ROLE OF IMAGING IN Evaluating potential cardiotoxicity

Kalliopi Keramida
MD, MSc, PhD
Accredited in heart failure by ESC/HFA
Predicted global cancer cases

Cases (millions)

- World
- Less developed countries
- More developed countries

Source: WHO GloboCan
The big C
Drugs in development*, 2010

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>0</th>
<th>200</th>
<th>400</th>
<th>600</th>
<th>800</th>
<th>1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
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<tr>
<td>Central nervous system</td>
<td>400</td>
<td>800</td>
<td></td>
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<tr>
<td>Infections</td>
<td>600</td>
<td>1,000</td>
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<tr>
<td>Pain and inflammation</td>
<td>800</td>
<td></td>
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<tr>
<td>Cardiovascular</td>
<td></td>
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<tr>
<td>Diabetes and metabolism</td>
<td>200</td>
<td>600</td>
<td>800</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood disorders</td>
<td></td>
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<td></td>
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<tr>
<td>Dermatological</td>
<td></td>
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</tbody>
</table>

*Top ten therapeutic areas for the world’s big pharmaceutical firms, includes drugs in Phase I, II, III or awaiting FDA approval.

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Estimated Number of Cancer Survivors in the US

Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Millions</th>
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</thead>
<tbody>
<tr>
<td>1970</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td></td>
</tr>
</tbody>
</table>

Childhood Cancer Survivors

Congestive Heart Failure – Stage C HF

Cumulative CHF incidence (%)

Time since diagnosis (years)

≥250 mg/m² anthracycline

<250 mg/m² anthracycline

General population

Cardio-oncology centers in Greece
The oncologist!
The patient has a cancer!

The cardiologist!
The patient has a cardiac disease!
Developing a Cardiology-Oncology Partnership
Optimize Cardiac Health

Best Cancer Care
Cardio-oncologist’s goals:

- To recognize and treat optimally the pre-existing CV risk factors
- To avoid the possibility that pre-existing cardiac disease be a barrier and lead to a reduction in the therapeutic opportunities of the patient
- To protect the patient from developing cardiac disease because of cancer therapy
Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines
**Proposed diagnostic tools for the detection of cardiotoxicity**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Currently available diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography:</td>
<td>• LVEF: &gt;10 percentage points decrease to a value below the LLN suggests cardiotoxicity.</td>
</tr>
<tr>
<td>- 3D-based LVEF</td>
<td>• GLS: &gt;15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.</td>
</tr>
<tr>
<td>- 2D Simpson’s LVEF</td>
<td></td>
</tr>
<tr>
<td>- GLS</td>
<td></td>
</tr>
<tr>
<td>Nuclear cardiac imaging (MUGA)</td>
<td>• &gt;10 percentage points decrease in LVEF with a value &lt;50% identifies patients with cardiotoxicity.</td>
</tr>
<tr>
<td>Cardiac magnetic resonance</td>
<td>• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.</td>
</tr>
<tr>
<td>Cardiac biomarkers:</td>
<td>• A rise identifies patients receiving anthracyclines who may benefit from ACE-Ils.</td>
</tr>
<tr>
<td>- Troponin I</td>
<td>• Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.</td>
</tr>
<tr>
<td>- High-sensitivity Troponin I</td>
<td></td>
</tr>
<tr>
<td>- BNP</td>
<td></td>
</tr>
<tr>
<td>- NT-proBNP</td>
<td></td>
</tr>
</tbody>
</table>
Core principles

- The same imaging modality and/or biomarker assay should be used for continued screening throughout the treatment pathway. Switching between modalities or assays is strongly discouraged.

- Modalities and tests with the best reproducibility are preferred.

- Imaging modalities that provide additional relevant clinical information are preferred (e.g. right ventricular function, pulmonary pressures, valvular function, pericardial evaluation).

- High quality radiation-free imaging is preferred, if available.
What to Look For – The Role of Echocardiography in Cardiotoxicity Diagnosis

- Systolic Function
- Diastolic Function
- RV function
- Valvular Disease
- Pericardium
Cardiotoxicity

• Decrease in LVEF more than 10 percentage points to a value below 50%

• >15% relative percentage reduction of GLS from baseline
Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes
Application to Patients Undergoing Cancer Chemotherapy

CONCLUSIONS: Noncontrast 3DE was the most reproducible technique for LVEF and LV volume measurements over 1 year of follow-up.
Treating Asymptomatic Chemotherapy-Induced Cardiac Dysfunction
A Chance That Cardiologists and Oncologists Should Not Miss

Graph showing percentages of responders over different time periods:
- 1-2 months: 65%
- 2-4 months: 54%
- 4-6 months: 28%

Time periods:
- 6-8 months: 0%
- 8-10 months: 0%
- 10-12 months: 0%
- >12 months: 0%
Assessment of Echocardiography and Biomarkers for the Extended Prediction of Cardiotoxicity in Patients Treated With Anthracyclines, Taxanes, and Trastuzumab

Heloisa Sawaya, MD, PhD, Igal A. Sebag, MD, Juan Carlos Plana, MD, James L. Januzzi, MD, Bonnie Ky, MD, MSCE, Timothy C. Tan, MBBS, PhD, Victor Cohen, MD, Jose Banchs, MD, Joseph R. Carver, MD, Susan E. Wiegars, MD, Randolph P. Martin, MD, Michael H. Picard, MD, Robert E. Gerszten, MD, Elkan F. Halpern, PhD, Jonathan Passeri, MD, Irene Kuter, MD, and Marielle Scherrer-Crosbie, MD, PhD

Peak systolic longitudinal myocardial strain and ultrasensitive troponin I measured at the completion of anthracyclines treatment predicted the subsequent development of cardiotoxicity; no significant associations were observed for left ventricular ejection fraction, N-terminal
Noninvasive Measures of Ventricular-Arterial Coupling and Circumferential Strain Predict Cancer Therapeutics-Related Cardiac Dysfunction

Narayan... Ky. JACC Imaging. 2016.

*<p<0.05

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
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<tbody>
<tr>
<td>Longitudinal strain</td>
<td>0.612</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>0.655*</td>
</tr>
<tr>
<td>Radial strain</td>
<td>0.624</td>
</tr>
<tr>
<td>Ea/Ees</td>
<td>0.703*</td>
</tr>
</tbody>
</table>
What to Look For – The Role of Echocardiography in Cardiotoxicity Diagnosis

- Systolic Function
- Diastolic Function
- RV function
- Valvular Disease
- Pericardium
Assessment of diastolic function

In patients with normal LV EF

- Average E/e' > 14
- Septal e' velocity < 7 cm/s or Lateral e' velocity < 10 cm/s
- TR velocity > 2.8 m/s
- LA volume index > 34 ml/m²

- <50% positive
- 50% positive
- >50% positive

- Normal Diastolic function
- Indeterminate
- Diastolic Dysfunction

How does cancer therapy affect diastolic function?

What is the prognostic significance of early changes?

Mitral Inflow

E/A ≤ 0.8 + E ≤ 50 cm/s or E/A > 0.8 - <2

3 criteria to be evaluated:

- 1-Average E/e' > 14
- 2-TR velocity > 2.8 m/s
- 3-LA Vold index > 34 ml/m²

When only 2 criteria are available

- 2 negative
- 1 positive and 1 negative
- 2 positive

Normal LAP
Grade I Diastolic Dysfunction

Cannot determine LAP and Diastolic Dysfunction
Grade*

1 LAP
Grade II Diastolic Dysfunction

3 LAP
Grade III Diastolic Dysfunction

†LAP

 ASE/EACVI GUIDELINES AND STANDARDS

Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

(J Am Soc Echocardiogr 2016;29:277-314.)
What to Look For – The Role of Echocardiography in Cardiotoxicity Diagnosis

- Systolic Function
- Diastolic Function
- RV function
- Valvular Disease
- Pericardium
Assessment of RV function

- Qualitative and quantitative assessment of RV function
Assessment of trastuzumab effect on both ventricles by 2D speckle tracking analysis

K. Keramida¹, J. Bingcang², R. Wensel³, P. Nihoyannopoulos⁴
¹Hammersmith Hospital, London, United Kingdom, ²Barts Health NHS Trust, Cardiology Department, London, United Kingdom, ³West Hertfordshire Hospitals, NHS Trust, Watford General Hospital, Cardiology, London, United Kingdom, ⁴Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom

<table>
<thead>
<tr>
<th>Group 1 N=22</th>
<th>Baseline</th>
<th>2 months after trastuzumab</th>
<th>p value</th>
<th>Group 2 N=15</th>
<th>Baseline</th>
<th>2 months after trastuzumab</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVGLS (%)</td>
<td>-21.66±3.38</td>
<td>-15.41±7.78</td>
<td>0.001</td>
<td>LVGLS (%)</td>
<td>-18.59±3.92</td>
<td>-17.31±8.92</td>
<td>0.615</td>
</tr>
<tr>
<td>RVGLS (%)</td>
<td>-20.53±4.98</td>
<td>-17.55±4.58</td>
<td>0.008</td>
<td>RVGLS (%)</td>
<td>-17.18±4.37</td>
<td>-17.96±1.94</td>
<td>0.494</td>
</tr>
<tr>
<td>RVFVWLS (%)</td>
<td>-24.82±4.61</td>
<td>-17.47±5.31</td>
<td>0.045</td>
<td>RVFVWLS (%)</td>
<td>-21.44±5.24</td>
<td>-22.87±3.77</td>
<td>0.164</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.94±3.2</td>
<td>61.29±4.43</td>
<td>0.592</td>
<td>LVEF (%)</td>
<td>62.17±2.52</td>
<td>60.50±3.12</td>
<td>0.118</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>23.16±3.40</td>
<td>24.31±3.30</td>
<td>0.249</td>
<td>TAPSE (mm)</td>
<td>21±2.71</td>
<td>22.3±2.83</td>
<td>0.253</td>
</tr>
<tr>
<td>TV S' (cm/sec)</td>
<td>13.50±2.31</td>
<td>13.87±2.36</td>
<td>0.620</td>
<td>TV S' (cm/sec)</td>
<td>12±1.41</td>
<td>13.2±2.09</td>
<td>0.181</td>
</tr>
<tr>
<td>RVID basal (mm)</td>
<td>33.37±2.73</td>
<td>33.44±3.36</td>
<td>0.923</td>
<td>RVID basal (mm)</td>
<td>34.6±3.44</td>
<td>34.2±3.67</td>
<td>0.693</td>
</tr>
<tr>
<td>RVID mid (mm)</td>
<td>26.44±2.22</td>
<td>26.94±3.27</td>
<td>0.552</td>
<td>RVID mid (mm)</td>
<td>27.9±2.51</td>
<td>29±3.39</td>
<td>0.129</td>
</tr>
<tr>
<td>RVID height (mm)</td>
<td>72.62±4.98</td>
<td>71.81±4.70</td>
<td>0.515</td>
<td>RVID height (mm)</td>
<td>68.9±3.9</td>
<td>70.9±5.60</td>
<td>0.115</td>
</tr>
</tbody>
</table>
Assessment of RV function

- **Pulmonary hypertension**
  - Chemotherapy: Dasatinib, Carfilzomib, cyclophosphamide
  - Stem cell bone marrow transplantation
  - Complications of metastatic cancer: thrombotic pulmonary tumor microangiopathy
What to Look For – The Role of Echocardiography in Cardiotoxicity Diagnosis

- Systolic Function
- Diastolic Function
- RV function
- Valvular Disease
- Pericardium
Assessment of valvular disease

- Radiotherapy
- Infective endocarditis
- Remodeling of LV and RV
- Tumor infiltration

- Aortic and mitral valve mostly affected
- Stenotic or regurgitant lesions
What to Look For – The Role of Echocardiography in Cardiotoxicity Diagnosis

- Systolic Function
- Diastolic Function
- RV function
- Valvular Disease
- Pericardium
Assessment of pericardial disease

- Pericardial effusion
- Pericardial constriction
- Pericarditis

- Radiation
- Metastatic cancer
- Chemotherapy:
  - anthracyclines
  - cyclophosphamide
  - bleomycin
Reduced contractile reserve after chemotherapy, despite normal LVEF and GLS.

Decreased cardiac reserve during chemotherapy is predictive of subsequent decline in LVEF.

In patients with intermediate or high pre-test probability of CAD who are undergoing regimens that may be associated with ischemia (fluorouracil, bevacizumab, sorafenib, and sunitinib).

In case of the development of cardiotoxicity, the transient recovery of LV function during stress echo may also predict a better outcome.

Cardiac MRI in cardio-oncology

- LV and RV volumes, function and strain
- Pericardial disease, specifically after radiation
- Detection of scarring or fibrosis by LGE
- Tissue characterization (inflammation, oedema) and ECVF quantification
- Detection of infiltration or mass
Nuclear cardiac imaging in cardio-oncology

- Detection of cardiotoxicity.
- Evaluation of cardiac perfusion.
- Stress test.

**Prechemo**

- LVEF: 68
- PFR: 3.36

**AC + Her**

- LVEF: 44
- PFR: 2.30
Nuclear and echo assessment

**MUGA**

\[
\begin{align*}
y &= 0.78x + 11.22 \\
r &= 0.88
\end{align*}
\]

**2D-TTE**

\[
\begin{align*}
y &= 0.36x + 30.45 \\
r &= 0.31
\end{align*}
\]

**3D-TTE**

\[
\begin{align*}
y &= 0.80x + 9.93 \\
r &= 0.91
\end{align*}
\]

1. CV risk assessment and cardio-toxicity prevention BEFORE therapy

2. Monitoring recommendations

3. CV surveillance and therapy DURING cancer treatment

4. CV monitoring and management AFTER cancer treatment => SURVIVORSHIP
Frequency of surveillance should be determined by health care providers based on clinical judgment and patient circumstances.

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

The precise timing and frequency of imaging and/or biomarker sampling will depend upon the specific cancer treatment, total cumulative dose of cardiotoxic chemotherapy, delivery protocol and duration and the patient’s baseline cardiovascular risk.

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines
CV risk assessment and cardio-toxicity prevention BEFORE therapy

<table>
<thead>
<tr>
<th>1) Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication-related risk</strong></td>
</tr>
<tr>
<td><strong>High (risk score 4):</strong> Anthracyclines, Cyclophosphamide, Ifosfamide, Clofarabine, Herceptin</td>
</tr>
<tr>
<td><strong>Intermediate (risk score 2):</strong> Docetaxel, Pertuzumab, Sunitinib, Sorafenib</td>
</tr>
<tr>
<td><strong>Low (risk score 1):</strong> Bevacizumab, Dasatinib, Imatinib, Lapatinib</td>
</tr>
<tr>
<td><strong>Rare (risk score 0):</strong> e.g. Etoposide, Rituximab, Thalidomide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Patient-related risk factors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy or heart failure</td>
</tr>
<tr>
<td>CAD or equivalent (incl. PAD)</td>
</tr>
<tr>
<td>HTN</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Prior or concurrent anthracycline</td>
</tr>
<tr>
<td>Prior or concurrent chest radiation</td>
</tr>
<tr>
<td>Age &lt;15 or &gt;65 years</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
</tbody>
</table>

**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)

CV risk assessment and cardio-toxicity prevention BEFORE therapy

**Very high cardiotoxicity risk:** initiate ACE-I / ARB, Carvedilol, and statins, starting at lowest dose and start chemotherapy in 1 week from initiation to allow steady state, up-titrated as tolerated

**High cardiotoxicity risk:** initiate ACE-I / ARB +/- Carvedilol +/- statins

**Intermediate cardiotoxicity risk:** discuss risk and benefit of medications

**Low cardiotoxicity risk:** none, monitoring only

**Very low cardiotoxicity risk:** none, monitoring only

Monitoring recommendations

2) Monitoring recommendations

**Very high cardiotoxicity risk:** TTE with strain before every (other) cycle, end, 3-6 months and 1 year, optional EKG, cTn with TTE during chemotherapy

**High cardiotoxicity risk:** TTE with strain every 3 cycles, end, 3-6 months and 1 year after chemotherapy, optional EKG, cTn with TTE during chemotherapy

**Intermediate cardiotoxicity risk:** TTE with strain, mid-term, end and 3-6 months after chemotherapy, optional EKG, cTn mid-term of chemotherapy

**Low cardiotoxicity risk:** Optional TTE with strain +/- EKG, cTn at end of chemotherapy

**Very low cardiotoxicity risk:** None

# Types of cardiotoxicity

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ anthracyclines</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>doxorubicin</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>epirubicin</td>
<td>Pertuzumab</td>
</tr>
<tr>
<td>idarubicin</td>
<td>Imatinib</td>
</tr>
<tr>
<td>➢ Mitoxantrone</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>«Irreversible»</td>
<td>Reversible</td>
</tr>
<tr>
<td>Dose dependent</td>
<td>Not dose dependent</td>
</tr>
<tr>
<td>After chemotherapy</td>
<td>During chemotherapy</td>
</tr>
<tr>
<td>Structural changes</td>
<td>No structural changes</td>
</tr>
</tbody>
</table>
CV surveillance and therapy DURING cancer treatment

Initial evaluation

- LVEF >50%
  - Reassessment at 250-300 mg/k2
    - No high risk
      - Reassessment at 450 mg/k2
        - Reassessment prior to each cycle
          - Discontinue if LVEF↓ ≥10% and LVEF ≤50%
    - High risk
      - Reassessment at 400 mg/k2
        - Reassessment prior to each cycle
          - Discontinue if LVEF↓ ≥10%

- LVEF <50%
  - Reassessment prior to each cycle
    - Discontinue if LVEF≤30%
CV surveillance and therapy DURING cancer treatment

Initial evaluation

LVEF ≥50%
- Reassessment at 12 weeks
  - Asymptomatic and stable LVEF
    - Reassessment at prior intervals

LVEF <50%
- Reassessment at 6 weeks
  - Asymptomatic and LVEF ↓ ≥10% or LVEF <40%
    - Discontinue trastuzumab
      - Heart failure therapy
        - Reassessment at 4 weeks
          - Risk-benefit assessment
            - Resume trastuzumab

Potential risk factors
- Risk-benefit assessment

Initiation of trastuzumab therapy
CV monitoring and management

AFTER cancer treatment => SURVIVORSHIP

- No routine cardiac imaging after completion of chemotherapy if LVEF and GLS are normal 6 months after and there are no additional factors increasing the patient’s risk.

- Assessment of cardiac function 4 and 10 years after completion of anthracycline therapy if >240mg/m² of doxorubin or >360mg/m² of epirubicin.

- In type 2 agents, echo at completion of therapy and after 6 months

ESMO guidelines, 2012.
Baseline pre-radiation comprehensive Echocardiography → Chest radiation exposure → Yearly targeted clinical history and physical examination

Screen for modifiable risk factors

Correct risk factors

Asymptomatic

Search for signs and symptoms suggestive of:
- Pericardial effusion/constriction
- Valvular heart disease
- LV dysfunction/heart failure
- Coronary artery disease
- Carotid artery disease
- Conduction system disease

New murmur → Echocardiography

CMR if suspicion of pericardial constriction

Signs/symptoms of heart failure

Angina

Neurological signs/symptoms

Carotid US

Screening Echocardiography 5 years after exposure in high-risk patients

10 years after exposure in the others

Functional noninvasive stress test for CAD detection (5-10 years after exposure in high-risk patients)

Re-assess every 5 years
WHOA! EASE UP ON THE CHEMO, NURSE. THAT'S HOW MUCH WE USE TO EUTHANIZE HORSES.

FACT: CHEMOTHERAPY CHEMICALS CAUSE PERMANENT DAMAGE TO THE HEART, LIVER AND KIDNEYS.

WWW.NEWSTARGET.COM

Thank you