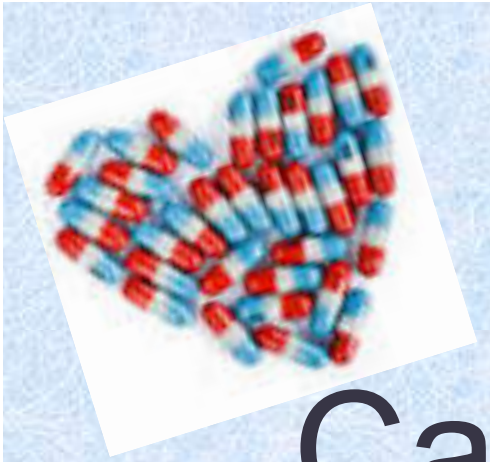


UNIVERSITÀ DEL PIEMONTE ORIENTALE

Cardiomiopatia da cardiotossicita'

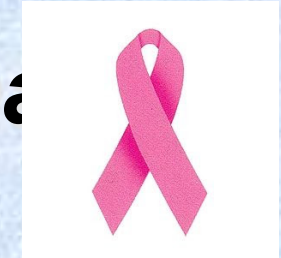
Dott.G.Francalacci
Clinica Cardiologica Novara

5 maggio 2016

Sig.ra Flora
anni 66

Paziente arruolata nel Registro Pilota Europeo **“Cardiac oncology toxicity (COT)”**

Anamnesi patologica prossima



Non precedenti cardiologici, familiarità per verosimile cardiomiopatia dilatativa, asma allergico.

Luglio 2015: carcinoma duttale Dx pT1c, N1a,G3(HER positivo, ER 100% Pg 60% ki-67=27%).

Quadrantectomia dx e svuotamento linfonodi ascellari. Veniva candidata a CT/RT adiuvante.

Ecocardiogramma pre CT

(eseguito in altro centro)

FE 56%, non deficit di cinetica segmentaria, diastole da iniziale alterato rilasciamento, insufficienza mitralica lieve/moderata, pressione sistolica polmonare stimata nei limiti di norma.

Rischio pre-CT

Rischio basso	Anamnesi negativa, No fdr FE normale	Sì CT FE ogni 3 mesi
Rischio intermedio	Anamnesi positiva per CAD e/o fdr. FE normale	Sì CT FE ogni 3 mesi Monitoraggio mensile. Se TnI o BNP, Terapia HF
Rischio alto	FE depressa (< 40%)	Trattare HF, rivalutare dopo 4 settimane. **CT** ?

Schema CT

4 cicli di **epirubicina/ciclofosfamide** dal 25/8 al 26/10/2015 e successivo avvio di **paclitaxel** settimanale per 12 settimane in associazione a **trastuzumab**

Visita ambulatoriale in Classe urgente
(11/12/15)

Dopo aver concluso 4 cicli di EC, 4 somministrazioni di paclitaxel e 2 di trastuzumab.

Comparsa di dispnea da sforzi lievi, tosse insistente ed ortopnea notturna.

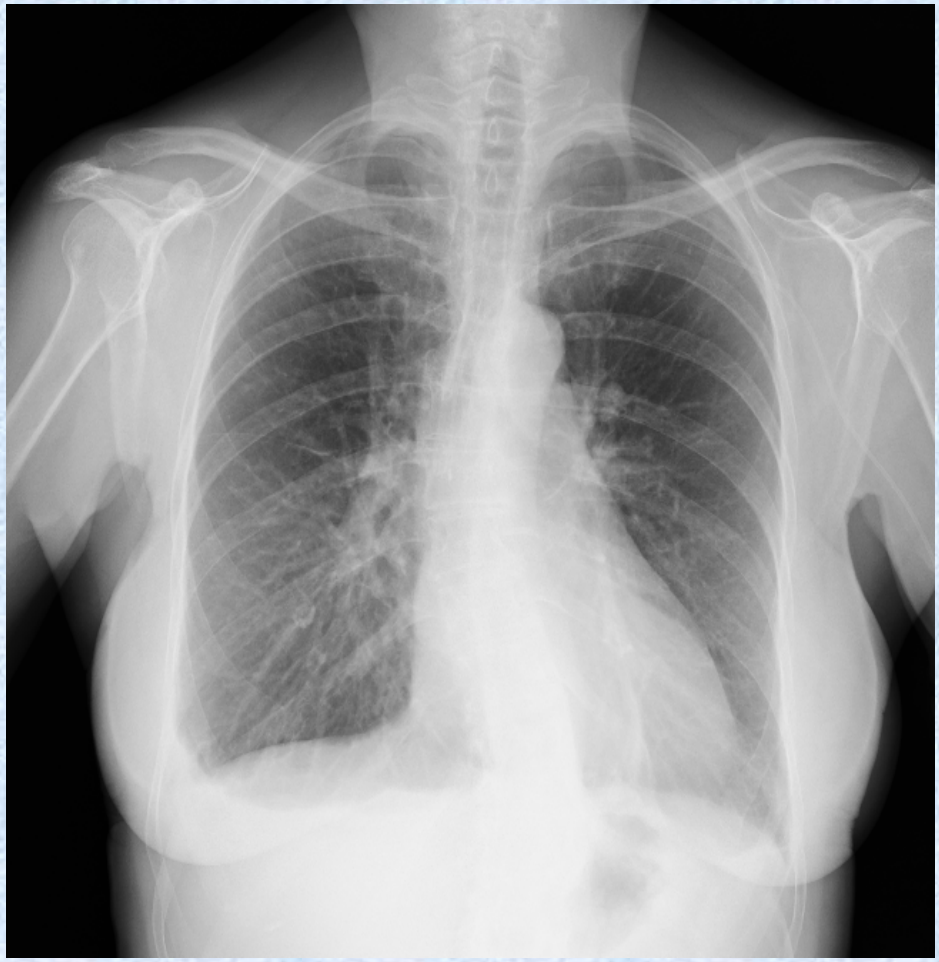
Alla RX torace: versamento pleurico dx.

All' esame obiettivo :PA 120/80 mmHg, toni tachicardici con effetto di galoppo. Al torace, riduzione del MV alla base di dx.

All' ecoscopia: moderata dilatazione del ventricolo sinistro, ipocinesia diffusa e riduzione della FE in modo moderato (40-45%), moderata-importante insufficienza mitralica, VCI lievemente dilatata e non collassabile.

Si ricovera.

Rx torace



Ematochimici

• emocromo con formula conservata.

• BNP 71 pg/ml (VN < 60) dopo 3 3 giorni di trattamento diuretico.

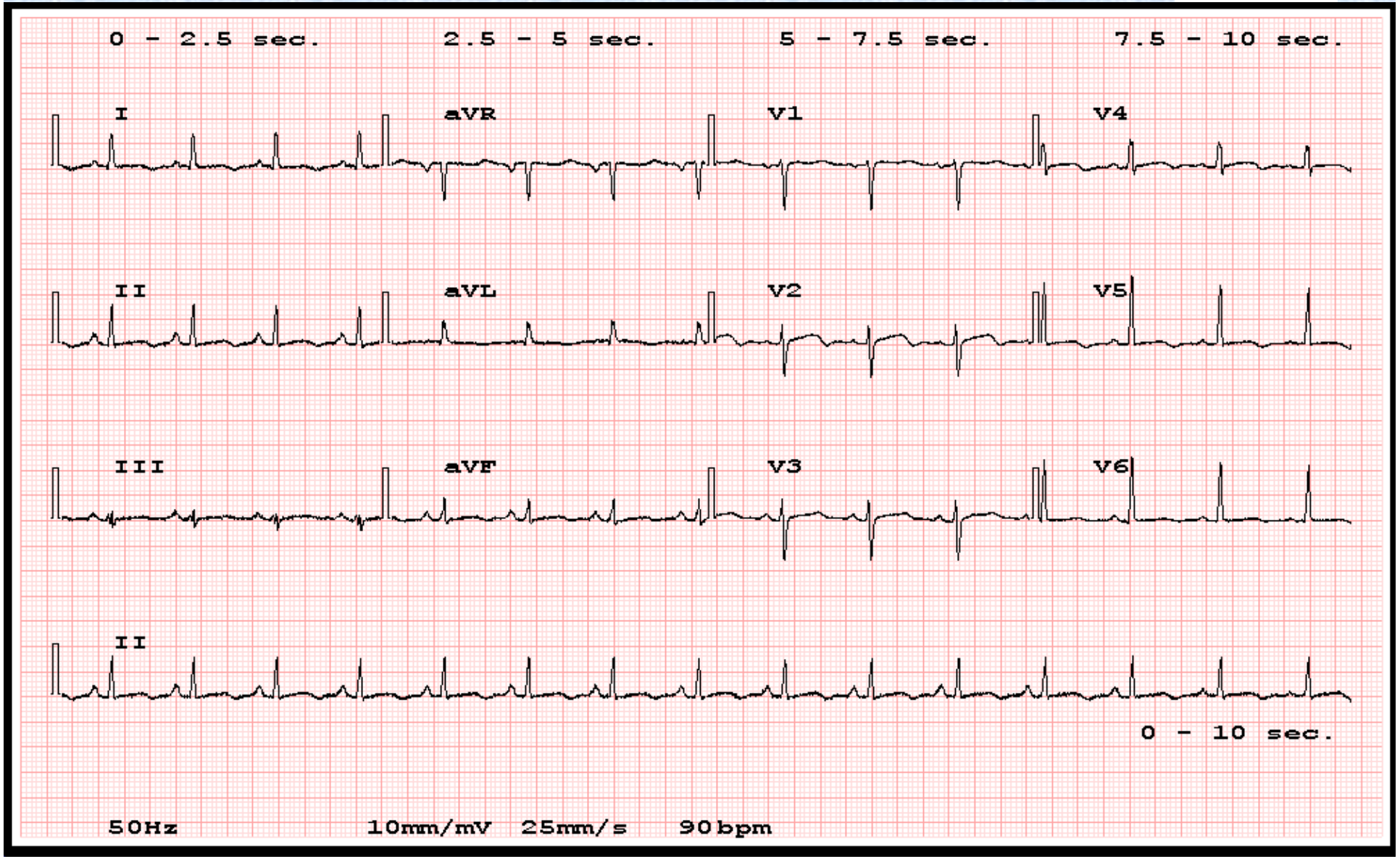
• PCR negativa.

• TnI negativa.

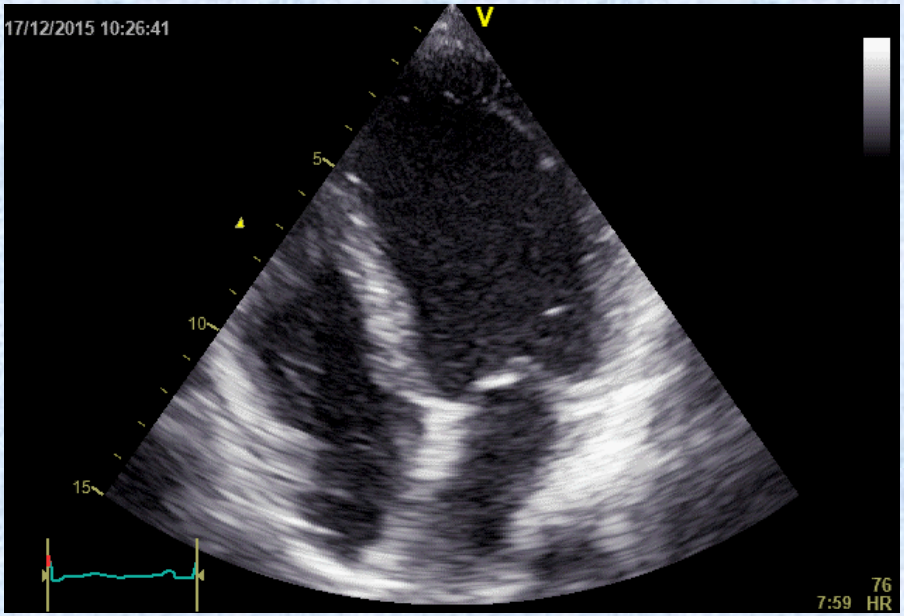
• funzione epatica e renale nella norma.

• EGA: Ph 7,44, PaCO2 35, PaO2 98mmHg, HCO3 24 mmHg.

ECG

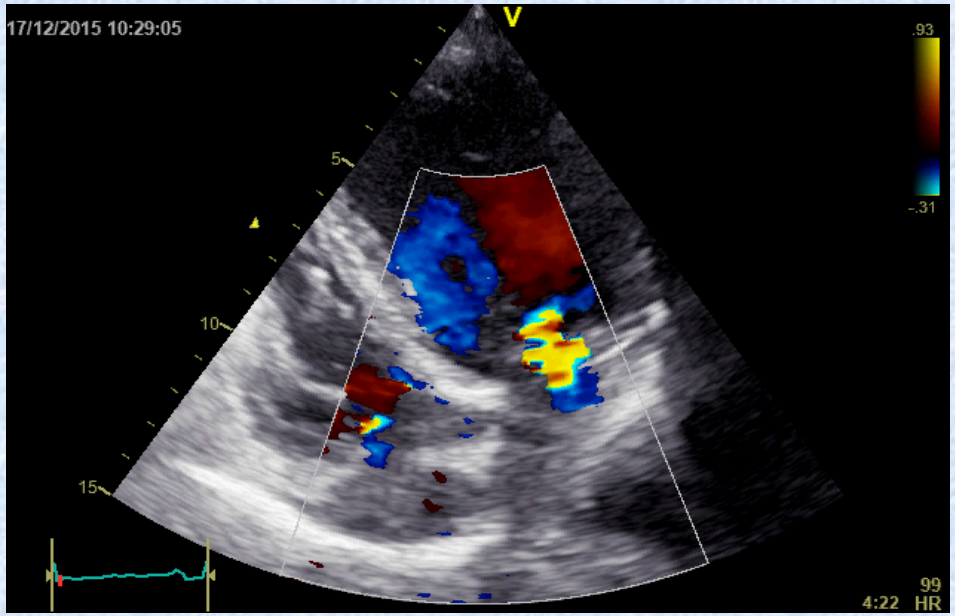

0 - 2.5 sec.
2.5 - 5 sec.
5 - 7.5 sec.
7.5 - 10 sec.
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
0 - 10 sec.
50Hz
10mm/mV
25mm/s
90bpm

Ecocardiogramma



FE 45% VTD 138 cc VTS 75 cc
Ipocinesia diffusa

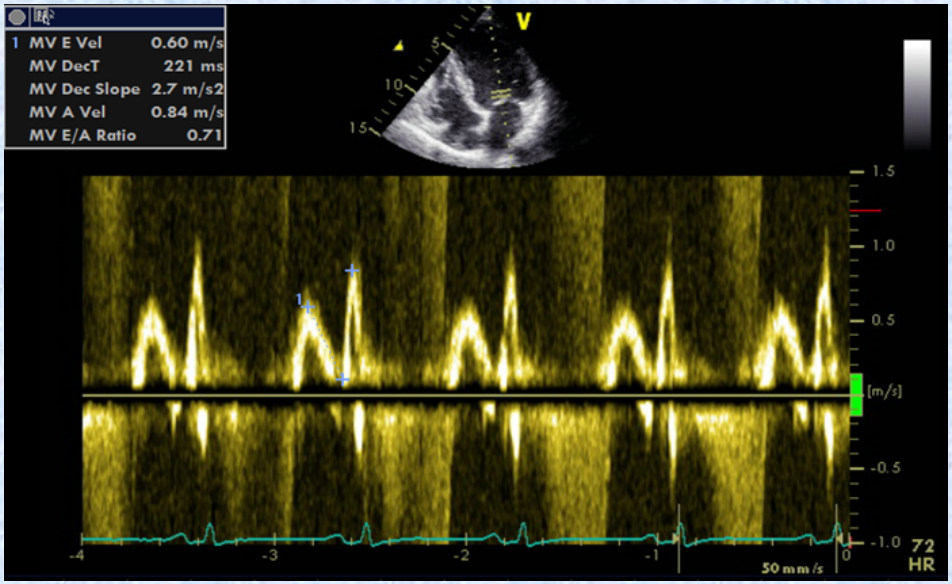
Insufficienza mitralica funzionale
Moderata.
IT lieve ,PAPS nella norma

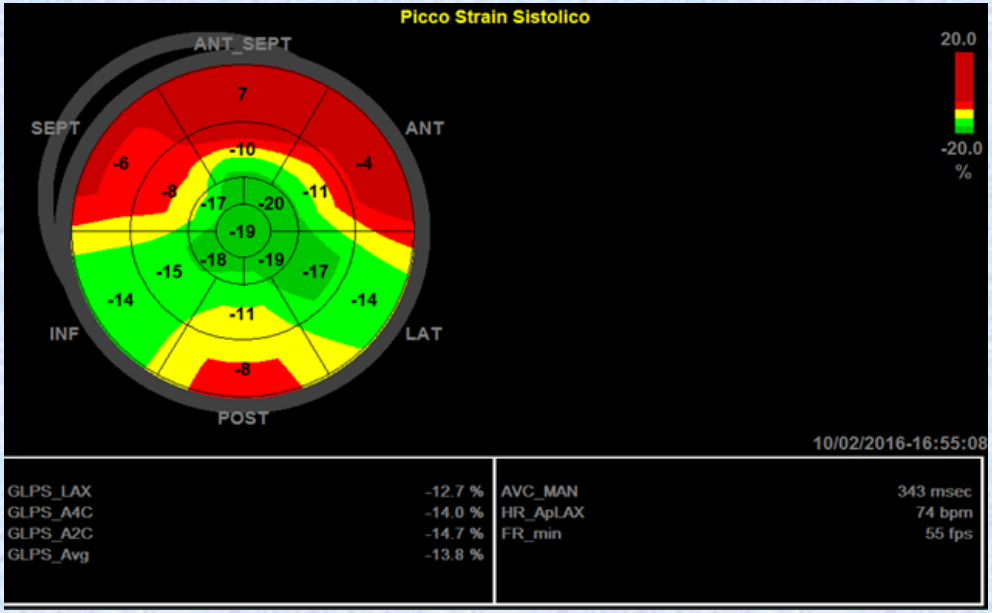


Diastole da alterato rilasciamento.

E’ 7 cm/s

E/E’ 8





Strain sistolico longitudinale globale :

- 12,7%

Strain Imaging: Detection of Early Cardiac Dysfunction

Sensitive measurement of myocardial systolic contractility

Much more sensitive than LVEF

Strain imaging:measures deformation of myocardium between two points .
(speckle tracking)

Strain Rate: Speed of the deformation

Strain sistolico longitudinale predice successiva cardiotossicità

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STATE-OF-THE-ART PAPERS

Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy

A Systematic Review

Paaladinesh Thavendiranathan, MD,*† Frédéric Poulin
Juan Carlos Plana, MD,‡ Anna Woo, MD,* Thomas I

Toronto, Ontario, Canada; Cleveland, Ohio; and Hobart,

Early Predictors of Cardiotoxicity

Studies/First Author (Ref. #)	Sensitivity	Specificity	PPV	NPV
Fallah-Rad et al. (44)*				
2% absolute (10.1% relative) decrease in LS	79%	82%	60%	92%
0.8% decrease in RS	86%	81%	60%	95%
Sawaya et al. (41)†				
10% decrease in GLS	78%	79%	50%	93%
Elevated hsTnI	67%	82%	50%	90%
10% decrease in GLS and elevated hsTnI	55%	97%	83%	89%
10% decrease in GLS or elevated hsTnI	89%	65%	40%	97%
Sawaya et al. (40)†				
GLS <19%	74%	73%	53%	87%
hsTnI >30 pg/ml	48%	73%	44%	77%
LS <19% and usTnI >30 pg/ml	35%	93%	67%	77%
LS <19% or usTnI >30 pg/ml	87%	53%	43%	91%
Negishi et al. (42)‡				
11% reduction in global GLS	65%	95%	—	—
3.6% reduction in global GLSR early diastole	82%	67%	—	—
6.4% reduction in global GLSR	73%	67%	—	—
Absolute GLS at 6 months <−20.5%	96%	66%	—	—
Mornos et al. (39)‖				
71% × ° reduction in GLS × LV twist	90%	82%	—	—
2.77% absolute (~13% relative) reduction in GLS	[illegible]	[illegible]	—	—
1.75° absolute reduction in apical rotation	70%	78%	—	—
Baratta et al. (37)‖				
≥15% decrease in GLS	86%	86%	—	—
≥10% decrease in GRS	86%	69%	—	—
≥15% decrease in GLS AND ≥10% decrease in GRS	71%	97%	—	—

Algoritmo –GLS(strain longitudinale)

GLS base -19% o >	nella norma	Sì CT no terapia cardiospecifica
GLS < -16%	Disfunzione subclinica	Terapia cardiospecifica
GLS-16%-19%	Zona grigia	Terapia cardiospecifica

Negishi-JASE -2013 26:493-8

- Il trattamento della cardiotossicità da trastuzumab non è differente dal trattamento dello scompenso cardiaco ed è indicato nelle linee guida sullo scompenso cardiaco.

Recommendations	COR	LOE	References
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF	I	A	314, 342–345
In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF	I	B	346–348
In patients with MI, statins should be used to prevent HF	I	A	104, 349–354
Blood pressure should be controlled to prevent symptomatic HF	I	A	27, 94, 311–313
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A	65, 344
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C	N/A
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B	355
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C	N/A

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and N/A, not available.

Circulation. 2013;128:e240-e327

Decorso e dimissione

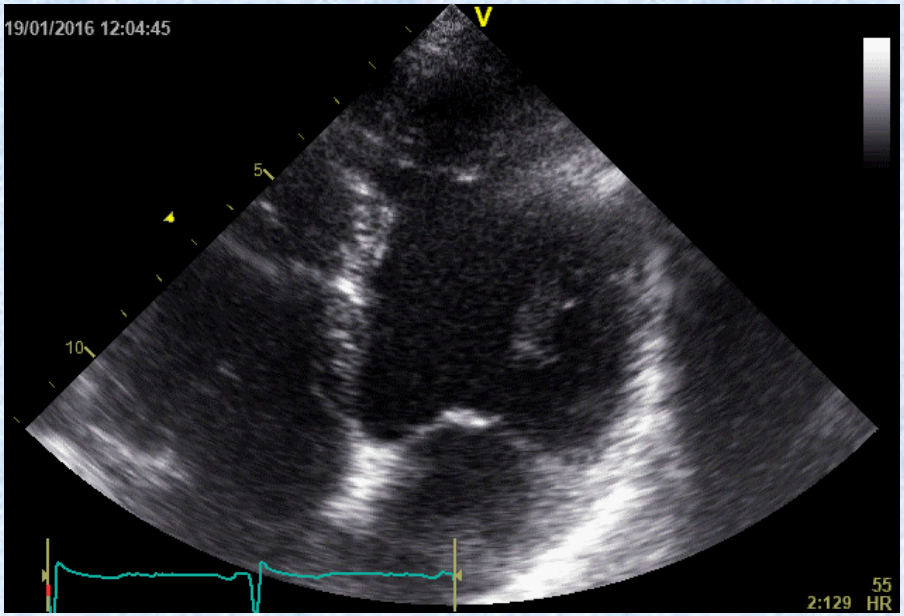
Rapido ricompenso di circolo dopo avvio di terapia diuretica e cardiospecifica. Risoluzione della sintomatologia e del versamento pleurico.

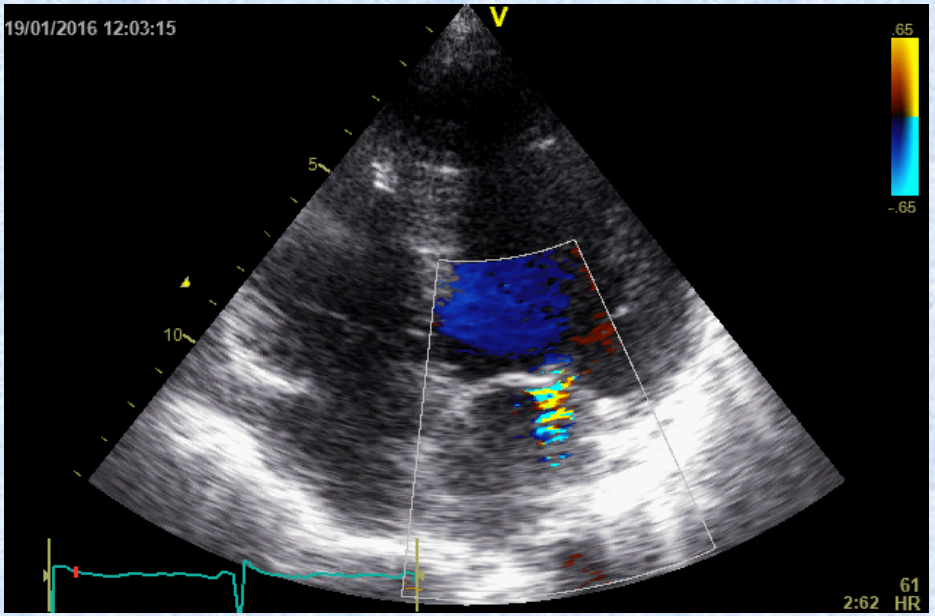
Dimessa con diagnosi di *scompenso cardiaco in quadro di cardiopatia esotossica*.

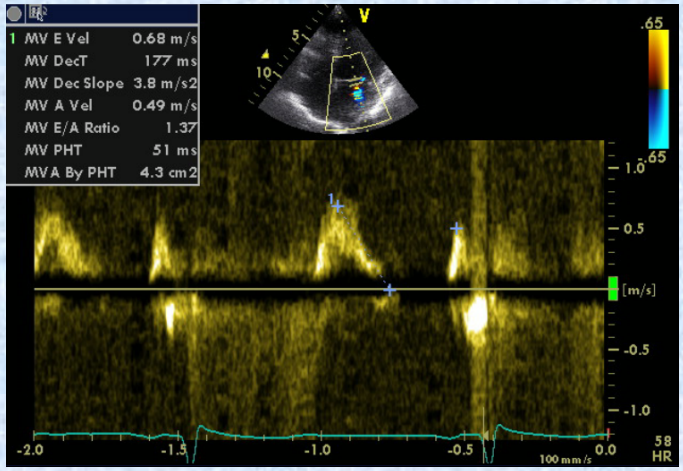
Terapia: furosemide/spironolattone 25/37mg, bisoprololo 1,25 mg, valsartan 40mg.

Sospensione temporanea CT → Rivalutazione Ecografica 3-4 settimane

Ecocardiogramma
(dopo 1 mese)







FE 55% **VTD** 117 cc **VTS** 53 cc

Diastole normale

E’ 10 cm/s

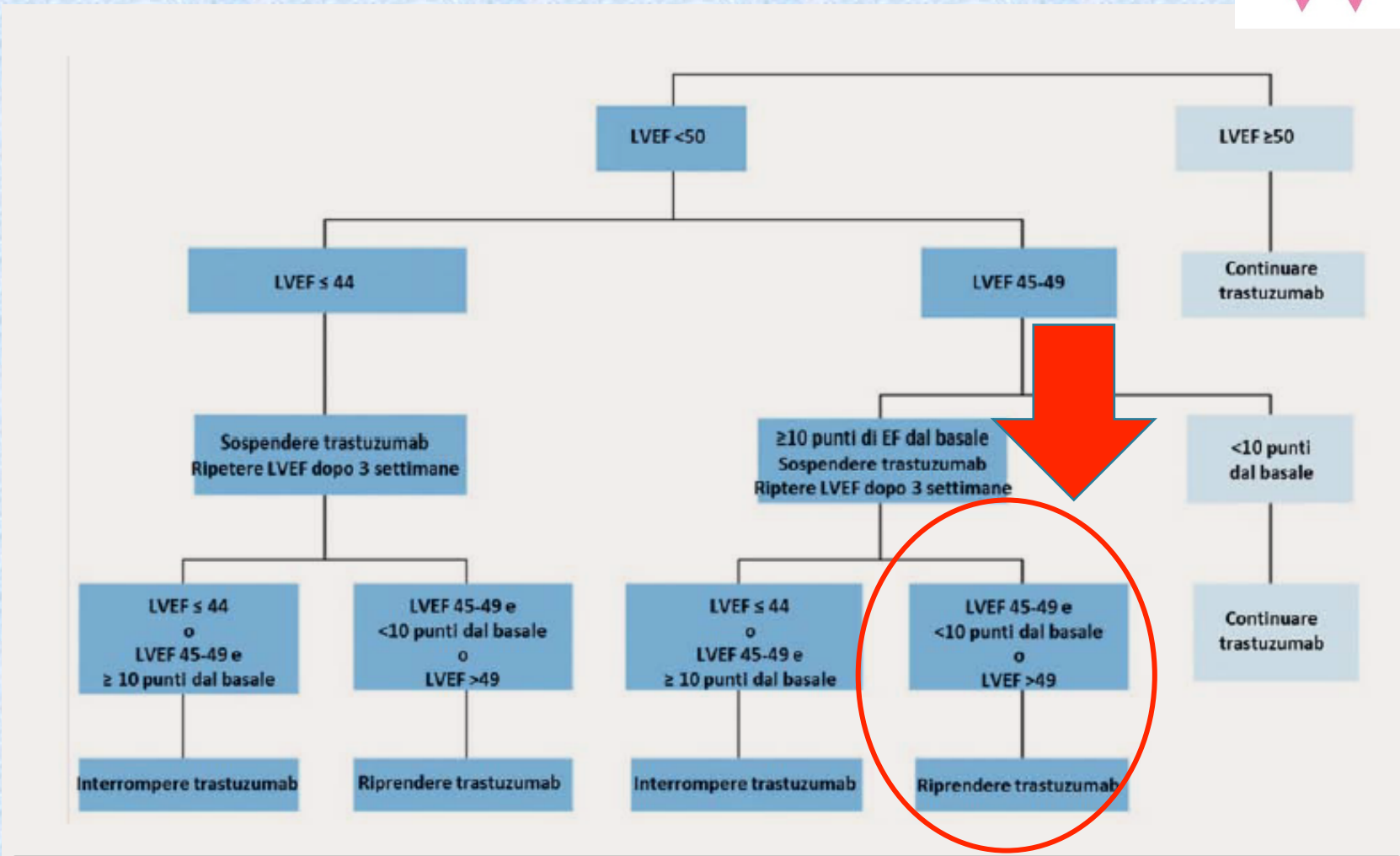
E/E’ 7

CT sì, CT no?

- Elevato rischio di recidiva della neoplasia mammaria (linfonodi positivi, recettori per HER-2 positivo).

- Miglioramento dell'FE 54% verso 45%.

Cardiotossicità da trastuzumab (algoritmo decisionale)



Riavvia trastuzumab monitorando mensilmente FE

Nuovo controllo clinico

Dopo 1 Mese ….

- Dopo un’unica somministrazione di trastuzumab, nuovo calo della funzione sistolica. NYHA 2

- FE 46%, diastole da alterato rilasciamento (E’ 6 cm/s), IM++, PAPS 40mmHg, IT+/++

- Riavvio betabloccante (sostituito in precedenza da ivabradina per ipotensione): prosegue con ARB+ lasitone.

Si sospende nuovamente trastuzumab

Visita cardiologica

3/2016

- NYHA 3

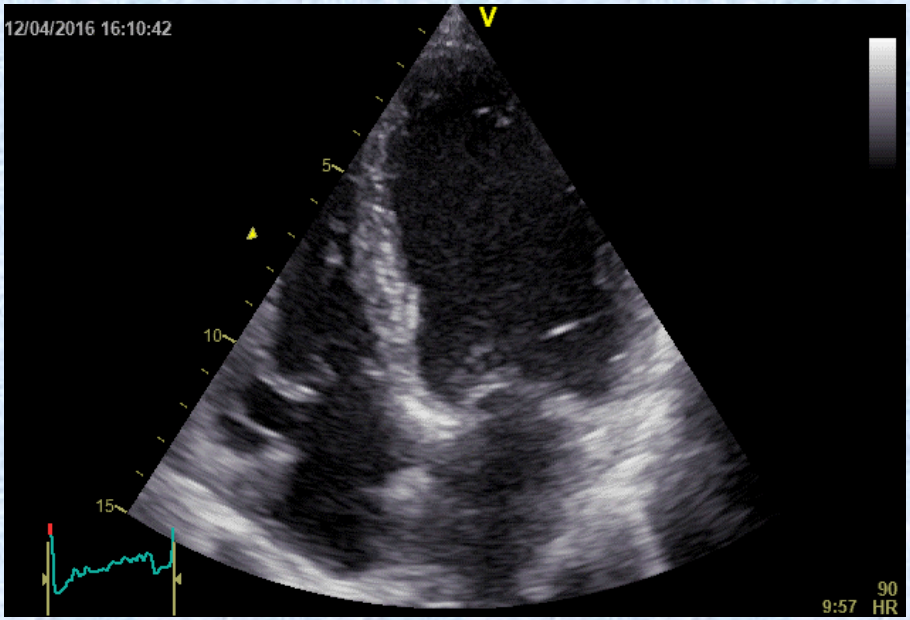
- Ecocardiogramma: FE 35% (VTD 115/ VTS 75), IM++/+++ funzionale, IT++ PAPS 40mmHg, diastole restrittiva.

Prosegue terapia cardiologica in atto mantiene sospeso Trastuzumab ma prosegue la RT.

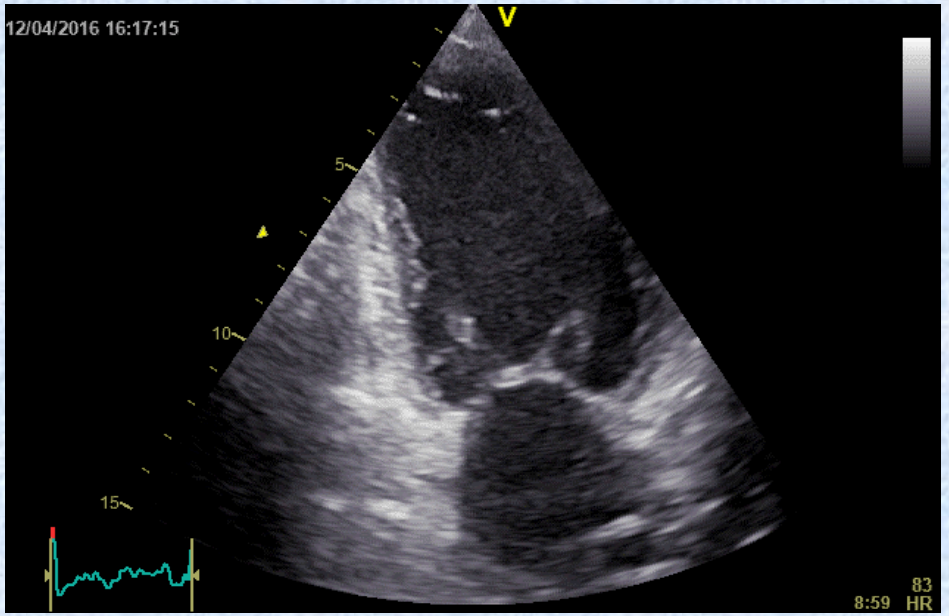
Il mese successivo… (12/04/16)

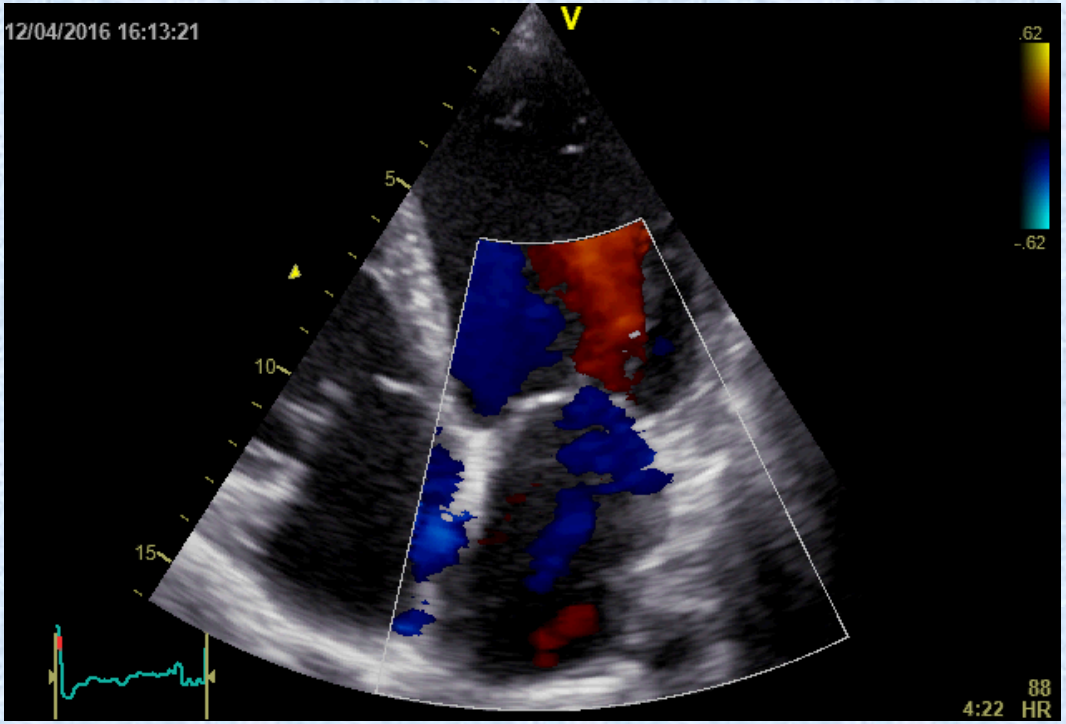
- NYHA 3
- Ha concluso il 4/04 RT (dose totale 50 Gy + Boost 9Gy).
- PA 100/80, Fc 85 bpm, toni validi e ritmici, SS 2/6 alla punta, non edemi declivi, lieve reflusso epato-giugulare, torace senza rumori umidi.

Ecocardiogramma 12/04/16



FE 35% VTD 115 ml VTS 75 ml





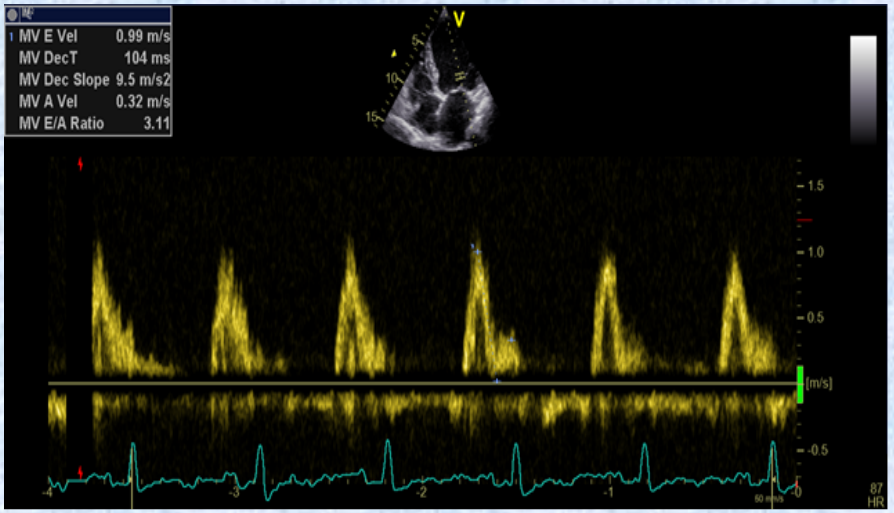
Insufficienza mitralica moderata-severa

ERO 0,3 cm^2

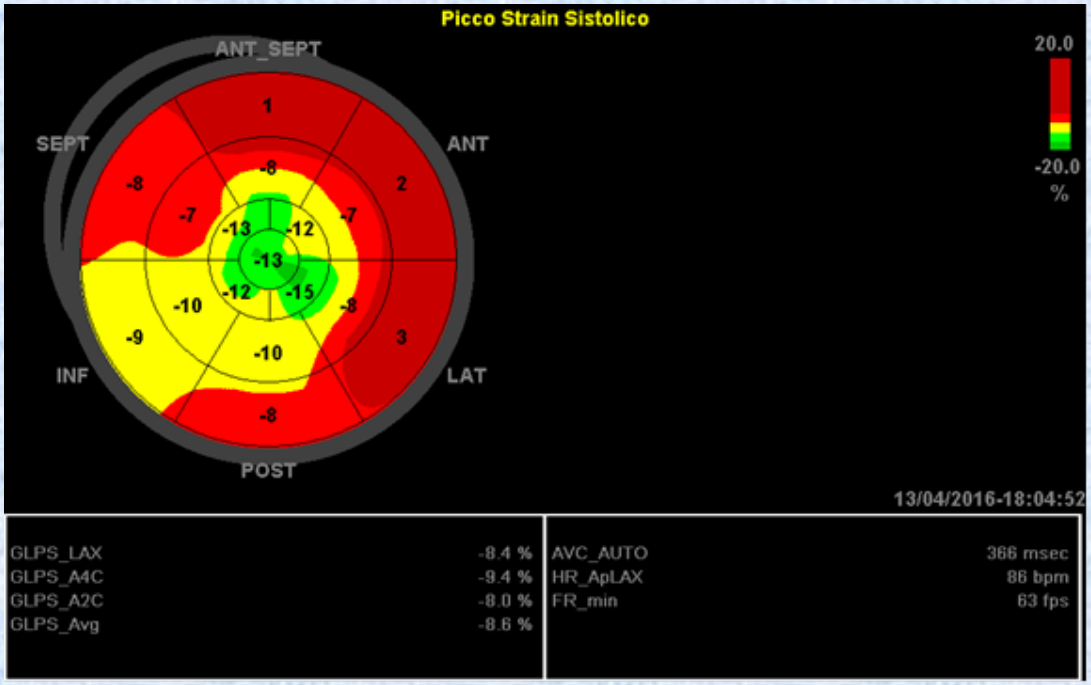
Diastole restrittiva

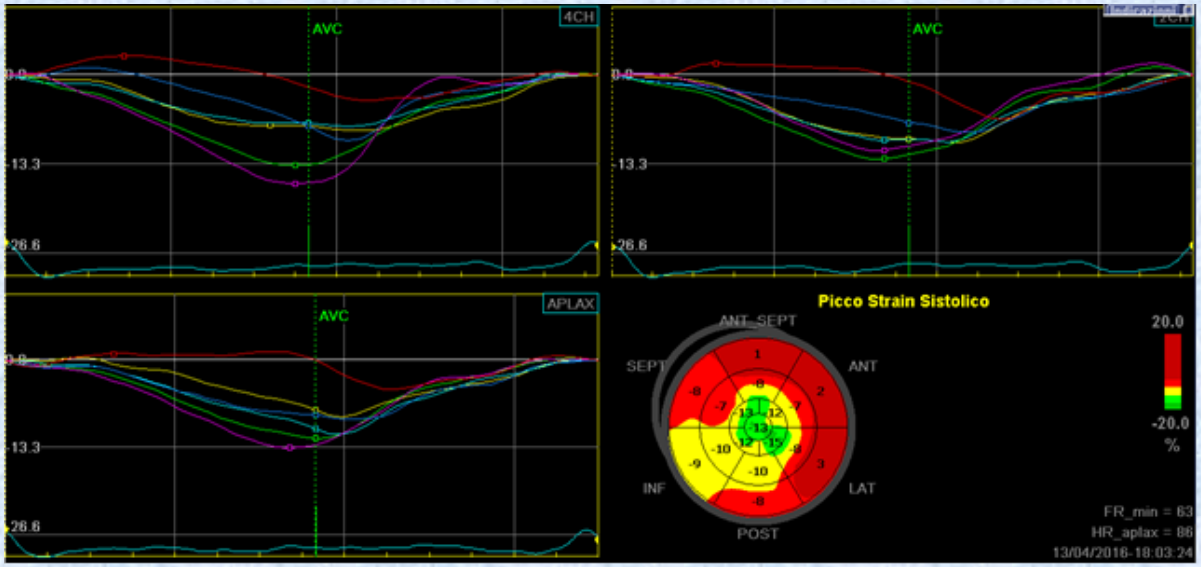
E’ 7 cm/s

E/E’ 14



Strain sistolico longitudinale globale:
-8,4%





Cosa fare?

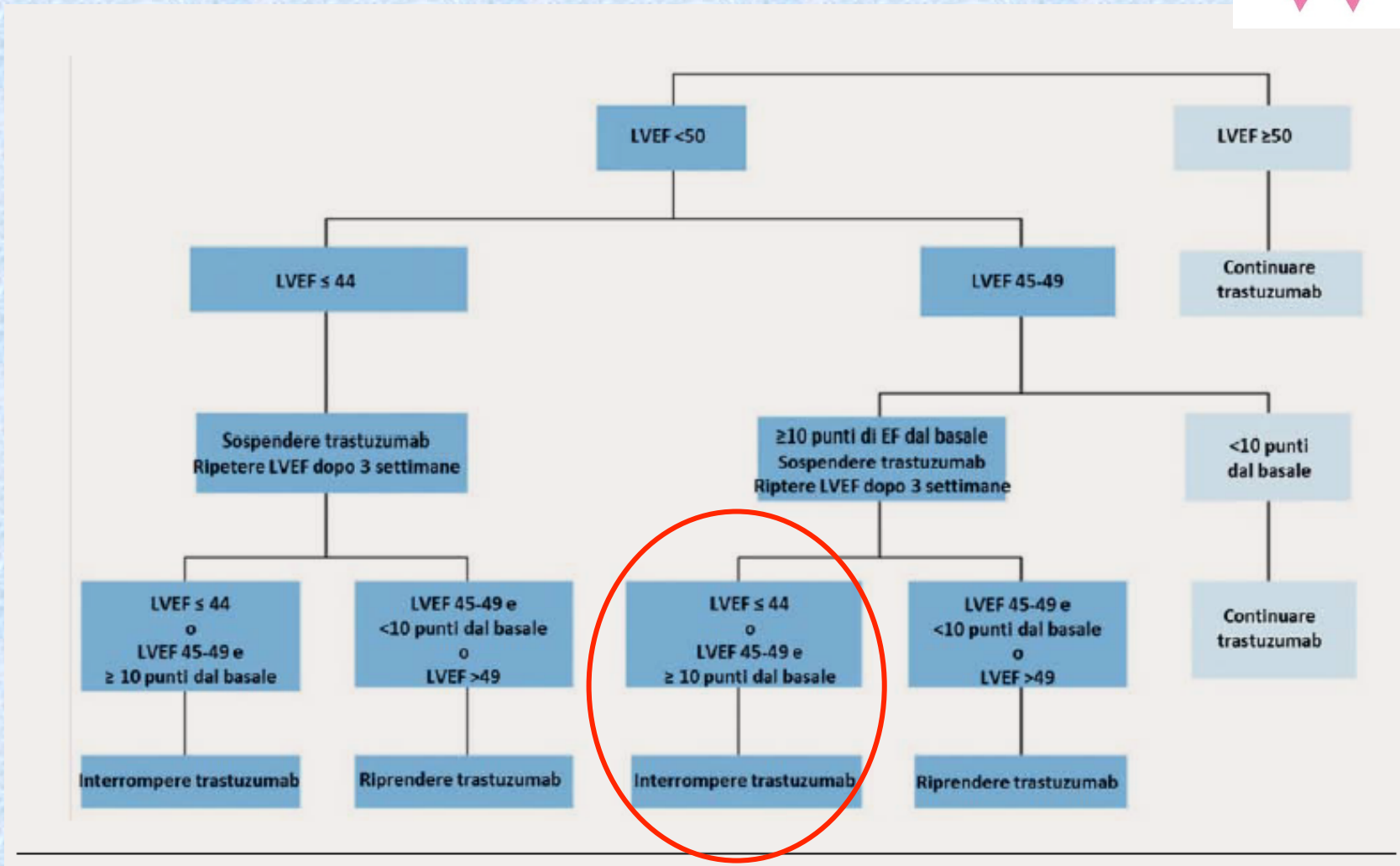


Figura 4.8 Algoritmo di Suter. Questo algoritmo, pubblicato su JCO in appendice al lavoro di Suter e coll. sulla cardiotossicità osservata nello studio HERA, suggerisce la gestione della cardiotossicità in corso di trattamento con trastuzumab sulla base dell'andamento della LVEF, Left Ventricular Ejection Fraction (Modificato da Suter et al, J Clin Oncol 2007).[116]

Cosa fare?

- Secondo calo FE
- Incrementa sartanico (Valsartan 80mg).
- Prosegue con bisoprololo 1,25mg, furosemide/ spironolattone 1cp/die e avvia digitale.

Se trastuzumab unica terapia possibile
Controllo ravvicinato FE
Se miglioramento riavvia. ??

Essendo secondo calo di FE dopo trastuzumab
STOP definitivo.

Cosa fare?

Monitoraggio del danno cardiaco

- Non vi e' ancora un' univoca indicazione sui tempi ,durata e frequenza dei controlli.
- Ogni percorso deve essere personalizzato e condiviso con il cardiologo e l' oncologo.
- Ottimizzare la terapia cardiologica per favorire poi la ripresa della terapia oncologica il prima possibile.
- Prevenzione primaria?

European Heart Journal Advance Access published February 21, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw022

AHA FASTTRACK
CLINICAL RESEARCH

Heart failure/cardiomyopathy

Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol

Geeta Gulati[1,2†], Siri Lagethon Heck[1,2†], Anne Hansen Ree[3,4], Pavel Hoffmann[5], Jeanette Schulz-Menger[6,7], Morten W. Fagerland[8], Berit Gravdehaug[9], Florian von Knobelsdorff-Brenkenhoff[6], Åse Bratland[10], Tryggve H. Storås[11], Tor-Arne Hagve[4,12], Helge Røsjø[1,2], Kjetil Steine[1,2], Jürgen Geisler[3,4], and Torbjørn Omland[1,2*]

Conclusioni: un trattamento con candesartan previene la cardiotossicità nelle pz trattate con AC+/- trastuzumab e RT.

Aims Contemporary adjuvant treatment for early breast cancer is associated with improved survival but at the cost of increased risk of cardiotoxicity and cardiac dysfunction. We tested the hypothesis that concomitant therapy with the angiotensin receptor blocker candesartan or the β-blocker metoprolol will alleviate the decline in left ventricular ejection fraction (LVEF) associated with adjuvant, anthracycline-containing regimens with or without trastuzumab and radiation.

Methods and results In a 2 × 2 factorial, randomized, placebo-controlled, double-blind trial, we assigned 130 adult women with early breast cancer and no serious co-morbidity to the angiotensin receptor blocker candesartan cilexetil, the β-blocker metoprolol succinate, or matching placebos in parallel with adjuvant anticancer therapy. The primary outcome measure was change in LVEF by cardiac magnetic resonance imaging. *A priori*, a change of 5 percentage points was considered clinically important. There was no interaction between candesartan and metoprolol treatments ($P = 0.530$). The overall decline in LVEF was 2.6 (95% CI 1.5, 3.8) percentage points in the placebo group and 0.8 (95% CI −0.4, 1.9) in the candesartan group in the intention-to-treat analysis (*P*-value for between-group difference: 0.026). No effect of metoprolol on the overall decline in LVEF was observed.

ACC.16
1354
JACC April 5, 2016
Volume 67, Issue 13
Heart Failure and Cardiomyopathies

Ipotesi per il futuro ??

RANOLAZINE AT THE END OF TRASTUZUMAB THERAPY PREVENTS LEFT VENTRICULAR DYSFUNCTION: IN VITRO AND IN VIVO STUDY

Poster Contributions
Poster Area, South Hall A1
Saturday, April 02, 2016, 10:00 a.m.-10:45 a.m.

Session Title: Heart Failure and Cardiomyopathies: Medical Therapy
Abstract Category: 27. Heart Failure and Cardiomyopathies: Therapy
Presentation Number: 1103-084

Authors: *Nicola Maurea, Carmela Coppola, Giovanna Piscopo, Domenica Rea, Gennaro Riccio, Gerolama Condorelli, Claudio Arra, Claudia de Lorenzo, Istituto Nazionale per lo Studio e la Cura dei Tumori Fondazione Giovanni Pascale, IRCCS, Italia, Naples, Italy*

Background: Trastuzumab (T) is used to treat HER2 positive breast cancer, but can produce cardiac dysfunction. The late INa inhibitor Ranolazine (R) protects from doxorubicin-induced oxidative stress and cardiac dysfunction. We aim at assessing whether R, administered after T treatment, reduces T cardiotoxicity in vivo and in vitro.

Methods: In vitro, rat H9C2 cardiomyoblasts and human fetal cardiomyocytes were treated with T for 3 days and then treated in the absence or presence of R for 3 days. Cell viability was determined by cell counts and MTT assays. In vivo, fractional shortening (FS) and ejection fraction (EF) were measured by M-mode echocardiography and radial and longitudinal strain (RS and LS) were measured using 2D speckle-tracking, in C57/BL6 mice, at 0, 2 and after 7 days of daily administration of T. These measurements were repeated after 5 days of R treatment initiated at the end of T treatment. We have divided mice in 4 groups. The first group (G1) was treated with T for 7 days. The second group (G2) was treated with T for 7 days and then treated with R for 5 days. The other 2 were control groups: CG1 (sham) and CG2 (no R). We have evaluated tissue expression of BNP by PCR analysis on heart tissue. Apoptotic pathway was assessed by western blotting, in lysates from murine hearts.

Results: R reduced T toxicity in H9C2 cardiomyoblasts and human fetal cardiomyocytes as evidenced by higher percentage of viable cells treated with T+ R with respect to cells treated with T alone ($p<0.01$). In vivo, after 7 days with T, FS decreased to 48.7±4.1%, $p<0.01$ vs 62.3±0.8% (sham), EF to 81.8±3.5%, $p<0.01$ vs 91.7±0.5% (sham), RS to 21±8.1%, $p<0.01$ vs 43.2±4% (sham), and LS to -11±3.7%, $p<0.01$ vs -38.8±6% (sham). In mice treated with R for 5 days after T treatment, the indices of cardiac function recovered: FS was

Trattamento con Ranolaziona potrebbe ridurre la cardiotossicità
in vitro (riduce apoptosi)
in vivo (miglioramento FE, Frazione di accorciamento, SR ma non SL).

E poi????...

- 15 gg dopo ….pressocche’ scomparsa la dispnea da sforzo,ripresa della normale attivita’ fisica .
- In attesa di nuovo controllo ecocardiografico…..

Casistica AOU Maggiore della Carità
Registro Europeo Cardiotossicità

33 pazienti arruolate

3 casi di cardiotossicità dopo trastuzumab, di cui 2 reversibili

- Pz 1 (66 aa) → associazione con antracicline, ipercolesterolemia.
- Pz 2 (68 aa) → antracicline, obesità, ipertensione.
- Pz 3 (65 aa) → antracicline.

CONCLUSIONI:

- Si attendono i dati **real life di un registro europeo sulla cardiotossicita'** nelle pazienti affette da CA della mammella:l'insieme dei dati di imaging con la misura della deformazione precoce miocardica in aggiunta alle variazioni dei biomarkers umorali prima e durante la chemioterapia potranno definire un percorso da seguire per limitare e trattare precocemente le complicanze cardiovascolari.
- **Questi dati potrebbero favorire gli sforzi dei cardiologi di coinvolgere gli oncologi in team multidisciplinari,non ci sono molte linee guida a riguardo ma ci stanno lavorando…**


Grazie per
l' attenzione!