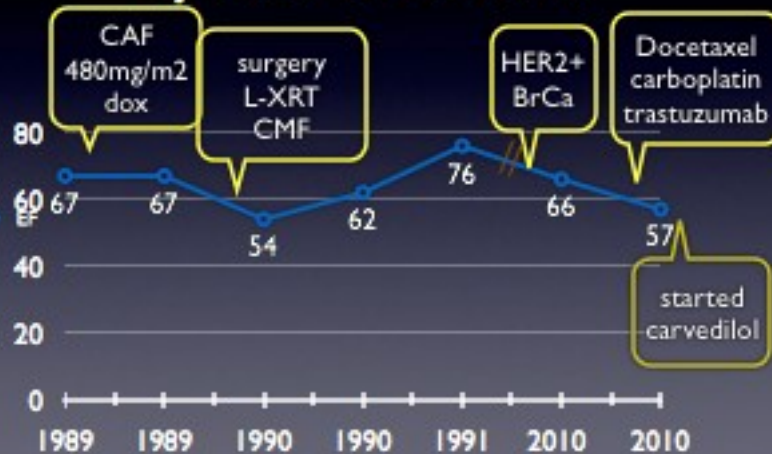


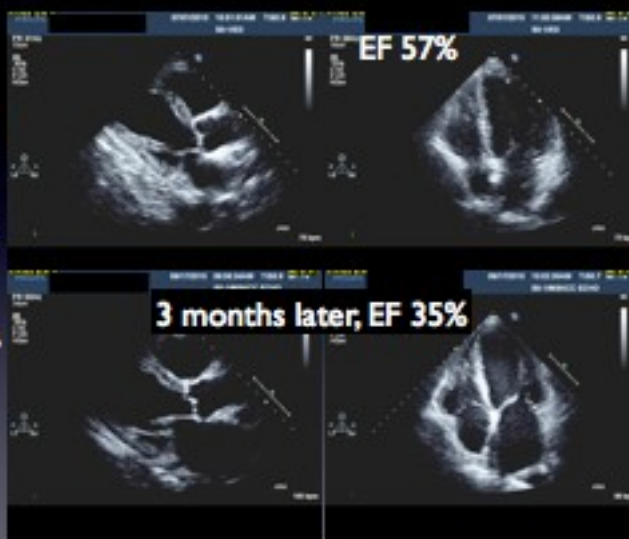
New Developments in Echocardiographic Detection of Cardiotoxicity

Carol L. Chen, MD
Memorial Sloan-Kettering Cancer Center
October 6, 2011
CSRC/ICOS

Detection of cardiotoxicity by LVEF is too late



At the next 3
month clinic
visit, (+)
symptoms of a
"cold"-
malaise,
dyspnea, cough,
wheezing,
edema,
orthopnea.

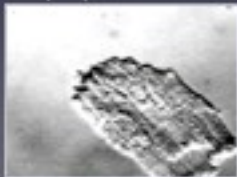


Why 2D-LV EF is inadequate

- Measurement of volume change.
- Is not direct measurement of contractility
- Subject to loading conditions.
- Well documented intra and interobserver variability.
- Visual estimate often affected by translational motion

What is myocardial strain?

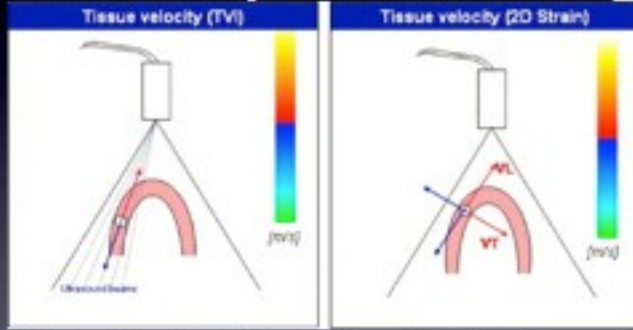
- Dimensionless index of myocardial contractility
- Strain: % of deformation from end-diastole to end-systole. $(L-L_0)/L_0$
- Strain rate: speed of the deformation (1/s)



Strain

- Strain to demonstrate abnormal myocardial contractility in settings of normal LVEF in:
 - CAD: predicts LV remodeling, CHF, death
 - HTN
 - Diabetes
 - CHF
 - Hypertrophic cardiomyopathy

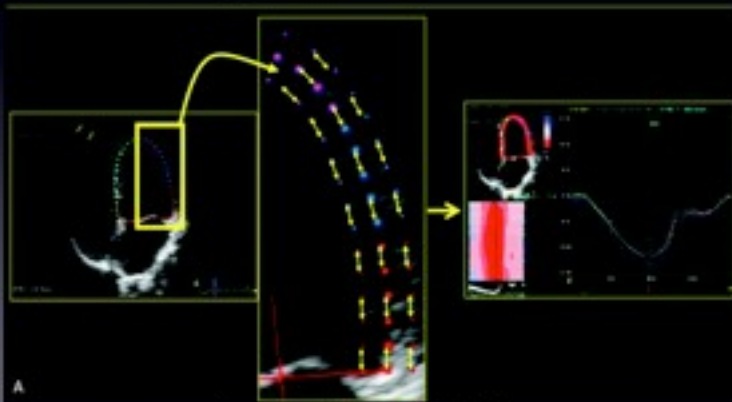
Tissue Doppler Strain and 2D speckle tracking



- Tissue Doppler strain is angle dependent and subject to noise
- 2D speckle strain is angle independent and less subject to noise

Perk et al. JASE 2010

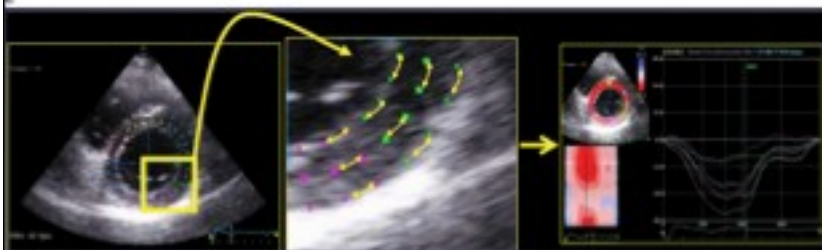
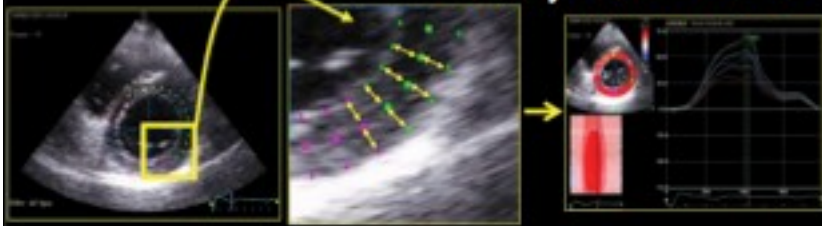
“Speckle” tracking: longitudinal strain



Mondillo et al. J Ultrasound Med 2011

Radial and circumferential strain

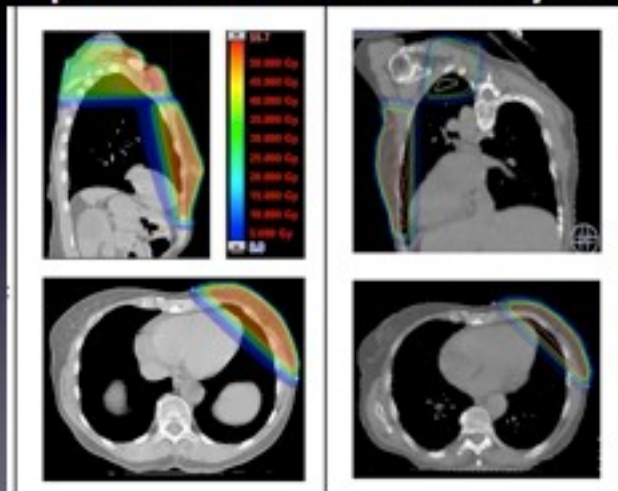
Mondillo et al. J Ultrasound Med 2011



Surveillance during treatment

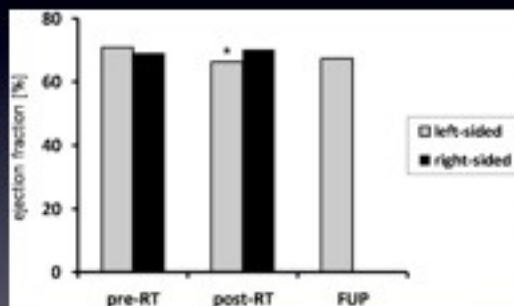
- i. radiation
- ii. anthracycline
- iii. trastuzumab
- iv. combination of above

Regional differences in radiation exposure and cardiac effects by strain

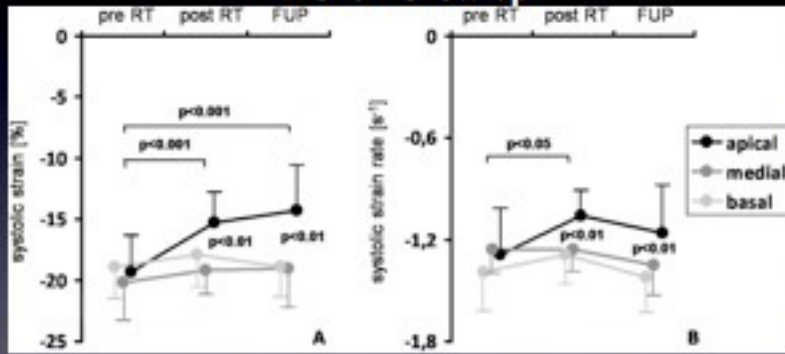


Conventional echo parameters

- All LVEF remained within normal limits
- Small decrease in EF post RT in left sided patients. When patients exposed to anthracyclines excluded, no significant change in EF at all.



Regional Differences Longitudinal strain and strain rate immediately after L-RT and 2 month follow up

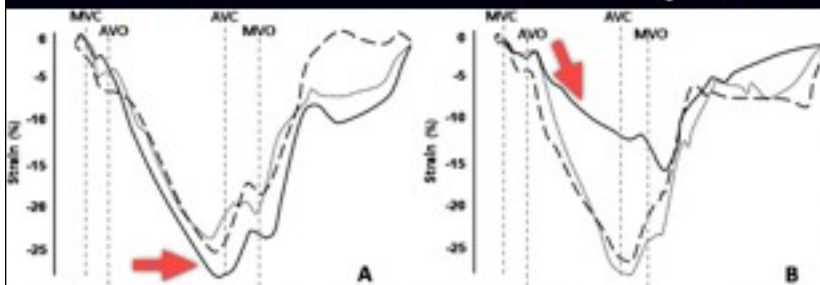


The function of the apical regions more affected than mid or basal segments.

Erven et al, Int J of Radiation Oncology 2011.

Decrease in strain in apex

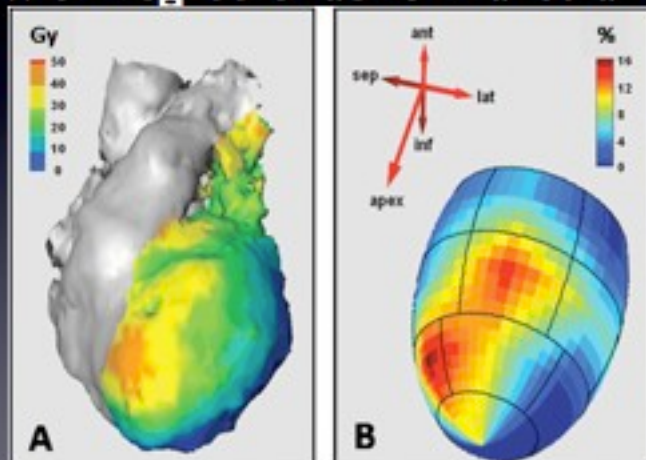
Baseline 2 months post L-RT



— apex
 - - - mid
 basal

Erven et al, Int J of Radiation Oncology 2011.

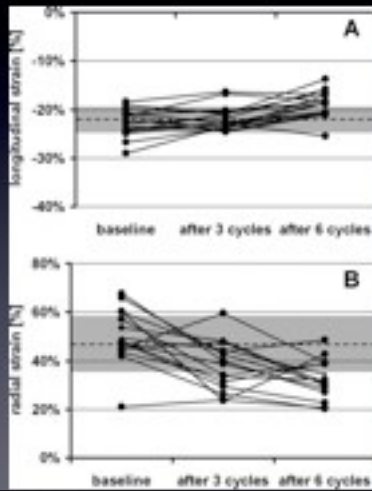
Radiation exposure correlates with degree of abnormal strain



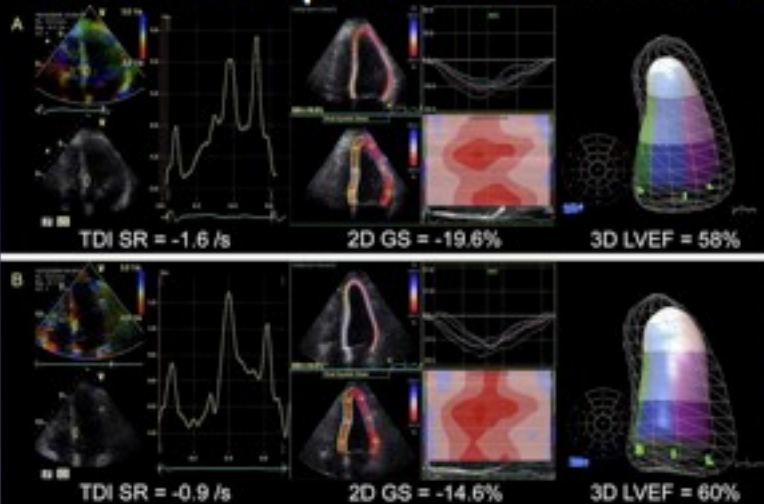
Erven et al, Int J of Radiation Oncology 2011.

Doppler Strain/Strain Rate Imaging Detects Early Cardiac Effects of Pegylated Liposomal Doxorubicin as Adjuvant therapy in Elderly patients with Breast Cancer. Jurcut, et al. JASE 2008.

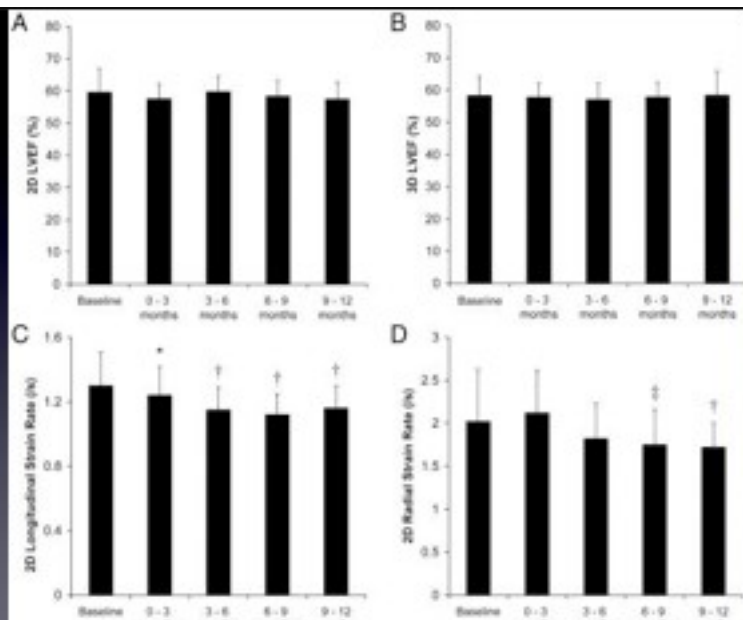
-----published normal value for average peak systolic strain \pm 1SD (gray area) for healthy women 50-79yo



Detection of preclinical dysfunction in breast cancer patients on trastuzumab

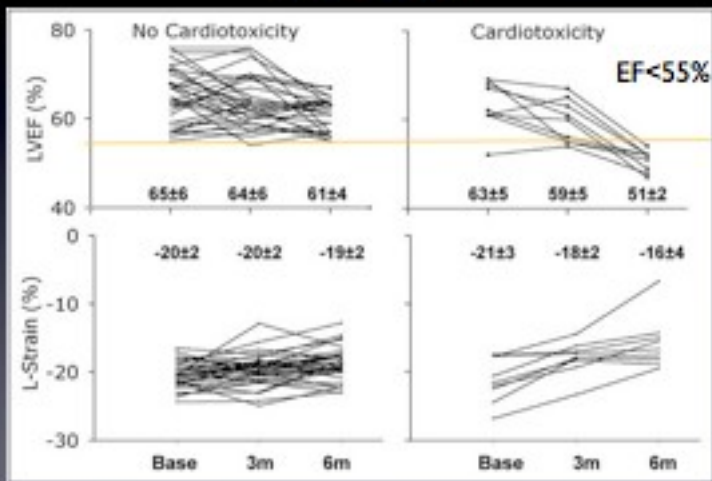


Hare et al. AHJ 2009



Hare et al. AHJ 2009

Early detection and prediction of cardiotoxicity in anthracycline+trastuzumab treated patients (Sawaya, et al. AJC 2011)



Univariate analysis of predictors of cardiotoxicity

	(-) cardiotoxicity (34)	(+) cardiotoxicity (9)	p value prediction of cardiotoxicity	OR
Elevation hsTnI at 3 months	6	6	0.006	9
Change in longitudinal strain at 3m	3% change	15% change	0.01	500
Change in radial strain at 3m	2%	22%	0.02	250

Sawaya et al.

Predictor of cardiotoxicity	sensitivity	specificity	PPV	NPV
10% decrease in longitudinal strain	78%	79%	50%	93%
elevated TnI (3months)	67%	82%	50%	90%
10% decrease in longitudinal strain and (+) TnI	55%	97%	83%	89%
10% decrease longitudinal strain or elevated TnI	89%	65%	40%	97%

Sawaya et al.

Anthracycline +Trastuzumab+XRT

- N=42
- Serial Echo, biomarkers, MRI
- 10 developed cardiomyopathy by 6 months (defined by 10% decline to <55%EF)
- all had decline in tissue Doppler (s'), global and radial strain preceded LVEF decline, MRI reveals delayed enhancement in all suggesting scar
- No change in TnT, ntBNP, CRP

Fallah-Rad, et al. JACC 2011

Surveillance of Survivors

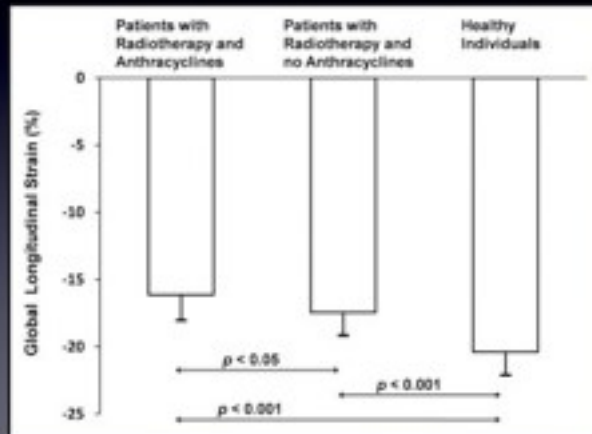
Pediatric survivors of doxorubicin

- Ganame, et al. JASE 2007. Cross-sectional study design. 56 asymptomatic patients, med age 12.7, mean 5 years after treatment for ALL, lymphoma, solid tumors or AML. median dose 240mg/m² (<300mg/m²)
- Findings: Abnormal diastolic function (pulmonary venous patterns, prolonged IVRT), reduced tissue Doppler-radial and longitudinal peak strain rate and strain.
- Cheung, et al. Heart 2010. Cross-sectional study design. 45 asymptomatic children, ALL- mean dose of doxorubicin 240mg/m² with normal LVEF.
- Findings: Reduced global 2D longitudinal, circumferential, radial strain and circumferential strain rate compared with healthy cohort. LV dyssynchrony index greater in patients than in control.

MSKCC preliminary data (Liu et al.)

- 85 consecutive adult cancer survivors of anthracycline therapy as child/young adult (<40 yo). median f/u 15 years since last treatment.
- Longitudinal 2D global strain
 - GE/EchoPacs, average of 18 segments
- Only 14% with abnormal LVEF (defined as <55%)
- 35% with abnormal average global 2D longitudinal strain (normative value < -18%)

Long term Survivors of Hodgkin's lymphoma treated by mediastinal XRT ± anthracycline



Tsai et al. AJC Feb 2011

Breast cancer survivors

- 70 women s/p completion of anthracycline-based therapy +/- adjuvant trastuzumab in prior 6 years compared with healthy cohort
- Normal LVEF
- Global longitudinal 2D strain decreased in treatment group
- 26% treatment group global strain below lower limit of healthy cohort.
- Radial strain not different between treatment and control

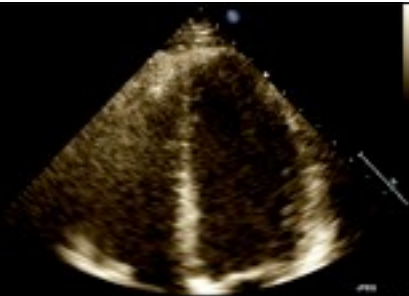
Ho, et al. Heart 2010;96:701

Issues with strain

- Clinical significance of decline in strain/SR in long term is still unclear.
- Many different measurements of strain
- Strain software remains proprietary and unique to each company. different normative values for different software by different vendors.
- ?self as baseline. ?Normative values
- Degree of abnormality which is clinically significant?
- Based on 2D Image
 - Foreshortening
 - Endocardial border resolution (apex)

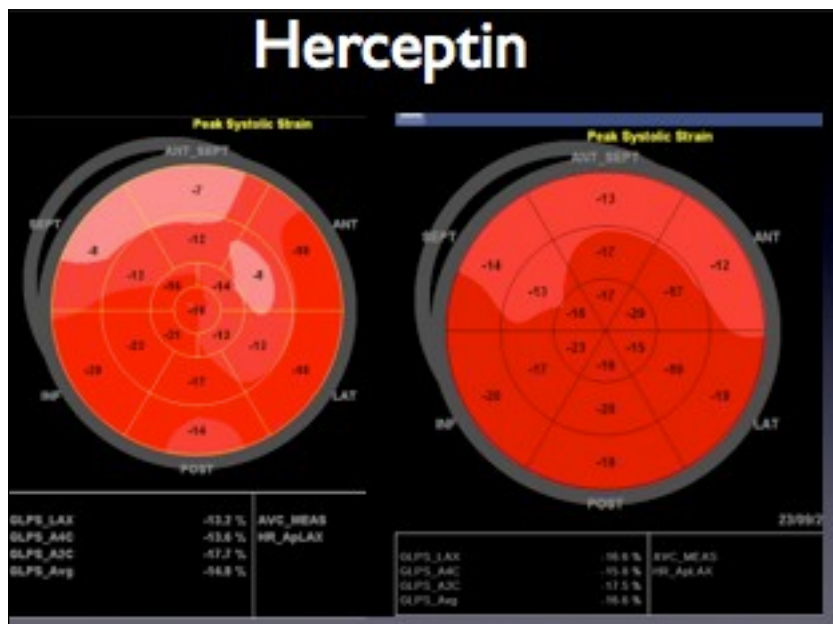
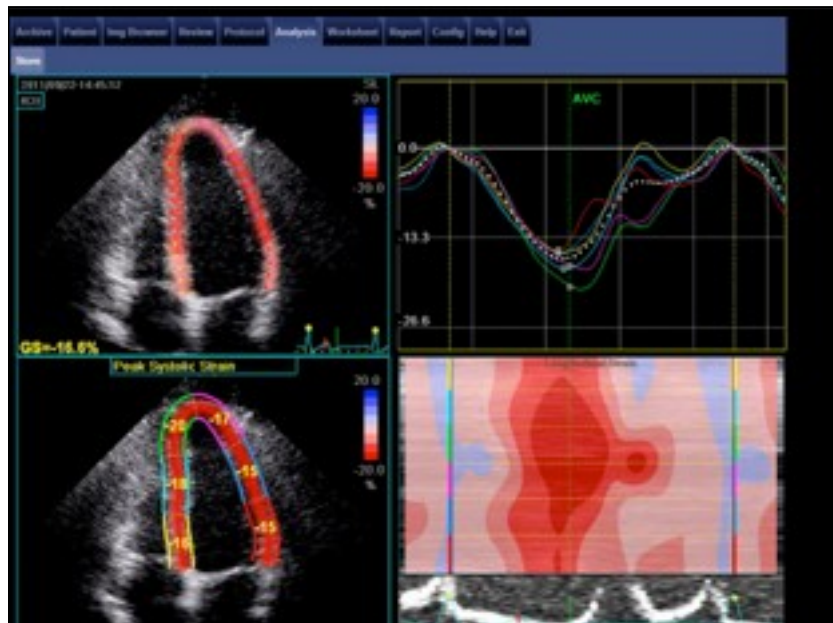
Potential current clinical uses

Baseline
echo
prior to
180mg/
m2 dox



After





Summary

- Strain has revealed early and sustained abnormal myocardial contractility in the setting of normal LVEF during and after radiation, anthracycline, trastuzumab therapy.
- 2D global longitudinal strain seems to be most feasible and reproducible
- Strain data is promising to identify higher risk group who should have closer follow up, continue/start cardiac medications. Larger populations with longer follow up is necessary to make this technology clinically relevant.