Cardio-oncology: Applying new echo technology to guide therapy

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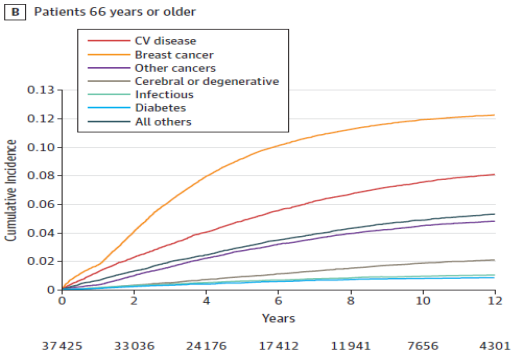
Disclosures

- **Janssen Advisory Board**
- **Takeda Advisory Board**

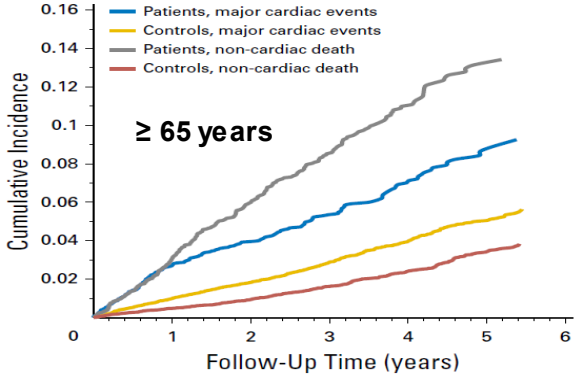
Outline

- **3D echocardiography in cardio-oncology**
- **Myocardial strain to potentially guide treatment**
  - **Baseline risk**
  - **Early detection and treatment**
- **Trials to guide practice**

Consequence of Myocardial Injury



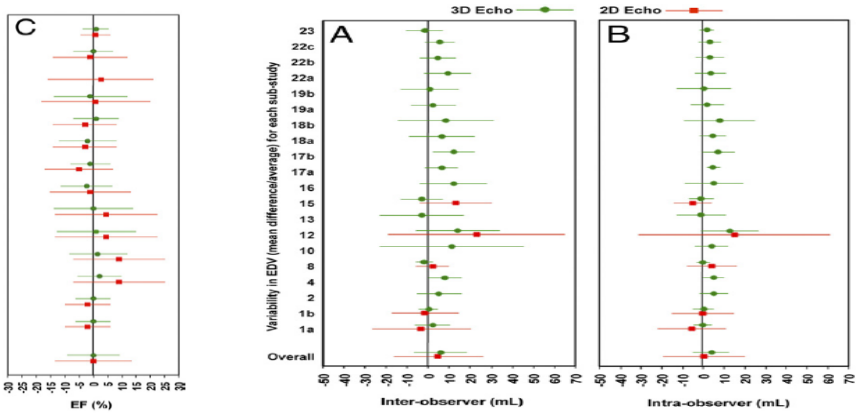
Abdel-Qadir et al, JAMA Cardiology Oct 2016



Thavendiranathan et al, JCO; 2016, Apr 18.

Detection of Cardiotoxicity

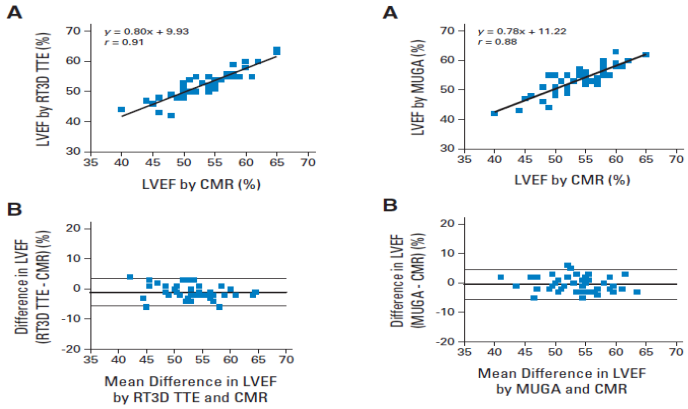
3D Left Ventricular EF



Dorosz JL et al. JACC, 2012; 15:1799

Detection of Cardiotoxicity

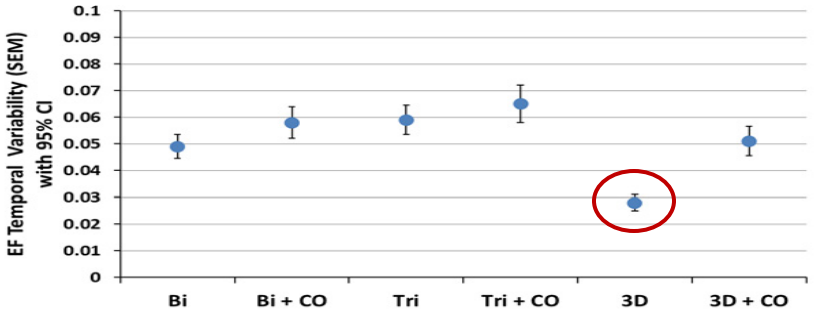
3D Left Ventricular EF



Walker et al. JCO, 2010; 28(21): 3429-3436.

Detection of Cardiotoxicity

Left Ventricular EF



	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)*

Thavendiranathan et al, JACC 2013 Jan 8;61(1):77-84.

Detection of Cardiotoxicity

Left Ventricular EF

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

2.1. LV systolic function.

- Echocardiography is the method of choice for the evaluation of patients before, during and after cancer therapy.
- Accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally 3DE).
- When using 2DE, the modified biplane Simpson technique is the method of choice.

3D Echocardiography Gaps

- Does 3D echocardiography identify cardiotoxicity earlier or more accurately?
- Does it provide incremental prognostic value?
- Does it guide earlier treatment?

Question

Which of the following is true about myocardial strain imaging?

1. Pre-cancer therapy strain can be used to guide cancer therapy
2. Cardiac meds guided by strain imaging prevents heart failure
3. Cardiac meds guided by strain imaging in survivors prevents LV systolic dysfunction
4. GLS measurements are more reproducible than 3D LVEF

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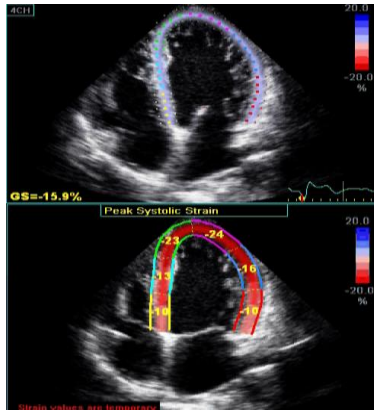
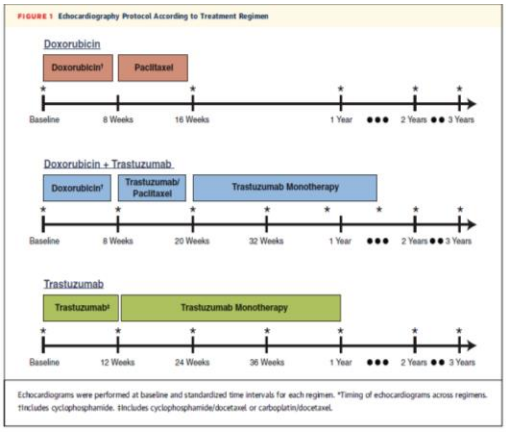
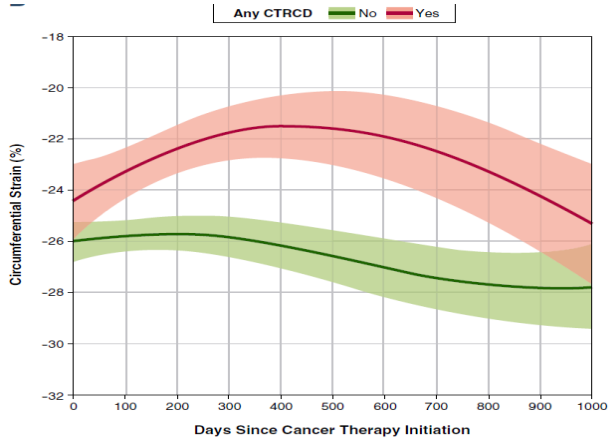
Myocardial strain

1. Pre-treatment risk assessment
2. Early detection of myocardial injury
3. Prediction of LVEF recovery
4. Subclinical disease in survivors



Pre-treatment risk assessment





Narayan HK et al, JACC: Cardiovascular Imaging, 2016

Pre-treatment risk assessment

TABLE 2 Associations of Strain, Strain Rate, and Ventricular-Arterial Coupling Parameters With Odds of CTRCD

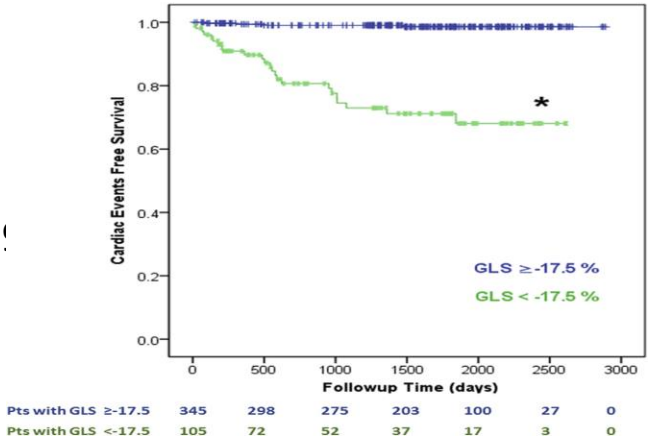
	Model 1* OR (95% CI)	p Value	Model 2† OR (95% CI)	p Value	Model 3‡ OR (95% CI)	p Value	ΔQIC§
Strain							
Longitudinal strain, %							
Baseline‖	1.13 (0.88–1.44)	0.34	1.24 (0.89–1.75)	0.21	1.25 (0.89–1.75)	0.20	-12.5
Change¶	1.17 (1.00–1.37)	0.051	1.26 (1.04–1.53)	0.017	1.25 (1.01–1.53)	0.037	
Circumferential strain, %							
Baseline‖	1.23 (1.10–1.36)	<0.001	1.28 (1.14–1.42)	<0.001	1.31 (1.16–1.47)	<0.001	-31.8
Change¶	1.13 (1.05–1.21)	0.002	1.17 (1.06–1.30)	0.002	1.21 (1.10–1.34)	<0.001	
Radial strain, %							
Baseline‖	1.00 (0.97–1.03)	0.97	0.99 (0.95–1.03)	0.74	0.98 (0.95–1.02)	0.39	-31.2
Change¶	0.98 (0.96–1.00)	0.075	0.97 (0.94–0.99)	0.034	0.97 (0.94–0.99)	0.015	
Change¶	1.12 (1.08–1.18)	<0.001	1.15 (1.07–1.23)	<0.001	1.17 (1.09–1.26)	<0.001	
Radial strain rate, 0.1/s							
Baseline#	1.00 (0.96–1.05)	0.99	0.99 (0.94–1.04)	0.65	0.98 (0.93–1.04)	0.56	-32.0
Change**	0.98 (0.95–1.01)	0.15	0.96 (0.93–0.99)	0.023	0.96 (0.93–0.99)	0.006	
Ventricular-arterial coupling							
Ea/Ees_{sb}							
Baseline††	1.40 (1.22–1.60)	<0.001	1.39 (1.21–1.59)	<0.001	1.38 (1.18–1.60)	<0.001	-15.0
Change‡‡	1.26 (1.14–1.40)	<0.001	1.26 (1.13–1.40)	<0.001	1.23 (1.10–1.37)	<0.001	

Every 1% difference in Circumferential strain at baseline 31% increase in odds of cardiotoxicity

Narayan HK et al, JACC: Cardiovascular Imaging, 2016

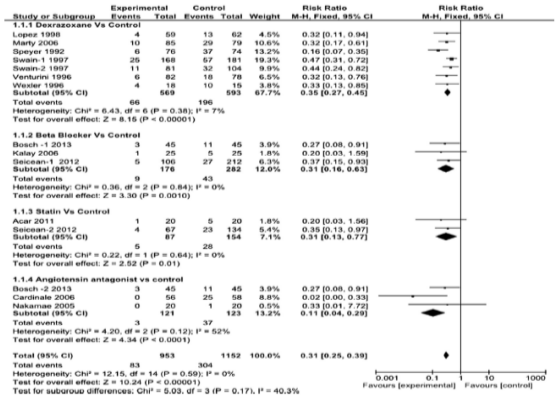
Pre-treatment risk assessment

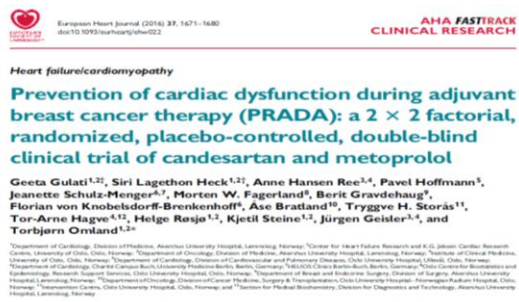
- 450 patients
- Hematological malignancy
- Anthracycline treated
- Followed for median 15[illegible] days
- 6% developed cardiac events (HF or death)
- Pre-treatment echo



Mohammed TA, et al JASE 2016; 29:522-27

Pre-treatment risk assessment





European Heart Journal (2016) 37, 1671–1680
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[1,12], Helge Røsjø[1,2], Kjetil Steine[1,2], Jürgen Geisler[3,4], and Torbjørn Omland[1,2*]

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See page 1681 for the editorial comment on this article (doi:10.1093/eurheartj/ehw133)

Kalam K and Marwick TH, European J of Cancer 2013

"Subclinical" Cardiac Injury

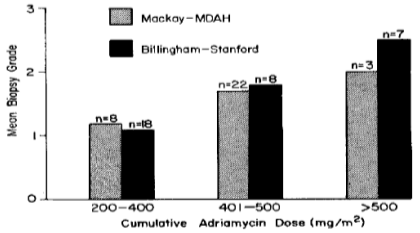


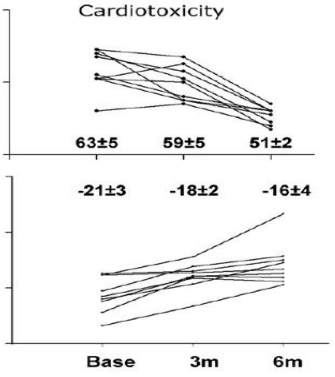
Fig. 2. Cardiac biopsy grade versus cumulative Adriamycin dose. The schedule of administration was by IV infusion over a 20-minute period every three to four weeks.

Table 7. Comparison of Biopsy Grades With Ejection Fractions (EF)

	Nuclear Scans (n = 173)		Echocardiogram (n = 146)	
Biopsy Grade	No. Patients	Mean EF	No. Patients	Mean EF
0	16	63%	16	65%
0.5	50	66%	43	66%
1.0	55	62%	46	67%
1.5	21	58%	19	61%
2.0	20	61%	15	62%
3.0	11	61%	7	65%

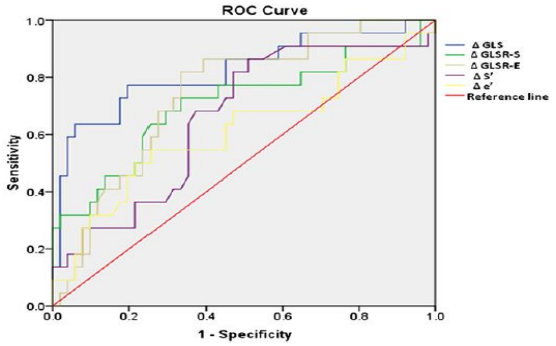
- 158 patients – various cancers, Adriamycin Rx
- Higher biopsy grades in pts with normal EF - even with moderate cumulative dose of Rx

Early Detection of Myocardial Dysfunction



N=43, 21% CTOX, AC followed by TZM

Sawaya H et al. Am J Cardiol 2011;107:1375



N=81, 30% CTOX, All trastuzumab, 40% A

Negishi K et al, JASE 2013, 26: 493-8

Prognosis

Table 3 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%

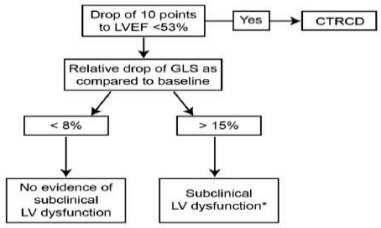
Thavendiranathan et al , JACC 2014

Management

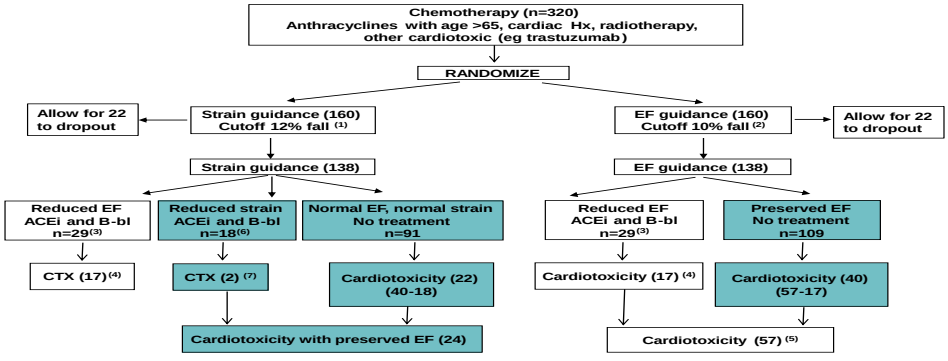
EXPERT CONSENSUS STATEMENT

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,



Treatment - SUCCOUR - RCT



Study PI: Dr. Thomas Marwick - **Tom.Marwick@bakeridi.edu.au**

North American PI: Dr. P. Thavendiranathan – **dinesh.thavendiranathan@uhn.ca**

Myocardial strain – recovery of ventricular function

- Newly diagnosed breast cancer, AC followed by trastuzumab (N=95)
- CTOX (ASE) in 19 (20%)
- Reversibility as per ASE = 13

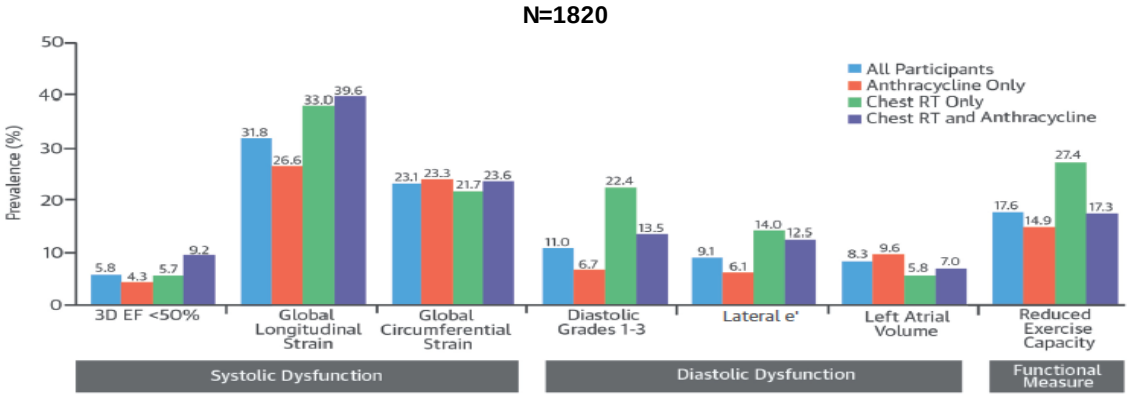
Echocardiographic Variables Shortly after AC Completion for Identifying Development of Cardiotoxicity in Patients with Breast Cancer Treated with Anthracyclines and Trastuzumab by Cox Regression Model

Variables	Univariate HR	Univariate 95% CI	Univariate P value	Multivariate HR	Multivariate CI	Multivariate P
LVEF						0.011
GLS						0.0001
LVEDVI						0.010
LVESVI						
LVEF decrea						
% GLS chan						

Patients with GLS at nadir absolute <15.8 less likely to recover – HR 0.39 (95% CI 0.18-0.74)

Hong-wen F et al. Echocardiography 2016

Strain in pediatric cancer survivors



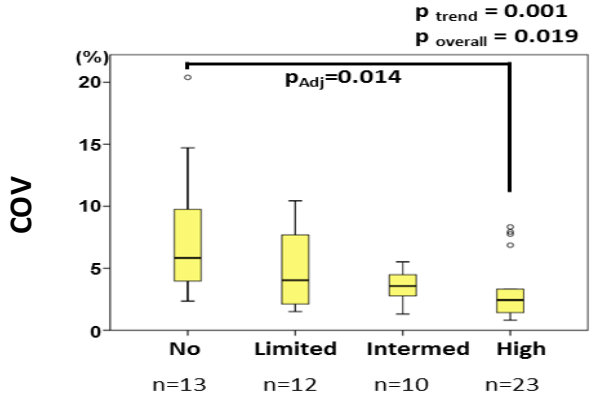
Armstrong GT et al, JACC 2016

Multi-center Reproducibility

	Core Lab value	Site value	Bias	LOA	ICC [95%CI]
GLS, %	-21.0±2.4	-20.4±2.1	0.7	3.1	0.845 [0.692, 0.919]
EF2D, %	61.7±3.5	63.8±5.3	2.0	9.8	0.513 [0.147, 0.725]
EF3D, %	61.6±4.6	62.0±4.7	0.5	8.0	0.750 [0.536, 0.866]

Negishi T et al, JACC CV Imaging, 2016, Oct 6
58 Readers from North America, Europe, Asia and Oceania

Experience and Reproducibility



No = 0 cases
Limited = 1-20
Intermediate = 21-100
High >100 cases
Expert > 1000 cases

Negishi T et al, JACC CV Imaging, 2016, Oct 6
58 Readers from North America, Europe, Asia and Oceania

Image Quality and Reproducibility

Image quality for measurement	GLS	EF	p (GLS vs. EF)
All	0.996 [95%CI 0.990, 0.999]	0.962 [0.900, 0.994]	<0.001
Good	0.997 [95%CI 0.990, 1.000]	0.961 [0.875, 0.997]	<0.001
Borderline	0.993 [95%CI 0.965, 1.000]	0.868 [0.421, 1.000]	<0.001
p (Good vs. Borderline)	0.01	<0.001	

Negishi T et al, JACC CV Imaging, 2016, Oct 6

Question

Which of the following is true about myocardial strain imaging?

1. Pre-cancer therapy strain can be used to guide cancer therapy
2. Cardiac meds guided by strain imaging prevents heart failure
3. Cardiac meds guided by strain imaging in survivors prevents LV systolic dysfunction
4. GLS measurements are more reproducible than 3D LVEF

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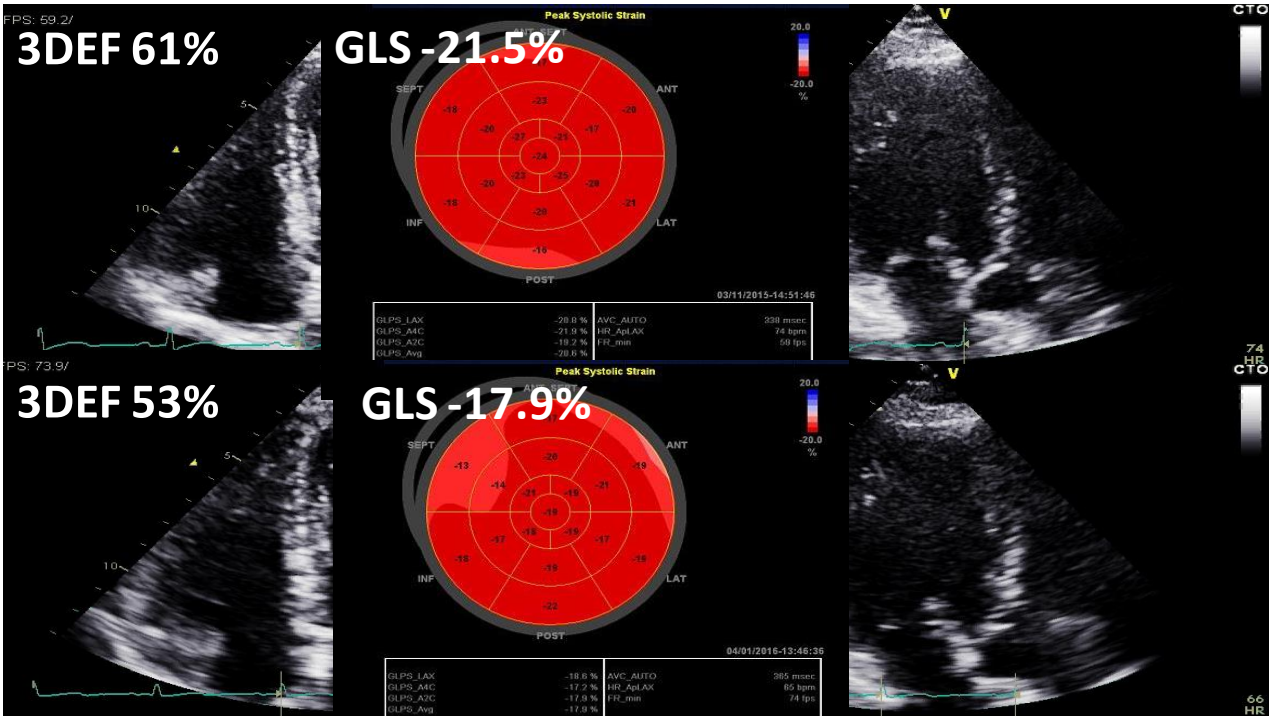
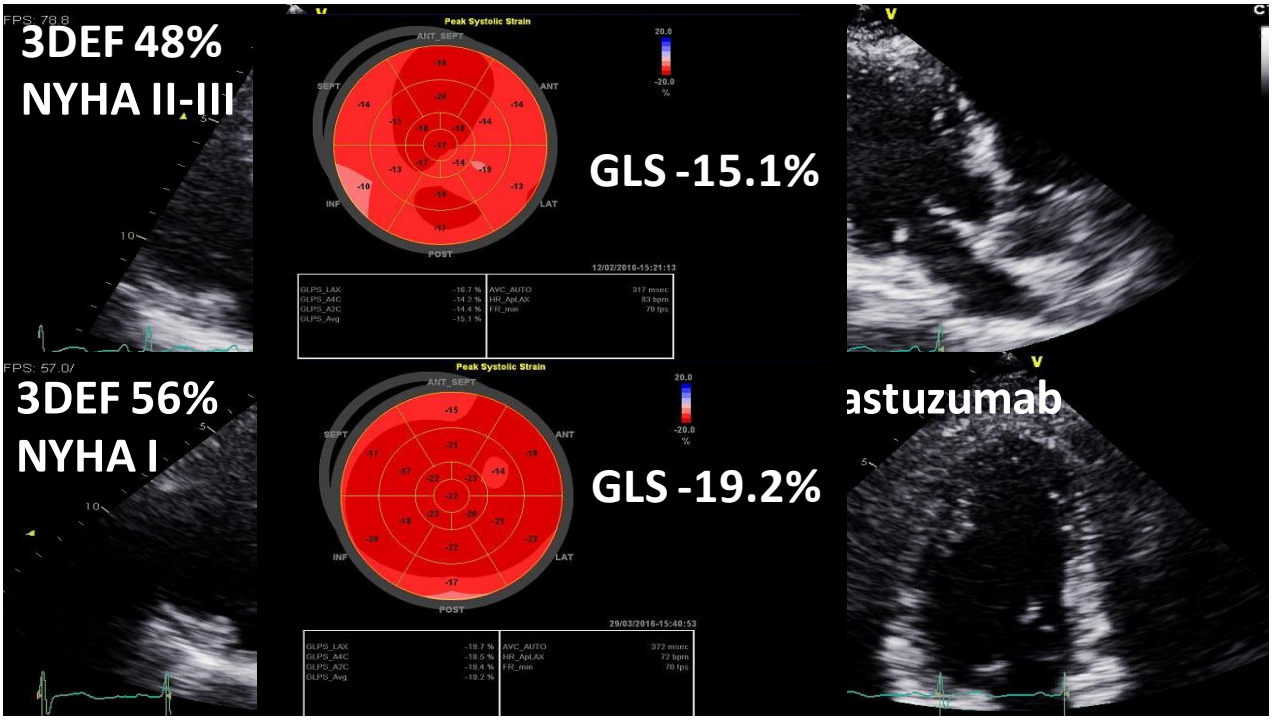
Case Example

- 51 year old woman, high risk HER2+, left sided breast cancer
- Treatment
  - Mastectomy, Epirubicin (300mg/m^2), Trastuzumab (17 cycles), refused radiation therapy, hormonal therapy
- No cardiovascular disease history, no CV risk factors, non-smoker, no medications, excellent functional capacity
- Baseline peaks systolic Circumferential strain -19.6% (mildly reduced)

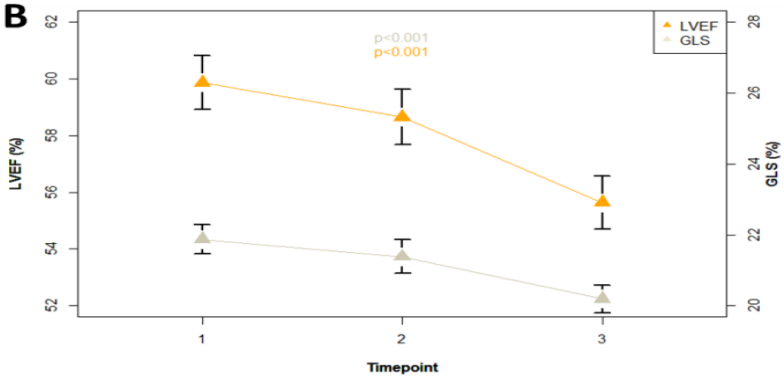




Case - Summary

Time	3D EF	MRI EF	GLS	E/A	E/e'	HsTpI	NYHA
Pre	61	56.7	-21.5	0.9	7.0	2	I
Post A	53	50.5	-17.9	1.1	8.7	48	I
1 month H	48	47.4	-15.1	1.6	11.3	102	II-III
6 weeks	56	55.5	-19.2	1.0	4.4	17	I
6 months	54	52.6	-17.8	1.2	6.1	8	I
9 months	53	-	-18.1	1.3	8.0	3	I
12 months	53	53.0	-17.1	1.3	5.0	2	I
24 months		-					I

Strain echo vs LVEF MRI



Unpublished Data

Summary

- Limited data - ?immunotherapy/ proteosome inhibitors? / immunomodulators?
- 3D EF more accurate reproducible
  - More accurate diagnosis ? Prognosis? Guide Rx?
- Value of strain
  - Circumferential strain – pre treatment risk
  - Longitudinal strain – LV dysfunction / recovery
  - LS / CS identifies subclinical disease in survivors
  - Strain is more reproducible than LVEF
- We need data on using these techniques to guide therapy and modify prognosis!


Thank you
Toronto General Hospital