every 3 months with LVEF/GLS during therapy and then at MD discretion
- If GLS<19 consider increased echo frequency and measure troponins

LVEF > 55%
- Follow up every 3 months with LVEF/GLS during therapy.
- If GLS < 19, consider increased echo frequency and measure troponins

* Consider confirmation by 3D/MUGA/MRI
Initiation of trastuzumab after regimen associated with Type 1 toxicity

Baseline evaluation of systolic function
LVEF: 3D (preferred)/ 2D (consider contrast)
GLS, Troponin I

- LVEF < 50%*
  - GLS <16%
  - Trastuzumab at discretion of clinician
  - Cardiology consultation

- EF 50-54%
  - + Tn I
  - Consider Cardiology consultation
  - F/U every 3 months during therapy.
  - F/U up at 6 months after completion of therapy and then at MD discretion.

- LVEF 55%
  - GLS>19%
  - Tn I
  - F/U every 3 months during therapy
  - F/U at 6 months after end of therapy and then at MD discretion.

* Consider confirmation by 3D/MUGA/MRI
** Consider more frequent monitoring if dose >300mg/m²

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Early detection of toxicity using biomarkers

Baseline cardiologic evaluation, ECHO

Type I and/or IIa regimen

TnI evaluation at each cycle

- TnI POS
  - Cardiology consultation
  - ECHO at end CT, 3, 6, 9 months
  - Clinical evaluation ± ECHO 6 m

- TnI NEG
  - ECHO 6 m

3DE

Nuclear – MUGA / eRNA
Future Imaging

- $^{123}$I-mIBG - Sympathetic neuronal imaging
- $^{111}$In-antimyosin – myocyte necrosis
- 99m Tc-annexin V – marker of apoptosis
- $^{111}$In-traxtuzumab – HER2/neu receptor marker

*Potential methods to identify pre-clinical cardiotoxicity and monitor Rx directed at reducing apoptosis*