BRIGHAM AND WOMEN'S HOSPITAL
| Heart & Vascular Center |

DANA-FARBER CANCER INSTITUTE

17th Annual Benjamin Schuster, MD Colloquium February 22nd, 2017:

Cardiovascular Oncology in 2017: Radiation induced CV Disease Survivorship

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

- Amgen Pharmaceuticals (Grant Support)
- Linda Joy Pollin Women’s Heart Center Innovation Award

Talk Outline

- **Part I: Radiation induced cardiovascular injury**
  - Risk factors
  - Practice guidelines pertaining to surveillance and testing
  - Cardiac surgery outcomes in pts with RIHD
  - Radiation-induced carotid disease and management
  - Refinements in radiation protocols to reduce cardiac exposure
- **Part II: Survivorship**
  - Guidelines for survivors of childhood and adult cancers
  - Adverse cardiometabolic profiles of cancer survivors
  - Prevalence and significance of impaired exercise capacity

RADIATION INDUCED CARDIOVASCULAR INJURY

CV Complications of Radiation Therapy

- ~50% of cancer patients receive RT[1]
- CV complications originally described in 1960s[2]

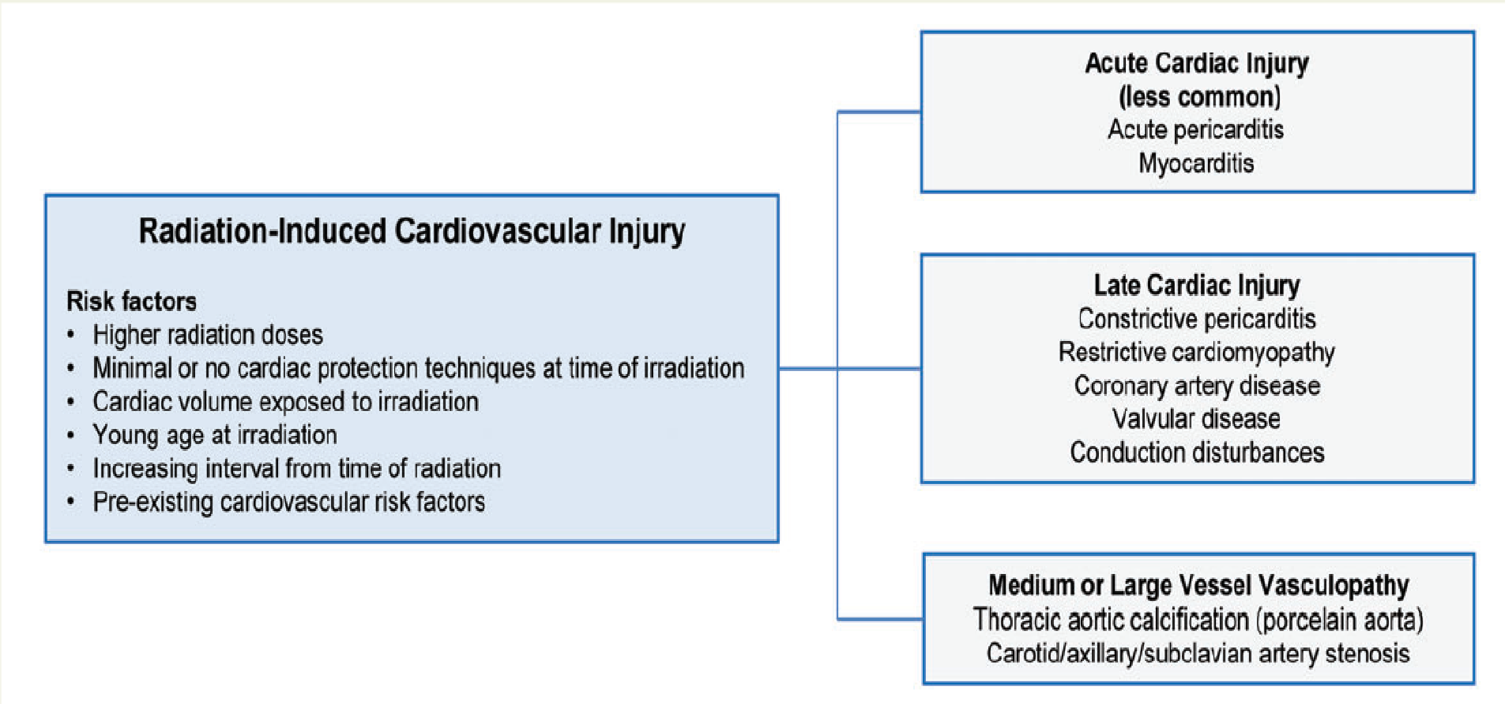


Figure 1 Classification of cardiovascular injury following radiation therapy.

Groarke JD. et al. Eur Heart J 2014; 35: 612-23.

[1]Cutter DJ et al. Tex Heart Inst J 2011;38:257-258
[2]Cohn KE et al. Medicine (Baltimore) 1967;46:281-298

Relative risk of RIHD in cancer survivors

	Hodgkin lymphoma: Relative risk	Breast cancer: Relative risk
Radiation induced heart disease	>6.3	2-5.9
IHD	4.2-6.7	1-2.3
Valve surgery	8.4-9.2	-
PPM	1.9	-
CHF	4.9	-
Cardiac death	2.2-12.7	0.9-2.0

Lancellotti et al. J Am Soc Echocar 2013; 26:1013-32
Ng A. BJH 2011; 154:23-31

Table 2 Risk factors of radiation-induced heart disease

Anterior or left chest irradiation location
High cumulative dose of radiation (>30 Gy)
Younger patients (<50 years)
High dose of radiation fractions (>2 Gy/day)
Presence and extent of tumour in or next to the heart
Lack of shielding
Concomitant chemotherapy (the anthracyclines considerably increase the risk)
Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight, ≥moderate hypertension, hypercholesterolaemia)
Pre-existing cardiovascular disease

High-risk patients definition: anterior or left-side chest irradiation with ≥1 risk factors for RIHD.

Lancellotti et al. J Am Soc Echocar 2013; 26:1013-32

The NEW ENGLAND JOURNAL of MEDICINE

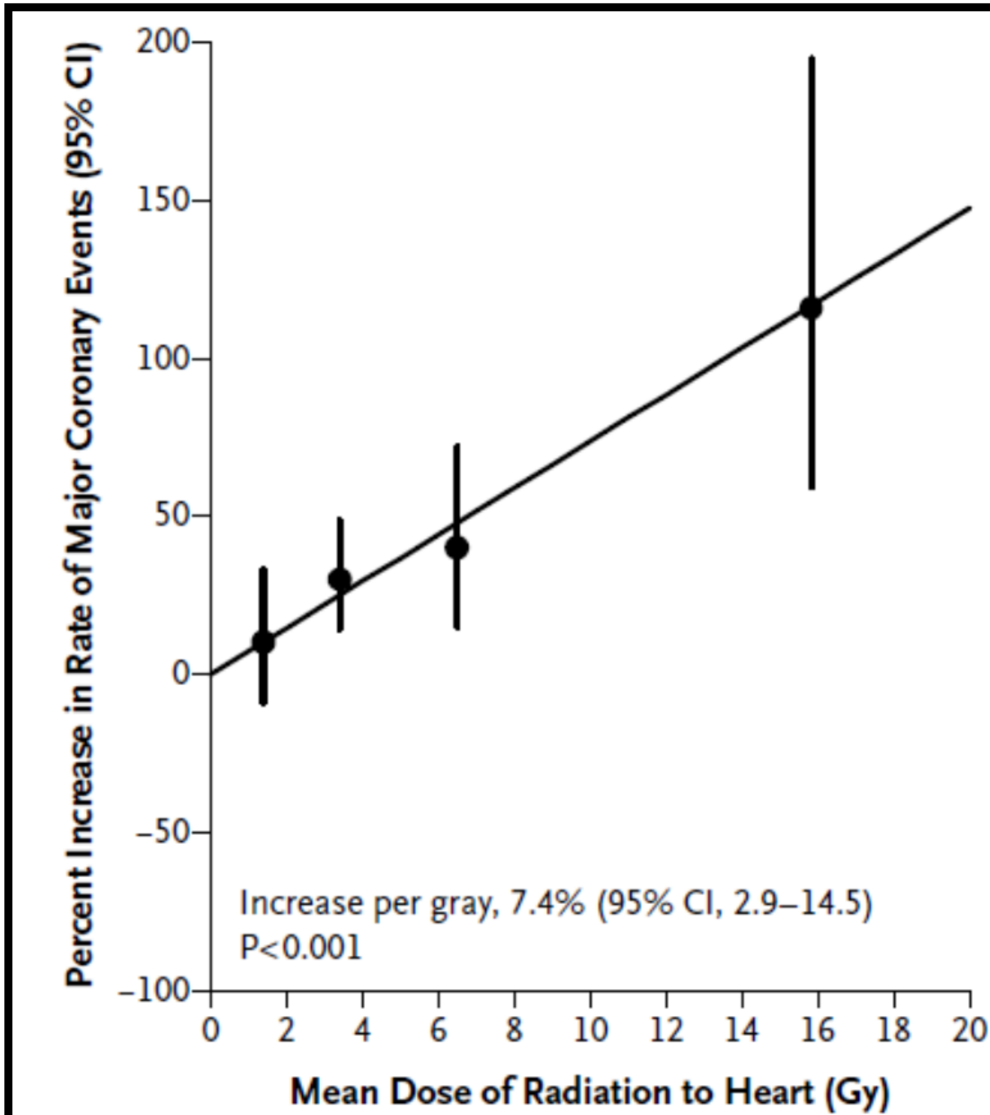
ESTABLISHED IN 1812 | MARCH 14, 2013 | VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

- 2168 women in Denmark and Sweden treated with RT between 1958-2001
  - 963 women with major coronary events (MI, revascularization, death from IHD)
- Mean dose to whole heart= 4.9 Gy (0.03-27.72)

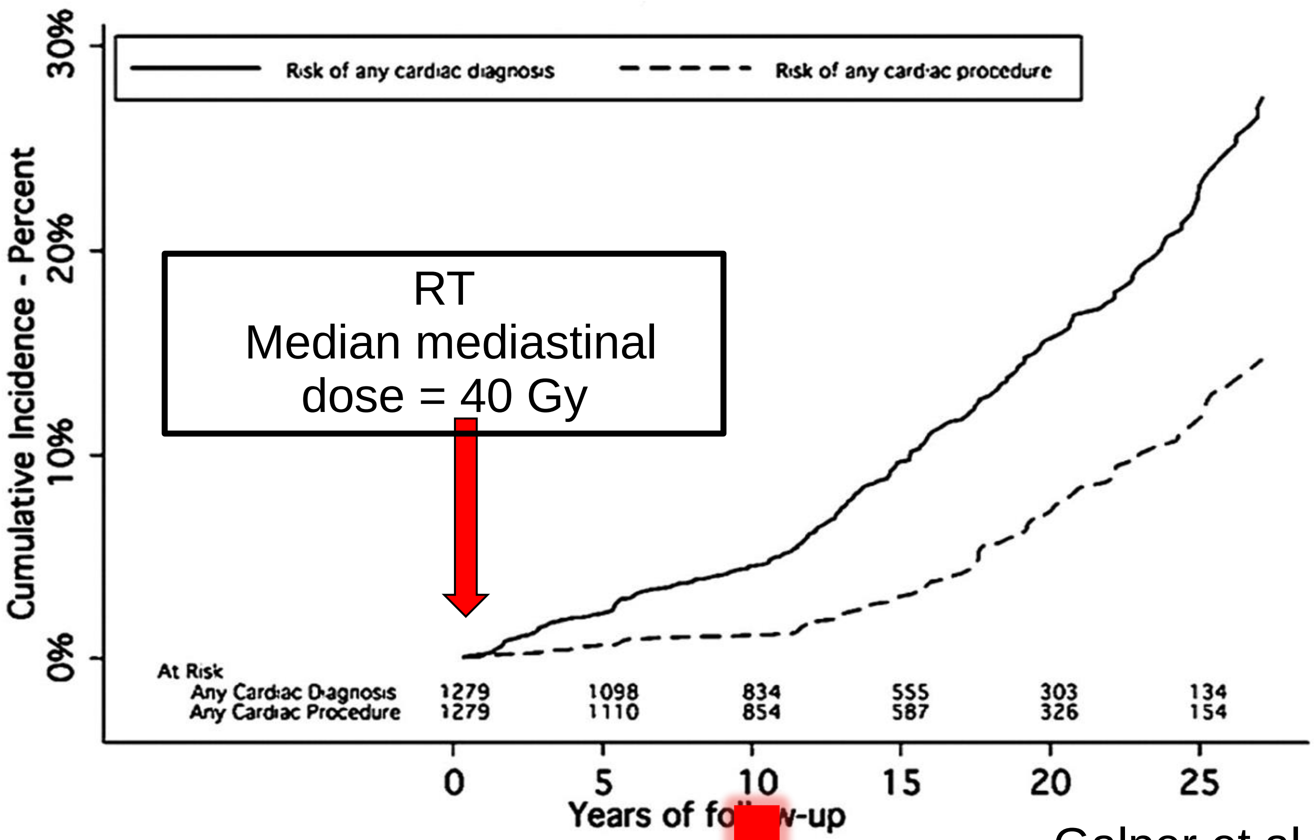
- Risk increases linearly with mean dose to heart
- Rate of major coronary events increases by 7.4% per Gy
- No apparent threshold below which there is no risk



**Major coronary event defined as MI, revascularization, or death from IHD

Darby et al. NEJM 2013;368:987-98

Cumulative incidence of cardiac diagnoses and cardiac procedures among 1279 HL patients treated from 1969-1989.



Galper et al. Blood 2011;117:412-8

National Comprehensive Cancer Network Clinical Guidelines endorse stress testing at 10 year intervals after treatment is completed in survivors of HL

{http://www.nccn.org/professional/physician_gls/pdf/hodgkins.pdf}

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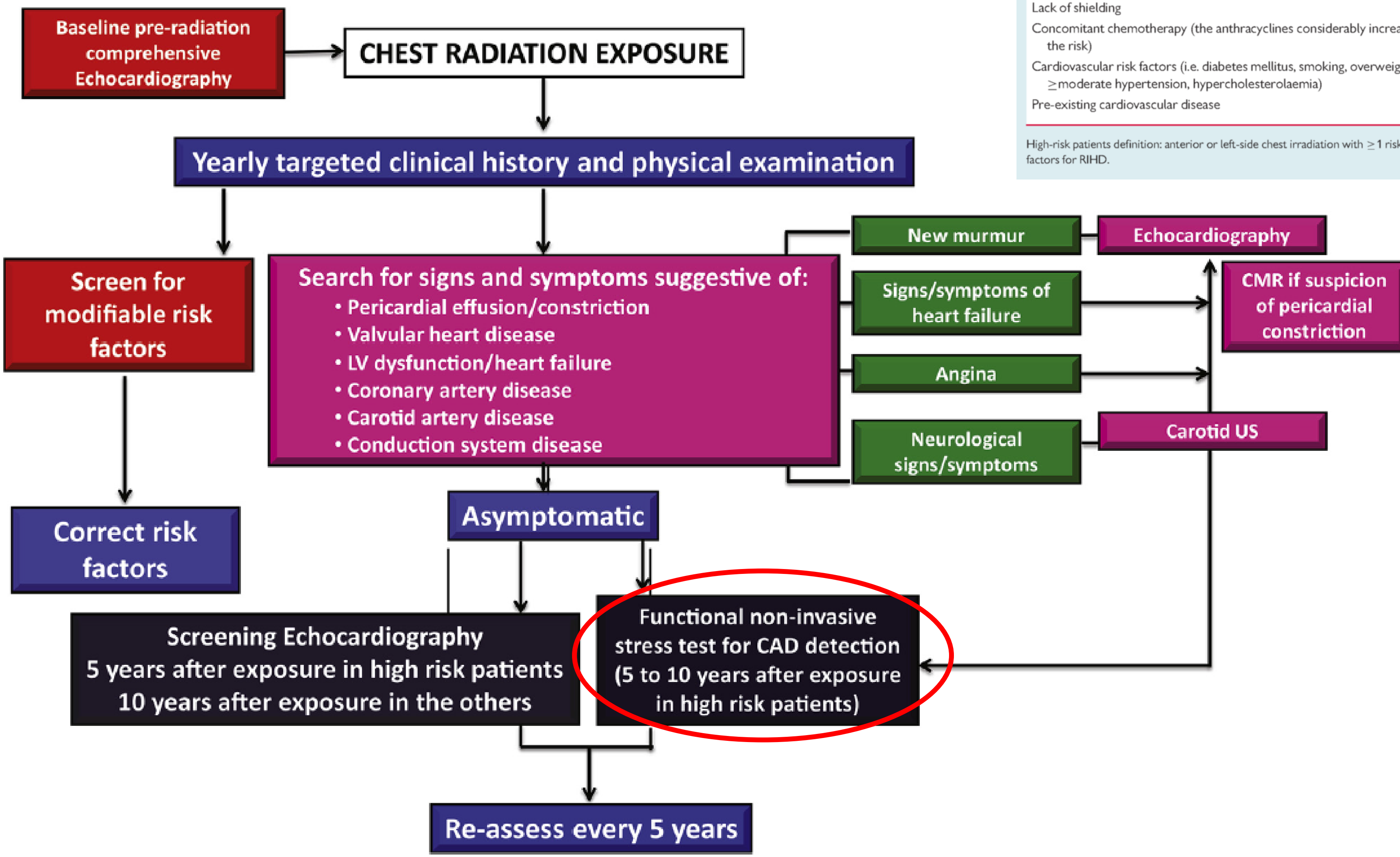

Lancellotti et al. J Am Soc Echocar 2013; 26:1013-32

Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (−2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

Darby et al. NEJM 2013;368:987-98

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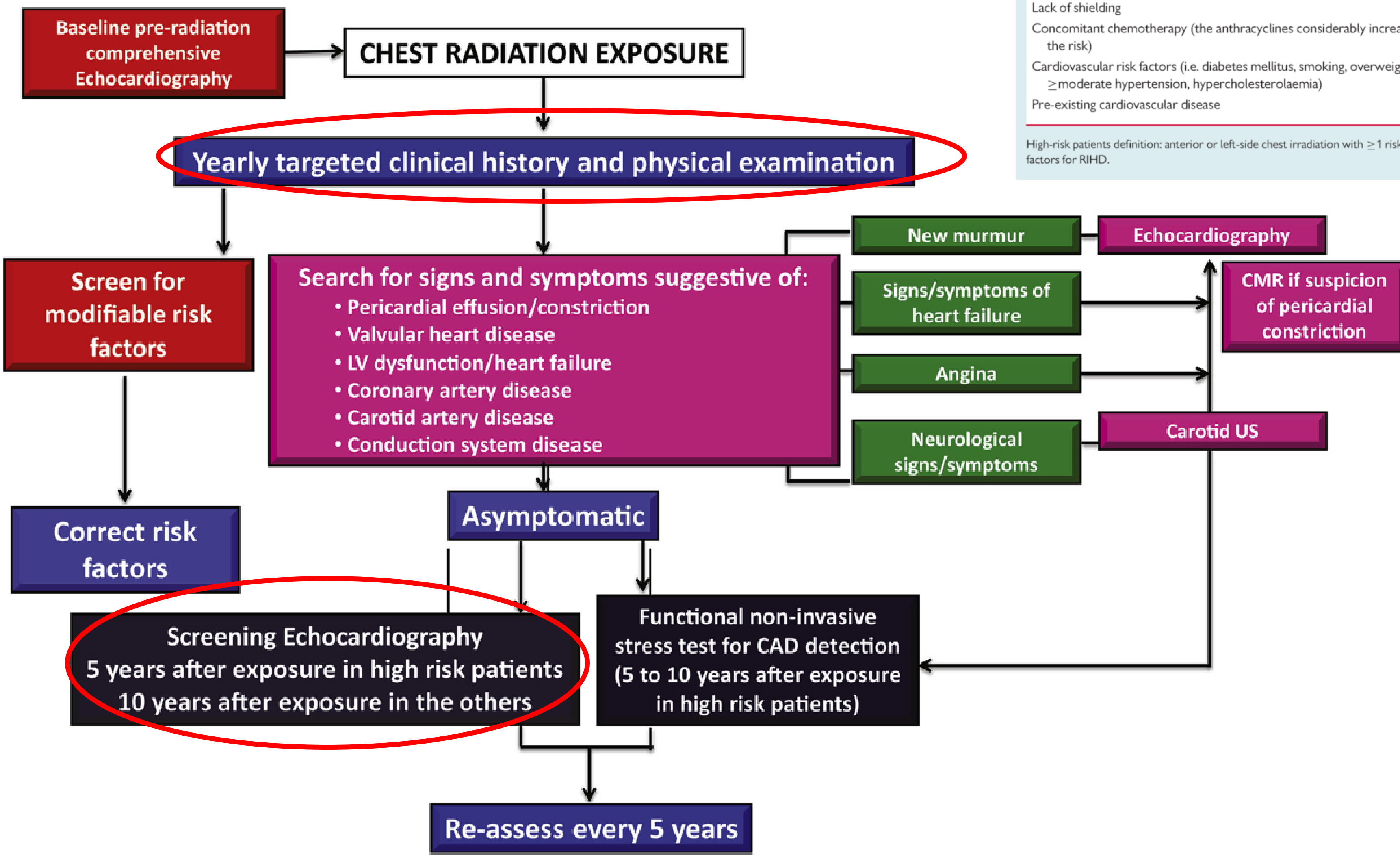


Lancellotti et al. J Am Soc Echocar 2013; 26:1013-32

European Heart Journal (2016) 37, 2768–2801
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

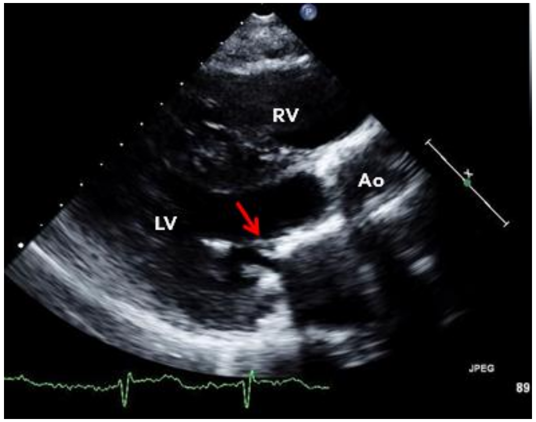
2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

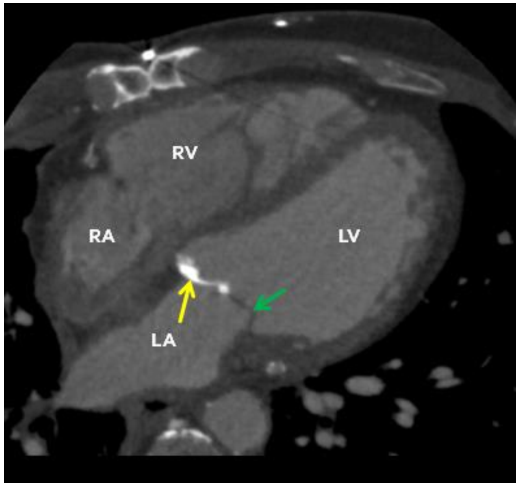
The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Echocardiography is the assessment method of choice, and 3D echocardiography may be useful, particularly for the evaluation of mitral valve commissures. Baseline and repeated echocardiography after radiation therapy involving the heart are recommended in patients with cancer for the diagnosis and follow-up of VHD.[80,85,95,148]

Echocardiographic features of radiation-induced valvular disease

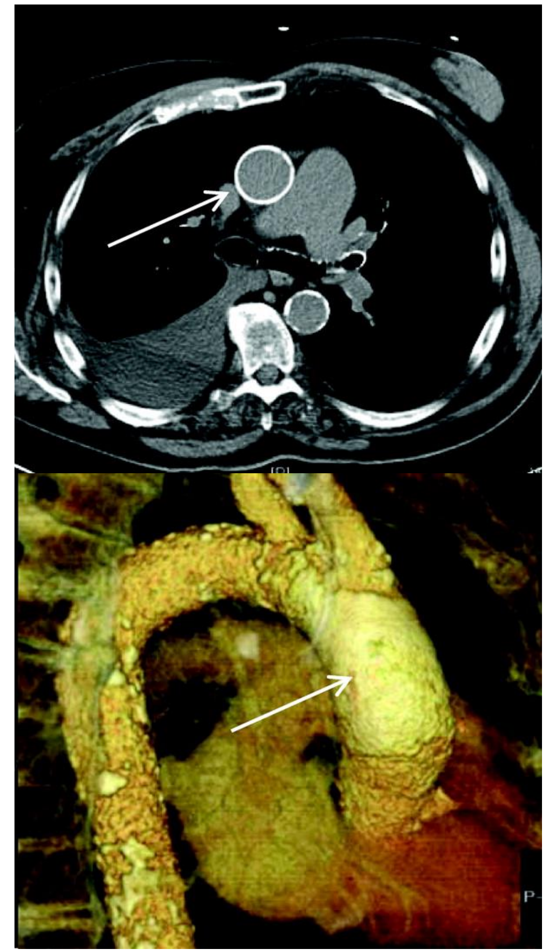
- Left sided valve disease is much more common than right sided valve disease
- Calcification of Ao root, AV annulus and leaflets, and aortic-mitral inter-valvular fibrosa
- Calcification of the MV annulus and leaflets with sparing of the valve tips and commissures





Cardiac surgery & RIHD

- Often multiple cardiac lesions
- Co-existing radiation induced pulmonary disease
- Co-existing vascular disease e.g. porcelain aorta
- Fibrosis of internal mammary artery
- ‘Hostile’ chest
- Tradition surgical risk scores do not consider prior RT and/or chemo: underestimate risk



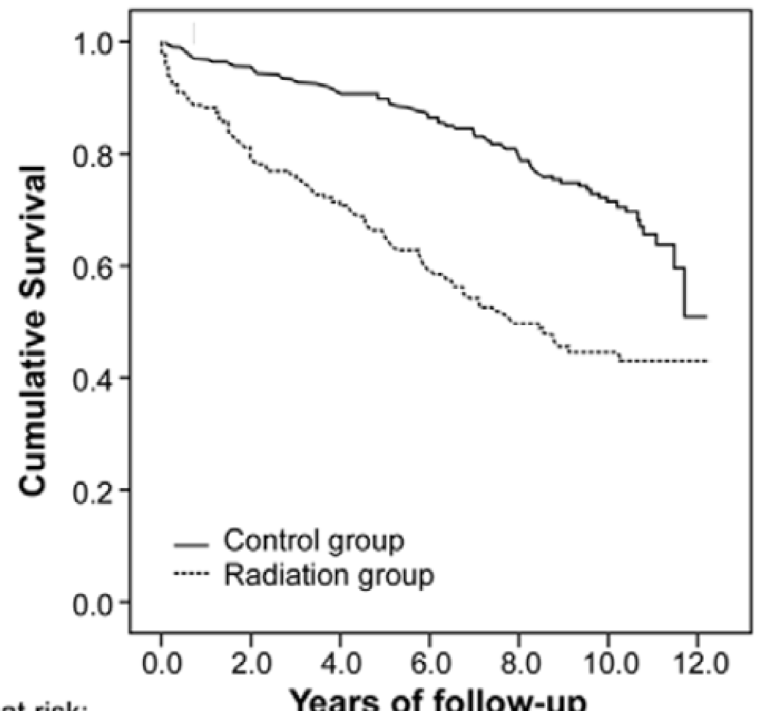
Source: Welt et al. Circ 2011;124:299-2948

Adverse outcomes following cardiac surgery in pts with RIHD

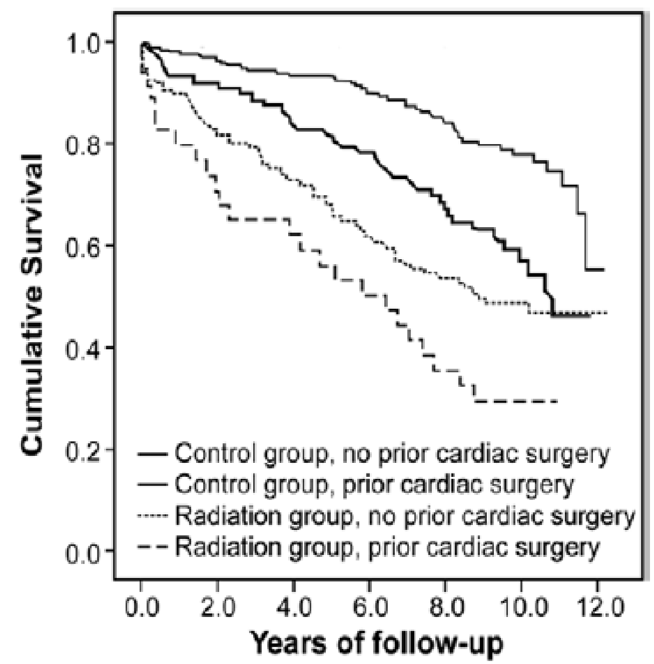
Variable	Radiation Heart Disease Group(n=173)	Comparison Group(n=305)	*P* Value
Age, y	63±14	63±14	0.9
Female sex, n (%)	130 (75)	226 (74)	0.5
Hypertension, n (%)	69 (40)	159 (52)	0.006
Diabetes mellitus, n (%)	27 (16)	74 (24)	0.07
Prior stroke, n (%)	18 (10)	24 (8)	0.2
Smoking history, n (%)	63 (36)	113 (37)	0.5
Proximal obstructive CAD, n (%)	78 (45)	117 (38)	0.09
Prior open heart surgery, n (%)	34 (20)	87 (29)	0.02
ICD, n (%)	8 (5)	3 (1)	0.01
EuroSCORE	7.8±3	7.4±3	0.12
Type of cardiothoracic surgery, n (%)			0.99
CABG	24 (14)	47 (15)	
CABG+1 valve	39 (23)	66 (22)	
CABG+≥ 2 valves	37 (21)	64 (21)	
1 Valve only	38 (22)	67 (23)	
≥ 2 Valves	28 (16)	47 (15)	
Other	7 (4)	13 (4)	
Bypass grafts, n	1.2±1.4	1.2±1.6	0.8

Wu et al. Circulation 2013;127:1476-1484

Variable	Radiation Heart Disease Group(n=173)	Comparison Group(n=305)	*P* value
Postoperative			
Perioperative length of stay, d	17±20	12±20	<0.001
Postoperative permanent atrial fibrillation, n (%)	28 (16)	12 (4)	<0.001
Postoperative permanent pacemaker, n (%)	18 (10)	14 (5)	0.02
Postoperative stroke, n (%)	1 (0.06)	5 (1.6)	0.3
Mortality within 30 d, n (%)	7 (4)	1 (0.3)	0.01



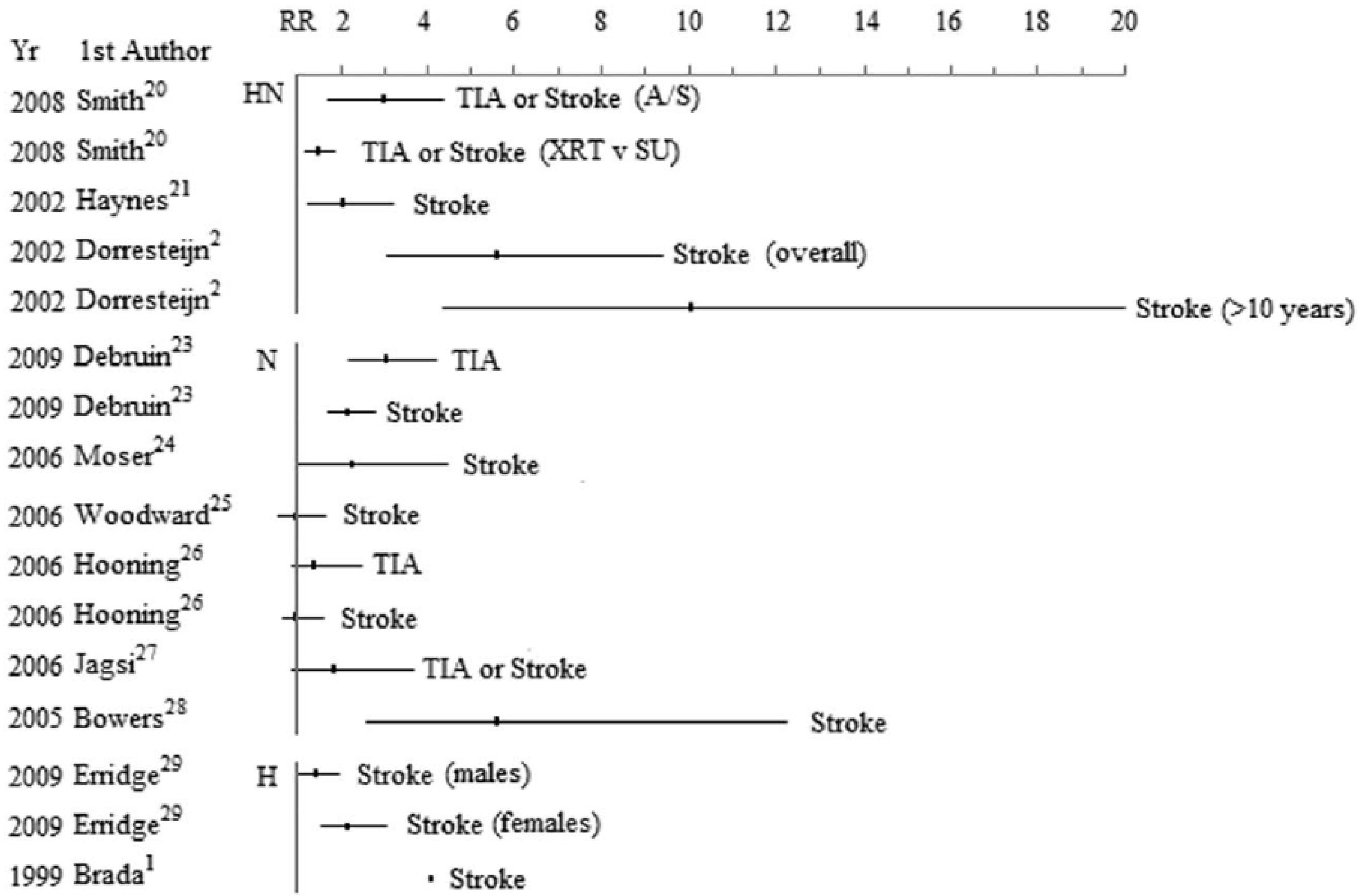
Number at risk:							
Control group	305	291	274	249	207	90	2
Radiation group	173	139	123	103	86	36	1



Number at risk:							
Control group, no prior cardiac surgery	218	211	201	183	153	66	2
Control group, prior cardiac surgery	87	80	73	66	54	24	0
Radiation group, no prior cardiac surgery	80	66	59	52	47	20	1
Radiation group, prior cardiac surgery	93	73	64	51	39	11	1

Radiation & Cerebrovascular disease

Relative risk of ischemic stroke and TIA



Plummer et al. Stroke 2011;42:2410-2418

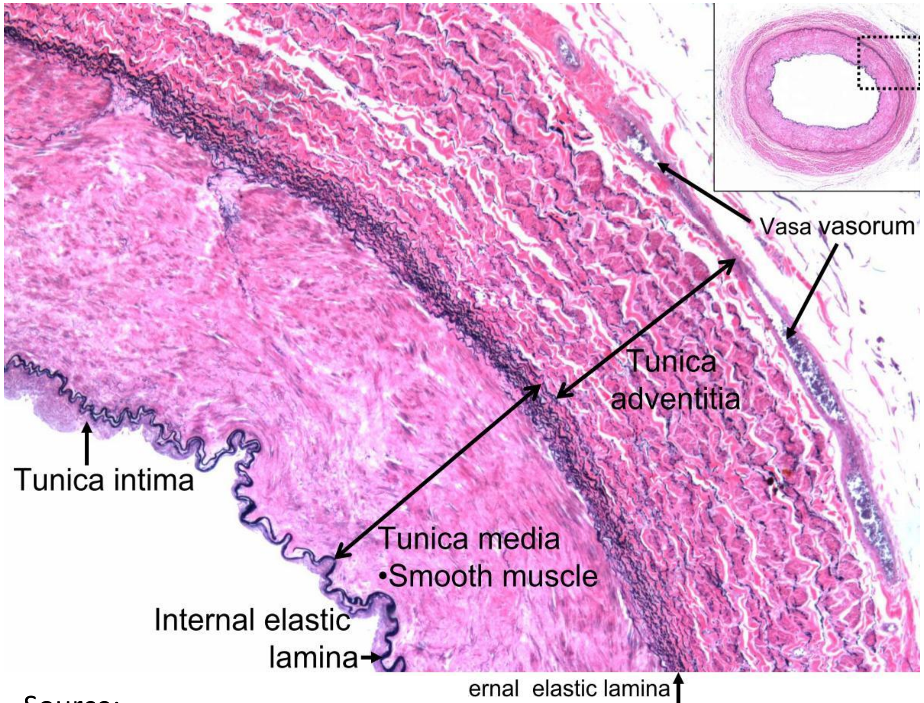
Radiation-induced carotid disease

- Increasing rates of hemodynamically significant stenosis with time from RT
- Often more extensive disease
- Involves longer segments of the carotid arteries
- More commonly involves the common carotid

Lancellotti et al. J Am Soc Echocar 2013; 26:1013-32
Yu et al. Stroke 2014;45:1402-1407

Pathogenesis of radiation-induced vasculopathy

- Likely a combination of:
  - A. Radiation injury to the vasa vasorum (→ ischemia of the vessel wall)
  - B. Radiation injury to intima-media (endothelium) →Accelerated form of atherosclerosis



Source: http://anatomy.kmu.edu.tw

European Heart Journal (2016) 37, 2768–2801
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Patients irradiated for head and neck cancer or lymphoma should undergo cerebrovascular ultrasound screening, especially beyond 5 years after irradiation. Duplex imaging may be considered at least every 5 years, or earlier and/or more frequently if the results of the first examination are abnormal. Other locations of post-radiation arterial lesions are usually discovered by clinical examination or when symptomatic.

Management of radiation induced carotid disease

- Radiation vasculopathy not addressed in current guidelines
- Effect of medical rx in limiting disease progression unclear
- Revascularization: Carotid endarterectomy versus (CEA) OR carotid angioplasty and stenting (CAS)?

CEA challenges associated with radiation-induced carotid disease

- Arterial wall fibrosis
- Tissue plane scarring
- Prosthetic infection
- Anastomotic dehiscence
- Surgically inaccessible proximal lesions
- Increased risk of wound complications
- Increased risk of restenosis

Yu et al. Stroke 2014;45:1402-1407

CEA versus CAS for radiation-induced carotid stenosis:

	Carotid artery angioplasty and stenting (n=361)	Carotid endarterectomy (n=172)	P value
Periop cerebrovascular events	3.9% (95% CI, 2.3-6.7%)	3.5% (95% CI, 1.5-8.0%)	0.77
Late (>30 days) cerebrovascular events	4.9/100 person-years (95% CI, 3.6-6.6)	2.8/100 person-years (95% CI, 2.0-3.9)	**0.014**
Cranial nerve injury	0%	9.2% (95% CI, 3.7-21.1%), mostly transient	**Significant**
Restenosis > 50%	5.4/100 person years (95% CI, 4.3-6.6)	2.8/100 person-years (95% CI, 1.9-4.0)	**0.003**

Fokkema et al. Stroke 2012;43:793-801

Carotid angioplasty/stenting in XRT-induced versus other carotid stenosis

	Radiation-induced carotid stenosis (n=65)	Atheroscelerotic carotid stenosis (n=129)	P value
Periprocedural stroke/death	1.5%	1.6%	1.00
Annual risk of stroke	1.2%	1.2%	0.89
Technical success	100%	100%	1.00
Instent restenosis	25.7%	4.2%	<0.001
Symptomatic instent restenosis	6.8%	0.8%	0.03

Yu et al. Stroke 2014;45:1402-1407

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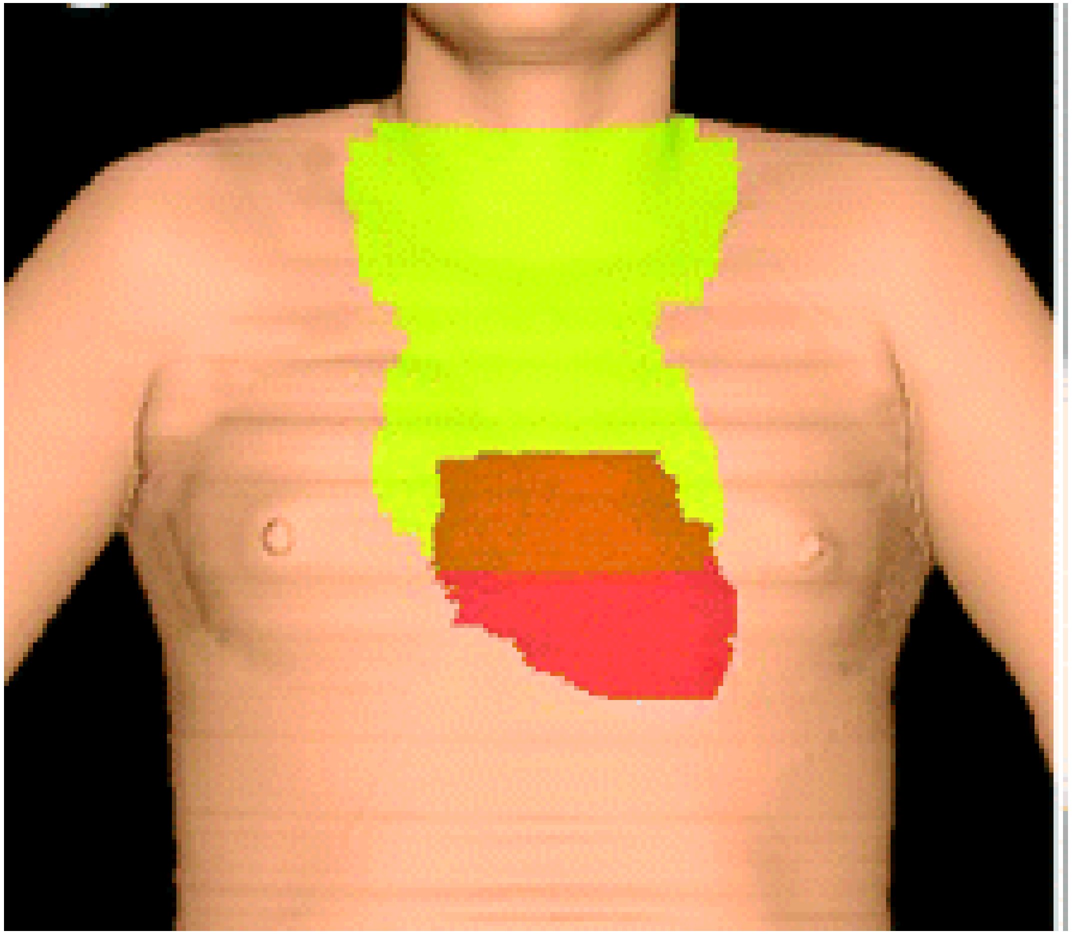
Stringent risk factor management is required to halt plaque progression. Antiplatelet therapy may be considered. Significant stenosis (e.g. carotid arteries) may require stenting or surgery.[201,202]

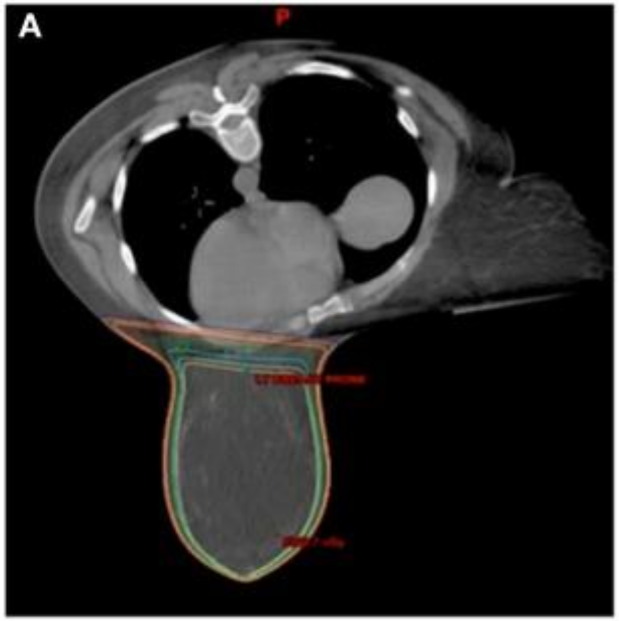
Changes in radiation field over time for HL

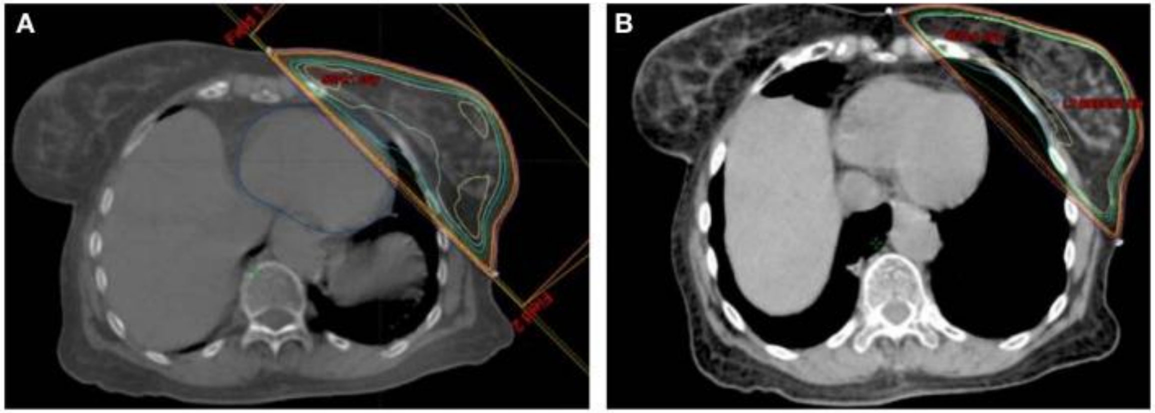


Hodgson DC Hematology 2011:323-329

Techniques to reduce cardiac exposure in RT for breast cancer

- CT assisted planning
- Prone position
- Deep inspiratory breath hold technique
- Intensity modulated radiation therapy
- Accelerated partial breast irradiation





Beck et al. Front Oncol 2014;4:327

Take home points regarding XRT

- Radiation-induced CV injury can manifest in many ways: CAD, valve disease, carotid disease, and PAD.
- Risk factors recognized
- Risk α mean radiation dose to heart
- Contemporary RT protocols refined to reduce radiation dose to heart…but risk not eliminated
- Annual history and exam
- Periodic ECG, functional stress testing, echo, US carotids
- Extra care with modifiable CV risk factors
- Educate patients regarding risk
- Cardiac surgery for RIHD is associated with increased risk

CANCER SURVIVORS:
* SURVIVORS OF CHILDHOOD CANCERS
* SURVIVORS OF ADULT CANCERS

Survivors of Childhood Cancers

- Current 5-year survival rates approach 80% → growing population of survivors
- Cardiac-specific disease is the most common non-cancer cause of death
- Compared with general population, childhood cancer survivors are at a:
  - 15-fold increased risk of developing CHF
  - 7-fold higher risk of premature cardiac death

Armenian et al. Lancet Oncol 2015;16:e123-e136
Lipshultz et al. Circulation 2013;128:1927-1995
Armstrong et al. J Clin Oncol 2009;27:2328-2338
Oeffinger et al. N Engl J Med 2006;355:1572-82

Cardiometabolic risk factors among adult survivors of childhood cancers

- Higher than expected frequency of obesity (especially women treated with cranial radiation as girls)
- Excessive adiposity and ↓ lean body mass (check waist circumference, not just BMI)
- Metabolic syndrome-type lipid abnormalities (Low HDL and high triglycerides) even without obesity (lipid panel every 2 years)
- Radiation exposure to hypothalamic-pituitary axis → late onset deficiency of GH → obesity, insulin resistance, and T2DM (screen for altered glucose metabolism every 3 years)
- Predisposition to HTN (monitor BP regularly)

Lipshultz et al. AHA Scientific Statement. Circulation 2013;128:1927-1995

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2006;355:1572-82.

SPECIAL ARTICLE

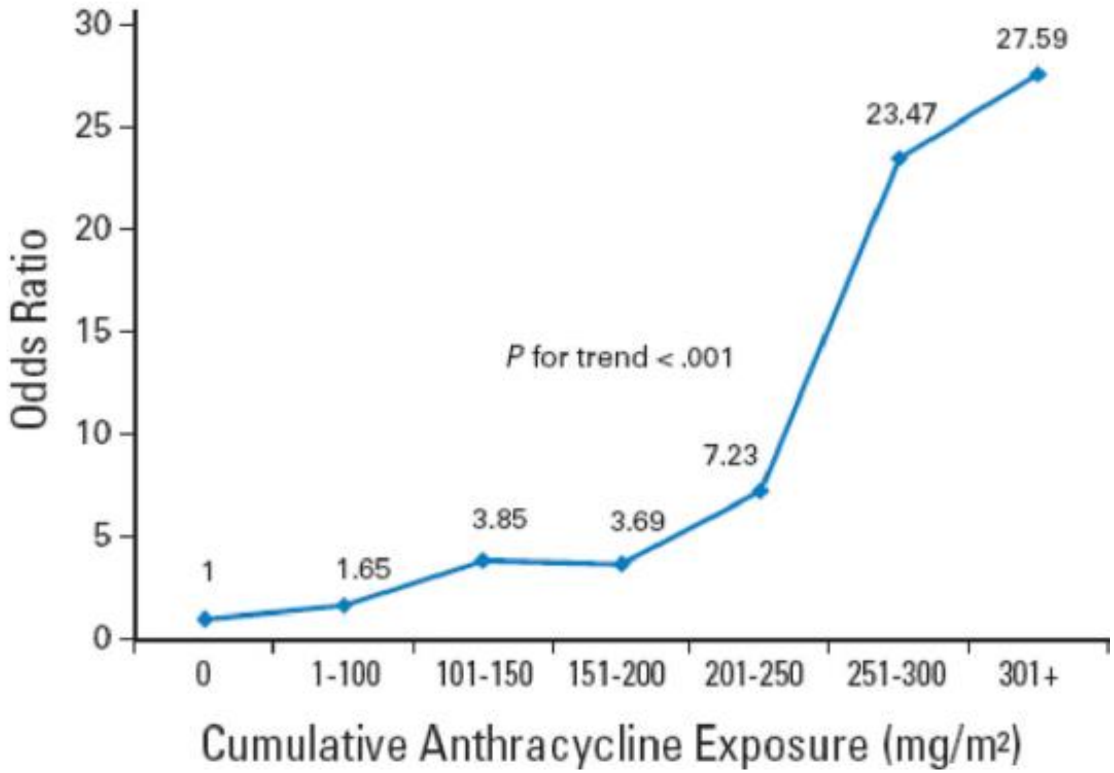
Chronic Health Conditions in Adult Survivors of Childhood Cancer

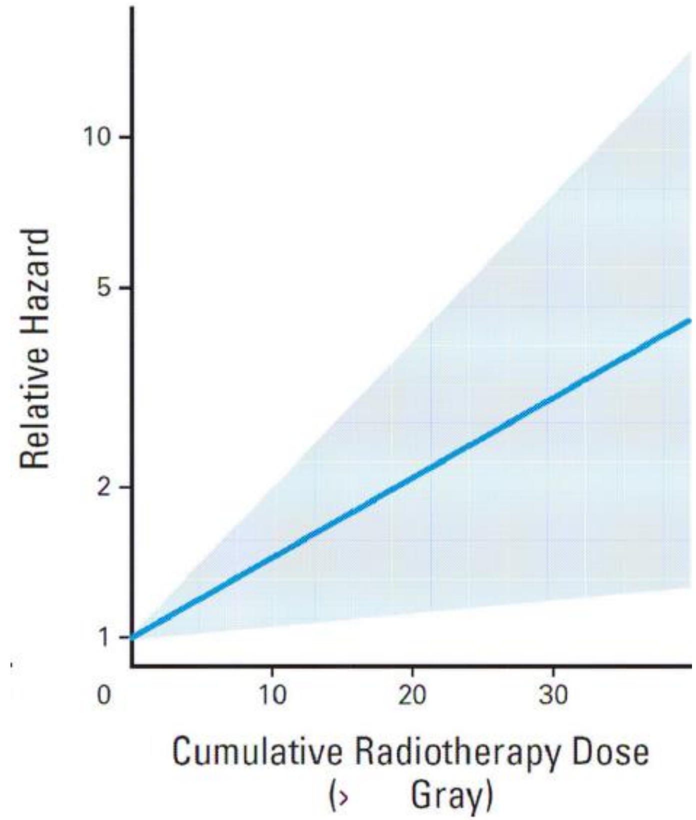
Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D., Toana Kawashima, M.S., Melissa M. Hudson, M.D., Anna T. Meadows, M.D., Debra L. Friedman, M.D., Neyssa Marina, M.D., Wendy Hobbie, C.P.N.P., Nina S. Kadan-Lottick, M.D., Cindy L. Schwartz, M.D., Wendy Leisenring, Sc.D., and Leslie L. Robison, Ph.D., for the Childhood Cancer Survivor Study*

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

Condition	Survivors (N=10,397)	Siblings (N=3034)	Relative Risk (95% CI)
	percent		
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1–25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)

Dose-response relationship for cardiomyopathy





Armenian et al. Lancet Oncol 2015;16:e123-e136

Lancet Oncol. 2015 March ; 16(3): e123–e136. doi:10.1016/S1470-2045(14)70409-7.

Recommendations for Cardiomyopathy Surveillance for Survivors of Childhood Cancer: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Saro H. Armenian[1], Melissa M. Hudson[2], Renee L. Mulder[3], Ming Hui Chen[4], Louis S. Constine[5], Mary Dwyer[6], Paul C. Nathan[7], Wim J.E. Tissing[8], Sadhna Shankar[9], Elske Sieswerda[3], Rod Skinner[10], Julia Steinberger[11], Elvira C. van Dalen[3], Helena van der Pal[12], W. Hamish Wallace[13], Gill Levitt[14], and Leontien C.M. Kremer[3]

Cardiomyopathy risk group definitions.

Risk Group	Anthracycline dose (mg/m^2)	Chest radiation dose (Gy)	Anthracycline (mg/m^2) + Chest radiation (Gy)
High	≥ 250	≥ 35	≥ 100 (Anthracycline) + ≥ 15 (Radiation)
Moderate	100 to < 250	≥ 15 to < 35	--
Low	< 100	--	--

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High	≥ 250	≥ 35	≥ 100 (Anthracycline) + ≥ 15 (Radiation)
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Low	< 100	--	--

- CMP surveillance **is recommended** for ***high risk survivors*** to begin no later than 2 years after rx, repeated at 5 years, and continued every 5 years thereafter
- CMP surveillance **is reasonable** for ***moderate/low risk survivors*** over same time frame

Ann Intern Med. 2014 May 20; 160(10): 672–683. doi:10.7326/M13-2498.

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

F. Lennie Wong, PhD[1], **Smita Bhatia, MD, MPH**[1], **Wendy Landier, PhD, RN**[1], **Liton Francisco, BS**[1], **Wendy Leisenring, ScD**[2], **Melissa M. Hudson, MD**[3], **Gregory T. Armstrong, MD**[3], **Ann Mertens, PhD**[4], **Marilyn Stovall, PhD**[5], **Leslie L. Robison, PhD**[3], **Gary H. Lyman, MD, MPH**[2], **Steven E. Lipshultz, MD**[6], and **Saro H. Armenian, DO, MPH**[1]

Ann Intern Med. 2014 May 20; 160(10): 661–671. doi:10.7326/M13-2266.

Routine echocardiography screening for left-ventricular dysfunction in childhood cancer survivors: a model-based estimation of the clinical and economic impacts

Jennifer M. Yeh, PhD[1], **Anju Nohria, MD**[2], and **Lisa Diller, MD**[3]

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD; Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

(*Circulation*. 2015;131:1981-1988. DOI: 10.1161/

- Prospective LVEF assessment at baseline, every 3 months during Rx and for the following year, and then every 6 months for the following 4 years in 2625 pts receiving anthracyclines
- Overall incidence of cardiotoxicity (LVEF decrease > 10 percentage points from baseline and < 50%) = 9%
- Median interval from end of chemo to cardiotox= 3.5 months
- 98% of cases occurred in the first year

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

Criteria for INCREASED RISK in survivors of adult cancers:

- Treatment that includes any of the following:
  - High-dose anthracycline (eg, doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2)
  - High-dose radiotherapy (RT; ≥ 30 Gy) where the heart is in the treatment field
  - Lower-dose anthracycline (eg, doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) in combination with lower-dose RT (< 30 Gy) where the heart is in the treatment field
- Treatment with lower-dose anthracycline (eg, doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age (≥ 60 years) at cancer treatment
  - Compromised cardiac function (eg, borderline low left ventricular ejection fraction [50% to 55%], history of myocardial infarction, ≥ moderate valvular heart disease) at any time before or during treatment
- Treatment with lower-dose anthracycline (eg, doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) followed by trastuzumab (sequential therapy)

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

What to do AFTER completion of cancer treatment?:

Recommendation 5.2. An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction. (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.3. Patients identified to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist or a health care provider with cardio-oncology expertise for further assessment and management.
(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.4. No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month post-treatment echocardiogram.
(Informal consensus; relative balance of benefits and harms; Evidence quality: insufficient)

Recommendation 5.5. Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care.
(Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Impaired exercise capacity

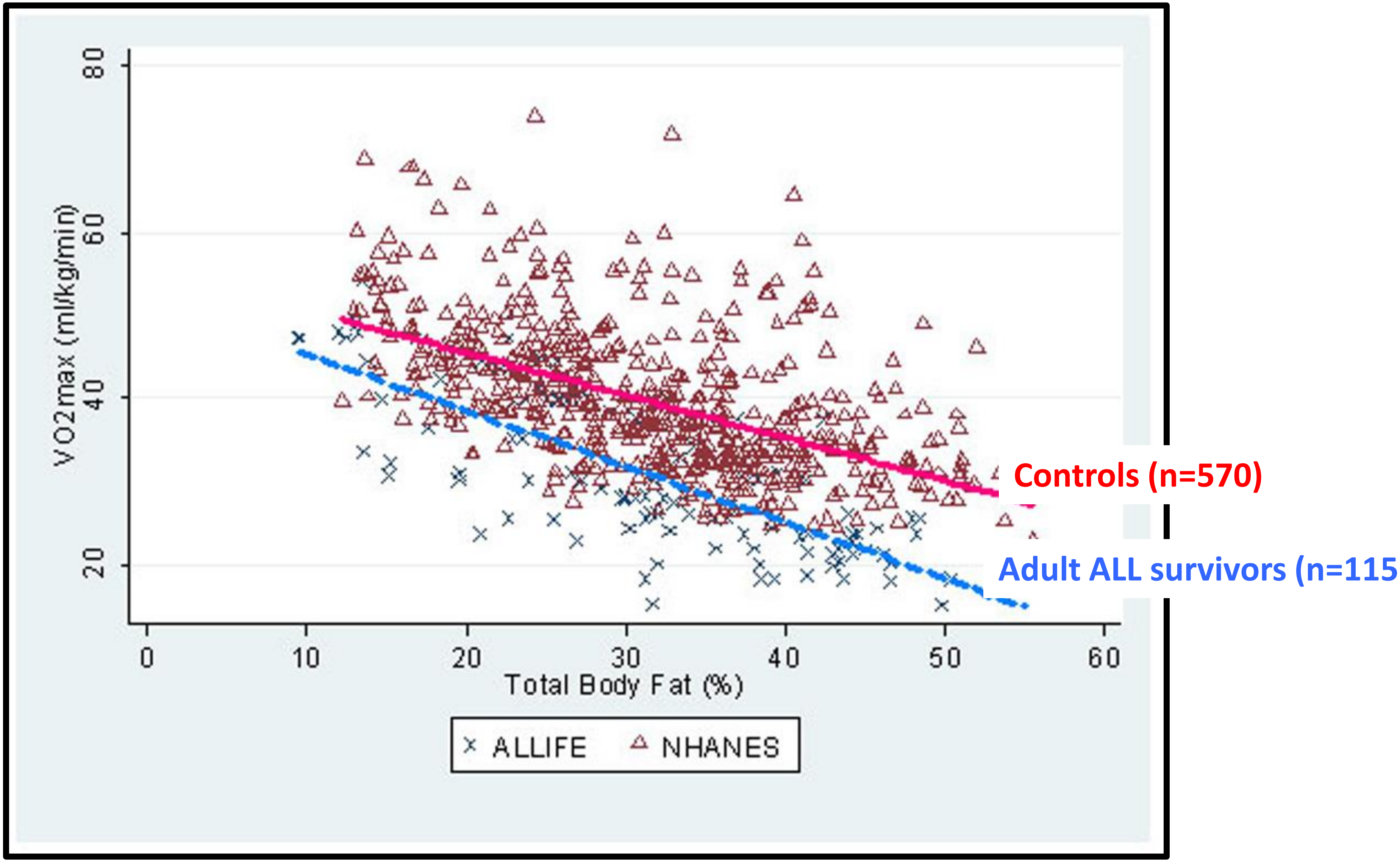
- Exercise capacity is below age and sex norms in as many as 31% of long term pediatric cancer survivors.

Pediatr Blood Cancer 2013;60:1358–1364

Reduced Cardiorespiratory Fitness in Adult Survivors of Childhood Acute Lymphoblastic Leukemia

Emily S. Tonorezos, MD, MPH,[1] Peter G. Snell, PhD,[2] Chaya S. Moskowitz, PhD,[1] Debra A. Eshelman-Kent, CPNP,[3] Jennifer E. Liu, MD,[1] Joanne F. Chou, MPH,[1] Stephanie M. Smith, MPH,[4] Andrea L. Dunn, PhD,[5] Timothy S. Church, MD, PhD,[6] and Kevin C. Oeffinger, MD[1*]

- Adult survivors of ALL are at increased CV risk
- Peak VO2 was measured in 115 ALL survivors (median age 23.5 years; range 18-37)
- Compared to age, gender, race/ethnicity controls from the 2003-2004 NHANES cohort



For any given percent body fat, ALL survivors had an 8.9 ml/kg/min lower VO2 max than non-cancer controls

Impaired exercise capacity

- Exercise capacity is below age and sex norms in as many as 31% of long term pediatric cancer survivors.
- Among survivors of adult cancers, impaired exercise capacity is prevalent:
  - "I can't go as far as I used to"
  - "I tire easily"
  - "I can't keep up with my husband anymore"

VOLUME 30 · NUMBER 20 · JULY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

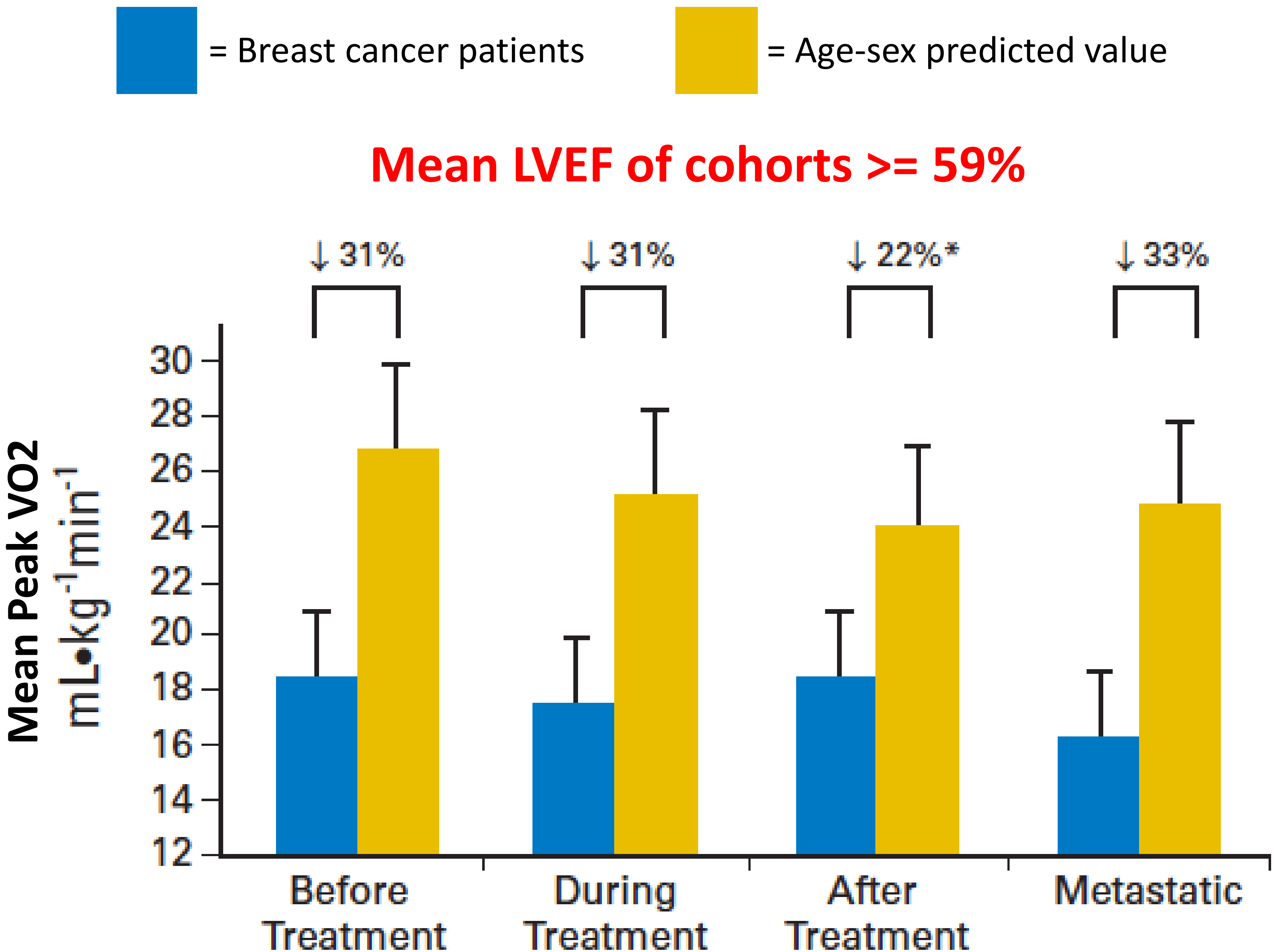
ORIGINAL REPORT

Cardiopulmonary Function and Age-Related Decline Across the Breast Cancer Survivorship Continuum

Lee W. Jones, Kerry S. Courneya, John R. Mackey, Hyman B. Muss, Edith N. Pituskin, Jessica M. Scott, Whitney E. Hornsby, April D. Coan, James E. Herndon II, Pamela S. Douglas, and Mark Haykowsky

- Evaluated cardiopulmonary function across the breast cancer continuum:
  - Before adjuvant therapy for nonmetastatic disease (n= 20)
  - During adjuvant therapy for nonmetastatic disease (n=46)
  - After adjuvant therapy for nonmetastatic disease (n=130)
  - During therapy for metastatic disease (n=52)

Mean LVEF of cohorts >= 59%



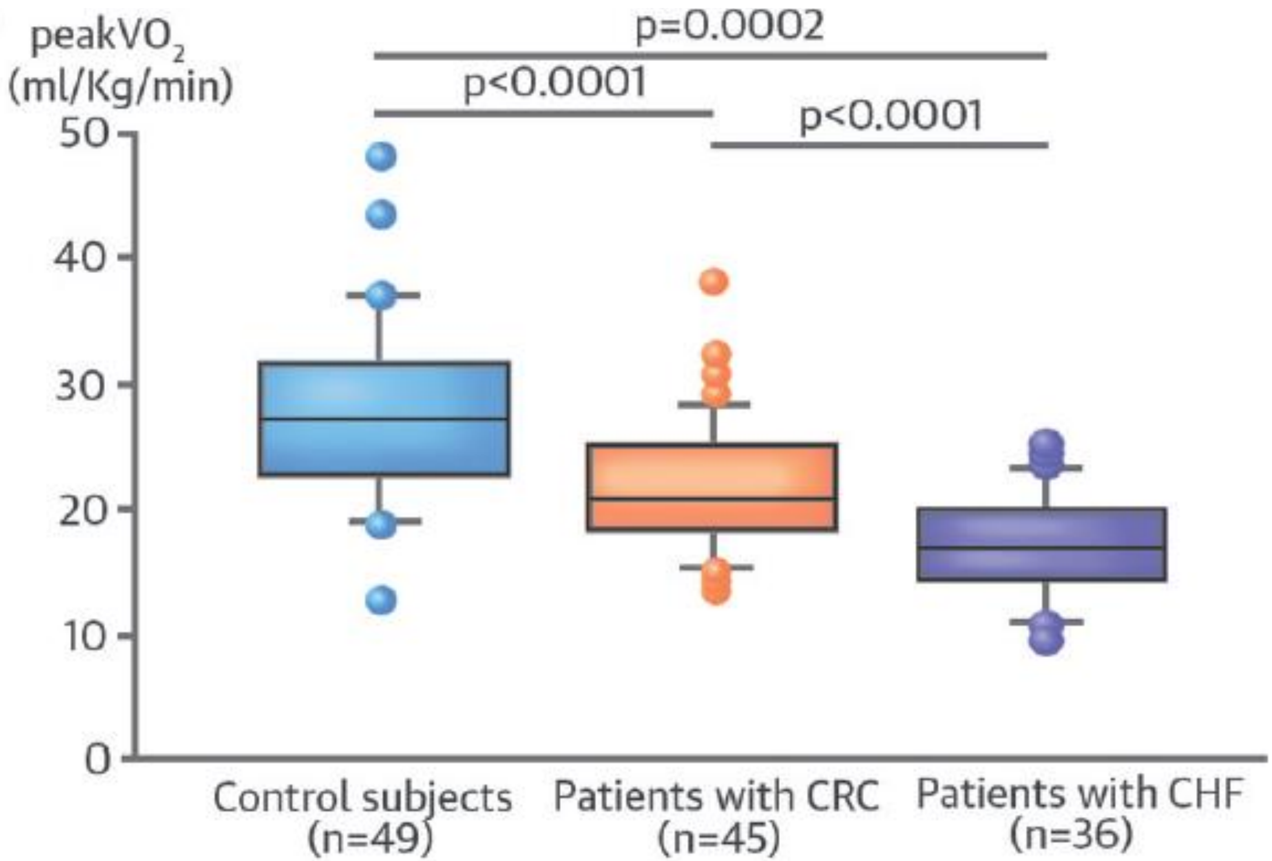
Jones LW, et al. J Clin Oncol 2012;30:2530-2537

Cardiovascular Function and Predictors of Exercise Capacity in Patients With Colorectal Cancer

Larissa Cramer,* Bert Hildebrandt, MD,† Thomas Kung,* Kristin Wichmann,* Jochen Springer, PhD,‡§
Wolfram Doehner, MD, PhD,*|| Anja Sandek, MD,* Miroslava Valentova,‡¶ Tatjana Stojakovic, MD,#
Hubert Scharnagl, PhD,# Hanno Riess, MD,† Stefan D. Anker, MD, PhD,*‡ Stephan von Haehling, MD, PhD*§

JACC 2014; 64:1310-9

- **Hypothesis:** similar patterns of cardiovascular pertubations are present in CRC and CHF
- **Methods:** Prospectively studied 3 groups:
  - CRC group (n= 50; 26 received chemo and 24 were chemo naïve)
  - CHF group (n= 51)
  - Control group (n=51)



Exercise capacity in colorectal cancer pts is severely impaired compared with age-matched controls (mean peak VO2 23% below controls)

Peak VO2 was only ~17% higher than that of HF pts

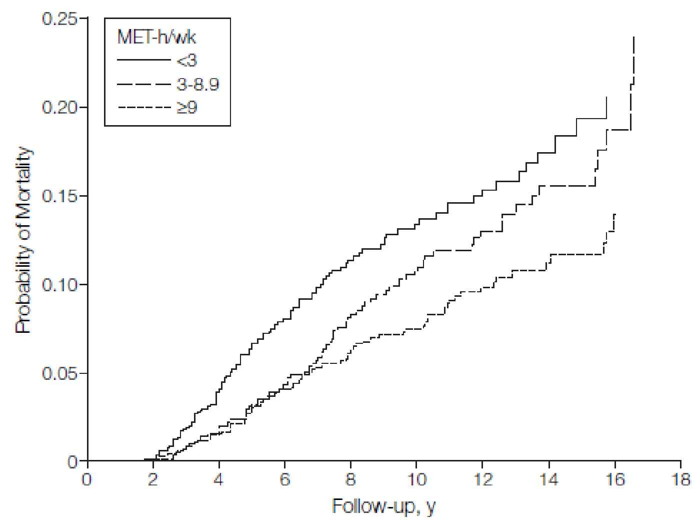
Independent of chemotherapy

Cramer et al. JACC 2014; 64:1310-9

Exercise capacity & prognosis

Table 2. Age-Adjusted and Multivariable-Adjusted Relative Risks According to Physical Activity Category After Breast Cancer Diagnosis

		Physical Activity After Diagnosis, MET-h/wk					
	Total (N = 2987)	**<3 (n = 959)**	**3-8.9 (n = 862)**	**9-14.9 (n = 335)**	**15-23.9 (n = 428)**	**≥24 (n = 403)**	***P* for Trend**
Total deaths	463	188	126	38	51	60	
Age-adjusted RR (95% CI)		1.00	0.69 (0.55-0.87)	0.53 (0.37-0.75)	0.56 (0.41-0.77)	0.67 (0.50-0.90)	.004
Multivariable-adjusted RR (95% CI)*		1.00	0.71 (0.56-0.89)	0.59 (0.41-0.84)	0.56 (0.41-0.77)	0.65 (0.48-0.88)	.003



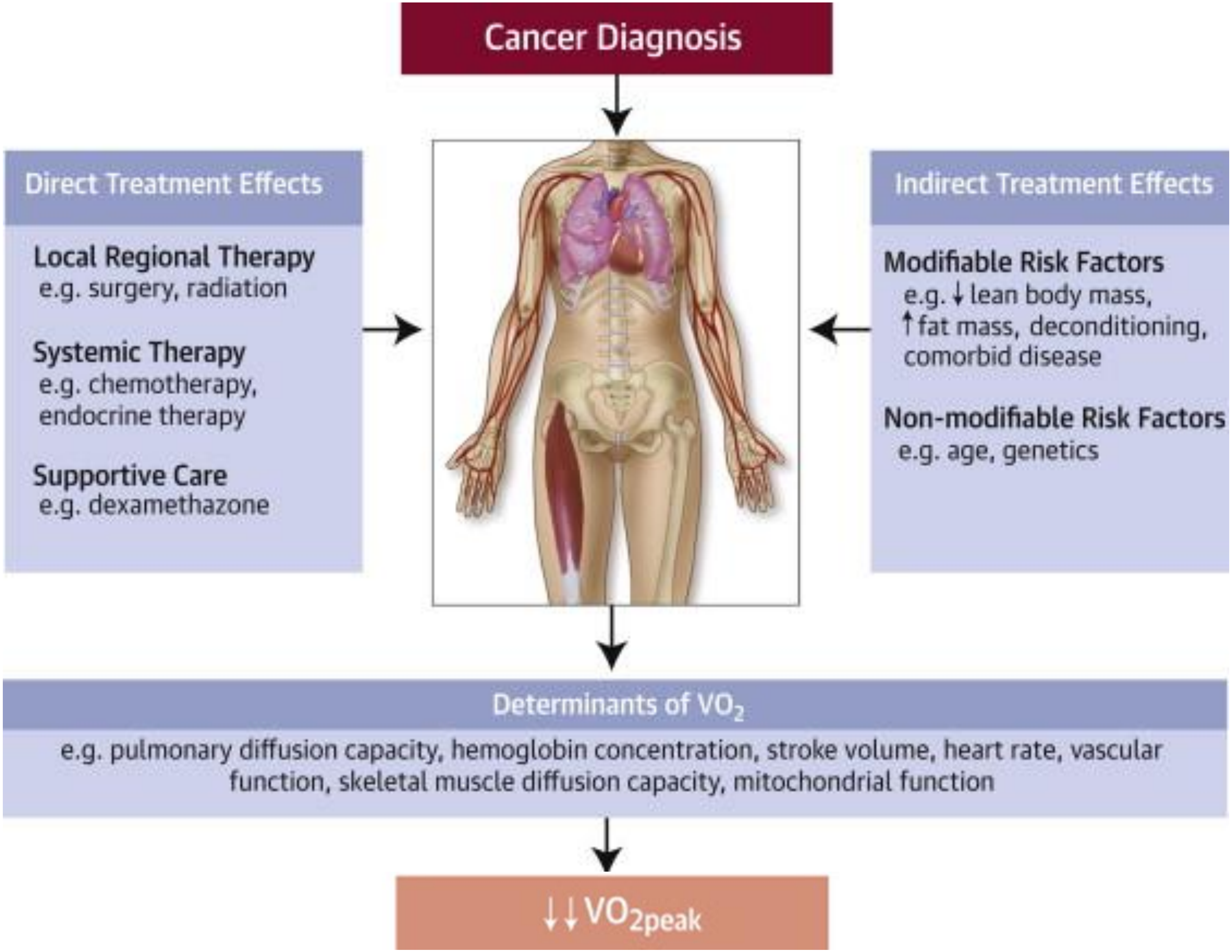
No. at Risk

Physical Activity, MET-h/wk									
<3	959	957	809	573	407	286	222	83	43
3-8.9	862	862	767	569	489	372	184	84	31
≥9	1166	1166	1066	773	692	449	290	164	86

Holmes et al. JAMA 2005;293:2479-2486

Impaired Exercise Capacity in Cancer Patients

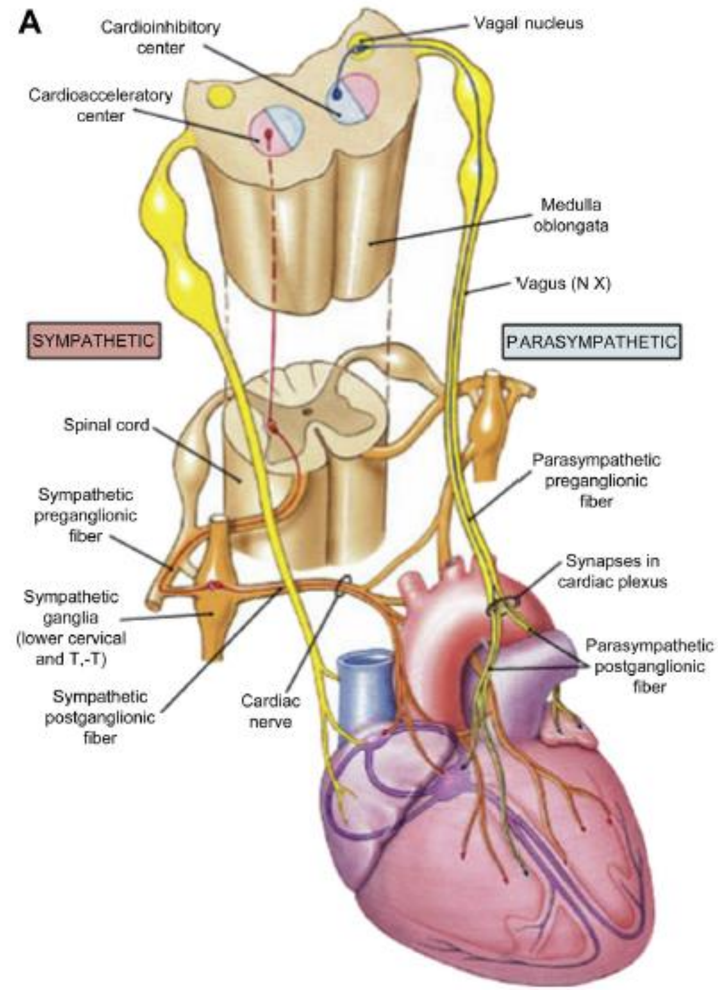
- Evidence of impaired exercise capacity
- Exercise capacity in cancer survivors influences:
  - All-cause mortality
  - Cancer mortality
  - ?? Cancer recurrence
- ∴ impaired exercise capacity in cancer patients that is prognostically significant.
- But why is exercise capacity impaired in cancer survivors?



Koelwyn GJ, et al. JACC 2014; 64:1320-2.

Impaired Exercise Capacity & Cardiac Autonomic Dysfunction

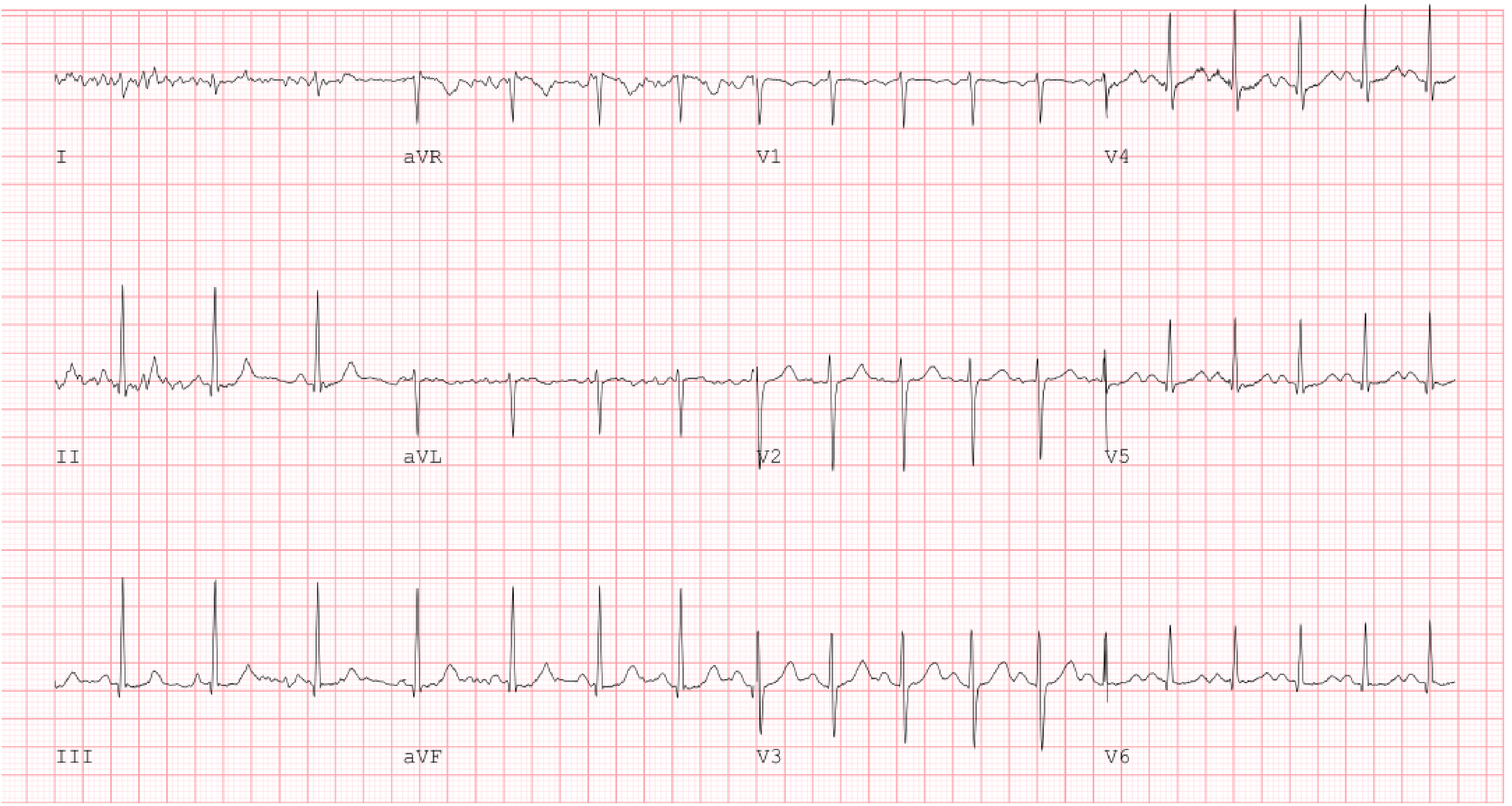
- Cancer- and cancer treatment-mediated injury to myocardium, pericardium, valves, coronaries, and large vessels well described…..
- Logical that the cardiac autonomic nervous system also vulnerable to injury?



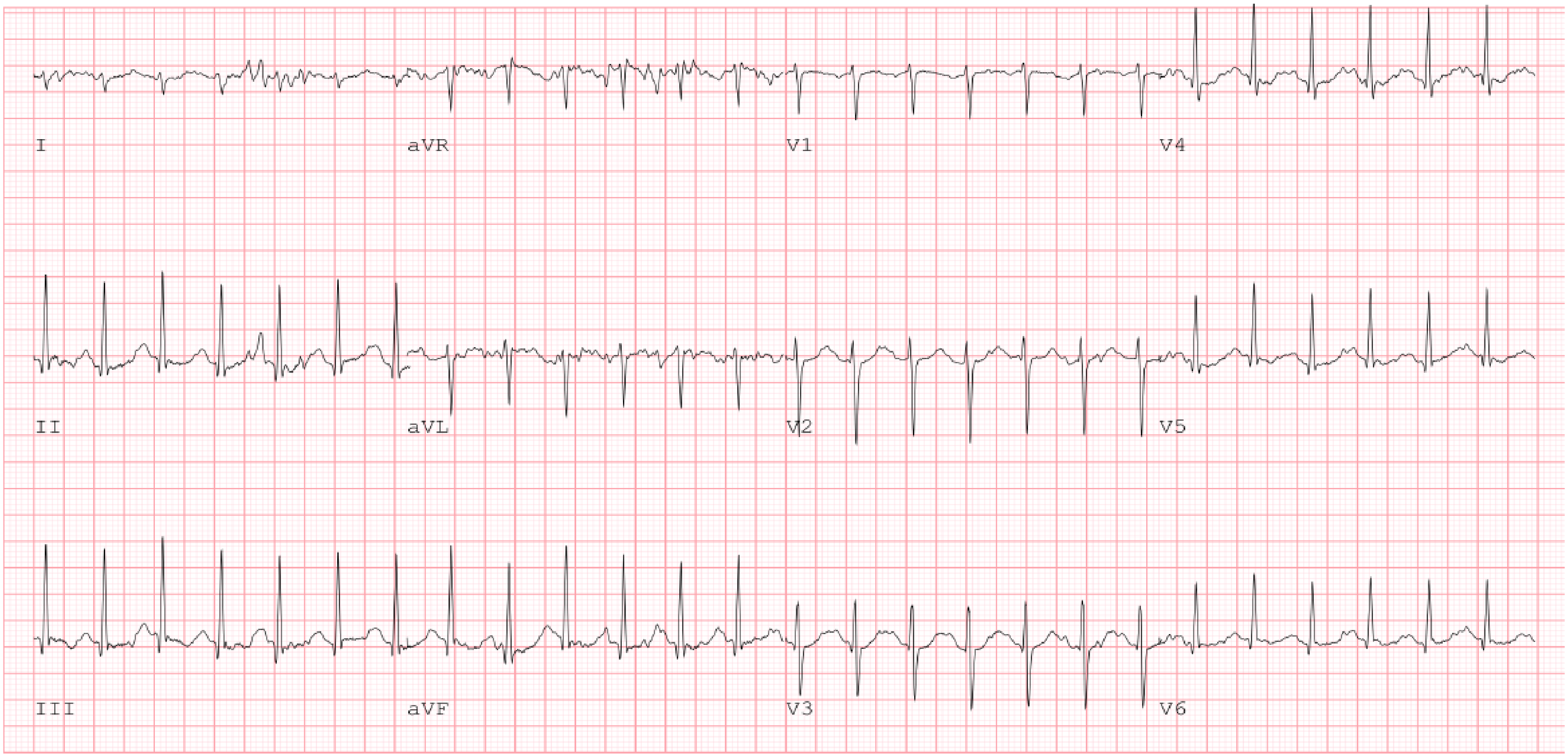
Case

- 34 year old female
- Stage IIa Hodgkin lymphoma 2003 (age 21)
  - 4 cycles ABVD chemotherapy (cumulative anthracycline dose=200 mg/m^2)
  - 36.6 Gy mantle radiation
- C/o exercise induced fatigue. No SOBOE
- Clinical exam:
  - HR at rest = 95 bpm, reg BP=119/85
  - Weight= 52kg
  - Unremarkable
- Labs:
  - Normal CBC, renal, liver profiles
  - TSH= 4.66 TC= 156 LDL= 66 HDL= 63
- TTE: LVEF=65%, normal diastology, normal valves

Resting ECG: HR = 107 bpm

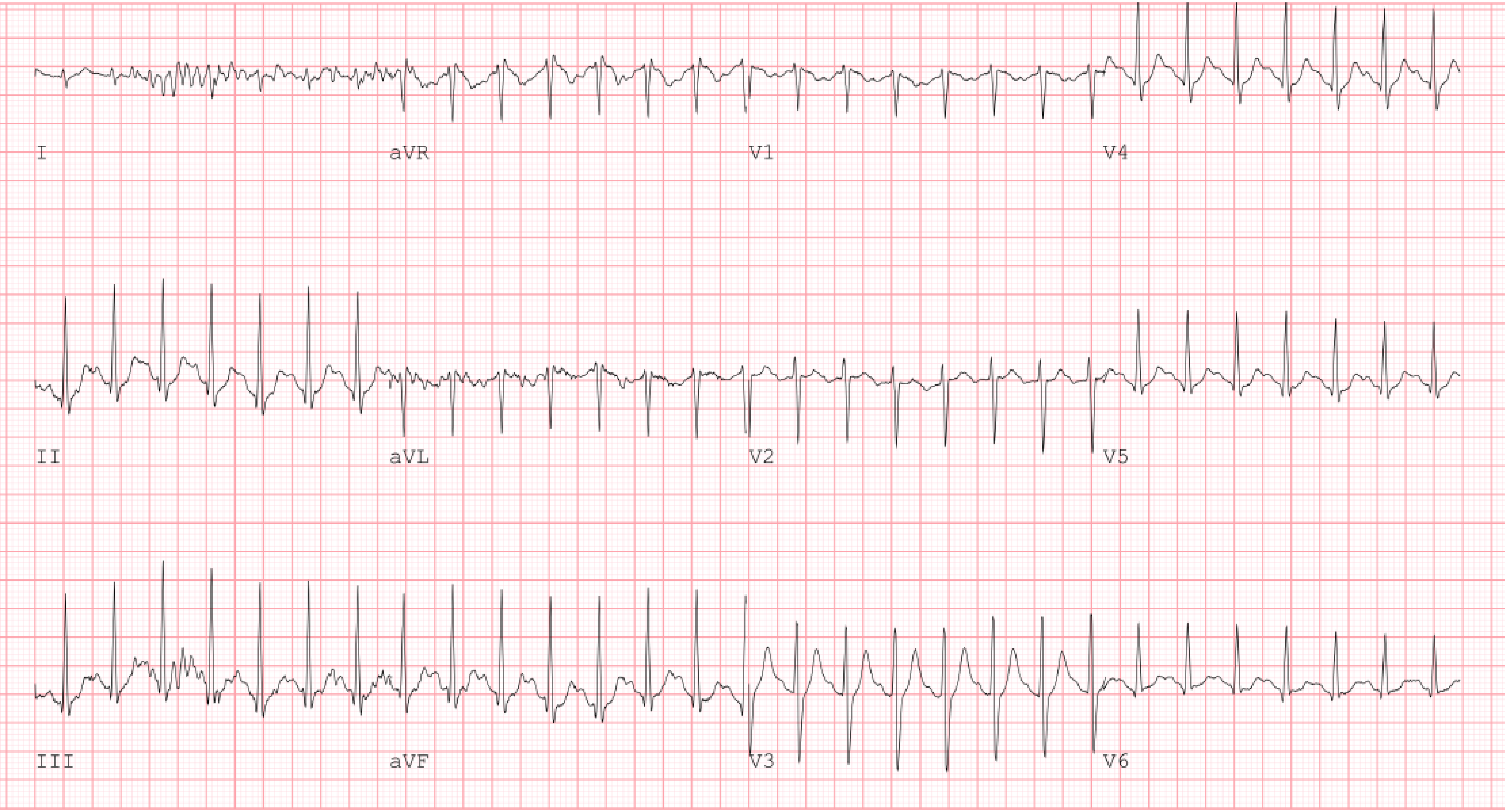


50 seconds into exercise: HR= 157 bpm

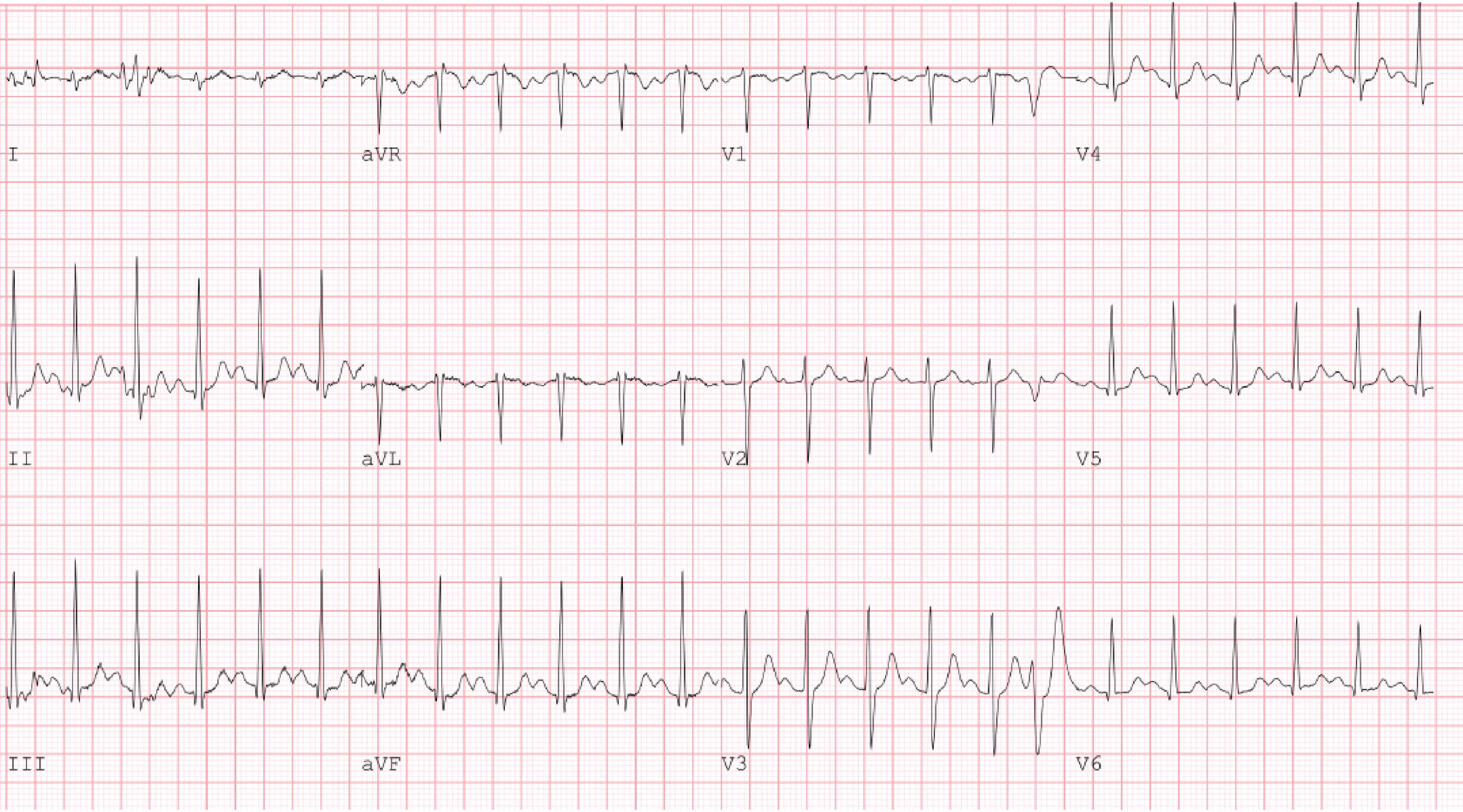


10 mins 2 seconds exercise: HR= 203 bpm

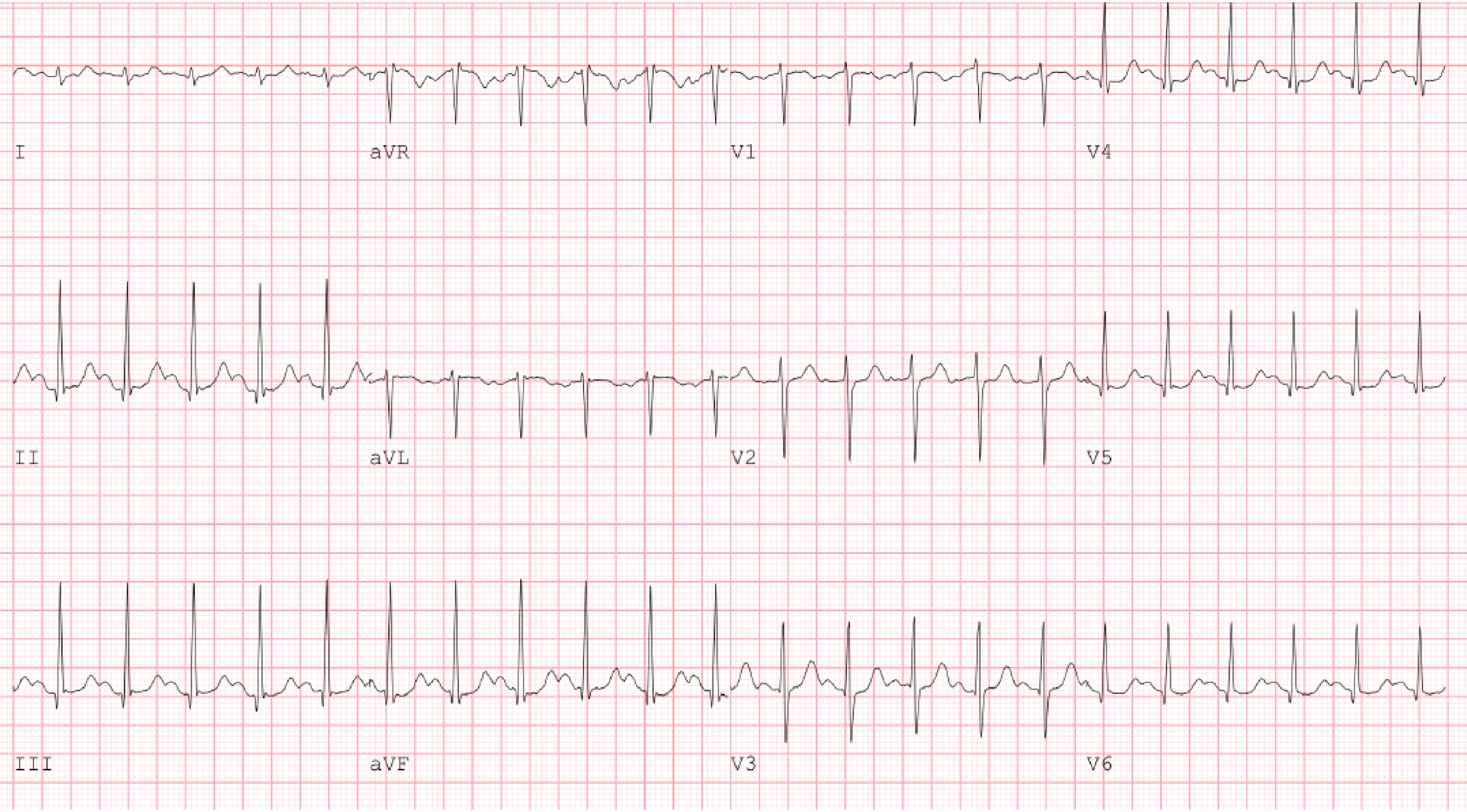
1 minute into recovery: HR= 176 bpm



3 minutes into recovery: HR= 141 bpm



14 minutes into recovery: HR= 131 bpm



What does this mean?

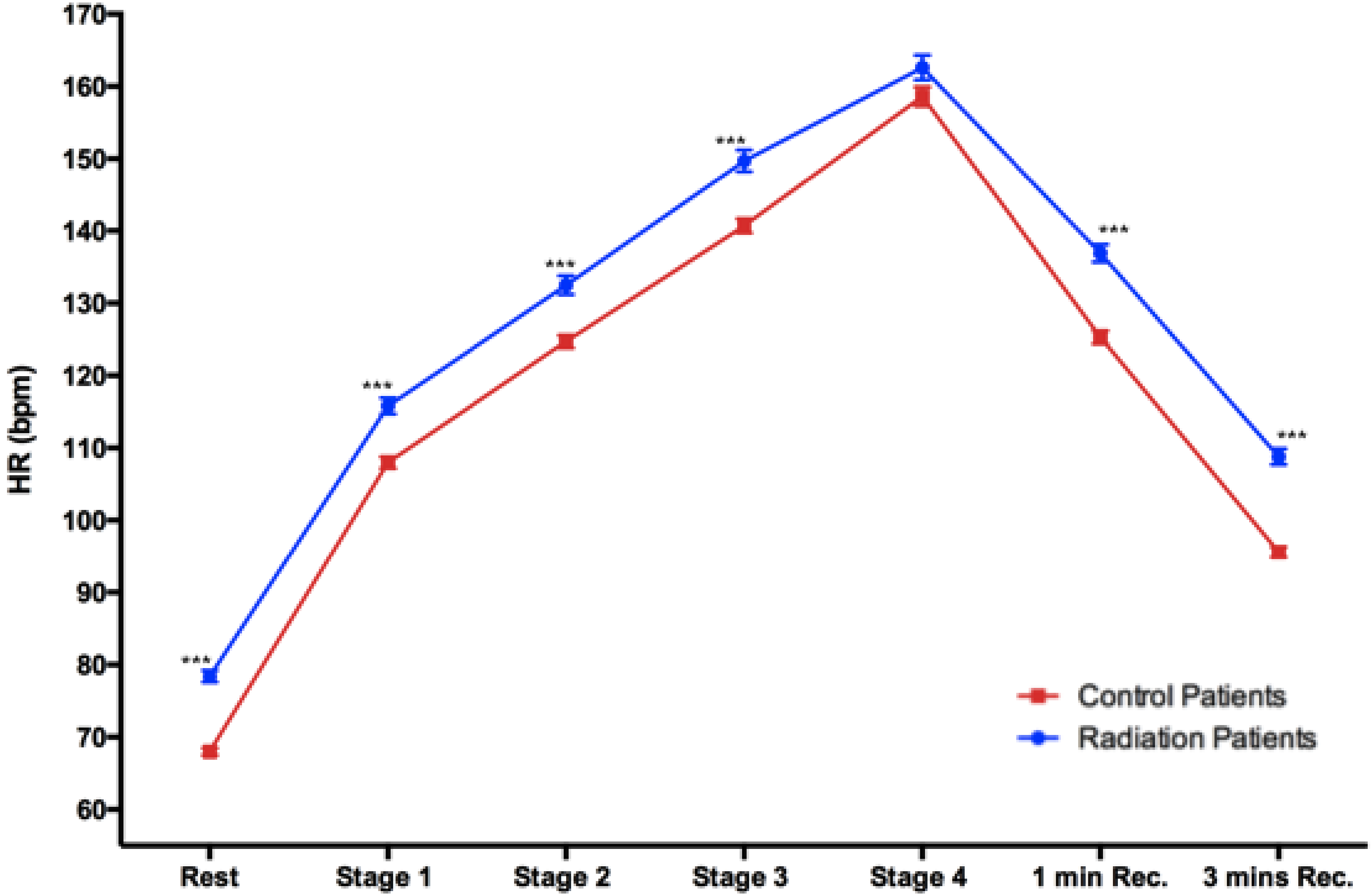
- 34 year old female HL survivor
  - 13 years post-anthracycline chemotherapy (200 mg/m2) and mantle radiation (36.6 Gy)
- Exertional fatigue
- No evidence of LV systolic or diastolic dysfunction
- Elevated resting HR, rapid HR acceleration after onset of exercise, and slow deceleration post-exercise

Abnormal Exercise Response in Long-Term Survivors of Hodgkin Lymphoma Treated With Thoracic Irradiation

Evidence of Cardiac Autonomic Dysfunction and Impact on Outcomes

John D. Groarke, MBBCh, MPH,*†‡ Varsha K. Tanguturi, MD,* Jon Hainer, BS,† Josh Klein, BA,†
Javid J. Moslehi, MD,*‡ Andrea Ng, MD,§ Daniel E. Forman, MD,*† Marcelo F. Di Carli, MD,*† Anju Nohria, MD*‡

	Radiation Patients (n = 263)	Control Patients (n = 526)	p Value
Age, yrs	49.9 ± 11.0	49.7 ± 10.8	0.77
Male	121 (46.0)	228 (43.4)	0.49
BMI, kg/m^2	26.3 ± 5.6	27.7 ± 6.0	0.002
Cardiovascular risk factors			
Hypertension	78 (30.0)	171 (32.5)	0.47
Diabetes mellitus	14 (5.3)	34 (6.5)	0.64
Hyperlipidemia	130 (49.4)	203 (38.6)	0.005
Family history of IHD	90 (46.2)	174 (45.9)	1.00
Smoking history	13 (4.9)	43 (8.2)	0.11
Congestive heart failure	26 (9.9)	60 (11.4)	0.55
Ischemic heart disease	41 (15.6)	52 (9.9)	0.03
Morise score	9 (3 to 12)	9 (4 to 12)	0.92
Cardiovascular medications			
Beta-blocker	58 (22.1)	120 (22.8)	0.86
Calcium-channel blocker	18 (6.8)	41 (7.8)	0.70
ACE inhibitor	33 (12.6)	79 (15.0)	0.39
Diuretic	23 (8.8)	54 (10.3)	0.53
Statin	96 (36.5)	146 (27.8)	0.01
Age at time of RT, yrs	30.0 ± 12.4	–	–
Interval from RT to ETT, yrs	19 (12–26)	–	–
Total radiation dose, Gy	38 (36–40)	–	–
Adjuvant anthracycline chemotherapy	121 (46.0)	–	–
LV ejection fraction, %*	59.0 ± 5.3	–	–



Number of observations in control cohort	526	522	480	348	168	526	526
Number of observations in radiation cohort	263	226	207	168	71	263	227

***=p<0.0001 by univariate comparisons

Likelihood of AD in HL survivors versus controls

	Unadjusted		Adjusted	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Primary endpoints				
Elevated resting heart rate	3.68 (2.65–5.12)	<0.0001	3.96 (2.52–6.22)*	<0.0001
Abnormal heart rate recovery at 1 min	4.57 (3.09–6.76)	<0.0001	5.32 (2.94–9.66)†	<0.0001

*Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, AVN-blocking medications, congestive heart failure/IHD, and anthracycline exposure. †Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, AVN-blocking medications, congestive heart failure/IHD, resting HR, exercise time, result of ETT, and anthracycline exposure. ‡Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, antihypertensive medications, congestive heart failure/IHD, resting HR, exercise time, result of ETT, and anthracycline exposure.

Groarke JD, et al. JACC 2015;65:573-83.

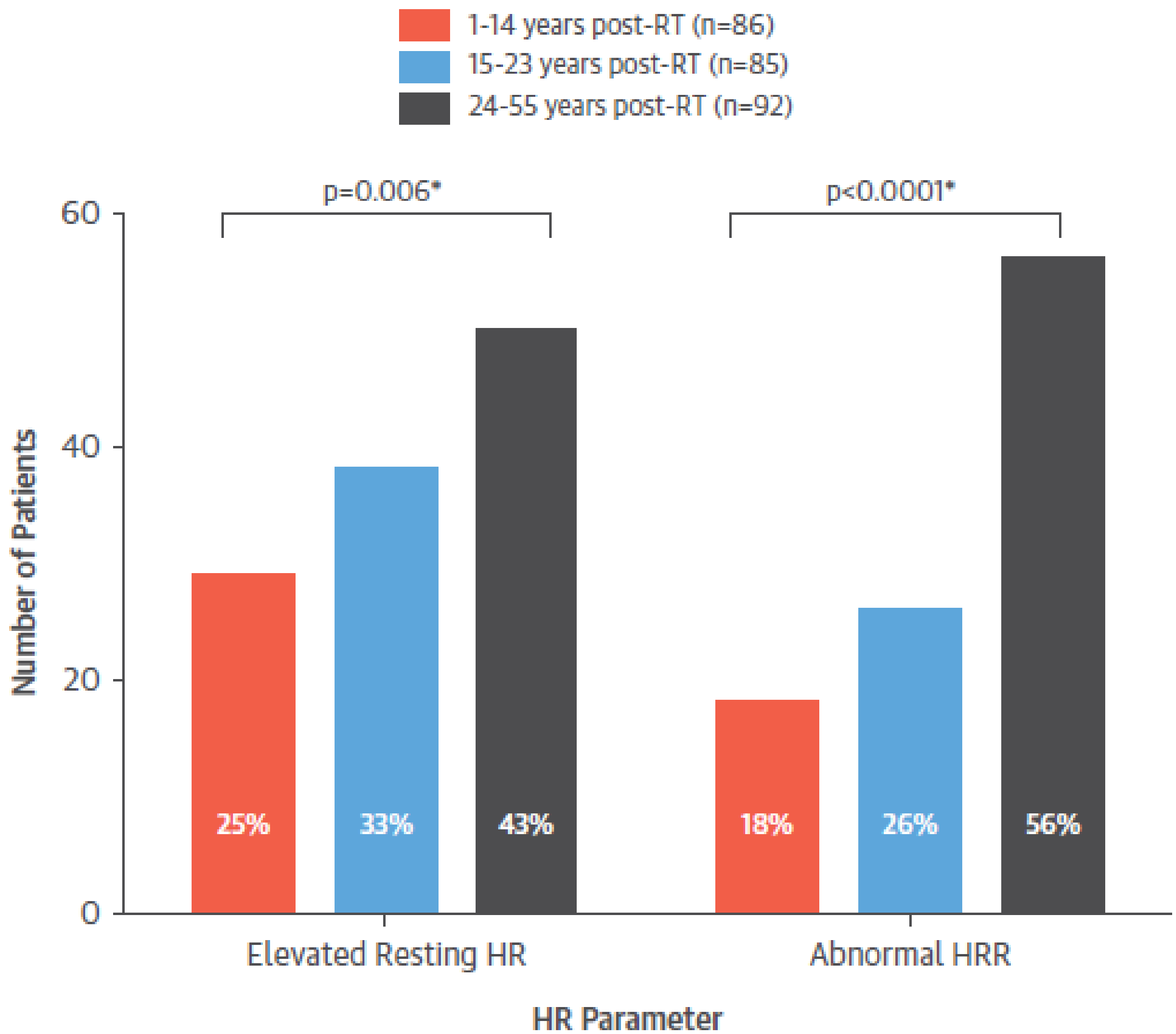
Functional Implications:
Reductions in exercise capacity

- Among HL survivors treated with RT:
  - Elevated resting HR associated with an adjusted* mean reduction of 1.1±0.4 in METs achieved during ETT ($p = 0.002$)
  - Abnormal HRR associated with an adjusted* mean reduction of 1.0±0.4 in METs achieved during ETT ($p = 0.007$)

*Adjusted for age, sex, CV risk factors, medications, indication for ETT, result of ETT

Groarke JD, et al. JACC 2015; 65:573-83

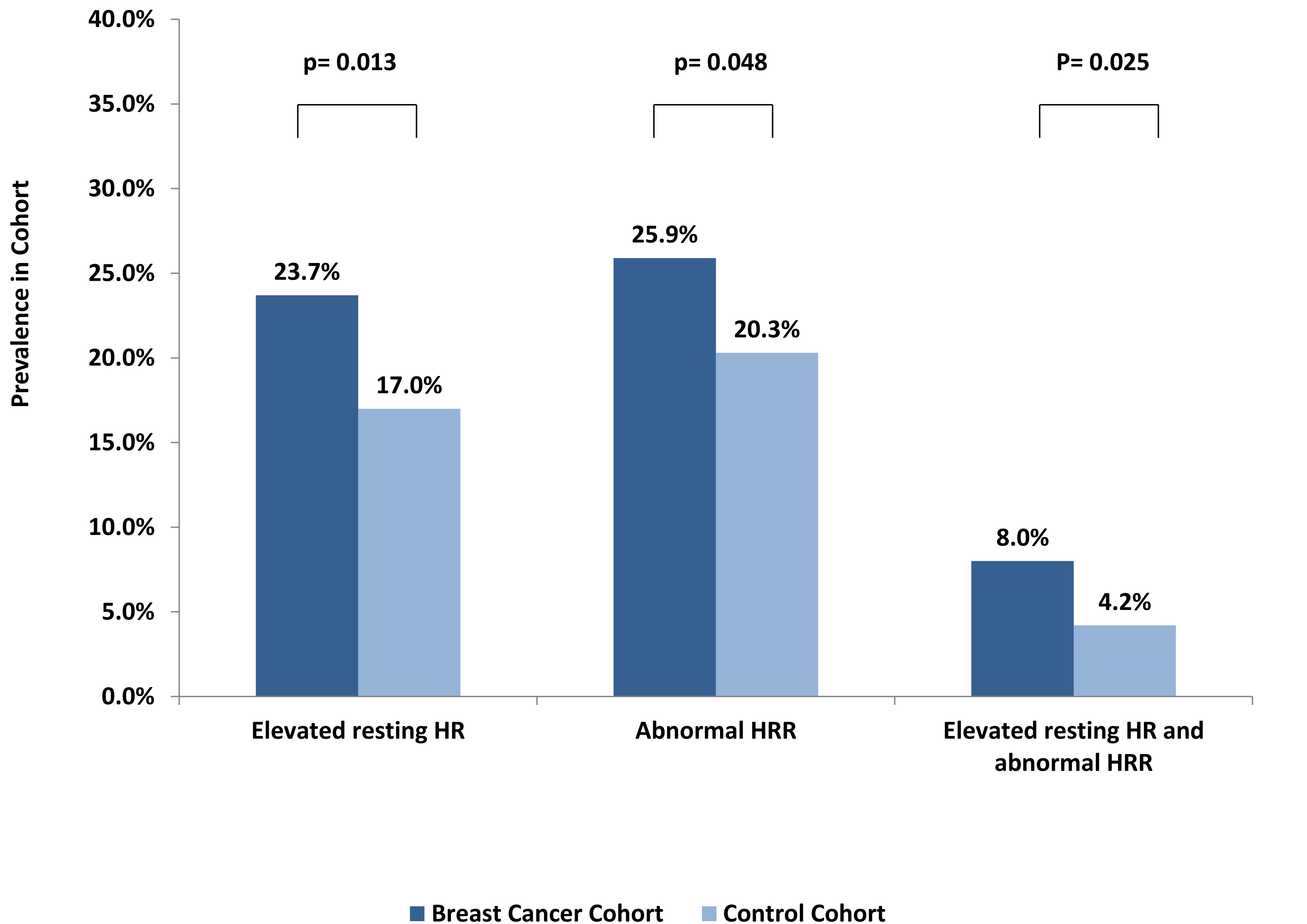
Prevalence of cardiac AD according to time from treatment



Groarke JD, et al. JACC 2015;65:573-83.

	Breast cancer cohort (n=448)	Control cohort (n=448)	p value
Age, years	62.6±10.0	62.5±10.0	0.92
BMI, kg/m²	27.0±5.2	28.8±6.3	0.0001
CARDIOVASCULAR HISTORY			
Morise risk score	13.5 (11.0, 16.0)	13.5 (11.0, 16.0)	0.66
Hypertension, n (%)	229 (51.1%)	254 (56.7%)	0.11
Hyperlipidemia, n (%)	221 (49.3%)	265 (59.2%)	0.004
Diabetes mellitus, n (%)	49 (10.9%)	86 (19.2%)	0.0007
Ischemic heart disease, n (%)	39 (8.7%)	61 (13.6%)	0.03
Smoking history, n (%)	23 (5.1%)	39 (8.7%)	0.05
Congestive heart failure, n (%)	28 (6.3%)	19 (4.2%)	
$^{\pi}$LVEF, %	64.4±9.8 (n=278)	66.9±9.3 (n=208)	0.004

Groarke JD, et al. ESC Congress 2016

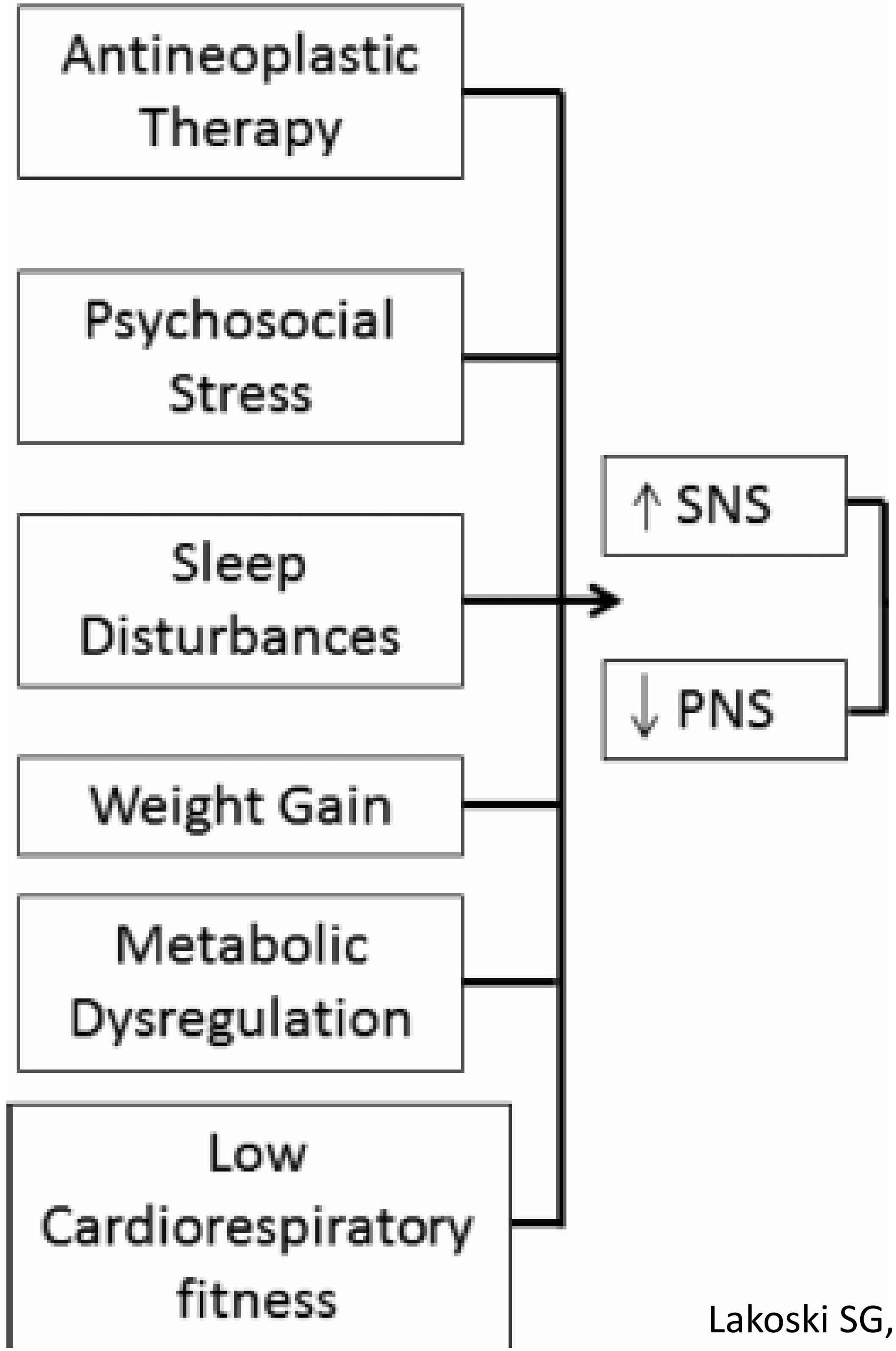


40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Prevalence in Cohort
p= 0.013
p= 0.048
P= 0.025
23.7%
17.0%
25.9%
20.3%
8.0%
4.2%
Elevated resting HR
Abnormal HRR
Elevated resting HR and abnormal HRR
Breast Cancer Cohort
Control Cohort

	Adjusted* mean reduction (SE) in METs achieved	p value
Elevated resting HR	-0.9 (0.3)	0.0003
Abnormal HRR	-1.3 (0.3)	< 0.0001
Elevated resting HR + Abnormal HRR	-1.9 (0.4)	< 0.0001

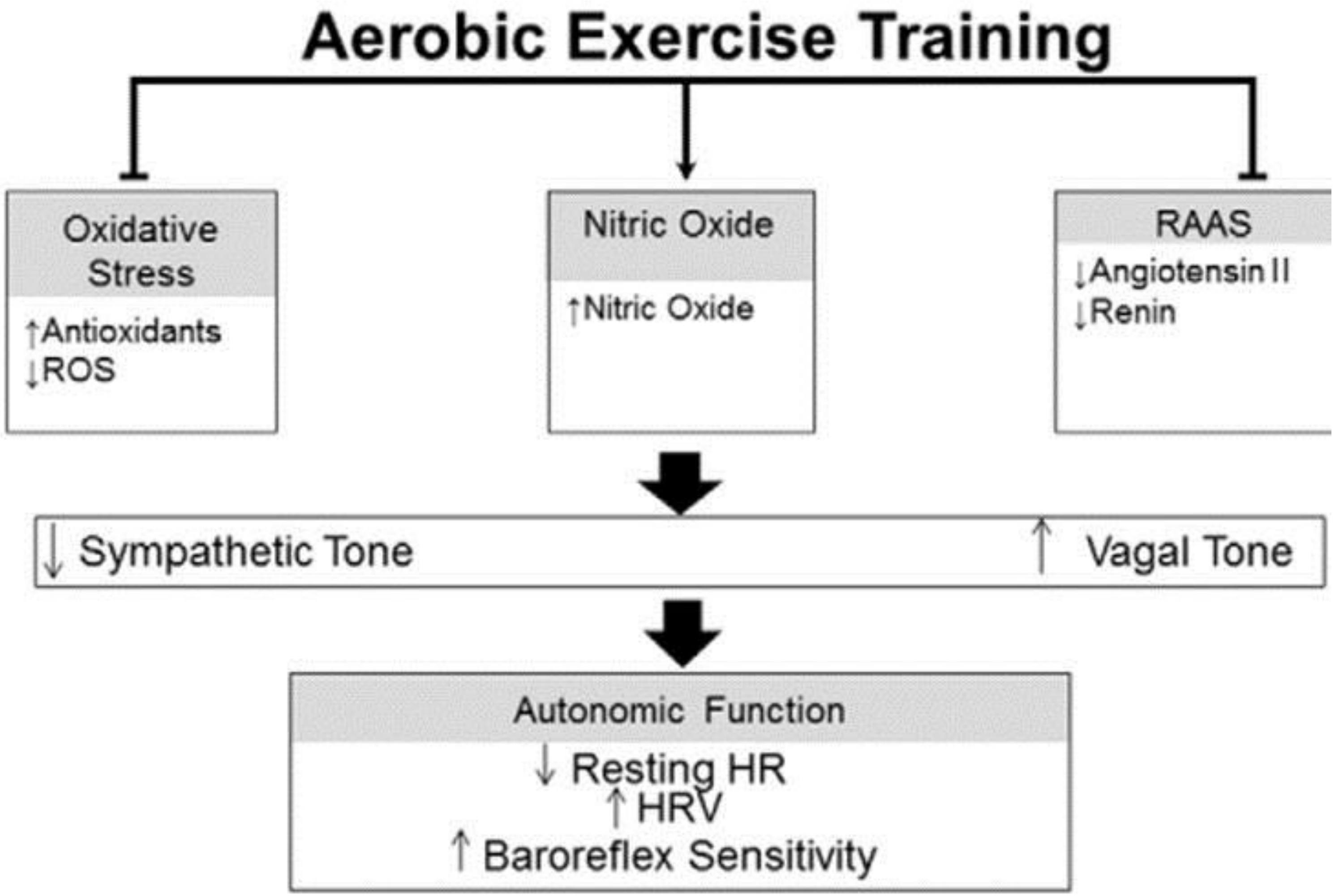
*Adjusted for age, BMI, hypertension, ischemic heart disease, hyperlipidemia, smoking history, diabetes mellitus, statin therapy, AV blocking drugs, result of ETT.

Groarke JD, et al. ESC Congress 2016



Lakoski SG, et al. Am Heart J 2015;170:231-41

Exercise Training



Scott et al. Int J Cardiol 2014;171:e50-e51

Summary of studies investigating the cardiovascular effects of exercise interventions after completion of breast cancer treatment

Author	Patient population	Exercise intervention	Outcome
Courneya et al. 2003 [62]	53 post-menopausal breast cancer survivors after completion of surgery, radiotherapy, and/or chemotherapy	Supervised aerobic exercise, 15 – 35 min/d at 70 % – 75 % of VO_{2peak}, 3 d/wk × 15 wks (n = 25); or control (n = 28).	↑ VO_{2peak} and ↑ self-reported QOL with aerobic exercise compared to control.
Daley et al. 2006 [73]	108 women treated for breast cancer 12 to 36 months previously	Supervised aerobic exercise, 50 min/d at 65 % – 85 % maximum heart rate and RPE 12–13, 3 d/wk × 8 wks (n =34); exercise-placebo, 50 min/d of light-intensity body conditioning/stretching, 3 d/wk × 8 wks (n = 36); or usual care (n = 38).	↑ fitness measured by submaximal walking test with aerobic exercise and exercise-placebo compared to usual care.
Hutnick et al. 2005 [74]	49 survivors of stage I–III breast cancer	Supervised aerobic exercise, 10 – 20 min/d at 60 % – 75 % of VO_{2peak}, plus resistance training, total session 40–90 min/d, 3 d/wk × 6 months (n = 28); or control (n = 21).	↑ VO_{2peak} and ↑ upper body strength
Pinto et al. 2005 [75]	86 women after completing treatment for stage 0–II breast cancer	Home-based aerobic exercise, 10 – 30 min/d at 55 % – 65 % of maximum heart rate, 5 d/wk × 12 wks (n = 43); or control (n = 43)	↑ fitness (↓ time for 1-mile walk test); no change in BMI or % body fat with aerobic exercise compared to control.
Schneider et al. 2007 [63]	113 women with breast cancer: 96 completed radiation and/or chemotherapy, and 17 undergoing concurrent cancer treatment with exercise	Supervised aerobic exercise, 60 min/d at 40 %–75 % of heart rate reserve, 2–3 d/wk × 6 months	↑ VO_{2peak}, ↓ SBP, ↓ resting heart rate, ↓ fatigue with aerobic exercise after completion of cancer treatment.

Yu AF, Jones LW. Cardiooncology 2016

Take home points on survivorship I

- Survivors of childhood cancers = cohort with adverse CV outcomes
- Unfavorable cardiometabolic profile: sarcopenic obesity, metabolic syndrome, insulin resistance --> regular surveillance of BMI, waist circumference, lipid panel, HbA1c
- Survivors of childhood cancers can be risk stratified based on cumulative anthracycline and radiation exposure
- CMP surveillance **recommended** for high risk survivors within 2 years of rx, and repeated q5 yrs (**reasonable** for moderate/low risk survivors)

Take home points on survivorship II

- Criteria for increased risk among survivors of adult cancers
- Echo 6-12 months after rx in asymptomatic ‘increased risk’ pts
- Evidence of impaired exercise capacity in cancer patients that is prognostically significant- multiple factors contribute to exercise limitation.
- Encourage cancer survivors of the need for exercise
- Aggressive optimization of modifiable CV risk factors
- Educate pts of risk, signs and symptoms of IHD, CVD, and PAD
- Providers should retain a high index of suspicion for CV disease and a low threshold for testing/intervention

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Thank You

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