XVII Congresso Nazionale SIEC

Napoli, 16-18 aprile 2015

IMAGING NEL PAZIENTE ONCOLOGICO

IMAGING TRADIZIONALE NEL PAZIENTE TRATTATO CON ANTIBLASTICI: IL VALORE DEL CONFRONTO DEI VIDEO

Dott. Stefano Oliva

IRCCS Istituto Tumori "Giovanni Paolo II"

Bari

La cardioncologia

DEFINIZIONE

La moderna cardioncologia nasce dall'esperienza degli ultimi 10 anni di un'aumentata incidenza di patologie cardiovascolari nei pazienti oncologici oramai guariti e trattati anche decenni prima…

Il cardioncologo è colui che, da cardiologo, affianca l'oncologo e l'ematologo nelle scelte terapeutiche e gestionali del paziente neoplastico al fine di prevenire (*se possibile*), identificare precocemente (*quando possibile*) e trattare (*sempre possibile*) le complicanze cardiovascolari legate al tumore e ai suoi trattamenti

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JOURNAL OF Cardiovascular Echography

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Review

Cardiovascular complications of conventional anticancer therapy

Stefano Oliva*, Agnese Maria Fioretti

Cardiology Unit, IRCCS National Cancer Institute "John Paul II" of Bari (Italy)

Received 28 April 2011; accepted 6 May 2011; available online 29 June 2011

Table 1 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 (Clolar) (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	+++

Table 1
Chemotherapy drugs associated to cardiotoxic late effects.

Drug	Cardiac side effect
Anthracycline	
• Doxorubicin	AR, LVD
• Epirubicin	AR, LVD
• Idarubicin	AR, LVD
Alkylating agents	
• Cyclophosphamide	LVD
• Ifosfamide	LVD
• Cisplatin	VTE
Antimetabolites	
• Clofarabine	
Antimicrotubule agents	
• Paclitaxel	MI, AR, LVD
• Docetaxel	MI, AR, LVD
Antimetabolites	
• Capecitabine	MI, AR
• Florouracil	MI, AR
Angiogenesis inhibitors	
• Lenalidomide	MI, VTE
• Thalidomide	VTE

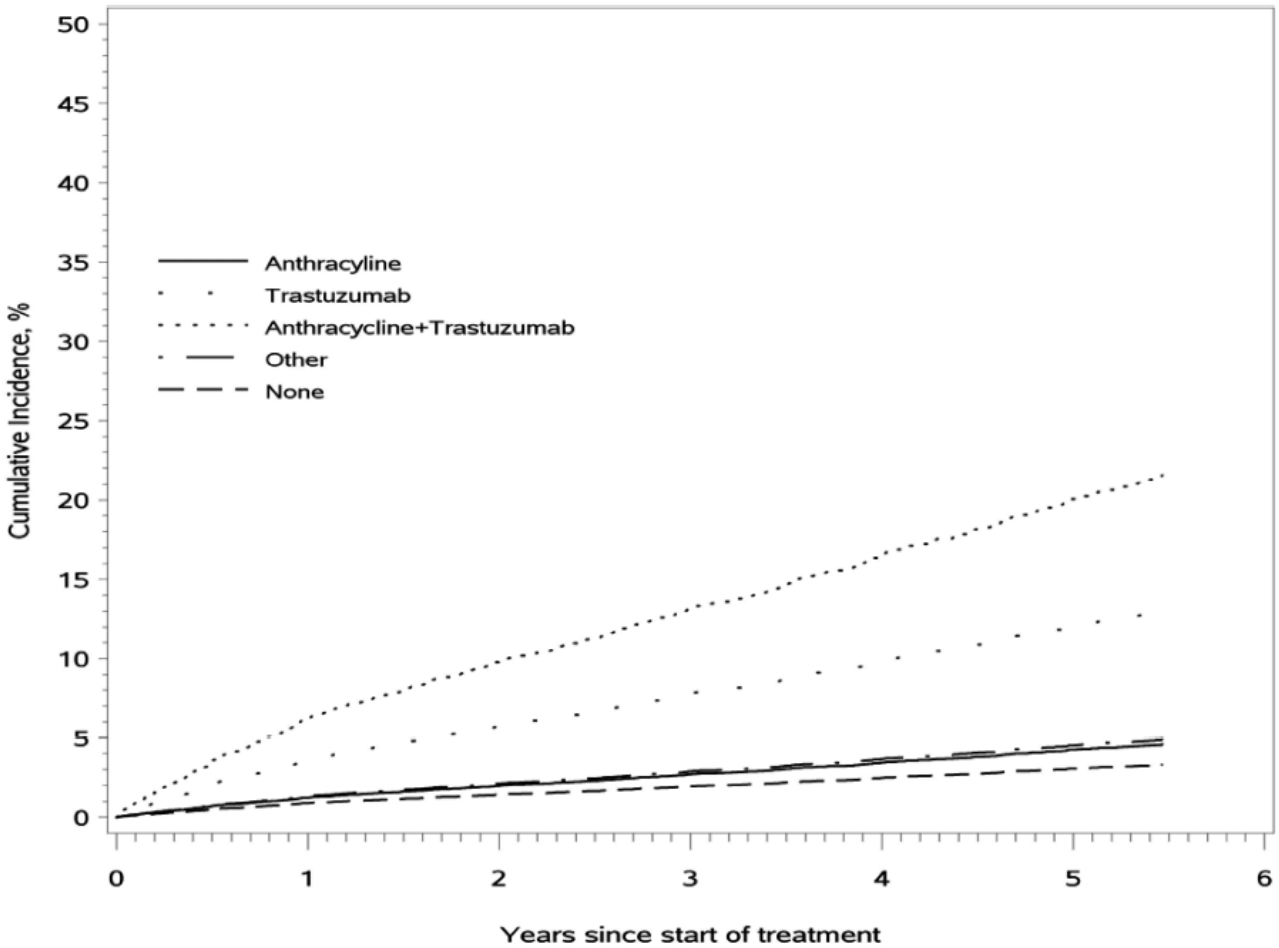
Legend: AR = Arrhythmias; LVD = Left Ventricular Dysfuntion; VTE = Venous Thromboembolism; MI = Myocardial Ischemia.

S. Oliva – JCECHO 2011;21:74-77

E. Yeh et al – JACC 2009;53:2231-2247

Risk of Heart Failure in Breast Cancer Patients After Anthracycline and Trastuzumab Treatment: A Retrospective Cohort Study

Erin J. Aiello Bowles, Robert Wellman, Heather Spencer Feigelson, Adedayo A. Onitilo, Andrew N. Freedman, Thomas Delate, Larry A. Allen, Larissa Nekhlyudov, Katrina A. B. Goddard, Robert L. Davis, Laurel A. Habel, Marianne Ulcickas Yood, Catherine McCarty, David J. Magid, Edward H. Wagner; for the Pharmacovigilance Study Team

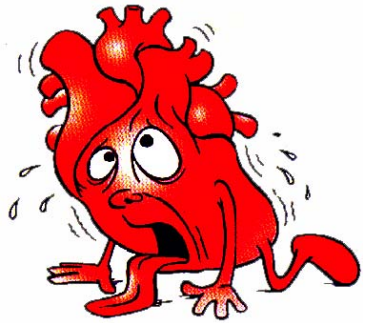


Bowles E.JA. et al – JNCI 2012

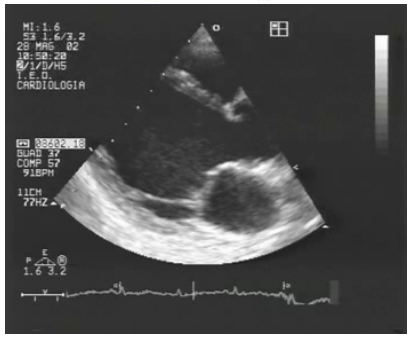
Quando è in gioco la vita…

…alcune cose passano in secondo piano!

Diagnosis of cardiotoxicity

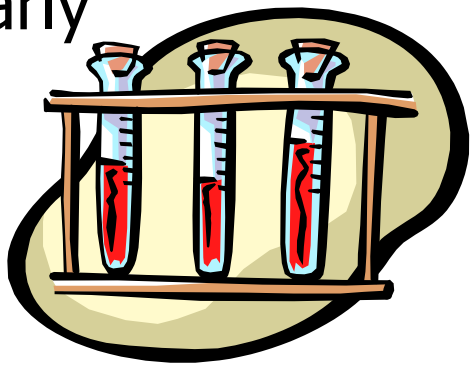


- Symptomatic → HF symptoms → very late



- Asymptomatic → ↓ LVEF → late ?

- Preclinical → myocardial injury → very early



per gentile concessione della Dott.ssa Cardinale

Cardiac toxicity in breast cancer survivors: review of potential cardiac problems

Table 1. Comparison of five different classifications of cardiotoxicity focusing on CHF

Classification system (reference)	Grade I	Grade II	Grade III	Grade IV
NYHA	No limitation of activities	Mild limitation of activity	Marked limitation of activity	Confined to bed or chair
American College of Cardiology/American Heart Association (3)	Stage A; at high risk but without structural heart disease or symptoms	Stage B; structural heart disease but without signs or symptoms	Stage C; Structural heart disease with prior or current symptoms	Stage D; Refractory CHF requiring specialized interventions
Clinical toxicity criteria, version 2.0*	Asymptomatic decline of resting EF ≥10% but <20% of baseline value	Asymptomatic but resting EF less than LLN for laboratory or decline of resting EF of ≥20% of baseline value; <24% SF	CHF responsive to treatment	Severe or refractory CHF or requiring intubation
Common terminology criteria for adverse events version 3.0 †	Asymptomatic, resting EF <60%-50%; SF <30%-24%	Asymptomatic, resting EF <50%-40%; SF <30%-24%	Symptomatic CHF responsive to intervention; EF <40%-20%; SF <15%	Refractory CHF or poorly controlled; EF <20%, intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated
Cardiac review and evaluation committee (5)	Decline in LVEF of at least 10% to <55% without signs or symptoms of CHF	Global decrease in LVEF	Signs or symptoms of CHF	Decline in LVEF of at least 5% to <55% with signs or symptoms of CHF

Brian RJ et al.- Clin Cancer Res 2008;14(1):14-24

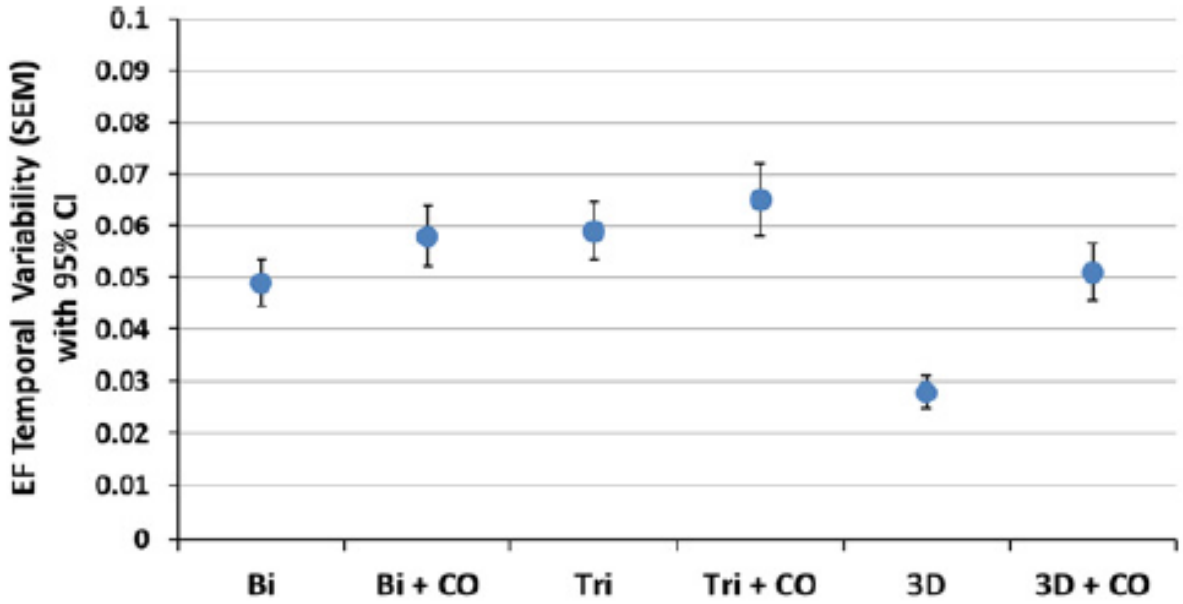
Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes

Application to Patients Undergoing Cancer Chemotherapy

56 pts (all female) with BC

5 echo (baseline, 3,6,9,12 months)

Stabile LV function (GLS ≤ -16%)



	Bi	Bi + CO	Tri	Tri + CO	3D	3D + CO
EF SEM 95% CI	0.049 (0.045–0.054)	0.058 (0.053–0.065)*	0.059 (0.054–0.065)	0.065 (0.058–0.072)	0.028 (0.025–0.031)	0.051 (0.046–0.057)*

Figure 3 Temporal Variability in EF

Tavendiranathan P et al, J Am Coll Cardiol 2013

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

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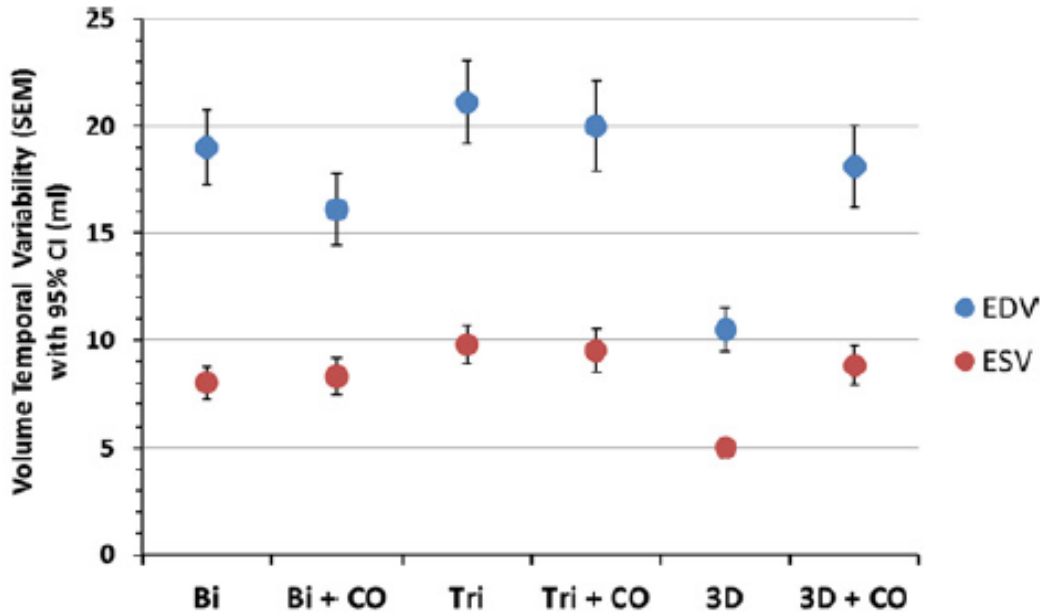


	Bi	Bi + CO	Tri	Tri + CO	3D	3D + CO
EDV SEM (ml) (95% CI)	19.0 (17.4–20.9)	16.1 (14.6–17.9)*	21.1 (19.3–23.2)	20.0 (18.0–22.2)	10.5 (9.6–11.6)	18.1 (16.4–20.2)*
ESV SEM (ml) (95% CI)	8.0 (7.3–8.8)	8.3 (7.5–9.2)	9.8 (8.9–0.7)	9.5 (8.6–10.6)	5.0 (4.6–5.5)	8.8 (8.0–9.8)*

Figure 4 Temporal Variability in EDV and ESV

Tavendiranathan P et al, J Am Coll Cardiol 2013

LVEF is not enough sensitive to detect cardiotoxicity

- ✓ Although LVEF is a robust predictor of cardiac outcome in the general population, it has low sensitivity for detection of small changes in left ventricular function
- ✓ In a recent study of cancer patients undergoing chemotherapy but free of heart failure (HF) symptoms, the upper limit of the 95% confidence interval of 2D measurement was 10% (range = 9.1 - 11.8).
- ✓ Therefore, **2D echocardiography appears to be reliable in the detection of differences only greater than 10% in LVEF.**
- ✓ It's most promising application, however, is in the use of myocardial strain and strain rate imaging to detect early cardiac injury.

Tavendiranathan P et al, J Am Coll Cardiol 2013;61:77-84

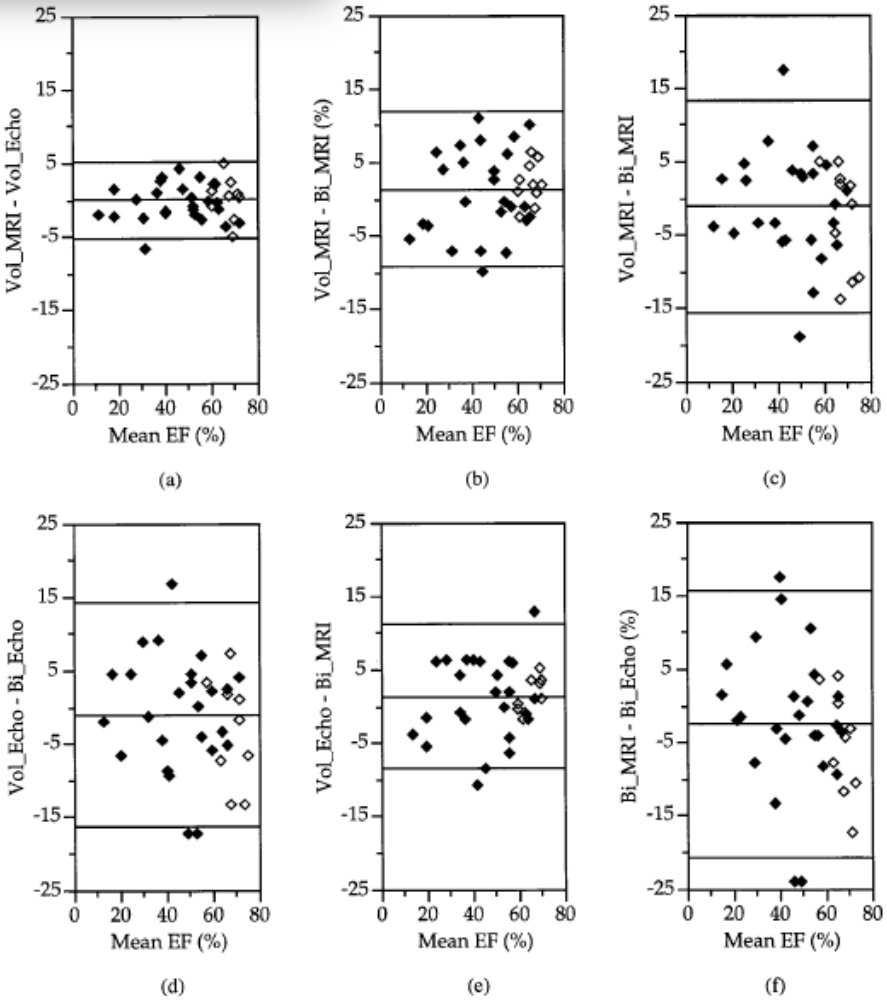
Importance of Imaging Method Over Imaging Modality in Noninvasive Determination of Left Ventricular Volumes and Ejection Fraction

Assessment by Two- and Three-Dimensional Echocardiography and Magnetic Resonance Imaging

RESULTS:

Biplane echocardiography understimed LV volume with respec to to the other three strategies (p<,01)

There were no significant differences (p>,05) between any of the strategies for the quantitative LVEF.



Chung ML et al – J Am Coll Cardiol 2000

Importance of Imaging Method Over Imaging Modality in Noninvasive Determination of Left Ventricular Volumes and Ejection Fraction

Assessment by Two- and Three-Dimensional Echocardiography and Magnetic Resonance Imaging

Table 2. Patient Classification by Systolic Function as Normal (A, LVEF ≥55%), Depressed (B, LVEF >35% to <55%) or Severely Depressed (C, LVEF ≤35%)*

Comparisons	A<–>B*	B<–>C†	A<–>C‡	Total Changes§
Volumetric MRI vs. volumetric echocardiography	2	0	0	2
Volumetric MRI vs. biplane MRI	3	3	0	6
Volumetric MRI vs. biplane echocardiography	6	5	0	11
Volumetric echocardiography vs. biplane echo	4	5	0	9
Volumetri bipl	5	3	0	8
Bipl e		3	1	10

*The ... ion differed between categories A and B. †The second column gives ... shows changes between category C (LVEF ≤35%) and category A (LVE... r of category changes among the 25 patients. LVEF ... agnetic resonance imaging.

La differenza tra l'eco e la RMN sta proprio nella capacità di quest'ultima di identificare le piccole variazioni di FEVS ai limiti della significatività

Chung ML et al – J Am Coll Cardiol 2000

Importance of Imaging Method Over Imaging Modality in Noninvasive Determination of Left Ventricular Volumes and Ejection Fraction

Assessment by Two- and Three-Dimensional Echocardiography and Magnetic Resonance Imaging

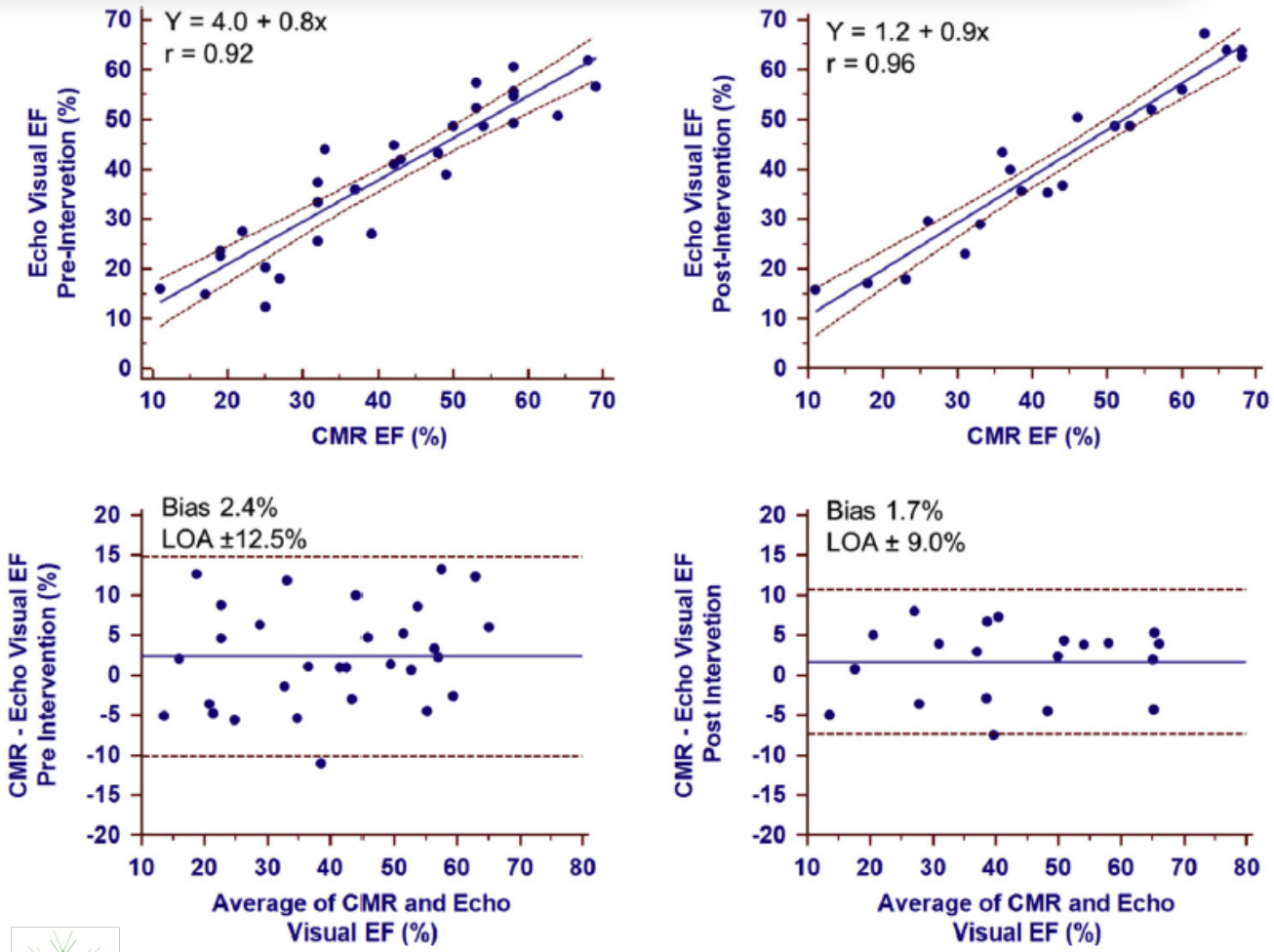
L'ecocardiografia appare la metodica con la più alta variabilità interosservatore ed intraosservatore

Table 3. Interc[illegible] Ejection Fraction*

	Volume MRI	Biplane MRI	lumetric Echocardiography	Biplane Echocardiography
Interobserver				
Variability (%)	3.6	13.4	8.3	17.8
Mean ± SD (%)	0.5 ± 1.5	−1.4 ± 5.9	−0.1 ± 3.8	1.3 ± 8.8
SEE	1.6	4.3	3.7	9.2
r^2	0.99	0.94	0.96	0.82
Intraobserver				
Variability (%)	5.1	13.0	6.9	13.4
Mean ± SD (%)	−1.1 ± 2.1	−2.0 ± 5.6	−0.4 ± 3.1	−0.9 ± 6.8
SEE	2.1	5.4	3.3	6.7
r^2	0.99	0.91	0.97	0.90

Chung ML et al – J Am Coll Cardiol 2000

Improved Interobserver Variability and Accuracy of Echocardiographic Visual Left Ventricular Ejection Fraction Assessment through a Self-Directed Learning Program Using Cardiac Magnetic Resonance Images



IRCCS Istituto Tumori di Bari
Unità Operativa di Cardiologia

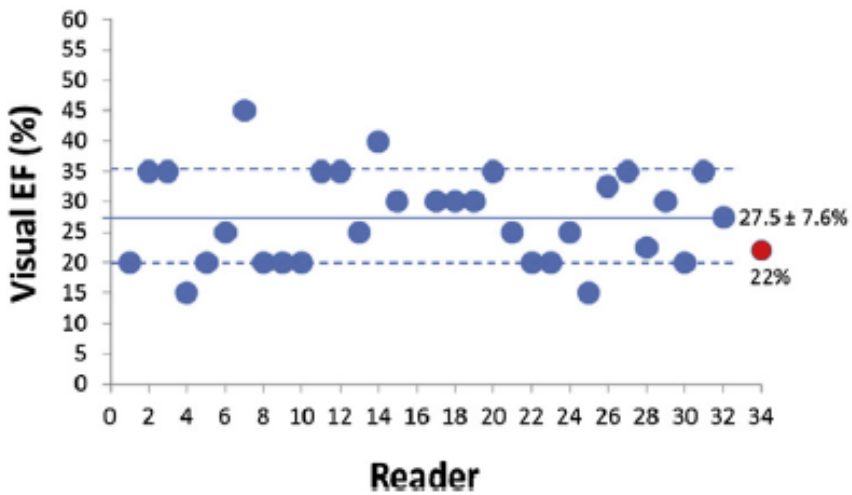
Tavendiranathan P et al, – J Am Soc Echocardiogr 2013;26:1267-73

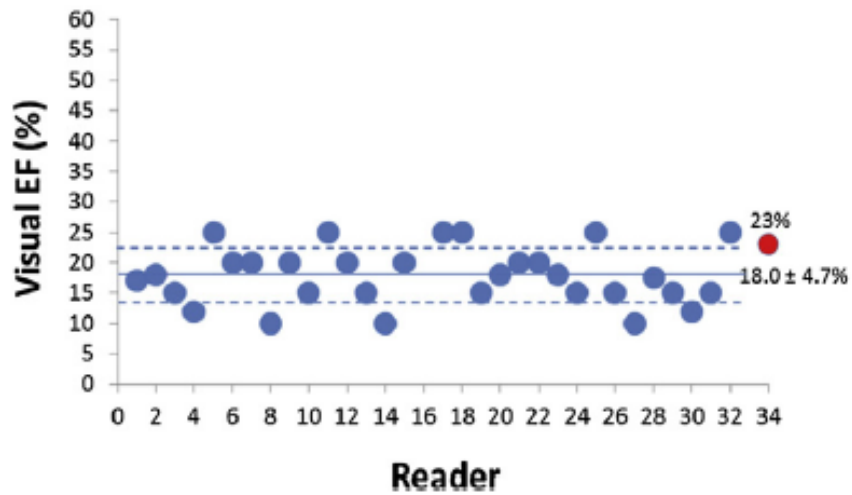
Improved Interobserver Variability and Accuracy of Echocardiographic Visual Left Ventricular Ejection Fraction Assessment through a Self-Directed Learning Program Using Cardiac Magnetic Resonance Images

Results: The baseline interobserver variability of ±0.120 improved to ±0.097 after the intervention. EF misclassification (defined as ±0.05 of CMR EF) was reduced from 56% to 47% ($P < .001$), and the intervention also resulted in a decrease in the absolute difference between CMR and echocardiography for all cases and all readers (from 0.07 ± 0.01 to 0.06 ± 0.01, $P = .0001$). This improvement was most prominent for the readers with lower baseline accuracy. A combined physician-sonographer EF estimate improved the precision of EF determination by 25% compared with individual reads.

1

2





Tavendiranathan P et al, – J Am Soc Echocardiogr 2013;26:1267-73

Il "confronto dei video": prospettive future

American Society of Echocardiography: Remote Echocardiography with Web-Based Assessments for Referrals at a Distance (ASE-REWARD) Study

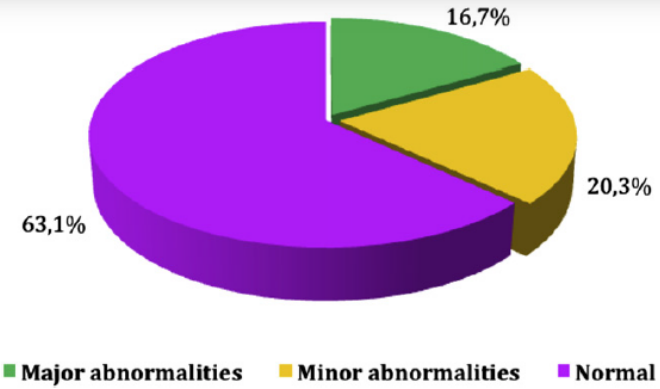


Figure 3 Distribution of the abnormal scans in the study subjects.

Table 1 Major echocardiographic abnormalities in the study patients (n = 170)

Echocardiographic abnormality	n (%)
Predominant valvular heart disease	49 (28.8)
Predominant LV systolic dysfunction	71 (41.8)
Regional	49 (28.8)
Global	22 (12.9)
Mixed valve disease and LV systolic dysfunction	7 (4.1)
Congenital heart disease*	23 (13.5)
Right-heart enlargement/pulmonary hypertension	9 (5.3)
Other abnormalities	12 (7.1)
Asymmetric septal hypertrophy	5 (2.9)
Concentric LV hypertrophy	3 (1.8)
Left atrial enlargement	3 (1.8)
Abnormal septal motion suggesting constrictive pericarditis	1 (0.6)

Shanemeet Singh et al – J Am Soc Echocardiogr 2013;26:221-33

Il "confronto dei video": prospettive future

American Society of Echocardiography: Remote Echocardiography with Web-Based Assessments for Referrals at a Distance (ASE-REWARD) Study

Conclusions: This study demonstrates the feasibility of performing sonographer-driven focused echocardiographic studies for identifying the burden of structural heart disease in a community. Remote assessment of echocardiograms using a cloud-computing environment may be helpful in expediting care in remote areas.

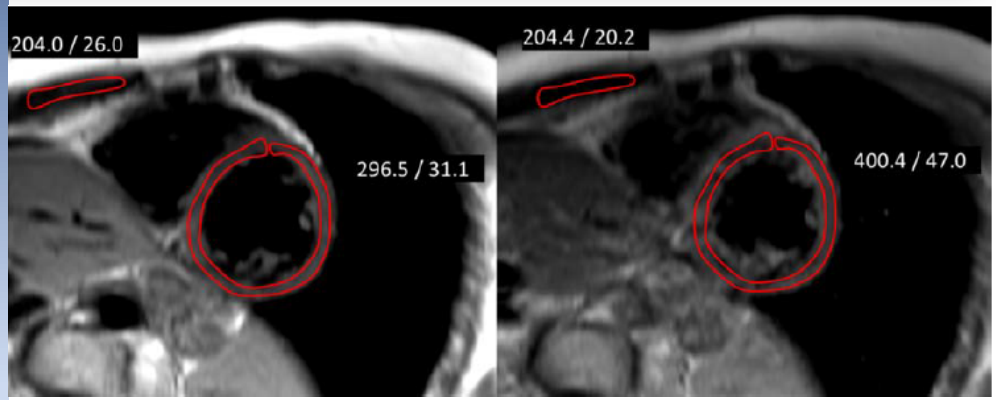
- Nella gestione dei lungosopravviventi, prioritaria è la fidelizzazione del paziente ad un programma di controlli periodici;
- Le strutture ospedaliere non riescono a soddisfare la richiesta (oltre 2.500.000 lungosopravviventi solo in Italia!);
- Necessita una collaborazione tra i Centri Ospedalieri (Oncologici e non), la Cardiologia Territoriale ed i Medici di Medicina Generale.

Shanemeet Singh et al – J Am Soc Echocardiogr 2013;26:221-33

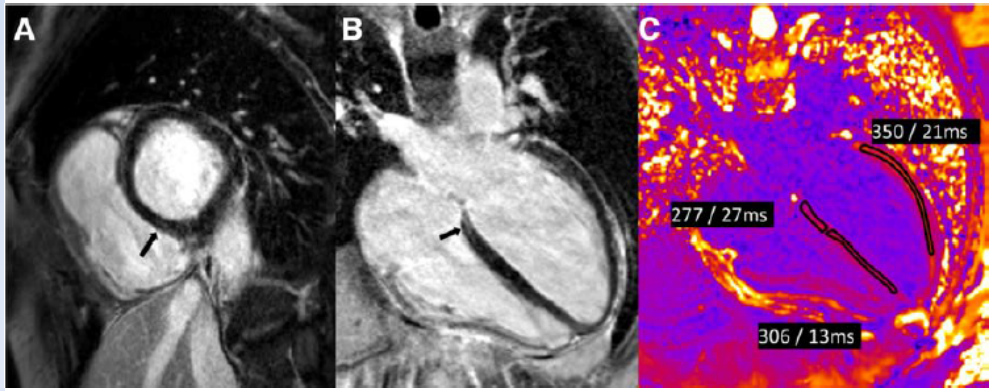
Cardiac MRI in the Assessment of Cardiac Injury and Toxicity From Cancer Chemotherapy

A Systematic Review

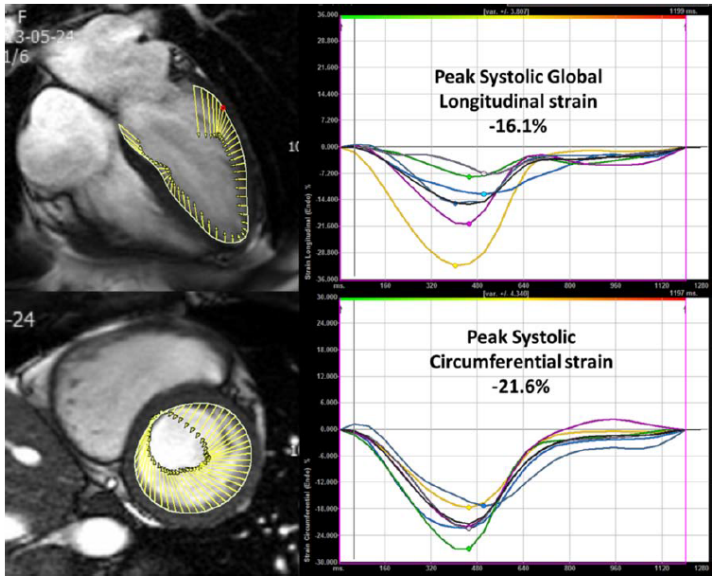
Paaladinesh Thavendiranathan, MD, MSc; Bernd J. Wintersperger, MD;
Scott D. Flamm, MD, MBA; Thomas H. Marwick, MBBS, PhD, MPH



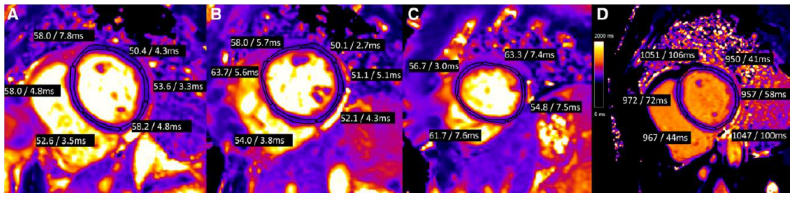
EARLY GADOLINIUM ENHANCEMENT



DELAYED ENHANCEMENT



STRAIN AND CMR



T1 AND T2 MAPS

La SIEC e l'ecocardio-oncologia: il nostro Core Lab

GRUPPO DI STUDIO SIEC DI ECOCARDIO-ONCOLOGIA

Scientific Coordinator:
Nicola Maurea M.D.– *INT" Pascale" (Napoli)*

PROYECT# 1

"EARLY DETECTION OF CARDIOTOXICITY IN CANCER PATIENTS"

Coordinator of project: Stefano Oliva M.D.

Prospective multicenterobservationalclinical study
Expected duration of the study: 48 months.

MANUALE ECOCARDIOGRAFICO

IDENTIFICAZIONE PRECOCE DELLA CARDIOTOSSICITA' DA FARMACI ANTITUMORALI

Il manuale fornisce le indicazioni per l'esecuzione della valutazione ecocardiografica dei pazienti inclusi nello Studio.

Centri partecipanti:

L'ecocardiografista responsabile di ogni centro partecipante dovrà leggere gli ecocardiogrammi da lui eseguiti e compilare la scheda ecocardiografica.

- Ogni esame ecocardiografico dovrà essere registrato su DVD/CD.
- Tutti i dati devono essere registrati in formato compresso DICOM dir.

Funzioni del Core Lab Ecocardiografico

a) Fase di validazione dei centri: si valuterà la qualità delle immagini e la riproducibilità (Core Lab) delle misurazioni effettuate sull' esame ecocardiografico, eseguito nel primo paziente randomizzato in ogni centro alla randomizzazione.
L'Eco Core Lab informerà l'ecocardiografista responsabile del risultato della valutazione via e-mail o via fax entro 3 giorni lavorativi dall'arrivo dell'esame.
Se ci saranno discordanze il Core Lab Eco contatterà l'ecocardiografista.

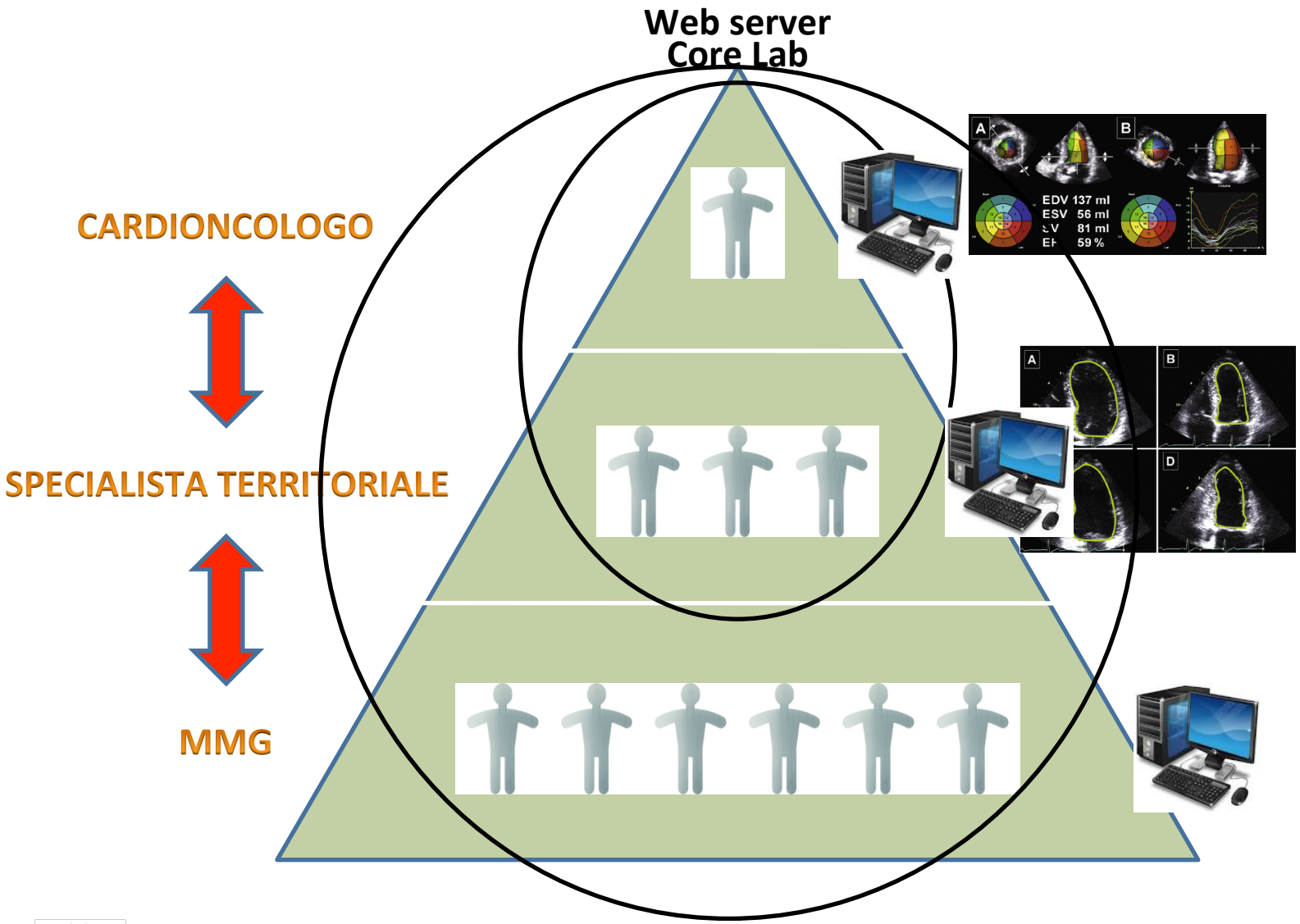
b) Fase di Controllo di Qualità: durante lo studio si effettuerà il Controllo di Qualità sia qualitativo che quantitativo del 20% degli esami effettuati in ogni centro. L'Ideale sarebbe la lettura centralizzata di tutti gli esami ecocardiografici inviati: ciò eviterebbe di ridurre la variabilità interosservatore.

L' Eco Core Lab ha il compito di rispondere a tutte le domande o dubbi riguardanti gli esami ecocardiografici dello studio inerenti qualsiasi quesito o problema tecnico sulla metodologia e/o sulle correzioni/commenti inviati dall'Eco Core Lab.

Per qualsiasi quesito o richiesta di informazioni contattare il Core Lab Ecocardiografico IEO:

Dr. Maurizio Civelli
Divisione di Cardiologia
Istituto Europeo di Oncologia
Tel: 02 57489539

Modello di organizzazione assitenziale cardioncologica



Conclusioni

- ✓ La diagnosi precoce della disfunzione ventricolare sinistra è indispensabile per l'efficacia terapeutica e la prognosi
- ✓ L'ecocardiografia (con il calcolo della FEVS) rimane la metodica strumentale di riferimento per la diagnosi di disfunzione ventricolare (nonostante necessiti di integrazione con nuove metodiche…)
- ✓ Il training dell'operatore (medico o tecnico) e/o la condivisione del dato migliorano l'outcome


fotografia di Emanuele Notarachille
Grazie dell’attenzione