Pediatric Survivors: Monitoring and Prevention of Cardiovascular Toxicities

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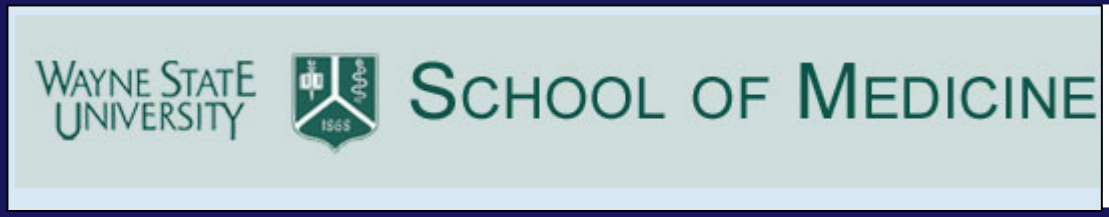
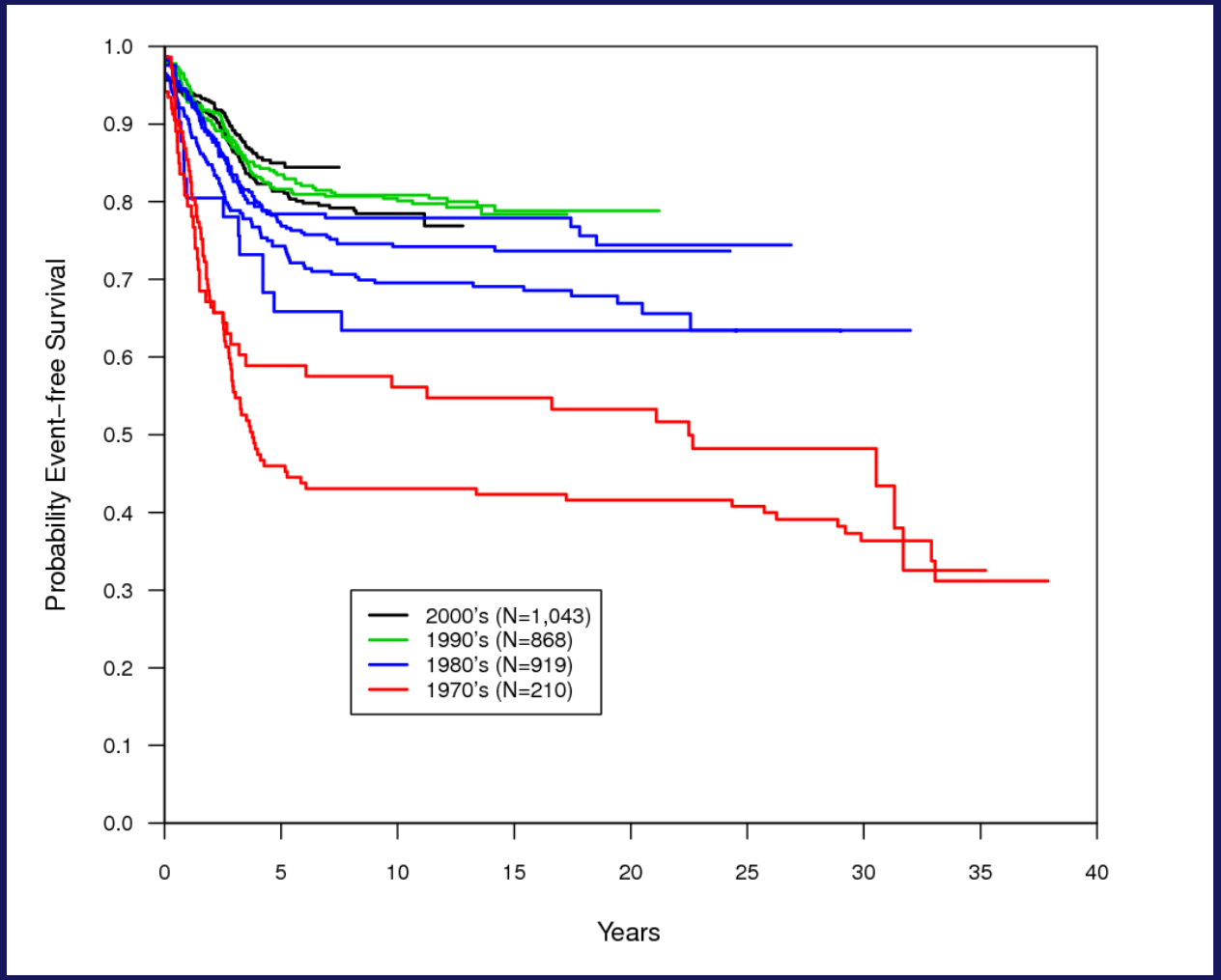


New Paradigm: Successful Treatment of Cancer is Determined by the Balance Between Oncologic Efficacy and Toxicity/Late Effects as Measured by Quality of Life for a Patient and Their Family Over a Lifespan

Lipshultz et al. J Clin Oncol 1993

Event-Free Survival in Children and Adolescents with Acute Lymphoblastic Leukemia on Consecutive DFCI ALL Consortium Trials, by Decade



- 81% 5-yr EFS
- 1:530 US Young Adults (20-45 years old) is a survivor of childhood cancer
- >50% of childhood cancer survivors have been treated with anthracyclines

Vrooman, Lipshultz, Sallan, PPC, 2014

National Cancer Institute Childhood Cancer Survivor Study (CCSS)

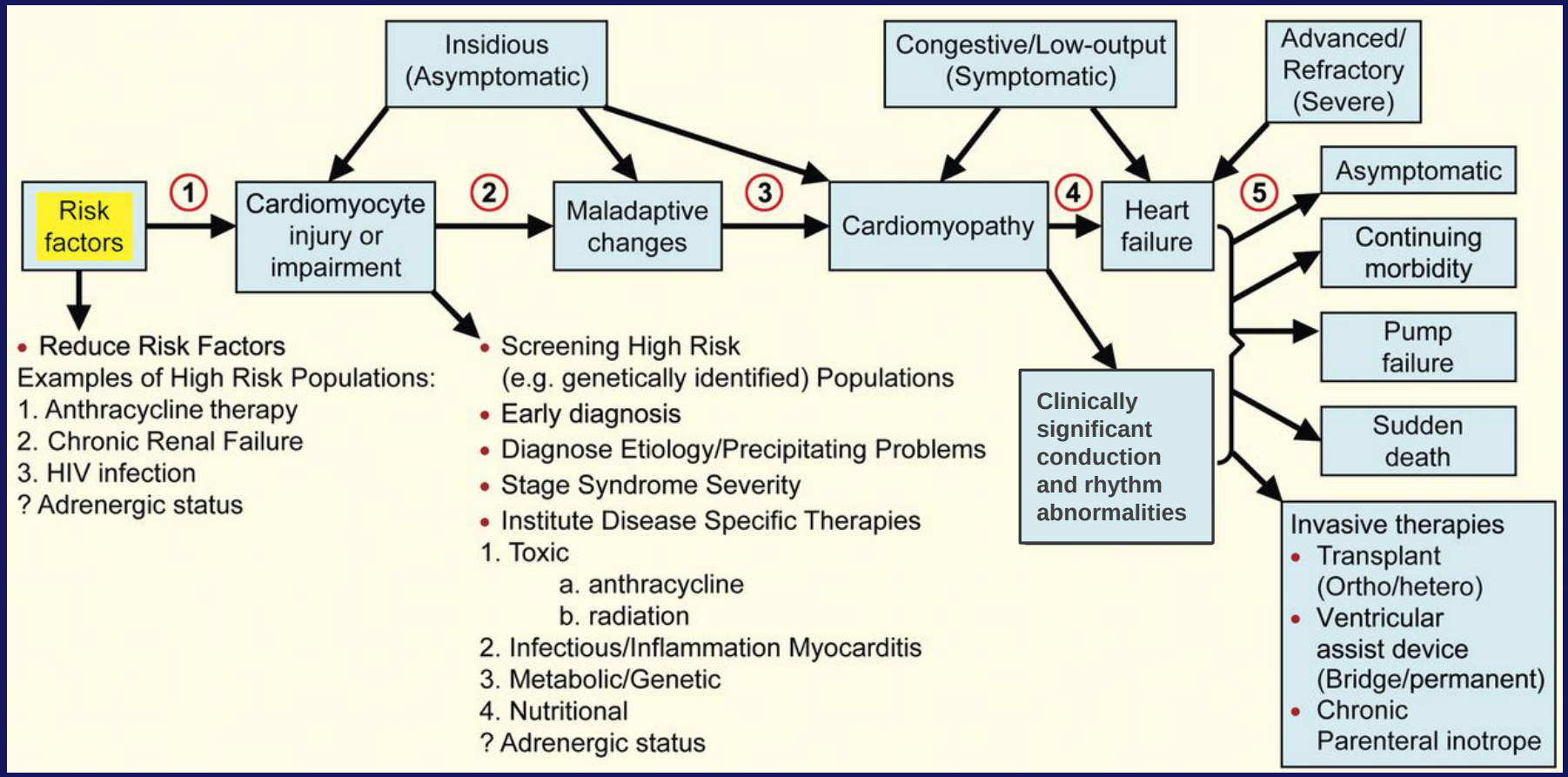
Common late effects and relative morbidity 30 years after childhood cancer treatment:

- Neurocognitive (severe cognitive dysfunction, RR* = 10.5)
- Psychological (depression, post-traumatic stress)
- Cardiopulmonary (decreased lung volume, heart dysfunction)
  (CAD, RR = 10.4; CHF, RR = 15.1; cerebrovascular accident, RR = 9.3)
- Endocrine (growth and fertility; ovarian failure, RR = 3.5)
- Musculoskeletal (major joint replacement, RR = 54.0)
- Second malignancies (RR = 14.8)

*RR = Relative risk of survivors vs. sibling controls

Institute of Medicine, American Cancer Society
Oeffinger et al., NEJM 2006

Stages in the Course of Pediatric Ventricular Dysfunction



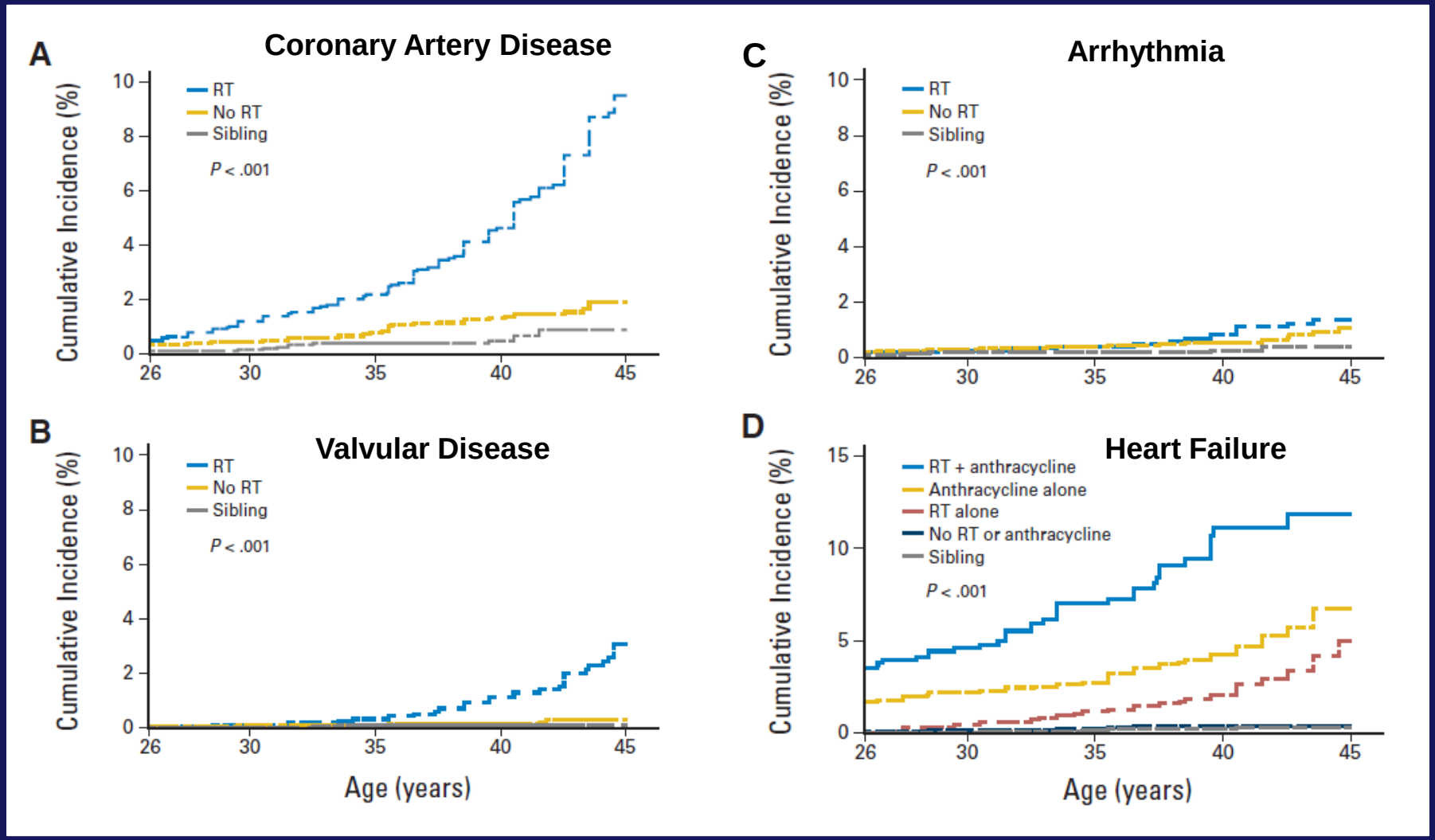
Preventive Strategies: Progressively less effective as the number increases.
Primary prevention is possible at number 1.
Secondary prevention is possible at numbers 2, 3, and 4.

Treatment Strategies: Greater impact with higher numbers but longer effects with lower numbers.
Treatment is possible at numbers 4 and 5 to reduce sequelae.

Biomarkers/Surrogate Endpoints:
Potentially more useful with lower numbers for alteration of course with interventions.
Potentially more useful with higher numbers for decisions about transplantation.

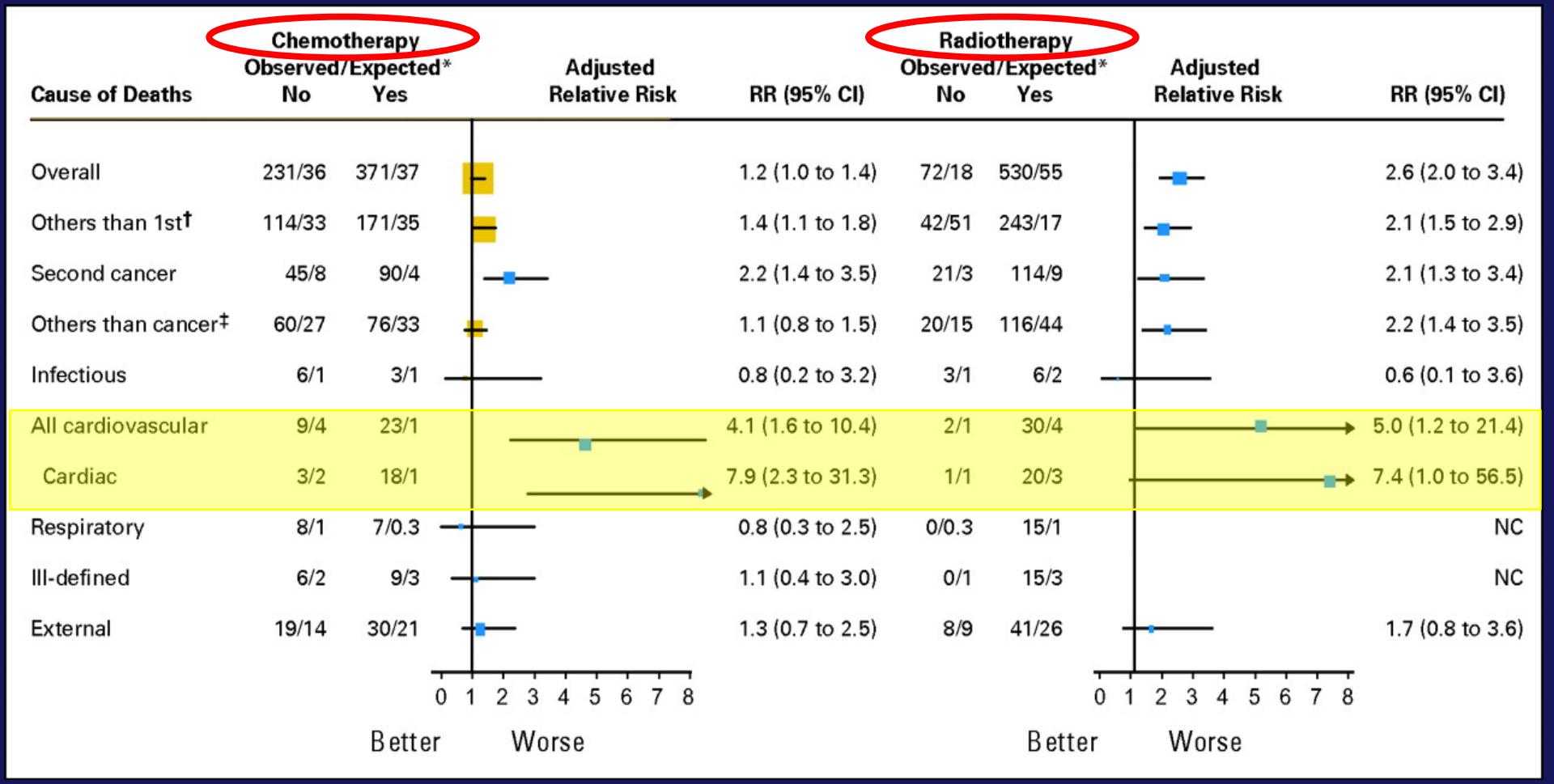
Lipshultz, et al., Prog Pediatric Cardiol 2000
Lipshultz, Eur Heart J 2012

NCI CCSS: Age-Specific Cumulative Incidence of Four Major Cardiac Outcomes in 10,724 5-year Survivors Compared to 3159 Siblings



Armstrong et al. JCO 2013

4,122 5-yr Childhood Cancer Survivors with 86,453 pt-yrs of Follow-up from France and UK, 27-year average F/U

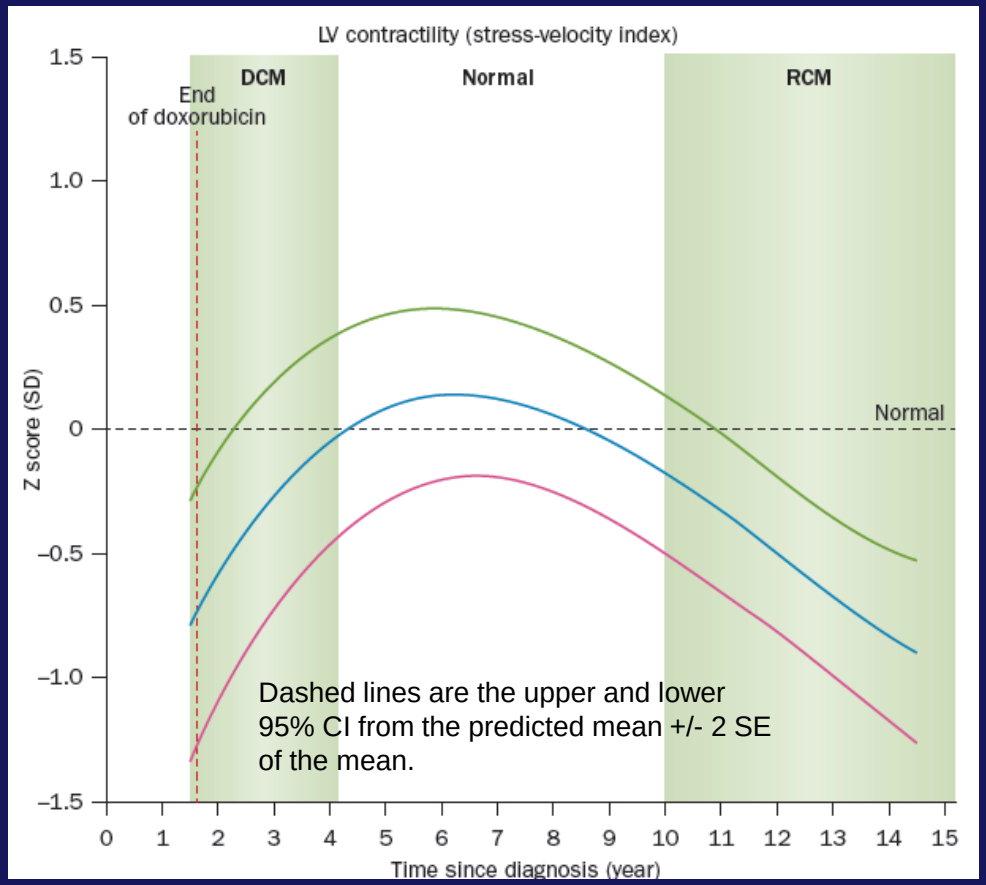


Tukenova, et al., JCO 2010

Left Ventricular Contractility (Health of Heart Muscle Cells) Progressively Worsens Over Time

Long-Term Follow-Up is Essential to See if an Early Doxorubicin "Hit" Results in Late Cardiotoxicity Associated with Progressive Cardiovascular Morbidity and Mortality

DFCI Cohort, High-Risk ALL, Avg age 4 yrs



Green & red lines are the upper and lower 95% CI from the predicted mean +/- 2 SE of the mean.

- >13 million US cancer survivors
- >50% anthracycline exposed

20-year Survivors

- >8-fold increased CV mortality
- >4-fold increased sudden death
- 10-fold increased atherosclerosis
- 5-fold increased myocardial infarction
- ↑ CV mortality from 15 to 25 yrs after Dox

30-year Survivors

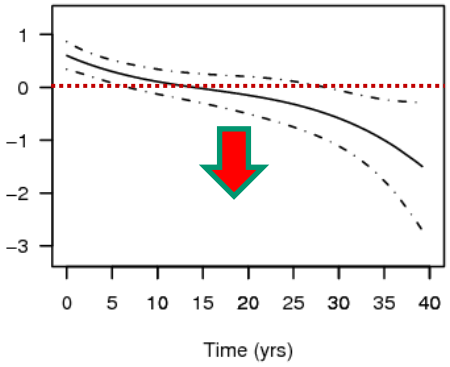
- >3-fold increased anthracycline–associated CV mortality
- 15-fold higher rates of heart failure
- 10-fold higher rate of other CV disease
- 9-fold higher rate of stroke

Mertens et al., JCO 2001
Mulrooney, BMJ 2009
Moller et al., JCO 2001
Tukenova et al., JCO 2010
Armstrong et al., JCO 2009
Oeffinger et al., NEJM 2006
Lipshultz et al., NEJM 1991
Lipshultz, et al., NEJM 1995
Lipshultz, et al., JCO 2005
Lipshultz et al., JCO 2010
Lipshultz et al., NEJM 2004

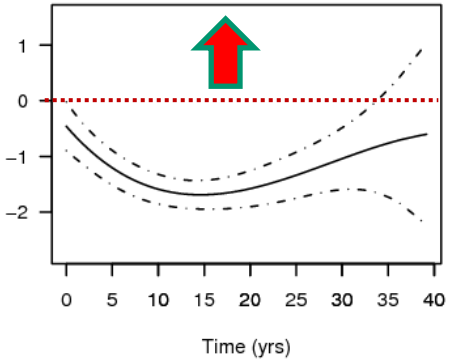
Hearts too small for body size after doxorubicin for childhood ALL: Grinch Syndrome

DFCI Childhood ALL Cohort, 115 HR-ALL patients

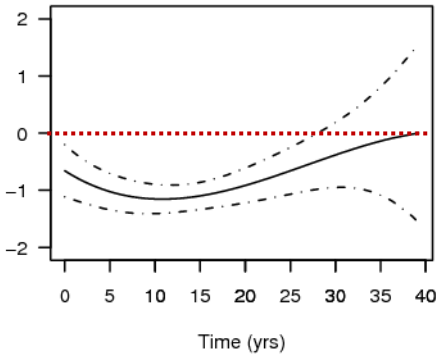
LV End Diastolic Dimension



LV Wall Thickness



LV Thickness-Dimension Ratio



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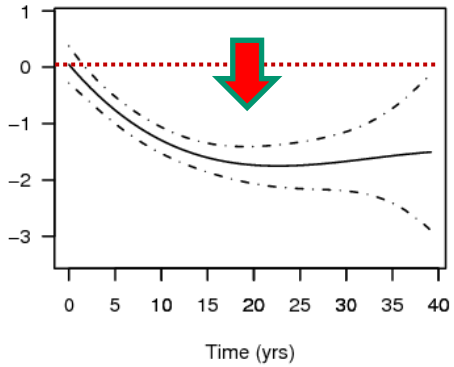
LV Mass



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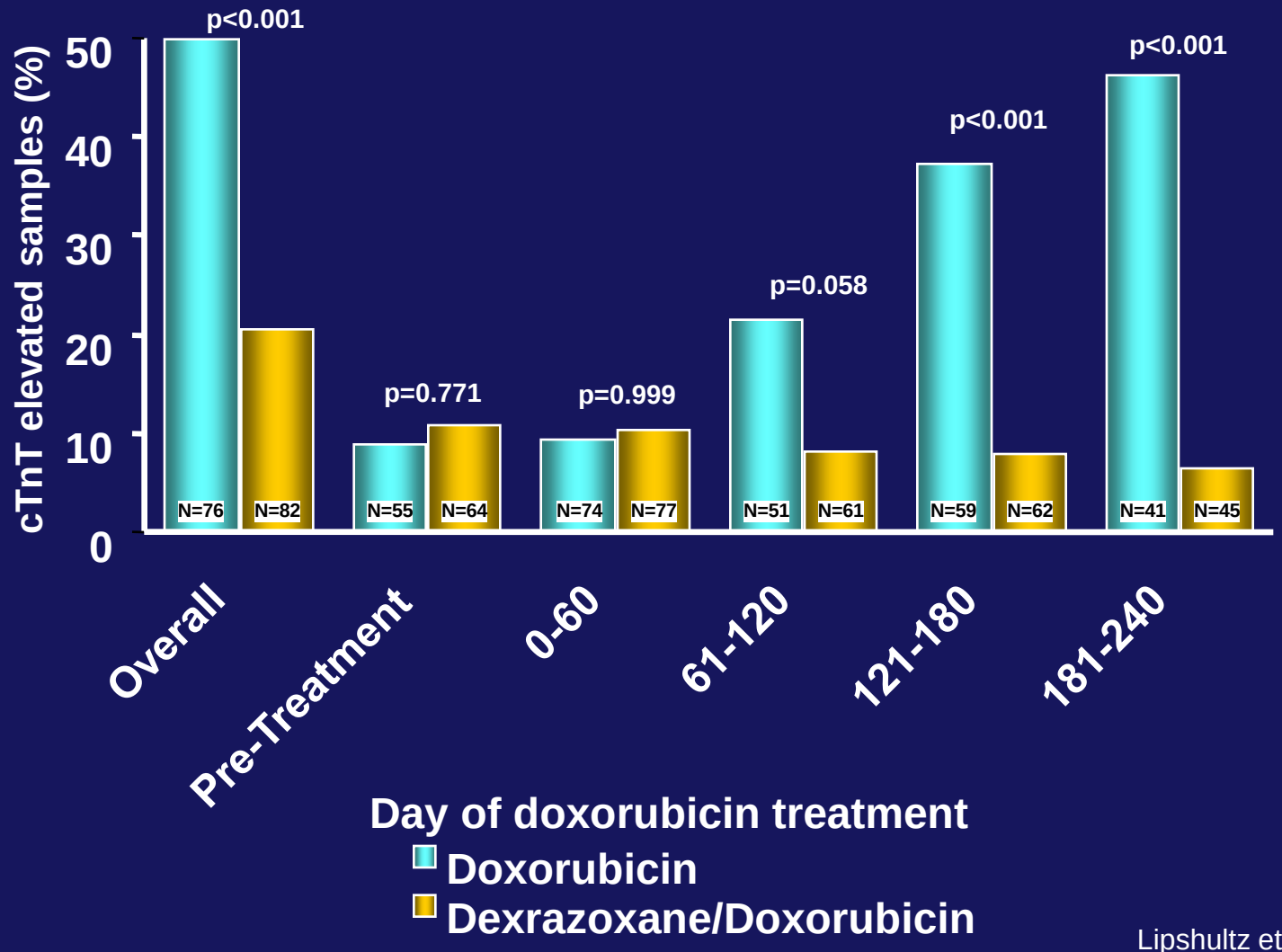
Average age at diagnosis: 4 yrs, Average cumulative dox dose: 352 mg/m^2

NCI DFCI 9501 Cohort: Dexrazoxane Reduces Myocardial Injury



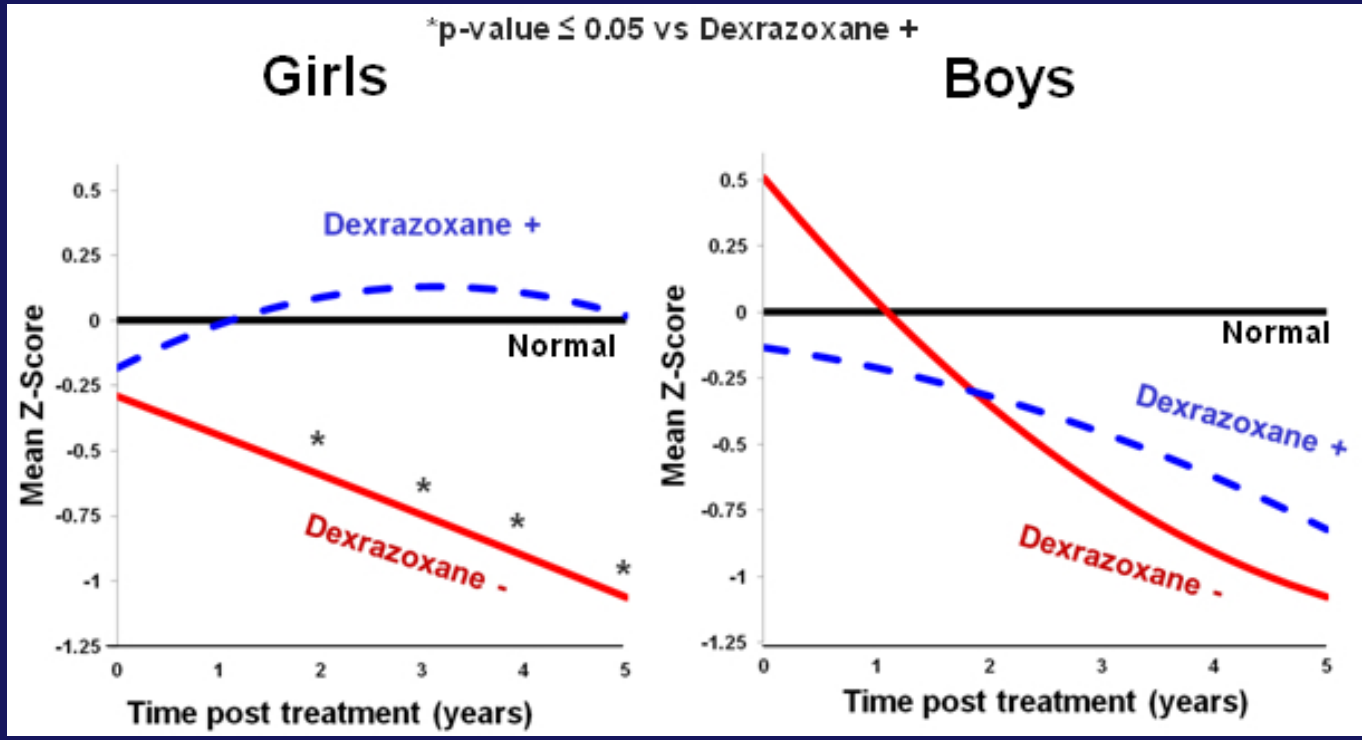
Lipshultz et al., NEJM 2004

Ventricular Remodeling in Systolic and Diastolic Heart Failure as a Function of Time

McMurray, Pfeffer, Heart Failure Updates 2003

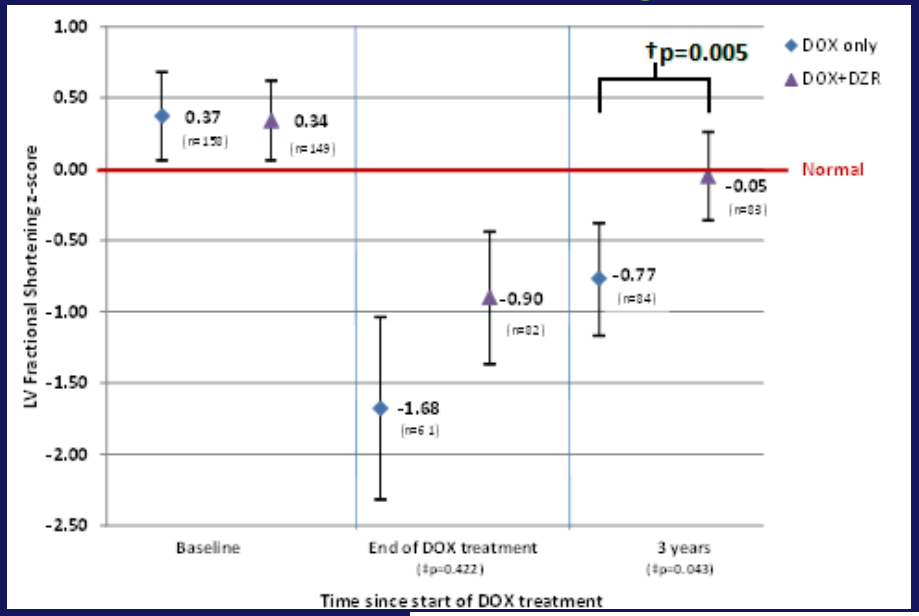
NCI DFCI ALL 9501 Cohort: Left Ventricular Thickness to Dimension Ratio in Doxorubicin-Treated Children; Dexrazoxane Blocks LV Remodeling

Lipshultz et al., Lancet Oncol 2010

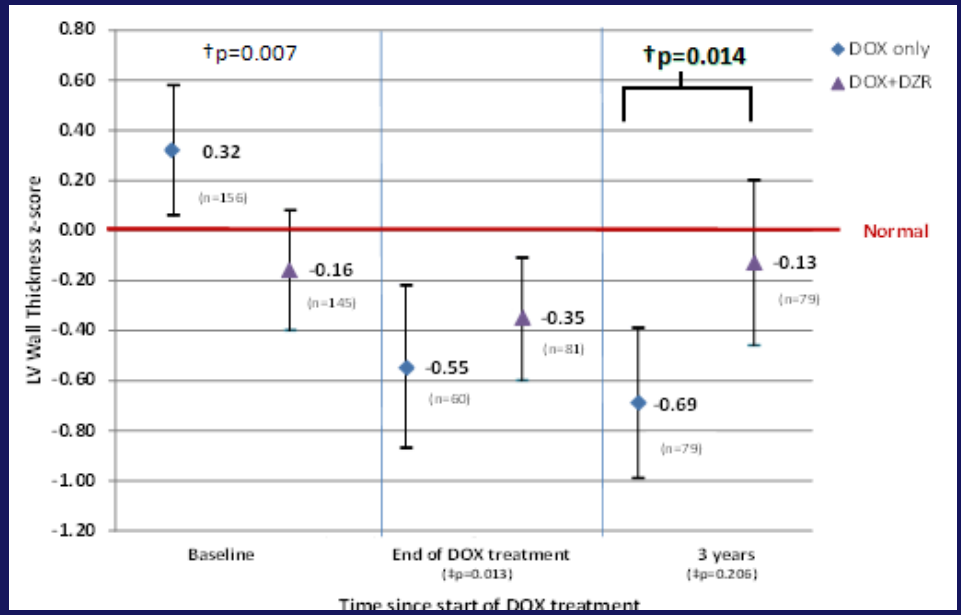


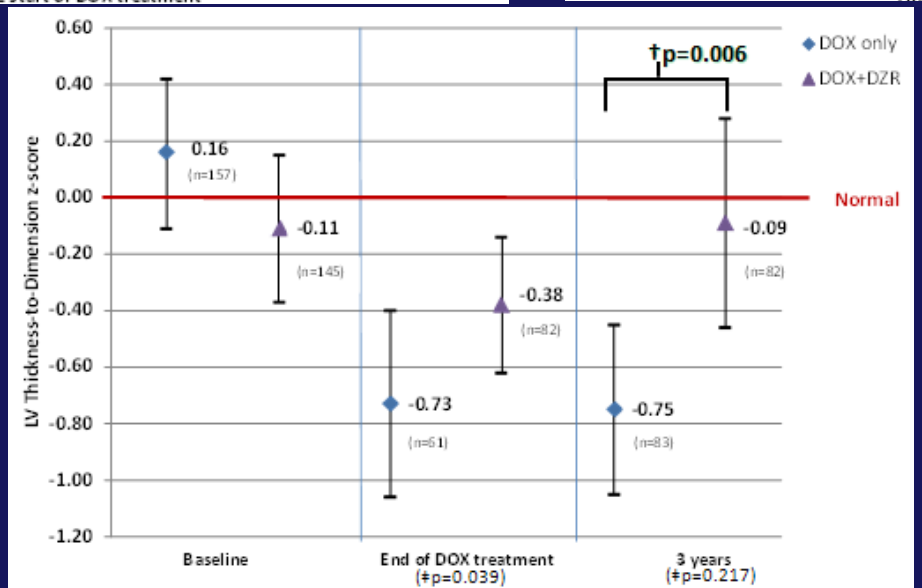
Second Study: NCI COG 9404 T-ALL: Dexrazoxane is Cardioprotective 3 Years After Doxorubicin

LV Fractional Shortening



LV Wall Thickness





LV Thickness-to-Dimension Ratio (LV Remodeling)

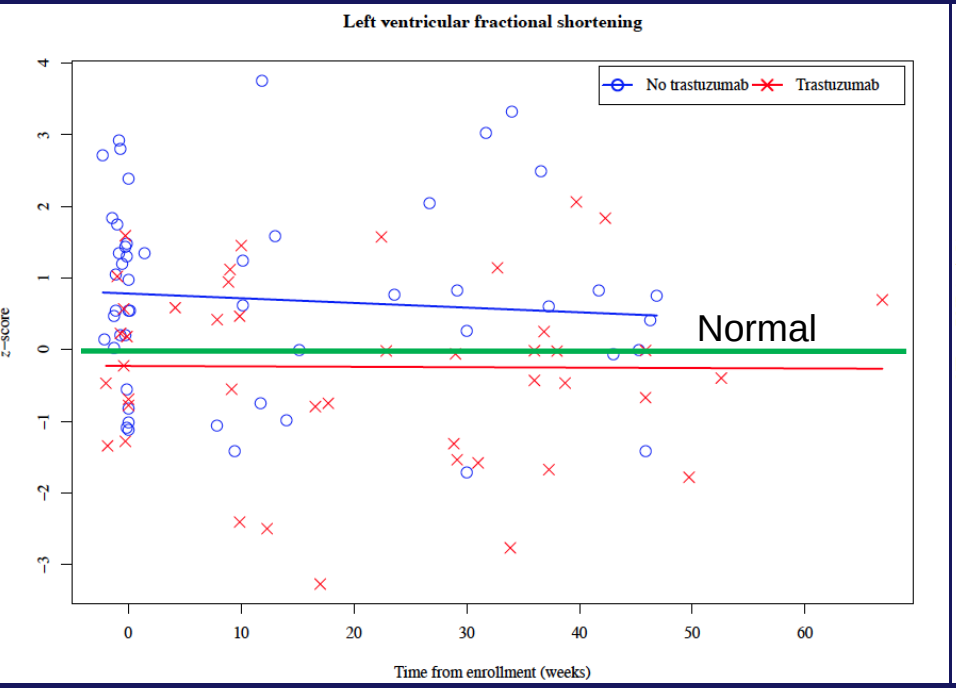
†p-value for difference between groups

‡p-value for differences in change of mean z-scores between groups

Asselin, BL…Lipshultz SE. JCO 2016

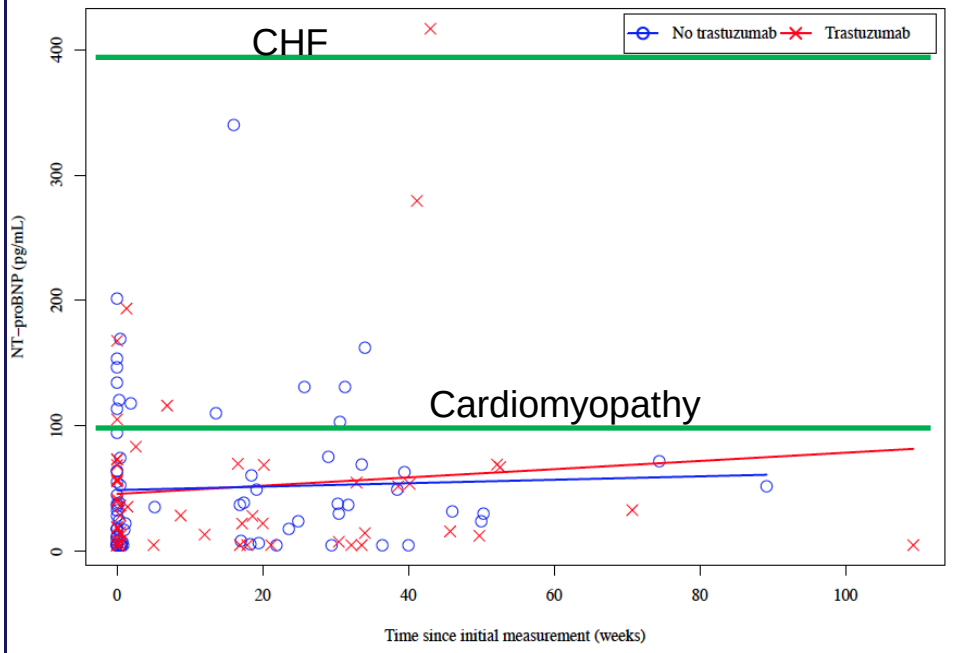
Third Study: Dexrazoxane is Cardioprotective for Additive Cardiotoxicity NCI COG AOST 0121

Herceptin/Dox Additive Cardiotoxicity Protected by Dexrazoxane



Both Groups Not Significantly Different from Normal

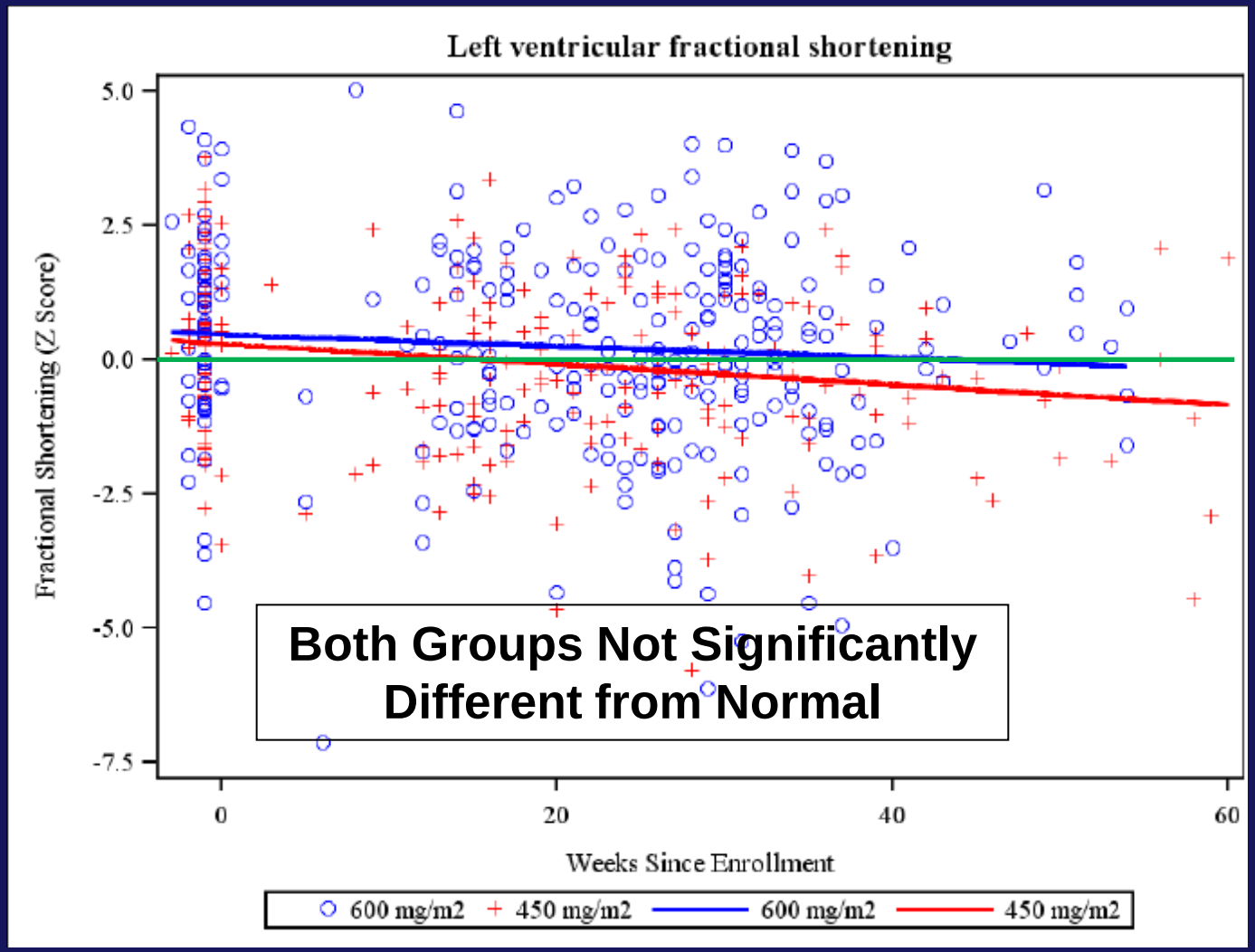
No Cardiomyopathy by NT-proBNP with Dexrazoxane



Both Groups Below the Cardiomyopathy Threshold

Kopp, Lipshultz, ASCO 2012
Ebb, Lipshultz, JCO 2012

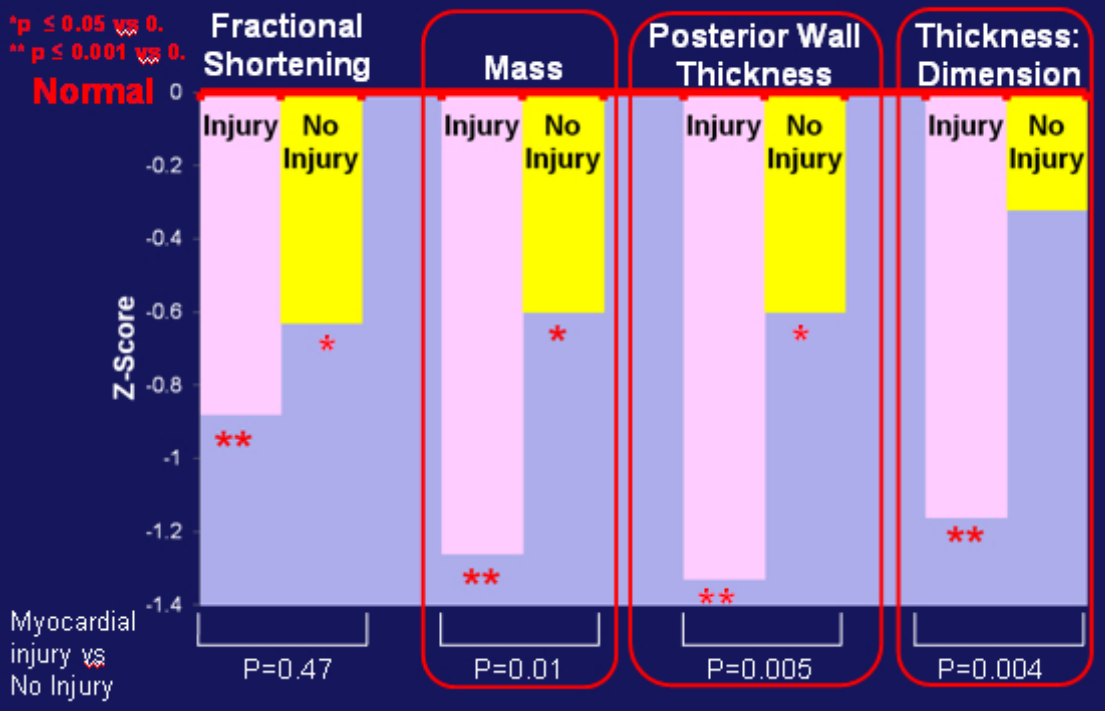
Fourth Study: Dexrazoxane is Cardioprotective with Doxorubicin Dose Escalation: NCI COG P9754: No Fall in LVFS slope going from 450 to 600 mg/m^2 of Doxorubicin when Dexrazoxane is used



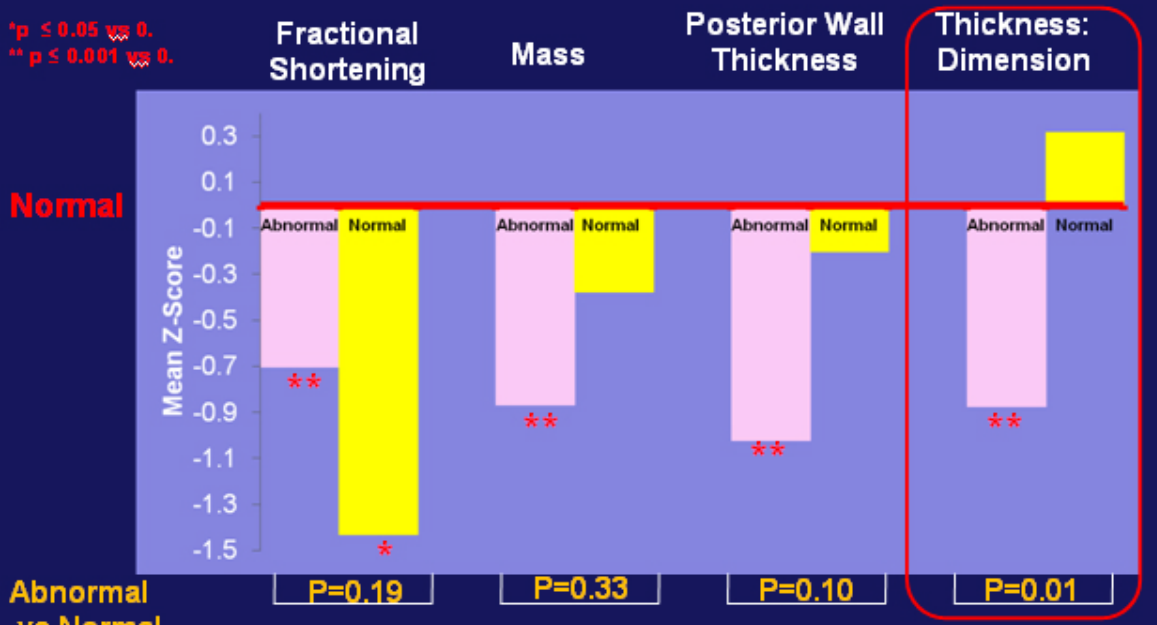
Schwartz CL…Lipshultz SE, Pediatr Blood Cancer 2015

Validate cardiac biomarkers as surrogate endpoints

Myocardial injury (measurable serum cardiac troponin T, ≥ 0.01ng/ml) during doxorubicin therapy is significantly related to lower left ventricular mass, wall thickness, and remodeling by echo more than 5 years later



Abnormal NT-proBNP (Cardiomyopathy, Age >1 yr ≥ 100 pg/mL; Age < 1yr abnormal ≥ 150 pg/ml) during the first 90 days of doxorubicin therapy is significantly related to LV remodeling (thickness to dimension ratio) by echo 4 years later



Lipshultz et al., JCO 2012

Associations Between HFE Mutations and Myocardial Injury During DOX Therapy

Biomarkers	OR*	95% CI	P
H63D			
abnormal cTnT	0.39	0.05-3.30	0.39
abnormal NT-proBNP	0.59	0.17-2.09	0.61
C282Y			
abnormal cTnT	**8.79**	**1.08-71.46**	**0.04**
abnormal NT-proBNP	1.49	0.31-7.19	0.62

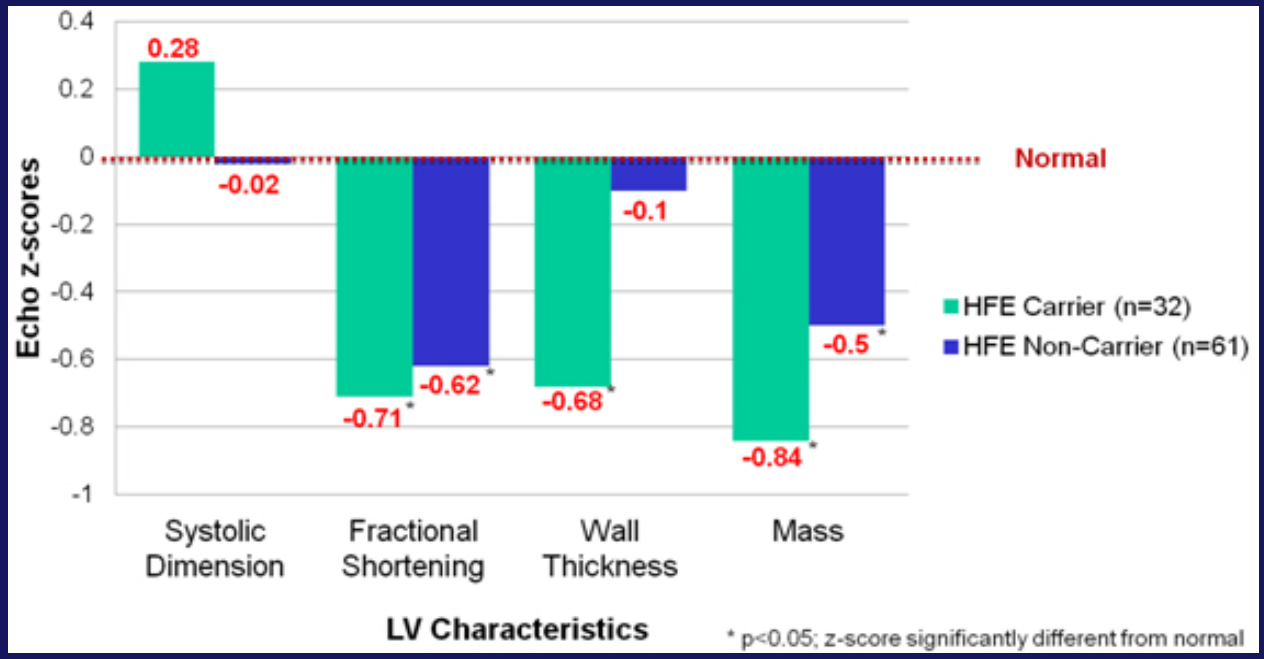
C282Y mutations were significantly associated with 8-fold increased risk of elevations in cTnT

- OR: Odds Ratio
- Abnormal cTnT: >0.01ng/ml;
- Abnormal NT-proBNP: ≥150 pg/mL in infants younger than 1 year or ≥100 pg/mL in children aged 1 year or older

* Adjusted for dexrazoxane

LV Characteristics by HFE Carrier 2 years after Randomization

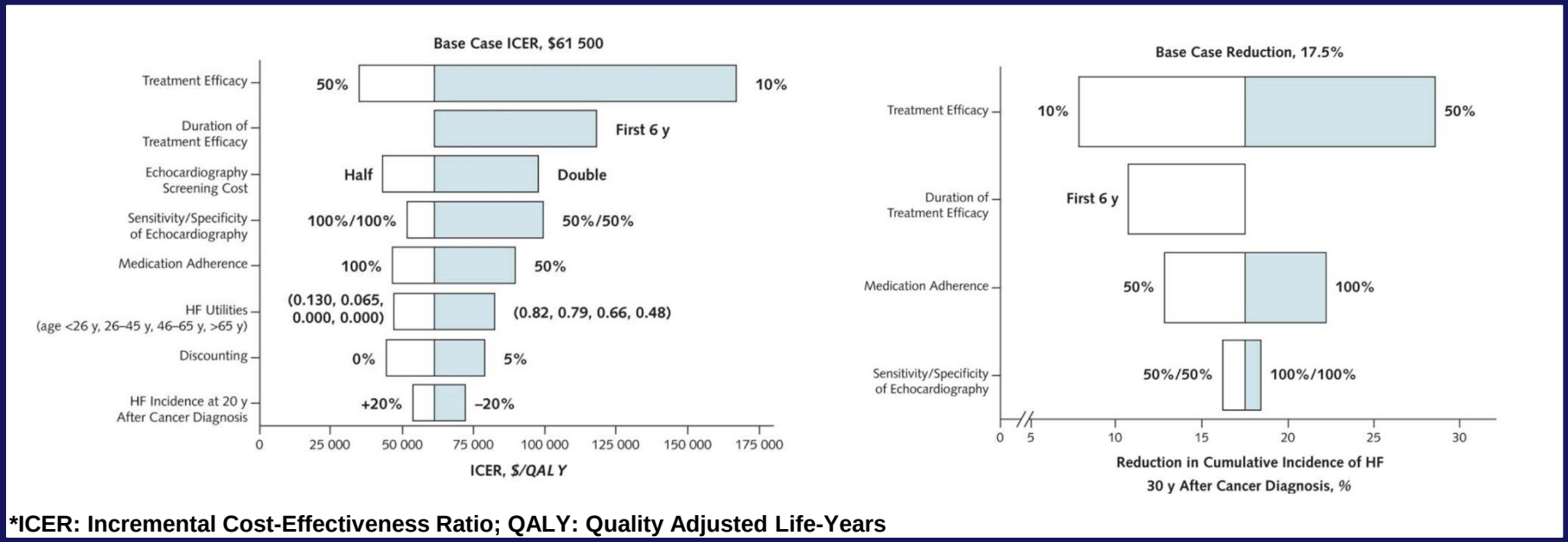
Carriers showed more dilated left ventricles, LV dysfunction, thinner posterior wall thickness, and reduced LV mass than normal



Lipshultz, et al. Cancer 2013
Krajinovic…Lipshultz, et al. Pharmacogenomics J. 2015

Efficacy and Cost-effectiveness of the Children's Oncology Group Long-Term Follow-Up Screening Guidelines for Childhood Cancer Survivors at Risk of Treatment-related Heart Failure

- The COG Guidelines versus no screening have an incremental cost-effectiveness ratio (ICER) of $61,500,
- Extend life expectancy by 6 months and quality adjusted life-years (QALYs) by 1.6 months, and
- Reduce the cumulative incidence of HF by 18% at 30 years after cancer diagnosis.
- However, less-frequent screenings are more cost-effective than the Guidelines, and maintain 80% of the health benefits



*ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality Adjusted Life-Years

Tornado diagrams of the one-way sensitivity analyses for ICER and the percent reduction in the cumulative incidence of HF at 30 years after cancer diagnosis, by varying key variables.

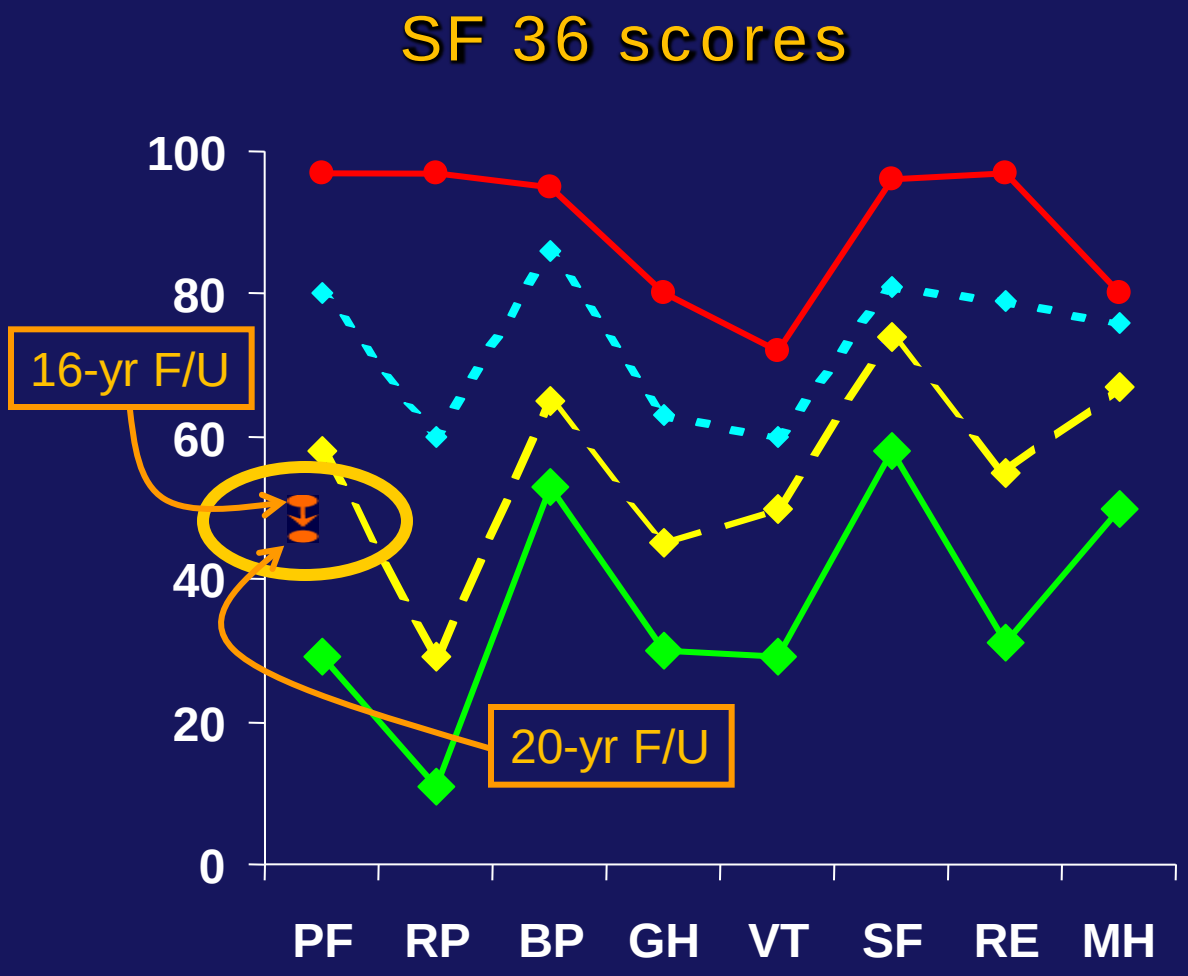
Wong LF. . . Lipshultz SE, Ann Intern Med 2014

16-Years After Mediastinal Irradiation for Adolescent Hodgkin Lymphoma There was Decreased Quality of Life and Physical Functioning

- All Rated Overall Health as Good or Better
- However on the General Health Survey:
  - 67% fatigue (half ≥ moderate problem)
  - 40% short of breath (1/3 ≥ moderate problem)
  - 10% significant problem with dizziness
  - 25% chest pain

Adams, Lipshultz et al., JCO 2004
Adams, Lipshultz, JCO 2006

QoL: Radiation Effects Are Similar to CHF



PF Physical Function
RP Role Limitation (Physical)
BP Bodily Pain
GH General Health
VT Vitality
SF Social Functioning
RE Role Limitation (Emotional)
MH Mental Health

Adams...Lipshultz, Prog Pediatr Cardiol 2015
Juenger et al., Heart 2002

Conclusions

- Cardiotoxicity associated with cancer therapeutics can be pervasive, persistent, and progressive but missed clinically
- Cardiovascular-related health burden will increase as this expanding population ages
- Genetic, environmental, and temporal factors interact to cause toxicity and identify high risk groups for safer treatment options and targeted interventions
- Dexrazoxane is cardioprotective and allows safe dose escalation and the use of additive cardiotoxic therapies
- Tailored follow-up and therapies (multi-agent cocktails) are needed and may be unique
- Screening for hemochromatosis gene mutations in children with newly diagnosed high-risk ALL might inform treatment decisions
- Validated cardiac surrogate cardiac endpoints are limited
- If you don't look, you don't know
- Survivor cardiac monitoring delays heart failure and improves QOL

"In Matters of the Heart, We're in This Together."