

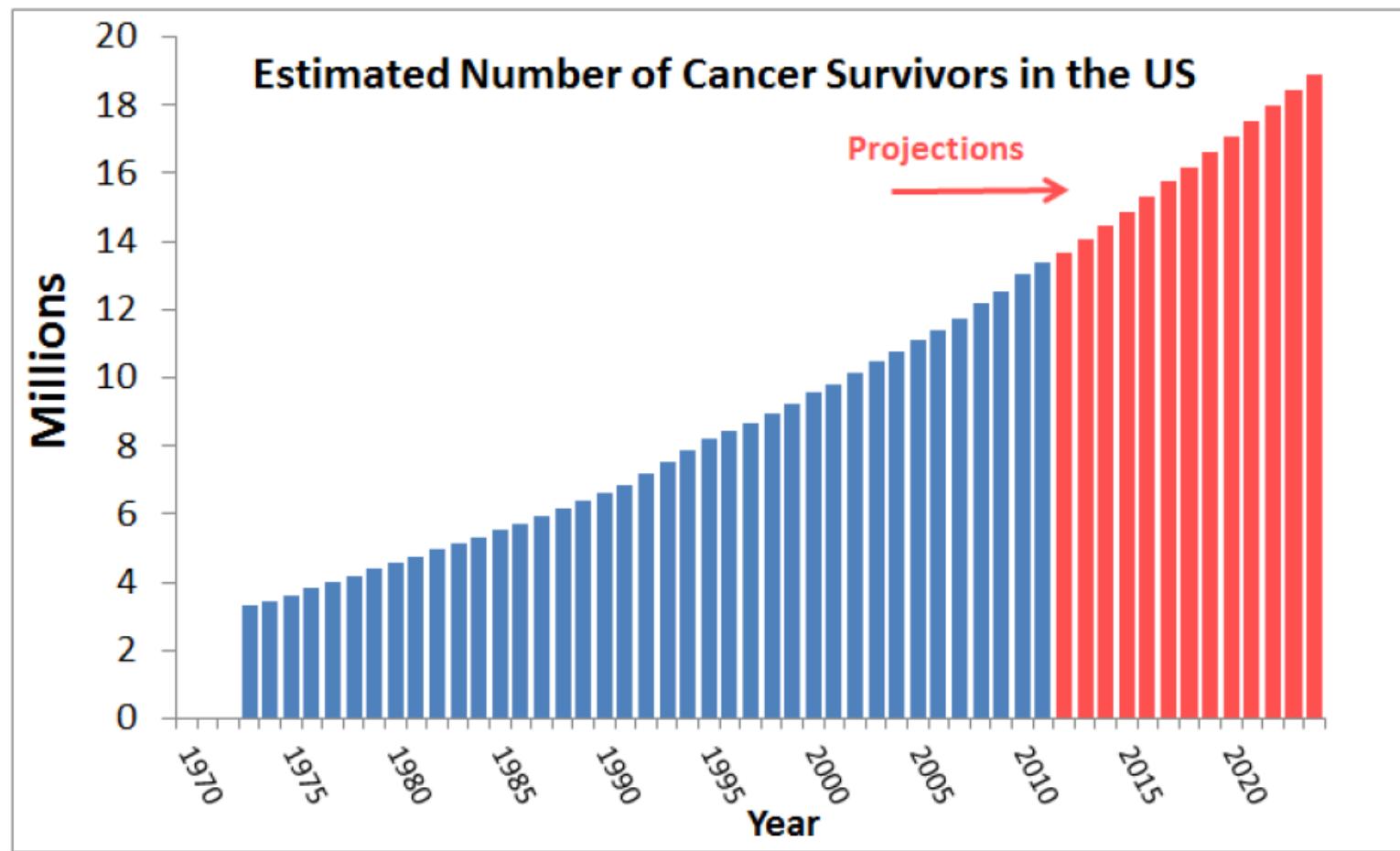


BIOMARCATORI ED IMAGING NELLA VALUTAZIONE DEL DANNO MIOCARDICO: L'ECOCARDIOGRAFIA

The poster features the logo of the IRCCS Ospedale Sacro Cuore Don Calabria and information about the 1st National Congress of Cardio-Oncology. It includes logos for ADm, AICO, SIE, ARCA, and SIC. The text specifies the date (25-26 GENNAIO 2019), location (IRCCS Ospedale Sacro Cuore Don Calabria, Sala Convegni Perez), and speakers (Presidenti Enrico Barbieri, Stefania Gori). The background features a stylized heart with a circuit board pattern.

Dr.ssa Laura Lanzoni
Laboratorio di Ecocardiografia
IRCCS Ospedale Sacro Cuore-Don Calabria
Negrar-Verona

Cancer – more patients, more survivors



De Santis C et al. Cancer J Clin 2014



1 in 8 women develops breast cancer

Complicanze cardiache da chemioterapia

Epidemiology of Anthracycline Cardiotoxicity in Children and Adults

Michelle A. Grenier and Steven E. Lipshultz

Semin Oncol, 1998

Long-term survivors of cancer represent one of the largest and ever-increasing groups of patients at risk for premature cardiovascular disease.^{8,9} A

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Chronic Health Conditions in Adult Survivors of Childhood Cancer

N Engl J Med,
2006

Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D.,
Toana Kawashima, M.S., Melissa M. Hudson, M.D., Anna T. Meadows, M.D.,
Debra L. Friedman, M.D., Neyssa Marina, M.D., Wendy Hobbie, C.P.N.P.,
Nina S. Kadan-Lottick, M.D., Cindy L. Schwartz, M.D., Wendy Leisenring, Sc.D.,
and Leslie L. Robison, Ph.D., for the Childhood Cancer Survivor Study*



CARDIOTOXICITÀ: UNO DEI MAGGIORI FATTORI LIMITANTI L'USO DELLA CHEMIOTERAPIA

Anti-HER2-Mediated Cardiotoxicity

From the **oncologist's** perspective:

- Interruption may lead to worse breast cancer outcomes

Parameter	Patients (total)	Patients (progressed)	Time to Progression (Years)	p-value
No therapy interruption	251	109	5.13 (4.11-9.53)	0.0005
Therapy interruption	14	14	3.51 (2.36-4.44)	

Source: Witzel L, *BMC Cancer* 2014

CARDIOVASCULAR ADVERSE EVENTS OF ANTICANCER AGENTS

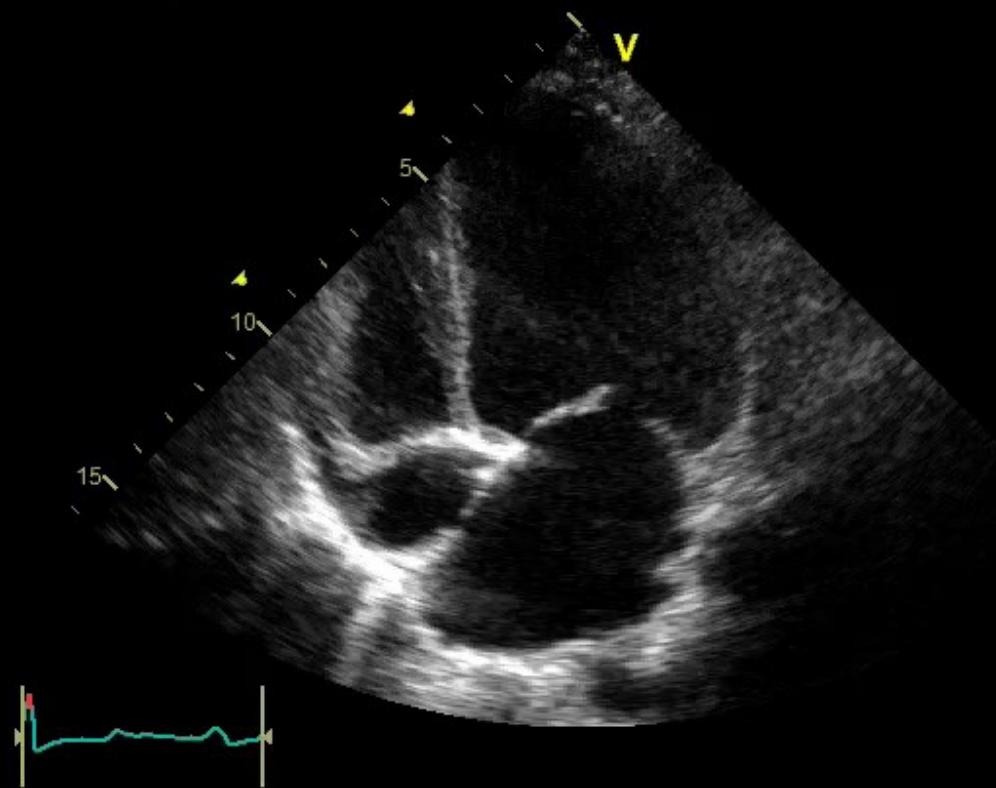
- **Myocardial dysfunction and heart failure**
- **Coronary artery disease**
- **QT prolongation**
- **Systemic hypertension**
- **Thrombotic disease**
- **Arrhythmias**
- **Myocardial infarction**
- **Valvular disease**

CTRCD:cancer therapy-related cardiac dysfunction

CANCER DRUG-ASSOCIATED CARDIOTOXICITY



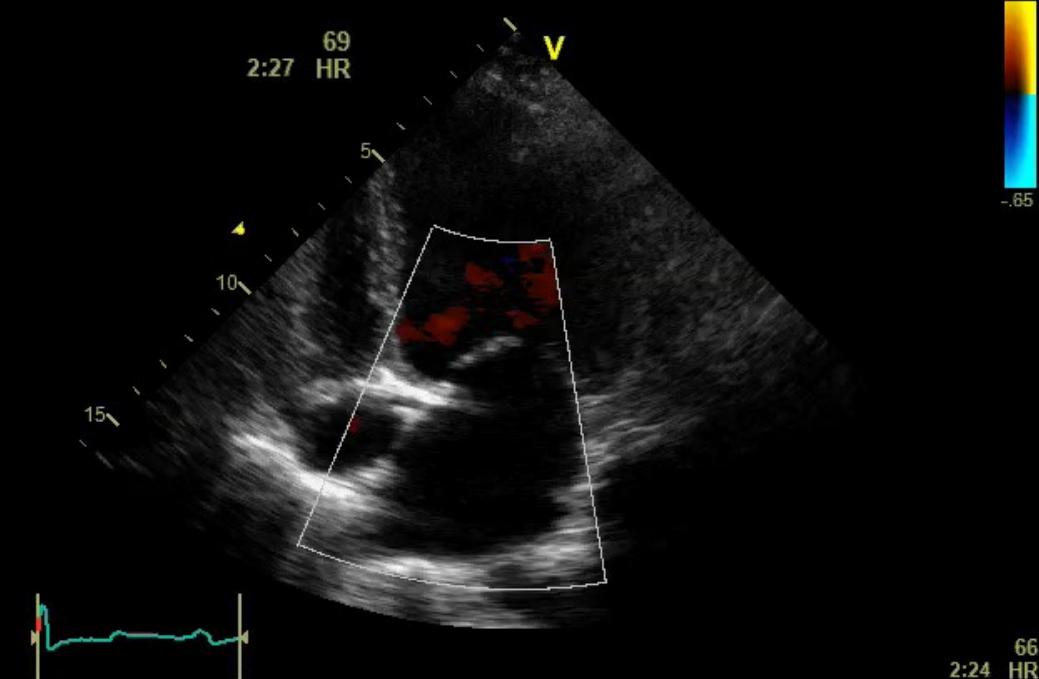
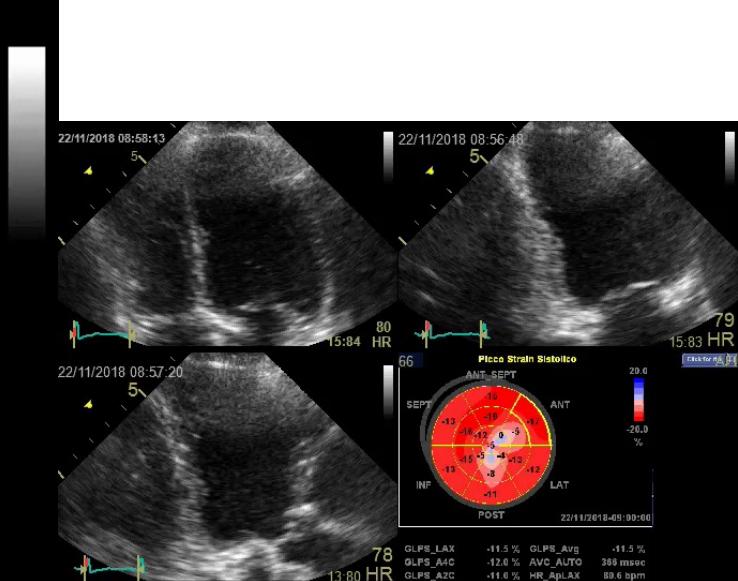
	Type I	Type II
Agent	Epirubicin	Trastuzumab
Cellular effects	Myocardium death	Dysfunction
Biopsy findings	Typical anthracycline changes	No typical changes
Dose response	Cumulative	Not cumulative
Reversibility	No	Generally reversible



Cardiac Dysfunction and Heart Failure

A.M. 32 aa

All'età di 9 anni trattata per
ependimoma sacrale
IFOSFAMIDE+
VINCRISTINA+Radioterapia
TP: B-Bloccante, ACE inib.



2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Advances in treatment have led to improved survival of patients with cancer, but have also increased morbidity and mortality due to treatment side effects.^{1,2} Cardiovascular diseases (CVDs) are one of the most frequent of these side effects, and there is a growing concern that they may lead to premature morbidity and death among cancer survivors.³ This may be the result of cardiotoxicity, which involves direct effects of the cancer treatment on heart function and structure, or may be due to accelerated development of CVD, especially in the presence of traditional cardiovascular risk factors.⁴

Table I Incidence of left ventricular dysfunction associated with chemotherapy drugs^{10–21}

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin)	3–5
400 mg/m ²	7–26
500 mg/m ²	18–48
Idarubicin (>90 mg/m ²)	5–18
Epirubicin (>900 mg/m ²)	0.9–11.4
Mitoxantrone >120 mg/m ²	2.6
Liposomal anthracyclines (>900 mg/m ²)	2
Aalkylating agents	
Cyclophosphamide	7–28
Ifosfamide	0.5
<10 g/m ²	17
12.5–16 g/m ²	
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20. ^a
Bevacizumab	1.6–4 ^b
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellaneous	
Everolimus	<1
Tensirolimus	<1

^aWhen used in combination with anthracyclines and cyclophosphamide.

^bIn patients receiving concurrent anthracyclines.

DIAGNOSTIC TOOLS FOR THE DETECTION OF CHEMO INDUCED CARDIOTOXICITY

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: - 3D-based LVEF - 2D Simpson's LVEF - GLS	<ul style="list-style-type: none"> LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity. 	<ul style="list-style-type: none"> Wide availability. Lack of radiation. Assessment of haemodynamics and other cardiac structures. 	<ul style="list-style-type: none"> Inter-observer variability. Image quality. GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	<ul style="list-style-type: none"> >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity. 	<ul style="list-style-type: none"> Reproducibility. 	<ul style="list-style-type: none"> Cumulative radiation exposure. Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	<ul style="list-style-type: none"> Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines. 	<ul style="list-style-type: none"> Accuracy, reproducibility. Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation. 	<ul style="list-style-type: none"> Limited availability. Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: - Troponin I - High-sensitivity Troponin I - BNP - NT-proBNP	<ul style="list-style-type: none"> A rise identifies patients receiving anthracyclines who may benefit from ACE-ls. Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation. 	<ul style="list-style-type: none"> Accuracy, reproducibility. Wide availability. High-sensitivity. 	<ul style="list-style-type: none"> Insufficient evidence to establish the significance of subtle rises. Variations with different assays. Role for routine surveillance not clearly established.



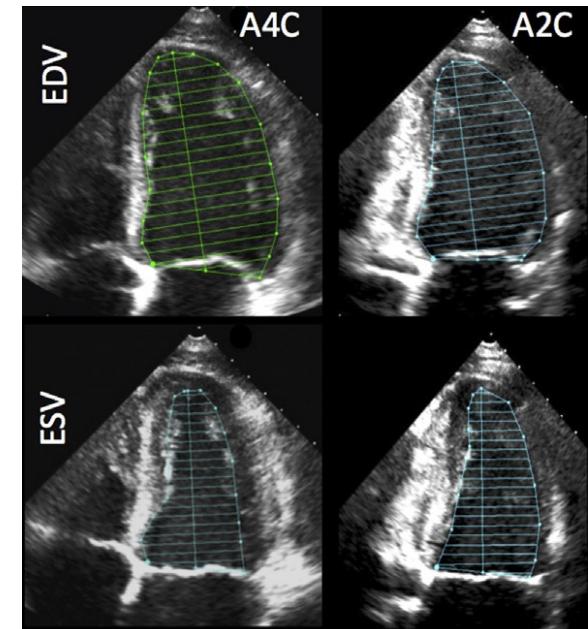
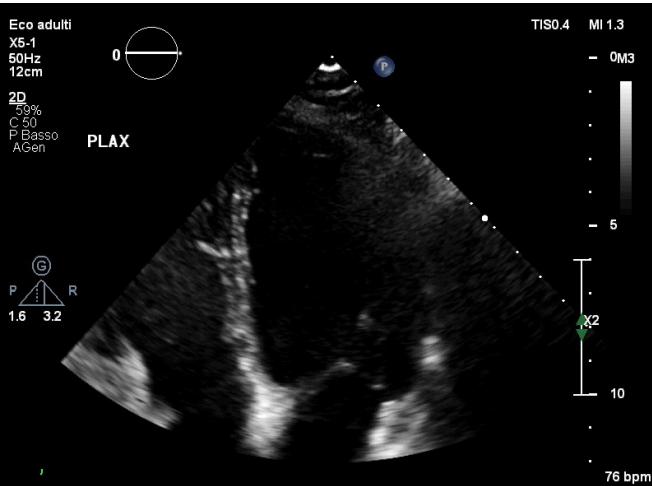
CARDIOTOXICITY DEFINITION

- The most common used definition in clinical practice and clinical trials is*:
 - A LVEF value <50% and a decrease >10% from its baseline value

DATO DA CONFIRMARE CON ECOCARDIOGRAMMA SUCCESSIVO A
2-3 SETTIMANE

ECO:funzione ventricolare 2D Biplana

- **PRO:** ampiamente disponibile, ripetibile, non costoso, sicuro, “rivedibile”
- **CONTRO:** eccesso di richieste, assunzioni geometriche, non sempre praticabile, dipendente dalle condizioni di riempimento, caratteristiche del paziente
- Valutazione FE con **metodo 2D, Simpson Biplano**
- Riproducibilità?? Variabilità temporale?

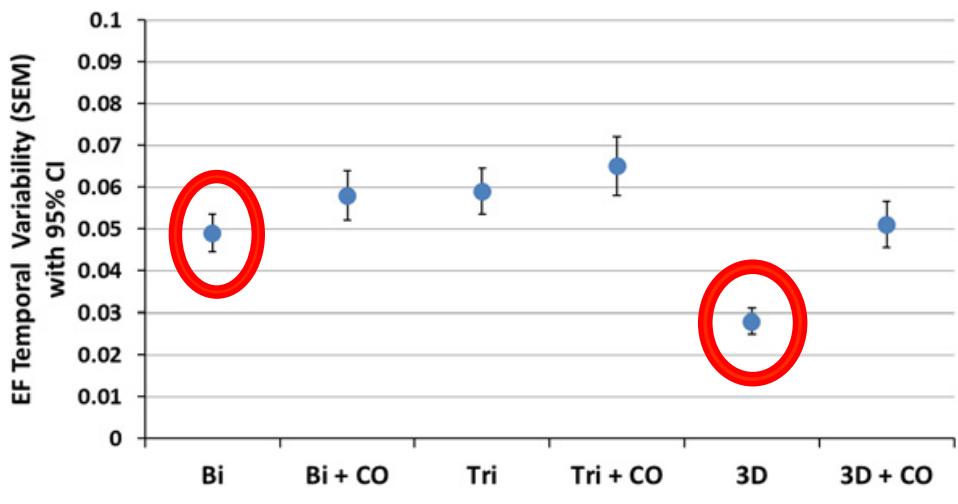


Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes

Application to Patients Undergoing Cancer Chemotherapy

Paaladinesh Thavendiranathan, MD, MSc, Andrew D. Grant, MD, Tomoko Negishi, MD,
Juan Carlos Plana, MD, Zoran B. Popović, MD, PhD, Thomas H. Marwick, MD, PhD, MPH

Cleveland, Ohio

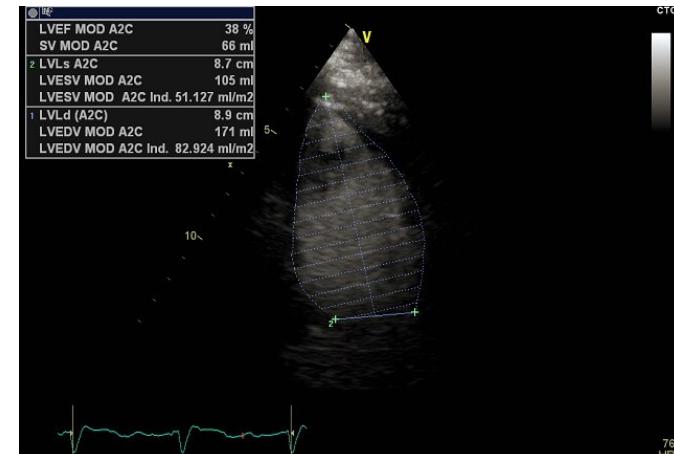
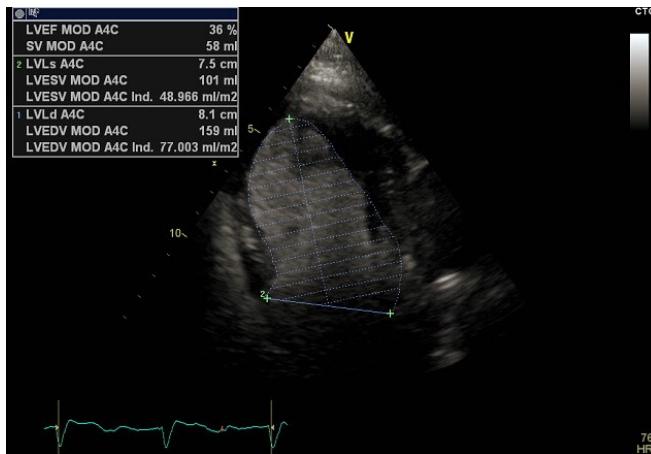


Il cambio di FEVS
che può essere
riscontrato con
metodica 2D con il
95% di confidenza è
l'11%.

LVEF assessed by 2DE often fails to
detect small changes in LV contractility

2D echo con Contrast

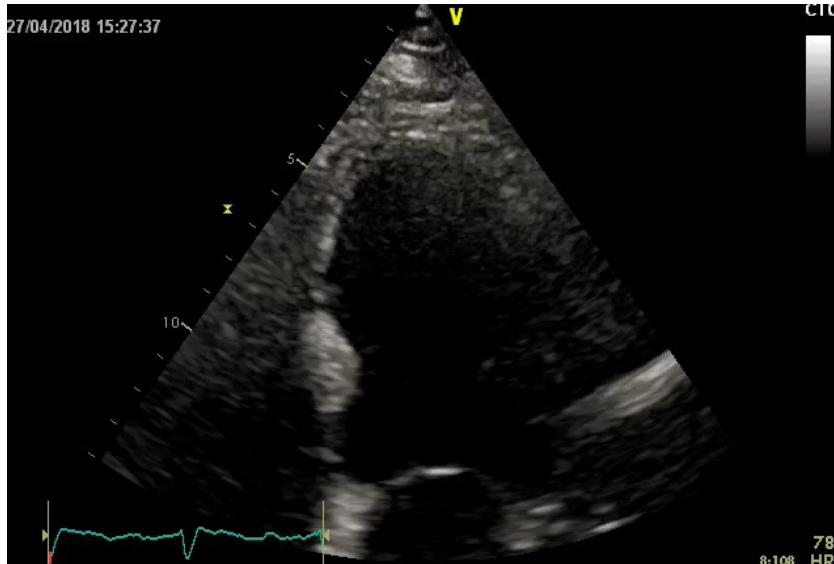
- **PRO:** migliora la visualizzazione del bordo endocardico e quindi le finestre acustiche subottimali, calcolo dei volumi e EF simili a MRI, minor variabilità interosservatore
- **CONTRO:** costoso, non sempre disponibile, artefatti, necessità di operatore esperto



Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017

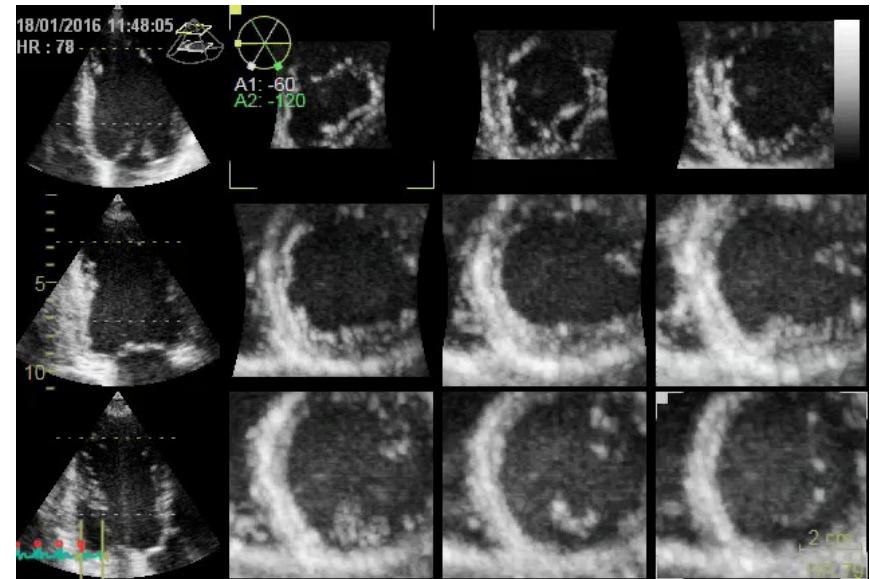
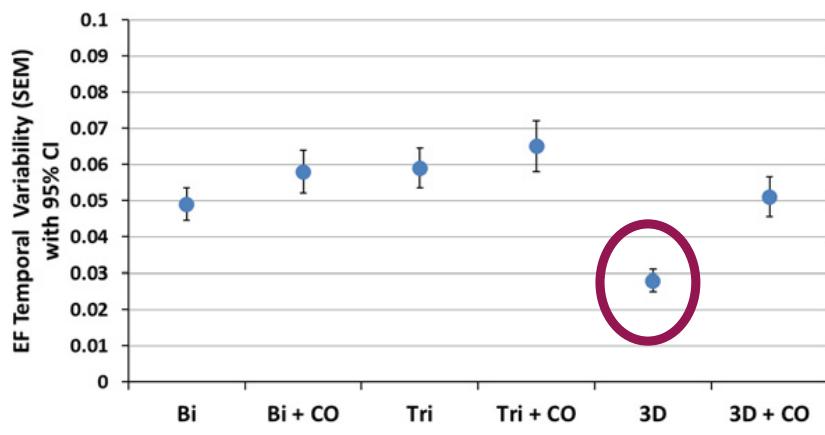
**Roxy Senior^{1*}, Harald Becher², Mark Monaghan³, Luciano Agati⁴, Jose Zamorano⁵,
Jean Louis Vanoverschelde⁶, Petros Nihoyannopoulos⁷, Thor Edvardsen⁸, and
Patrizio Lancellotti⁹**

Contrast 2D echocardiography should be considered irrespective of image quality when clinical management depends on accurate measurements of LVEF such as monitoring of patients treated with cardiotoxic drugs and when implantation of ICD or CRT devices are considered (Class IIa, Level B).



3D Echo

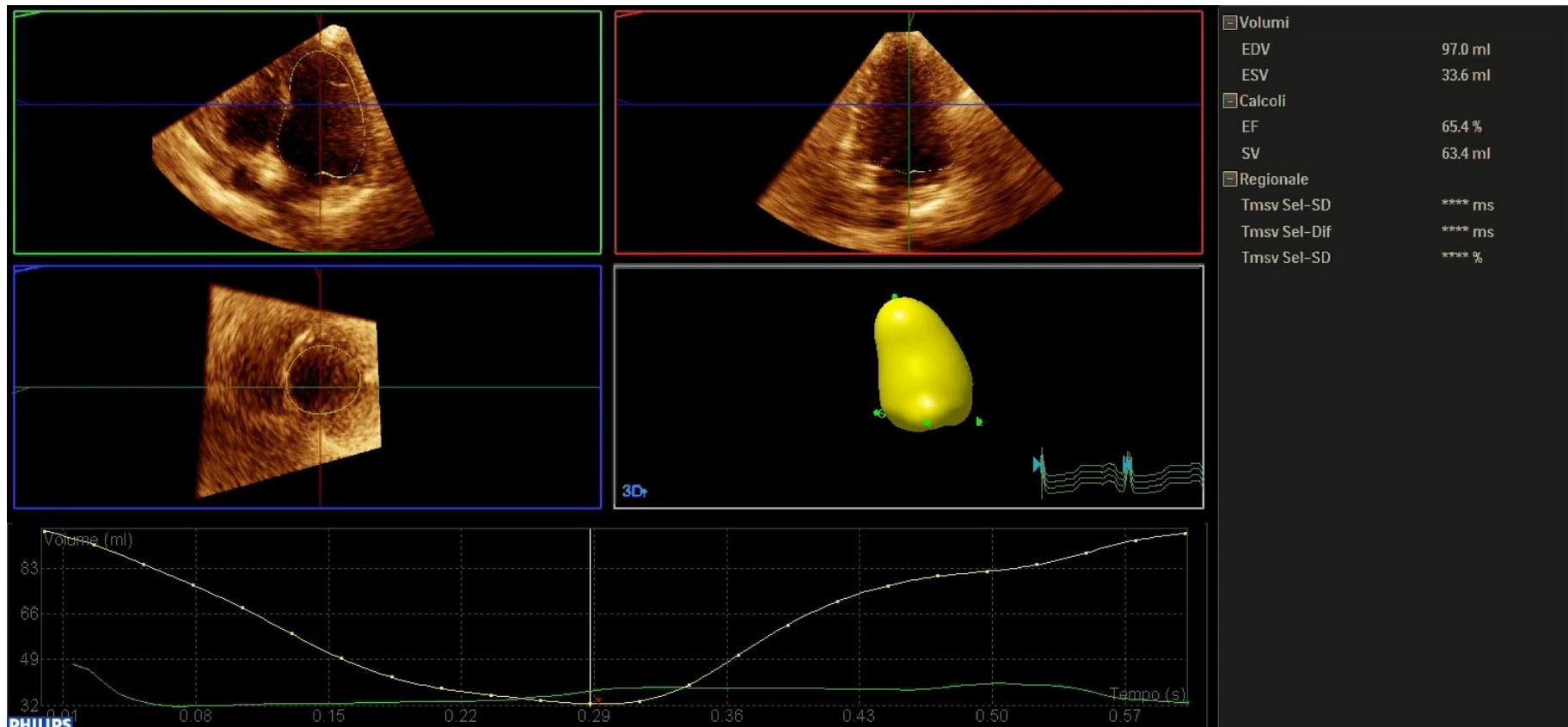
Il calcolo dei volumi del ventricolo sinistro in ecocardiografia 3D non risente degli errori indotti dalle assunzioni geometriche del metodo Simpson né da errori nell'acquisizione di immagini off-axis del ventricolo sinistro.



TECNICA DI PRIMA SCELTA
PER ASE/EACVI ED ESC!

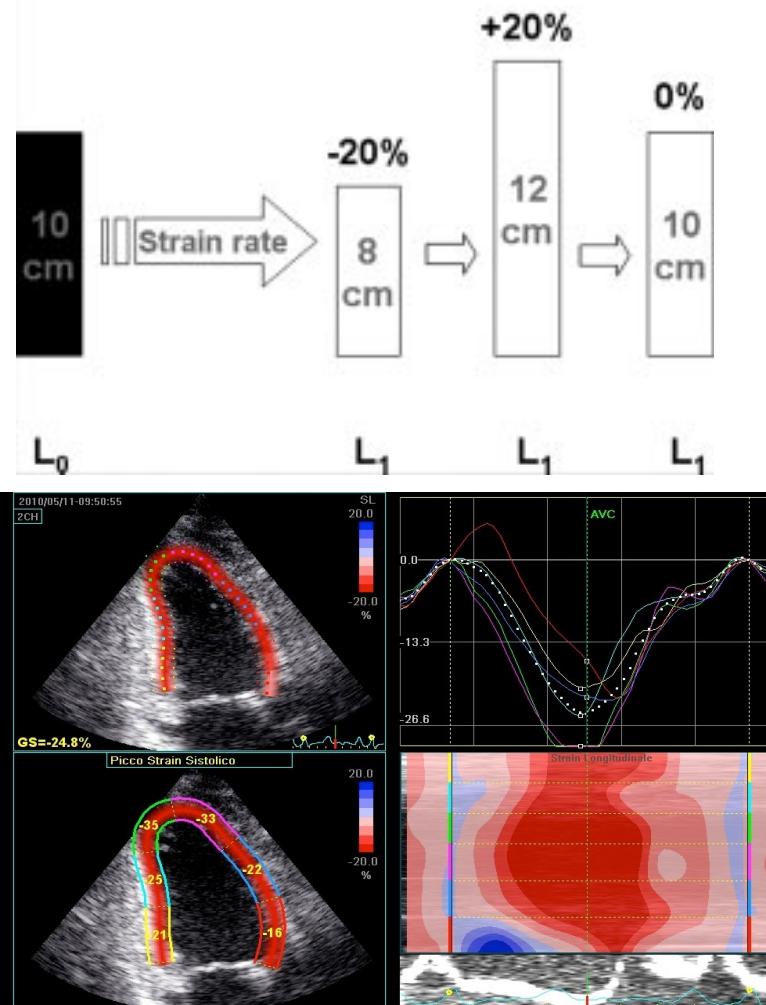
PRO: ECO 3D è il metodo più riproducibile accuratezza simile a CMR (**Gold standard**) ed è il metodo con minor variabilità temporale.

CONTRO: ridotta diffusione nel territorio della metodica 3D , software avanzati ed analisi in post processing, caratteristiche del paziente.

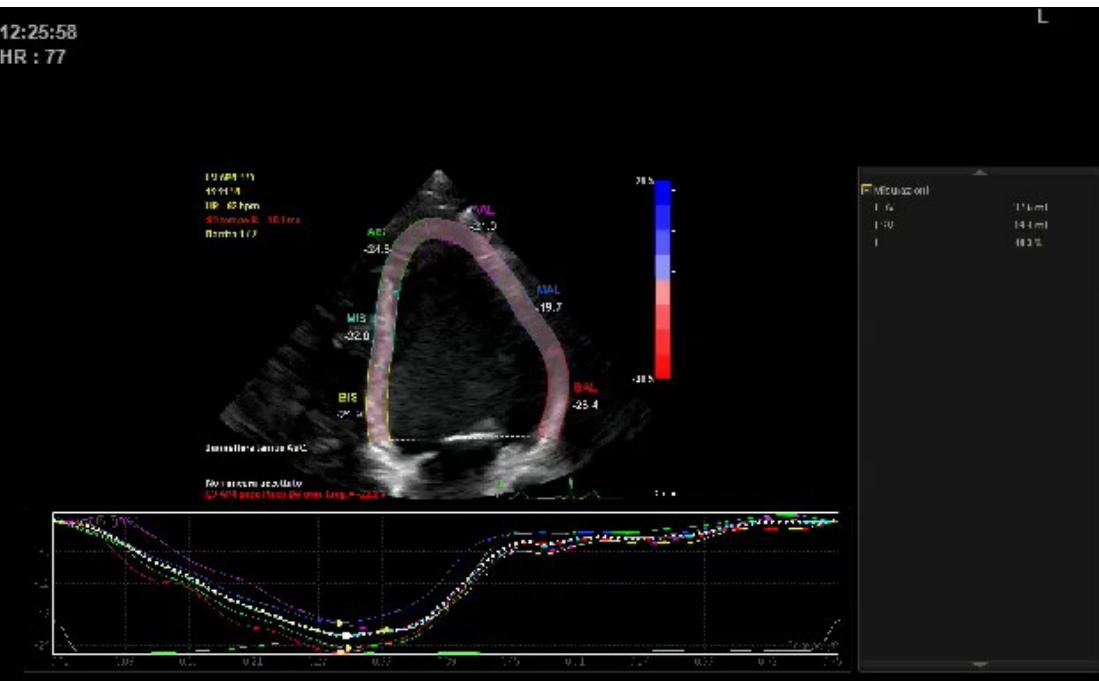


GLS: deformazione miocardica

$$\text{Strain } (\epsilon) = \frac{L_1 - L_0}{L_0}$$



DEFORMAZIONE
MIOCARDICA: accorciamento
di un segmento miocardico
rispetto alla dimensione
originale



LVEF e GLS

- Un calo di EF valutabile avviene solamente dopo un perdita consistente di tessuto miocardico per cui il suo riconoscimento può essere tardivo; alterazioni di GLS possono precedere il calo di EF.
- Valore normale di GLS: – 20% ± 2

GLS e FEVS

...STE appears therefore as the imaging technique of choice for detection of sub-clinical LV dysfunction...

PRO: Più RIPRODUCIBILE DI FE, sensibile, tecnica semiautomatica

CONTRO: dipende dalla qualità dell'esame, valori NON confrontabili tra diversi tipi di macchine ecografiche

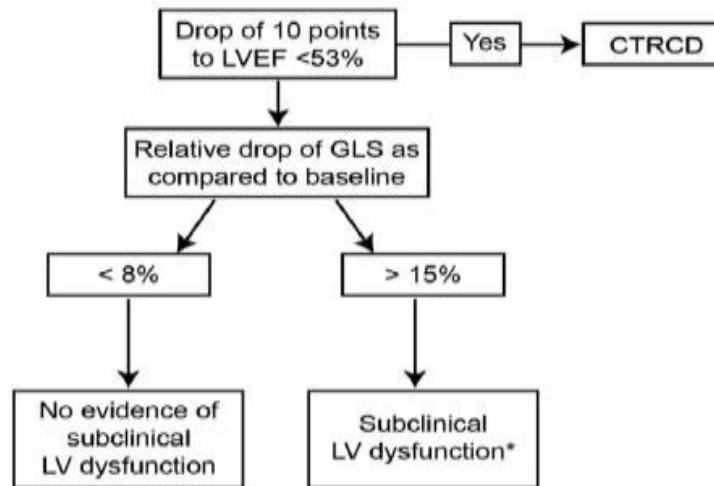
LA RIDUZIONE DI GLS PREVEDE LA COMPARSA DI CARDIOTOSSICITÀ IN MODO INDIPENDENTE ED ADDITIVO ALLA FE, CON UNA MAGGIORE SENSIBILITÀ.

Management

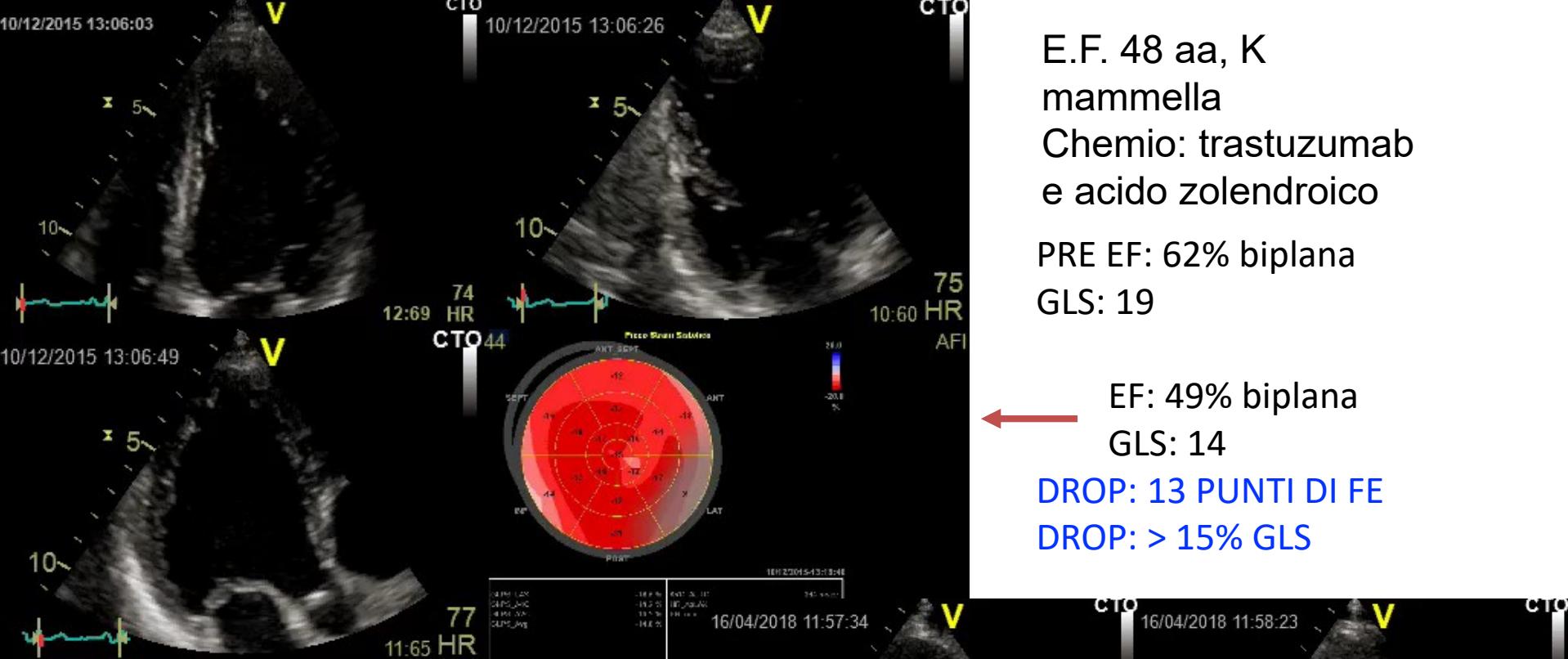
EXPERT CONSENSUS STATEMENT

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

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD,

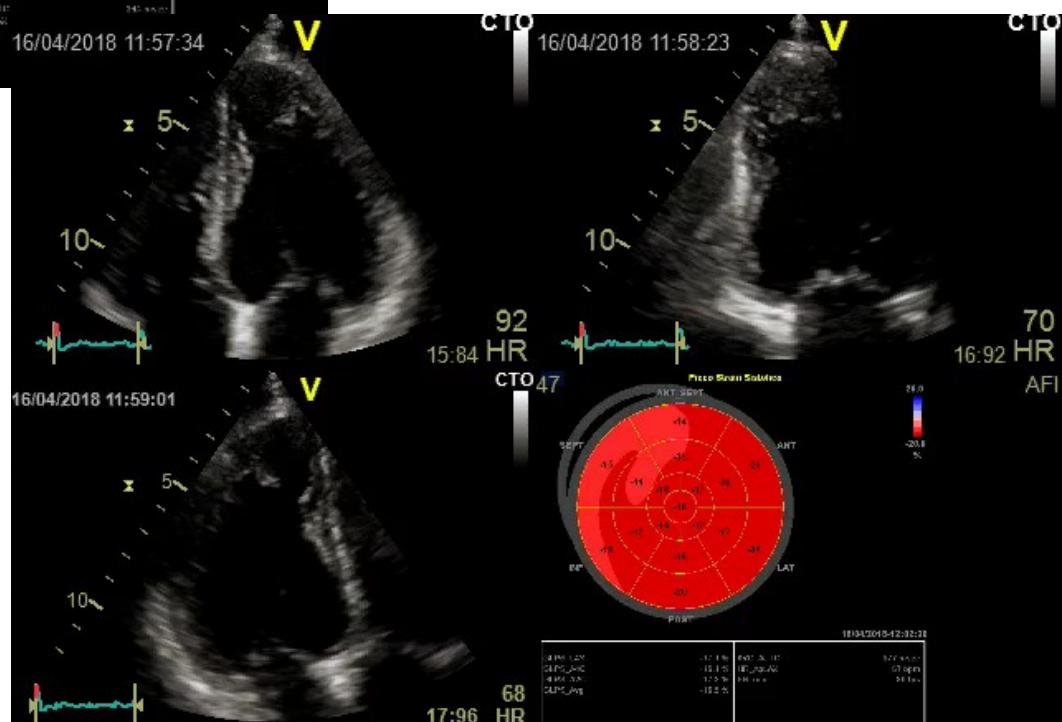


Early detection of sub-clinical LV dysfunction using GLS

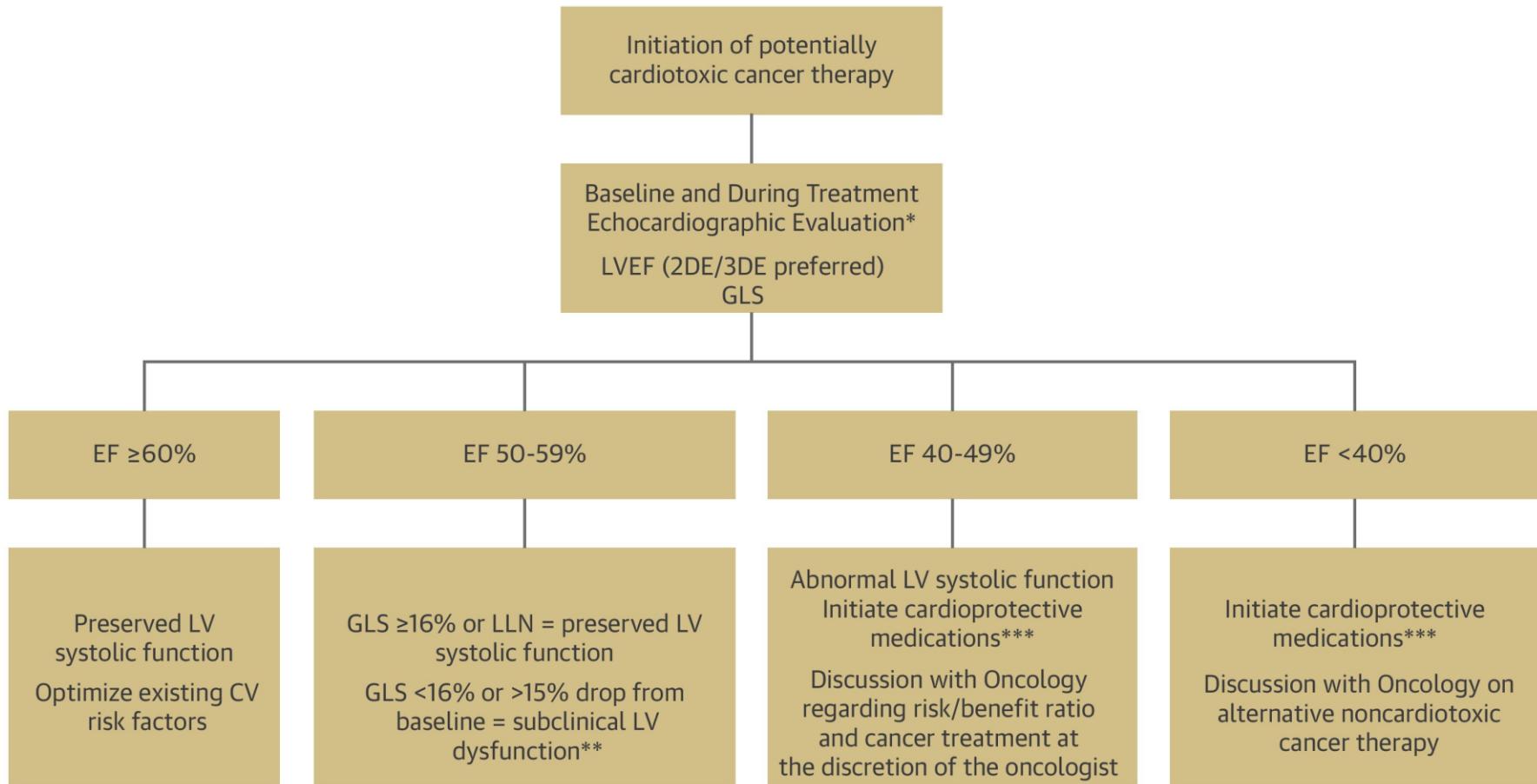


Inizio terapia cardioprotettiva
Stop temporaneo terapia
cardiotossica,
RIPRESA FE E GLS

EF: 54%
GLS: 18



CENTRAL ILLUSTRATION: Echocardiography-Guided Clinical Decision Making



Liu, J. et al. J Am Coll Cardiol Img. 2018;11(8):1122-31.

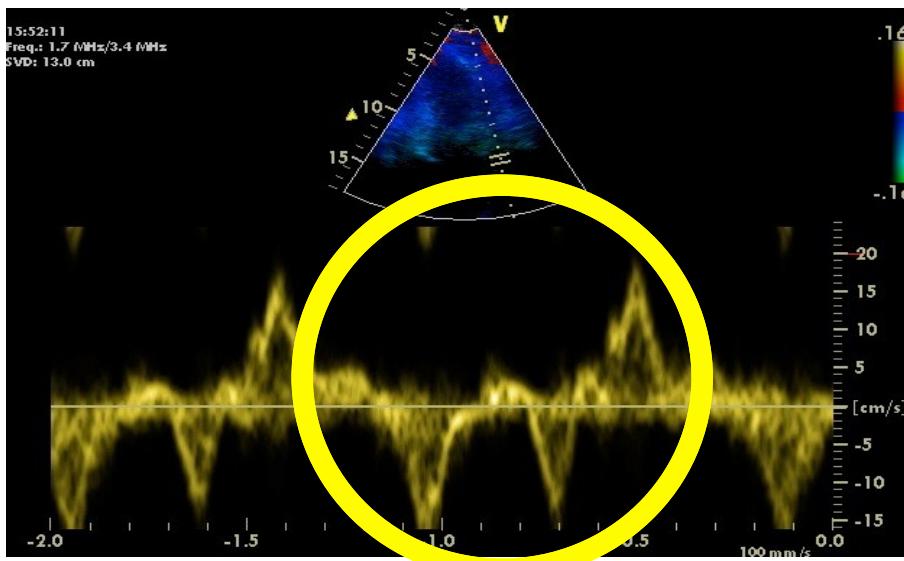
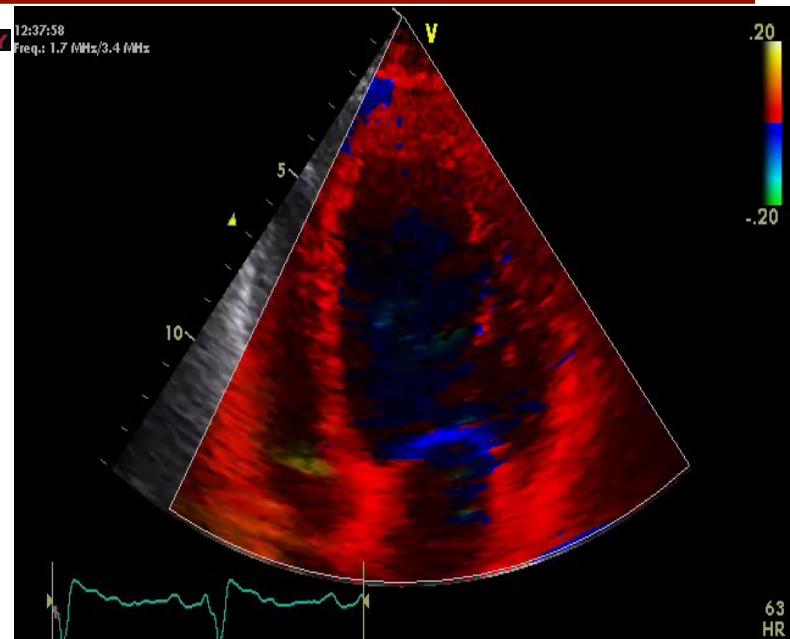
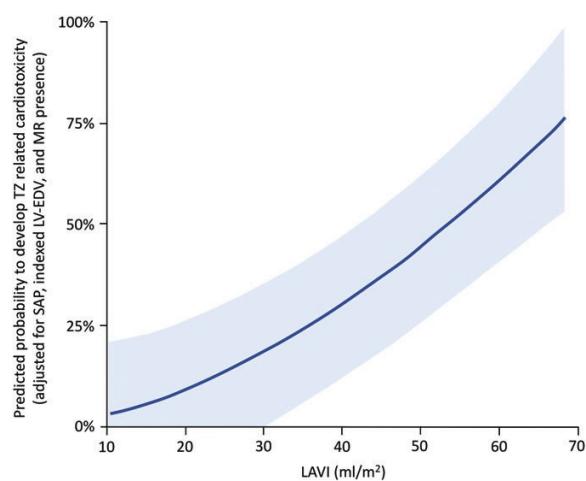
ALTRI PARAMETRI DI FUNZIONE VENTRICOLARE SINISTRA

WILEY CARDIOLOGY

CLINICAL INVESTIGATIONS

Left atrial volume in patients with HER2-positive breast cancer: One step further to predict trastuzumab-related cardiotoxicity

Corinna Bergamini¹ | Giulia Dolci¹ | Andrea Rossi¹ | Flavia Torelli¹ | Luca Ghiselli¹ |
Laura Trevisani¹ | Giulia Vinco¹ | Stella Truong¹ | Francesca La Russa² | Giorgio Golia¹ |
Annamaria Molino² | Giovanni Benfari¹ | Flavio Luciano Ribichini¹



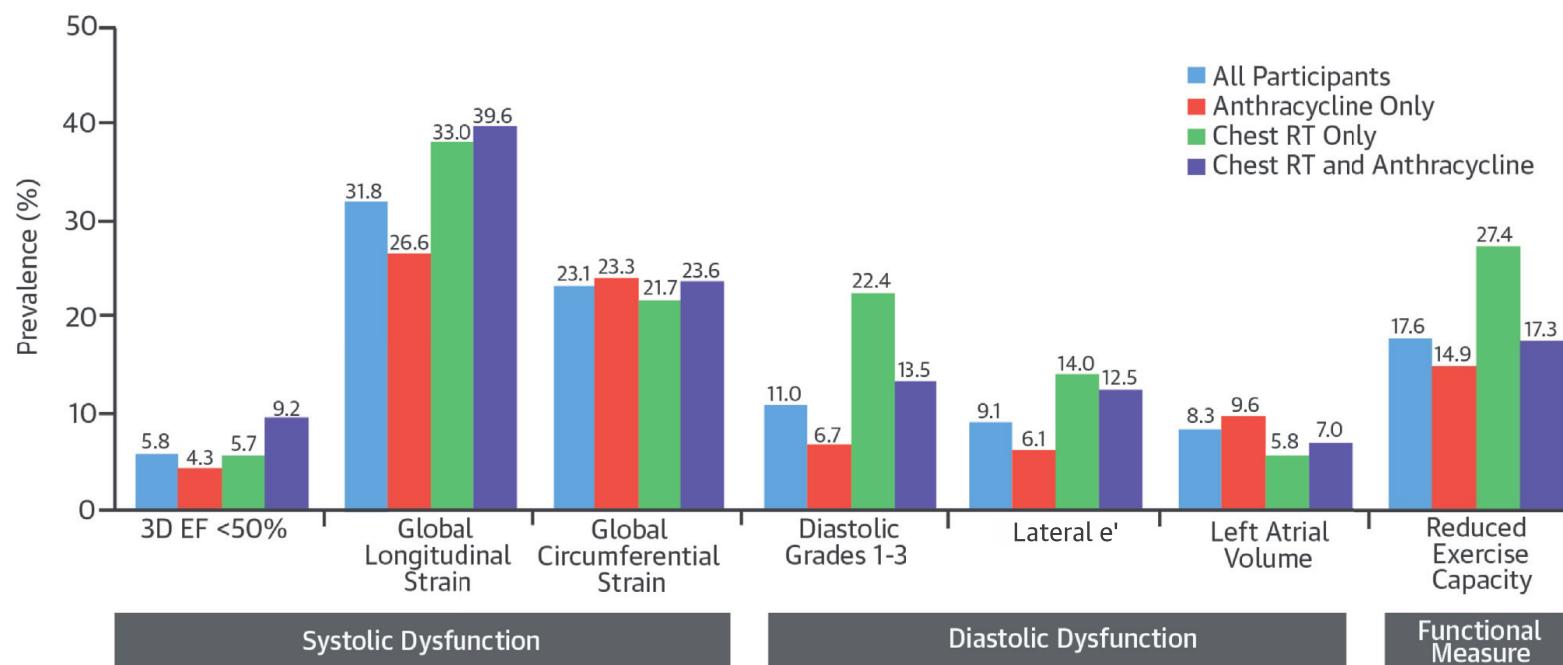
FUNZIONE DIASTOLICA?
DISFUNZIONE
VENTRICOLARE DESTRA?
RUOLO ECO DA STRESS?



Comprehensive Echocardiographic Detection of Treatment-Related Cardiac Dysfunction in Adult Survivors of Childhood Cancer

Results From the St. Jude Lifetime Cohort Study

CENTRAL ILLUSTRATION Prevalence of Cardiac Dysfunction and Reduced Exercise Capacity in Adult, 10-Year Survivors of Childhood Cancer

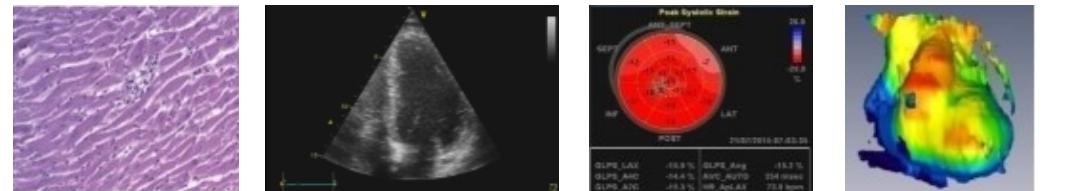


Armstrong, G.T. et al. J Am Coll Cardiol. 2015; 65(23):2511-22.

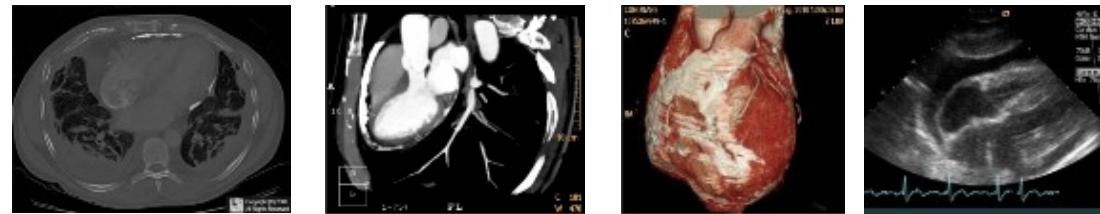
EF = ejection fraction; RT = radiotherapy; 3D = 3-dimensional.

NON SOLO MIOCARDIO.....

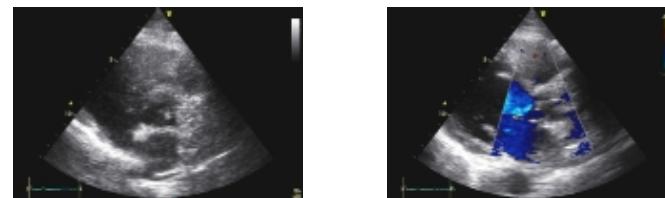
Myocardium



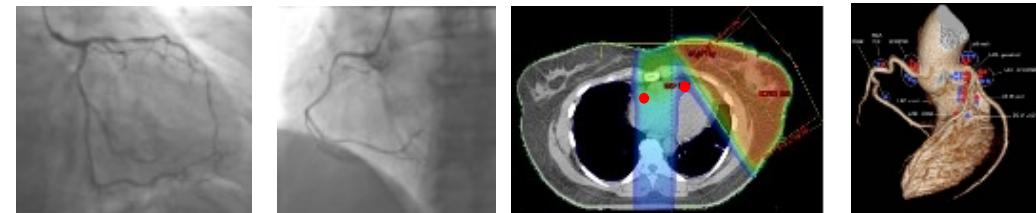
Pericardium



Valves



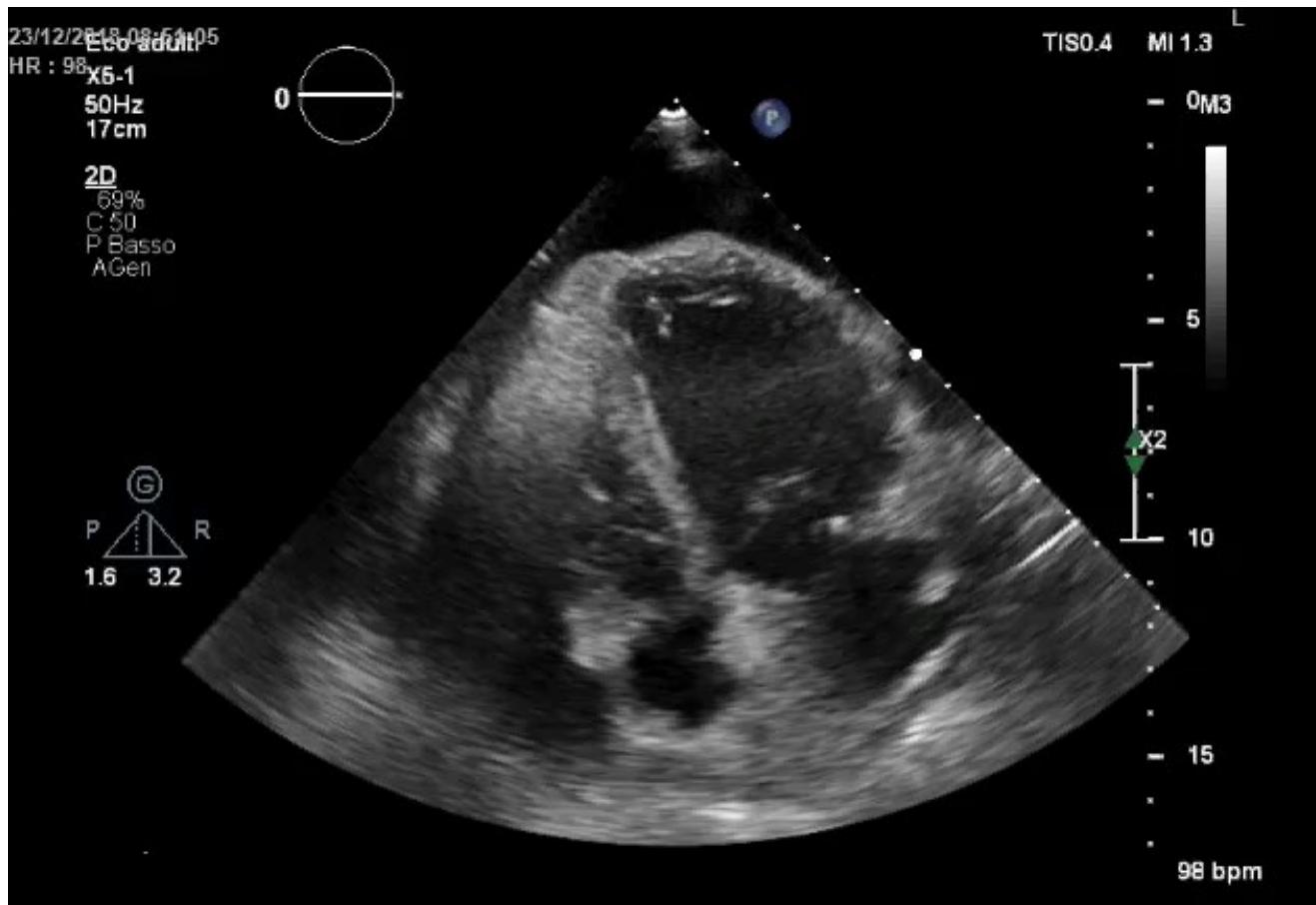
Coronaries



Conduction



..... PERICARDIO



K.M.52 aa, 2011 K mammella trattata con
quadrantectomia, radioterapia e ormonoterapia
2018 recidiva polidistrettuale trattata con chemioterapia

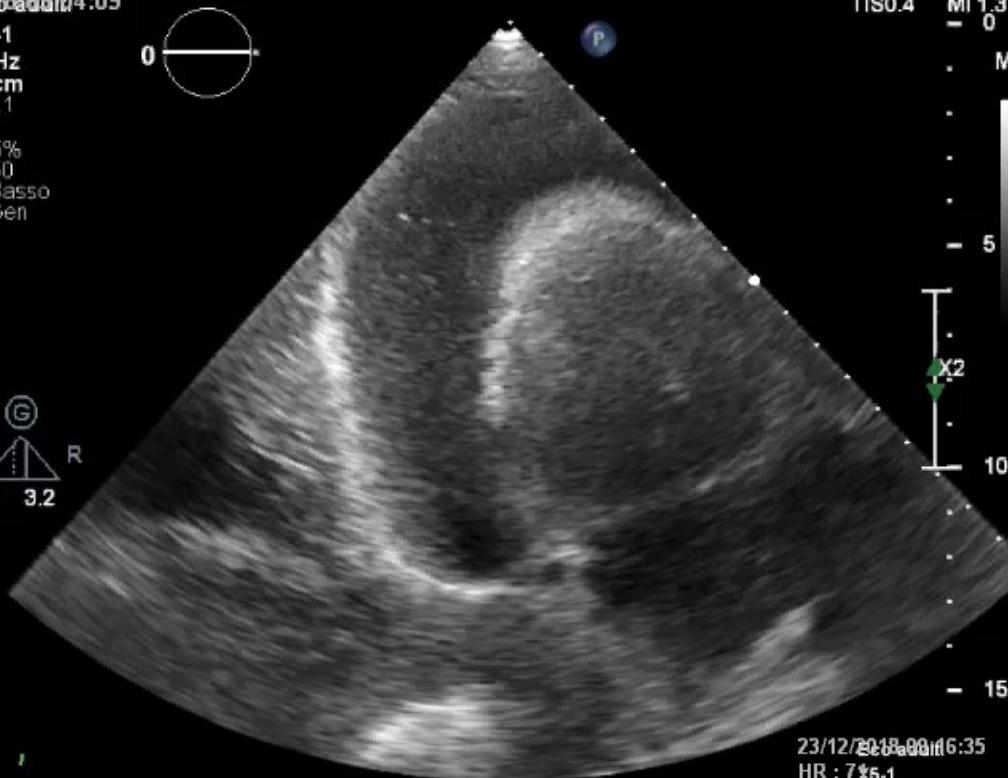
MALATTIE DEL PERICARDIO
COMUNI NEL PAZIENTE
ONCOLOGICO:
-metastasi cardiache
-chemio e radioterapia

23/12/2018 00:04:09

HR : 86.1
50Hz
17cm
Z 1.1
2D
75%
C 50
P Basso
AGen



(G)
P R
1.6 3.2



23/12/2018 00:16:35

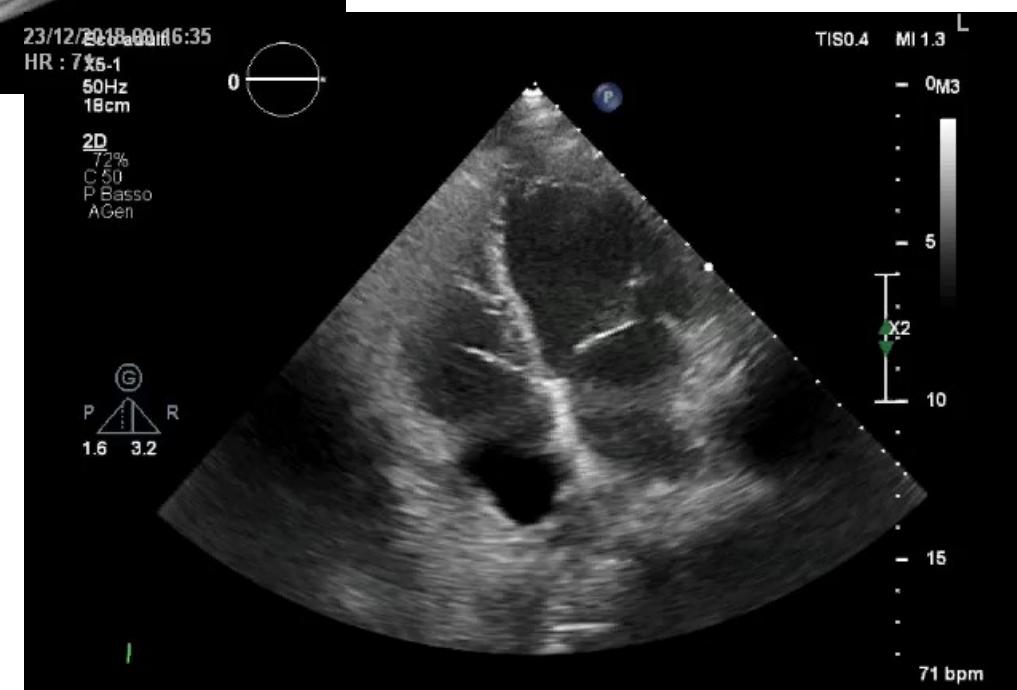
HR : 75.1
50Hz
18cm
2D
72%
C 50
P Basso
AGen



(G)
P R
1.6 3.2

Citologia liquido pericardico:
**NEGATIVA PER CELLULE
NEOPLASTICHE**

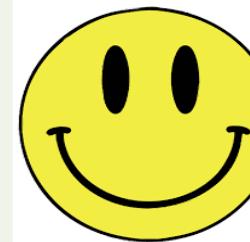
PERICARDIOCENTESI ECOGUIDATA



71 bpm

.....VALVOLE

<u>CAUSA</u>	RADIOTERAPIA >10%, 10-20 anni post trattamento
FISIOPATOLOGIA	Danno endoteliale, fibrosi e calcificazioni
POSIZIONE	PREVALENTEMENTE VALVOLA AORTICA E MITRALE, FIBROSA INTERVALVOLARE
TIPO	Insufficienza>> stenosi Stenosi>> aorta
VALUTAZIONE	<u>ECO:</u> RADICE AORTICA E CUSPIDI VALVOLARI ANULUS E LEMBI MITRALICI <u>TIPICO</u> NON COINVOLGE I MARGINI LIBERI E LE COMMISSURE DELLA VALVOLA MITRALE
TRATTAMENTO	Sostituzione valvolare o TAVI



B.M.M. 70 aa

Linfoma di Hodgkin circa
30 anni fa, chemio e
radiotrattato

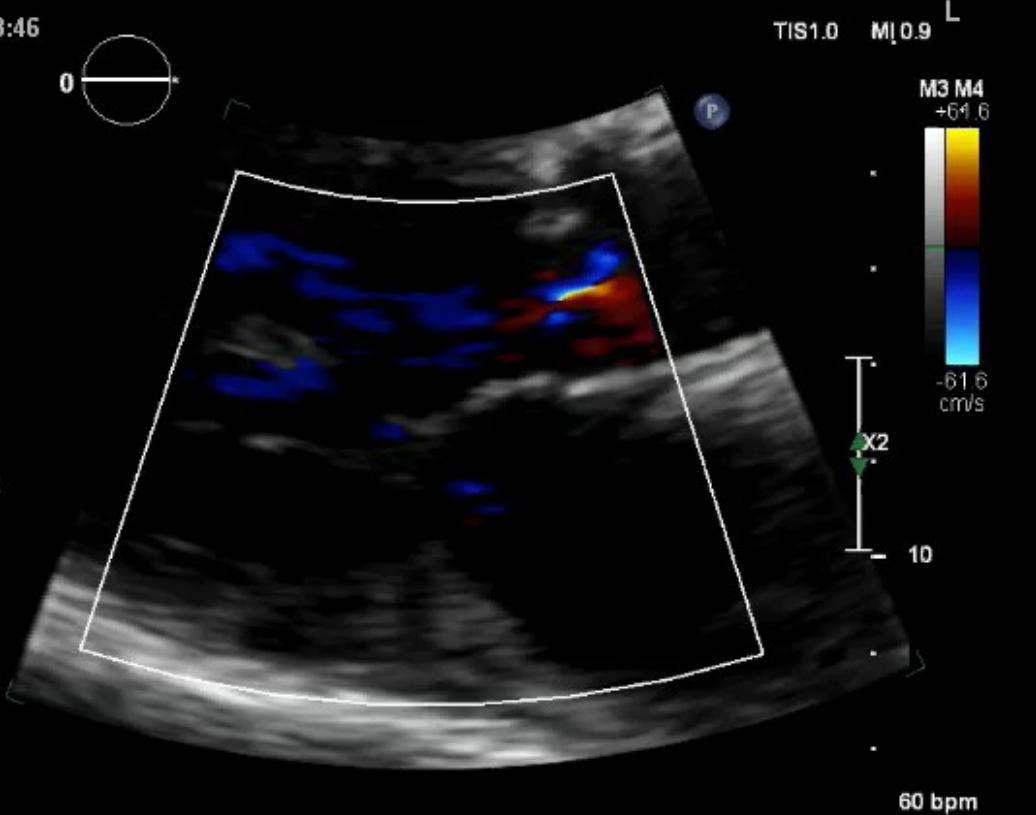
07/12/2018 12:03:46

HR : 60±1
22Hz
12cm

2D
60%
C 50
P Bassa
Agen

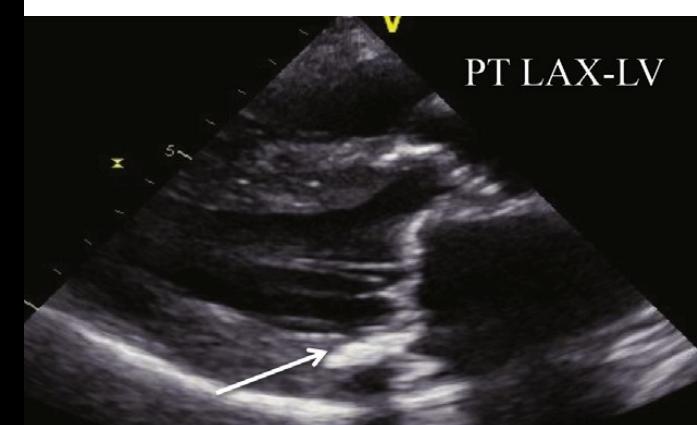
CF
50%
4000Hz
WF 399Hz
2.5MHz

(G)
P 1.6 R 3.2



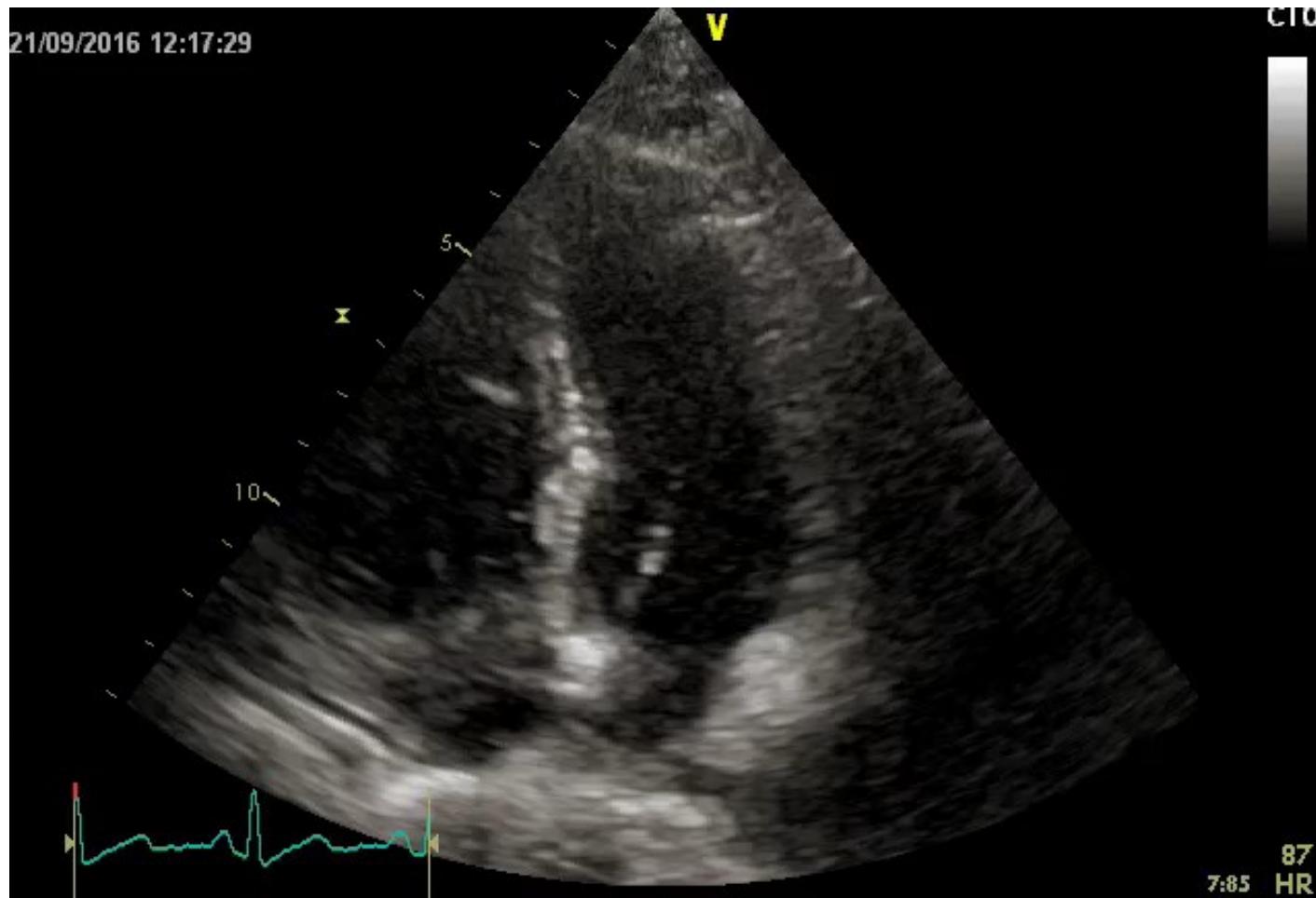
Alla CGF: stenosi critica del TCCS ostiale.

ECO: FEVS 40% biplana
IM medio-severa
IA: media



.....TROMBOEMBOLISMO

21/09/2016 12:17:29



M.M. 43 aa
K mammella
operato
TP adiuvante con
Epirubicina e
ciclofosfamide
Tp
estroprogestinica

RMN cuore:
...esilissimo
peduncolo di
raccordo con la
parete infero-laterale
in adiacenza con
valvola di Eustachio
...non in
corrispondenza di
PICC....

REPERTO ACCIDENTALE....

CONCLUSIONI

- Per valutare la comparsa di cardiotossicità è indicata l'ecocardiografia 3D (se possibile) o 2D biplana associata a GLS
- Diagnosi precoce essenziale
- Aspetti ancora da approfondire: disfunzione diastolica, volume atriale sinistro, funzione ventricolare destra

CONCLUSIONI

- L'esame ecocardiografico di un paziente oncologico richiede tempo, strumentazione adeguata e competenza
 - Integrare diverse tecniche di imaging
 - Stretta collaborazione tra cardiologo e oncologo dello stesso centro!



2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

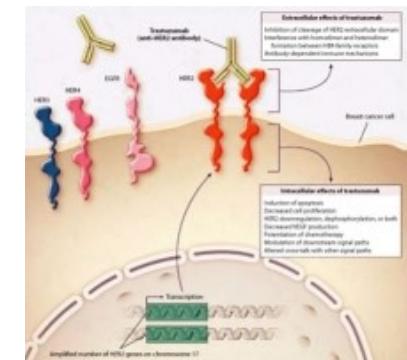
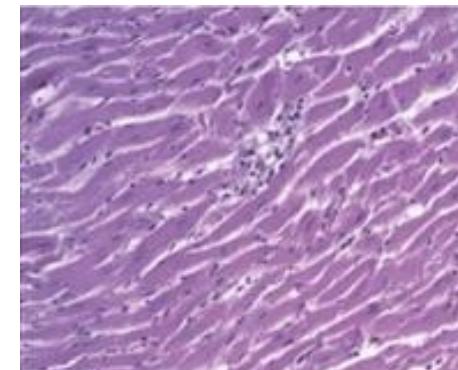
Echo Measurements	Action
EF decreases >10% but not below 50%	repeat EF measurement shortly after and during the duration of cancer treatment
EF decreases >10% to EF <50%, asymptomatic	may be considered as stage B HF (in particular with high BNP) ACE inhibitors (or ARBs)+beta-blockers
EF decreases >10% to EF <50% with heart failure	ACE inhibitors (or ARBs)+beta-blockers
GLS decreases > 15% EF remains >50%	No change in chemotherapy!

“Classical” chemotherapy: Type 1 CTRCD

Targeted molecular therapies: Type 2 CTRCD

Chemotherapy Associated With Left Ventricular Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3-26*	+++
Epirubicin (Ellence) (10)	0.9-3.3	++
Idarubicin (Idamycin PFS) (8)	5-18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11-13)	7-28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clofar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3-8	++
Monoclonal antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7-3	++
Trastuzumab (Herceptin) (20-28)	2-28	++
Proteasome inhibitor		
Bortezomib (Velcade) (10,17)	2-5	++
Small molecule tyrosine kinase Inhibitors		
Dasatinib (Sprycel) (10)	2-4	++
Imatinib mesylate (Gleevec) (34,35)	0.5-1.7	+
Lapatinib (Tykerb) (32)	1.5-2.2	+
Sunitinib (Sutent) (36,37)	2.7-11	+++



Yeh ET et al. J Am Coll Cardiol 2009
 Ewer MS, Ewer SM. Nat Rev Cardiol 2010

CORONARY ARTERY DISEASE/ACUTE CORONARY SYNDROME

M.B. 40 yrs
No FDR/ storia di CVD

Seminoma
Chemio: cisplatino,
etoposide e bleomicina

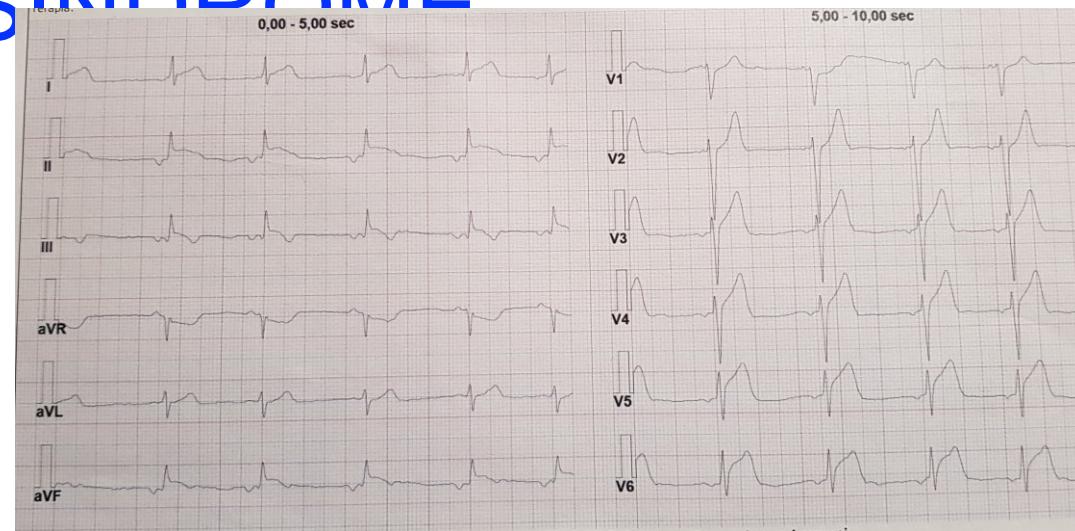
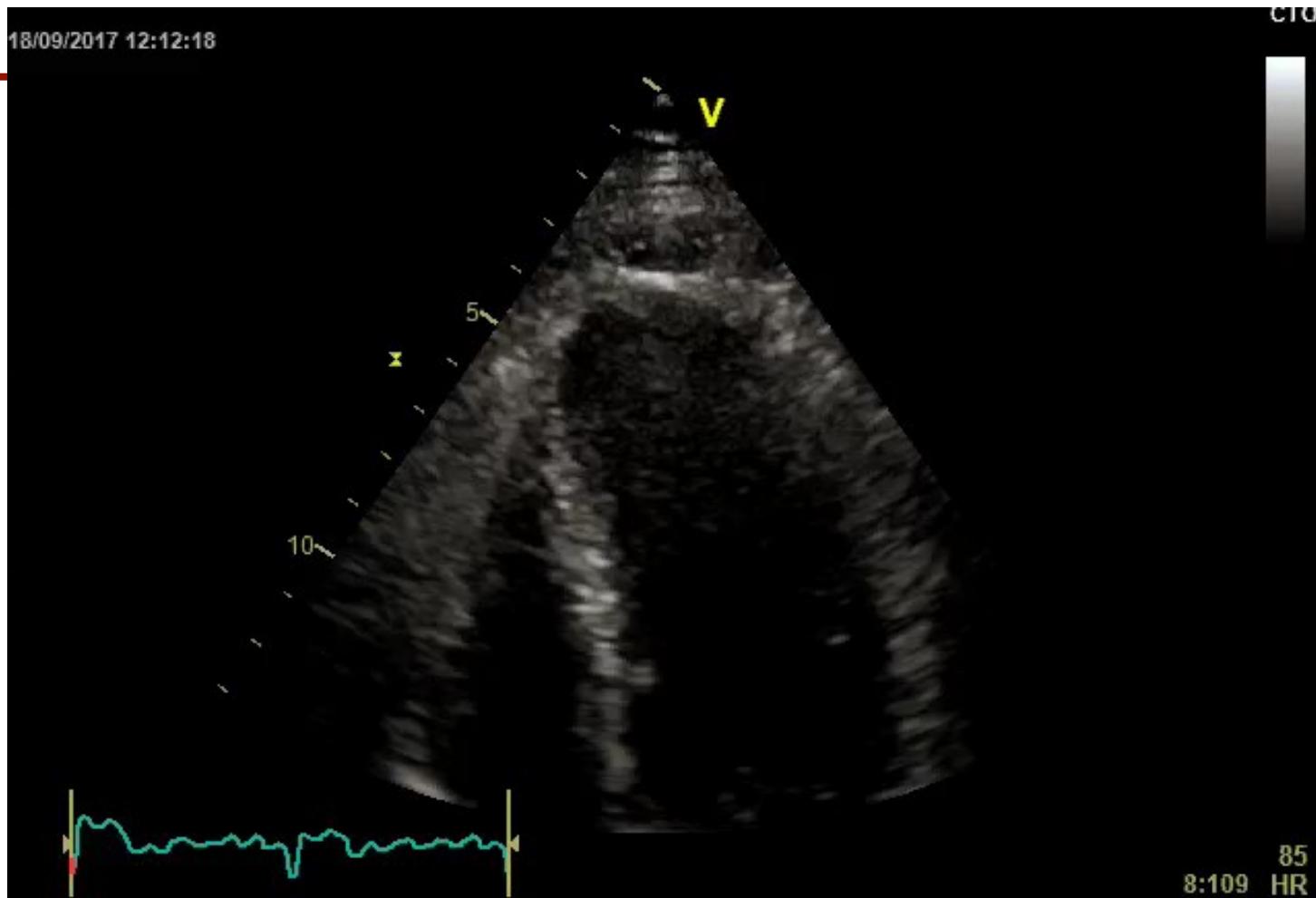


Table 7 Pathophysiological mechanisms of coronary artery disease in cancer treatment^{7,60,81,99,117–123}

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	<ul style="list-style-type: none">• Endothelial injury• Vasospasm	<ul style="list-style-type: none">• Up to 18% manifest myocardial ischaemia• Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	<ul style="list-style-type: none">• Procoagulant status• Arterial thrombosis	<ul style="list-style-type: none">• 20-year absolute risk of up to 8% after testicular cancer• 2% risk of arterial thrombosis
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	<ul style="list-style-type: none">• Procoagulant status• Arterial thrombosis• Endothelial injury	<ul style="list-style-type: none">• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiotherapy	<ul style="list-style-type: none">• Endothelial injury• Plaque rupture• Thrombosis	<ul style="list-style-type: none">• 2–7-fold increased relative risk of myocardial infarction• Cumulative 30-year coronary events incidence of 10% in Hodgkin lymphoma survivors• Risk proportional to irradiation dose

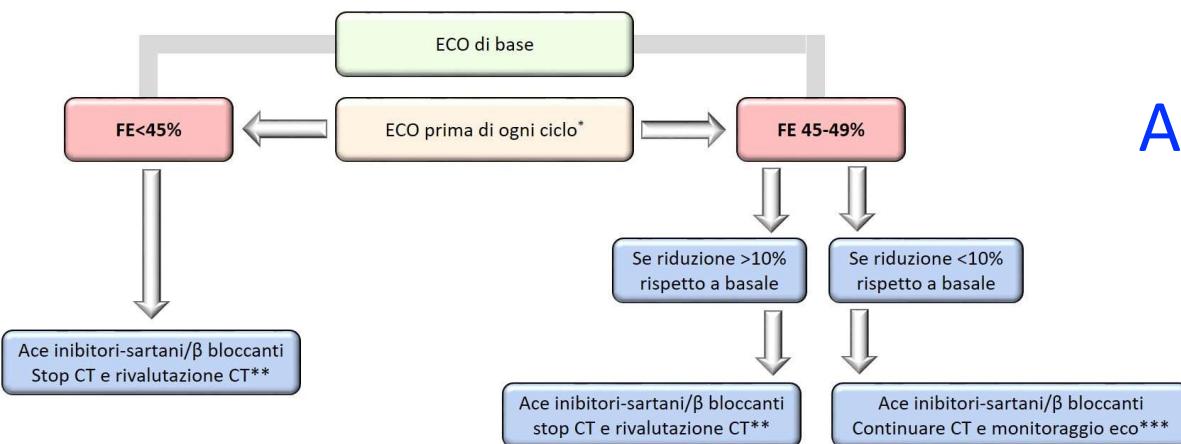
18/09/2017 12:12:18

CTO



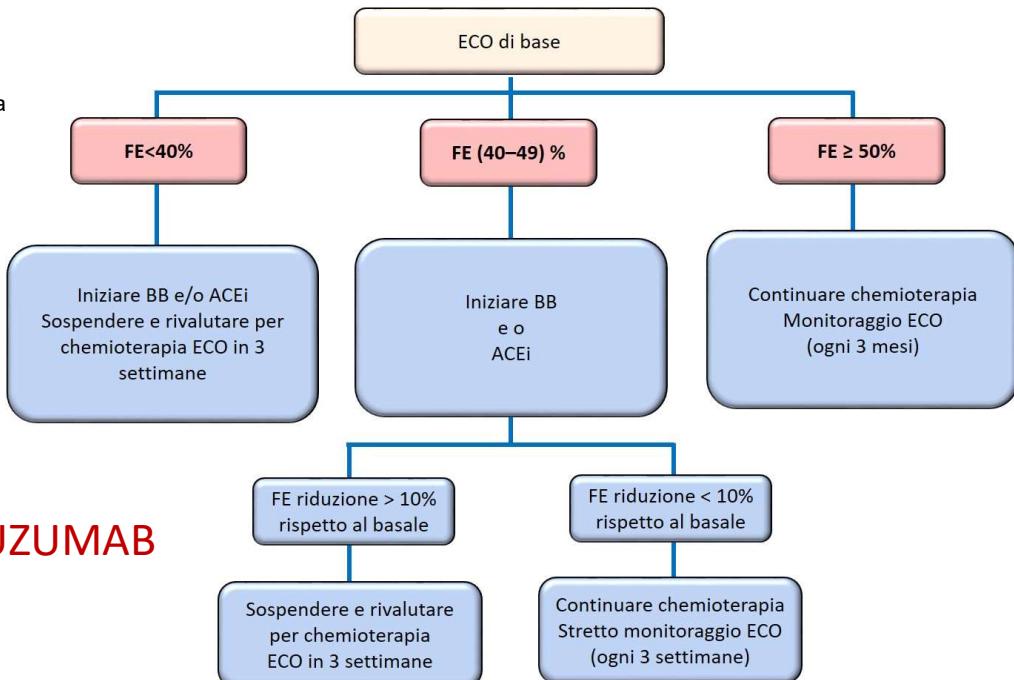
MECCANISMO DI ISCHEMIA:
EFFETTO VASOSPASTICO
INSTABILITÀ/ROTTURA DI PLACCA
TROMBOSI ARTERIOSA ACUTA

VALUTAZIONE ECOCARDIOGRAFICA E ~~TRATTAMENTI~~



CONSENSUS ANMCO/AICO/AIOM

* se FE <50% valutazione ecocardiografica prima di ogni ciclo
 ** valutare eventuale chemioterapia alternativa
 *** alla fine della chemioterapia o dopo dose cumulativa >250 mg/m², nel follow-up in base al rischio cardiovascolare del paziente.



CENTRAL ILLUSTRATION: Cardiovascular Complications of Cancer Therapy

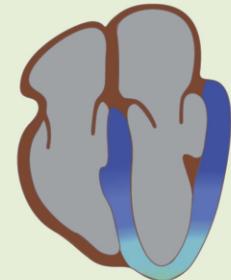
CARDIOVASCULAR COMPLICATIONS OF CANCER THERAPY

STAGES OF THE EVALUATION

Risk Stratification → Early Detection of Injury → Prediction of Recovery → Detection of Injury in the Survivor

CLINICAL CONDITIONS TO BE EVALUATED

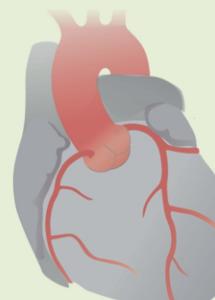
LV Dysfunction



Pericardial Disease



CAD



Pulmonary Hypertension



Aortopathy



IMAGING MODALITIES ARMAMENTARIUM

ECHO



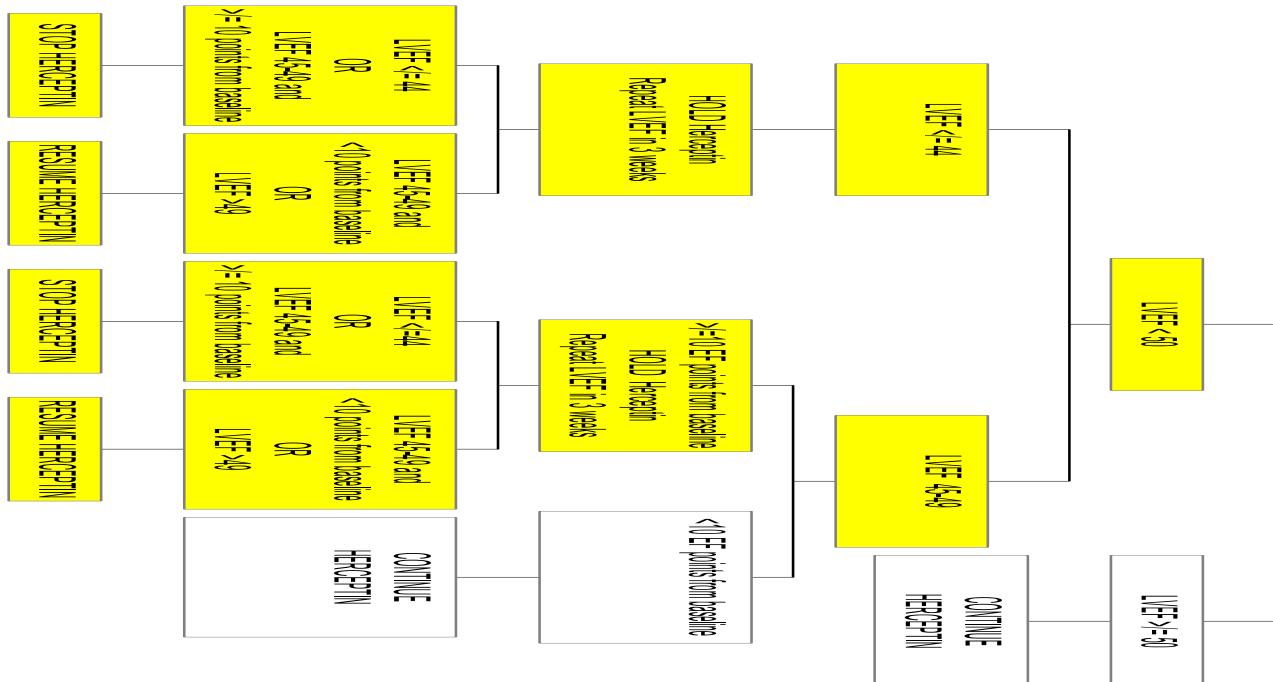
Nuclear/PET

Cardiac CT

CMR

STUDIO HERA

Figure 4 Algorithm for continuation and discontinuation of Heraceptin® based on interval LVEF assessments



2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility

Ciro Santoro¹, Grazia Arpino², Roberta Esposito¹, Maria Lembo¹,
Immacolata Paciolla², Cinzia Cardalesi², Giovanni de Simone³, Bruno Trimarco¹,
Sabino De Placido², and Maurizio Galderisi^{1*}

