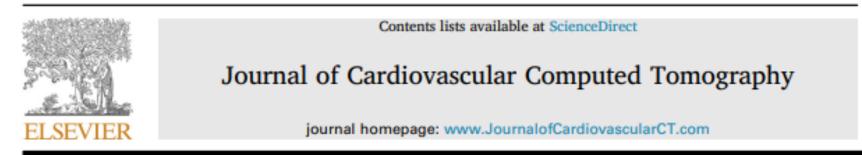
Imaging Modalities And Cardiovascular Screening For Cardiomyopathy And Non-Cardiomyopathy Events In Cancer Patients

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Summary Recommendations Coronary Artery Disease screening in Newly Diagnosed Cancer or Survivorship

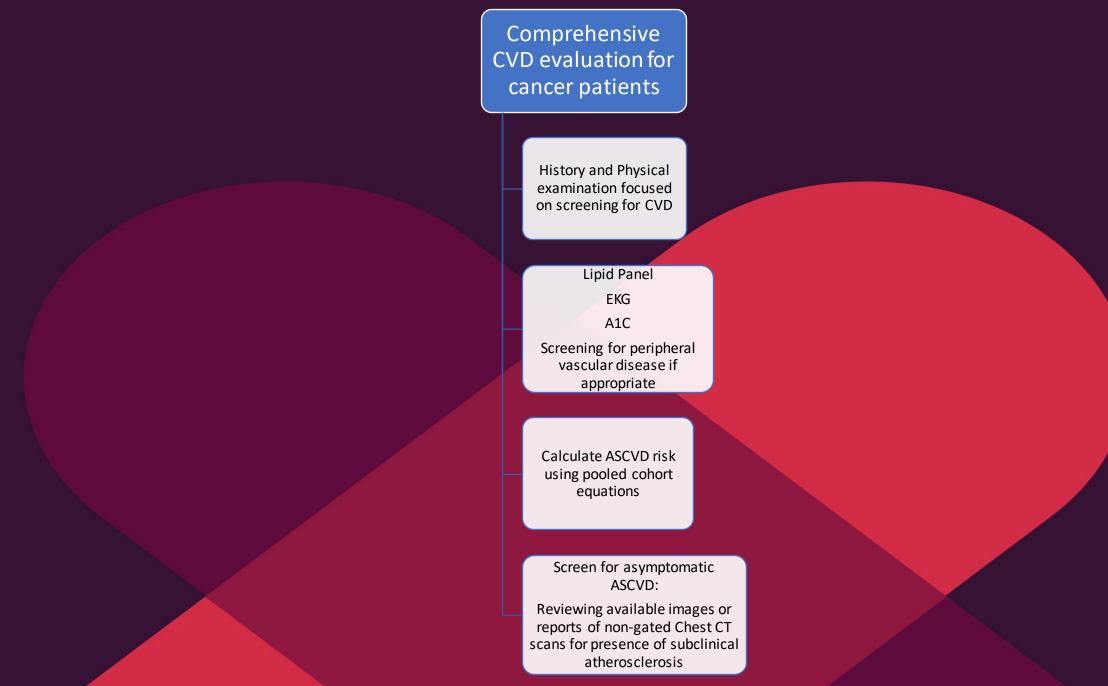


Practice guidelines

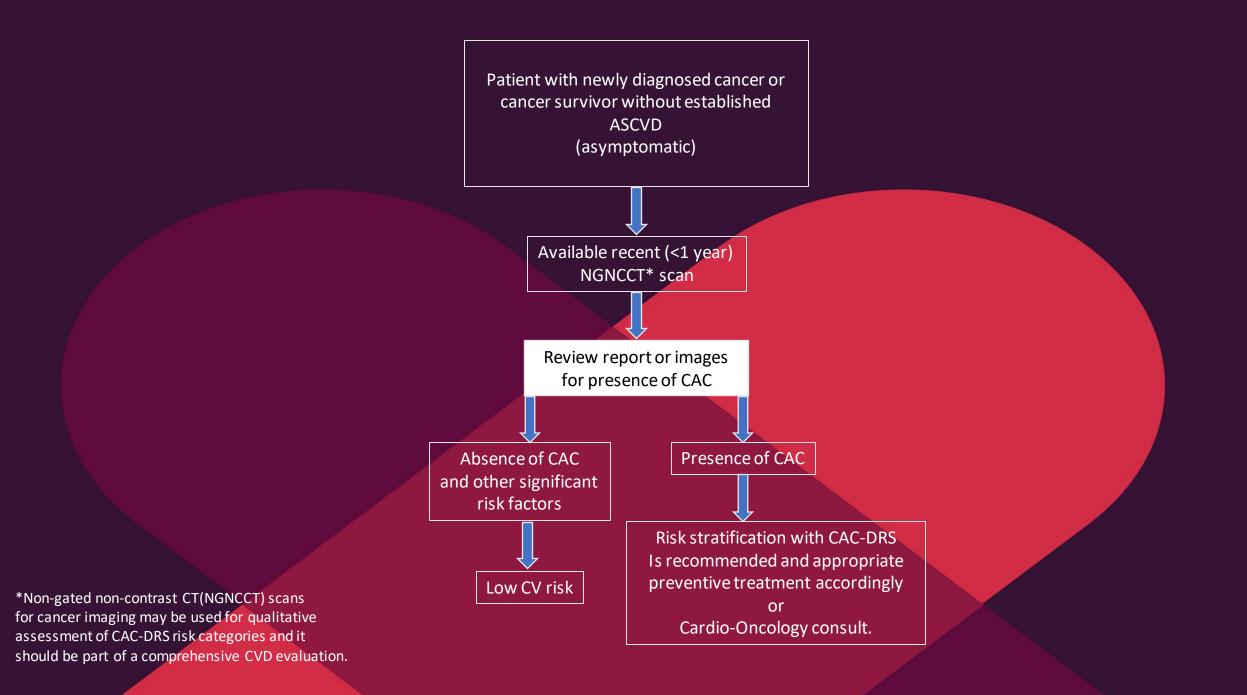
Cardiac computed tomographic imaging in cardio-oncology: An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT). Endorsed by the International Cardio-Oncology Society (ICOS)

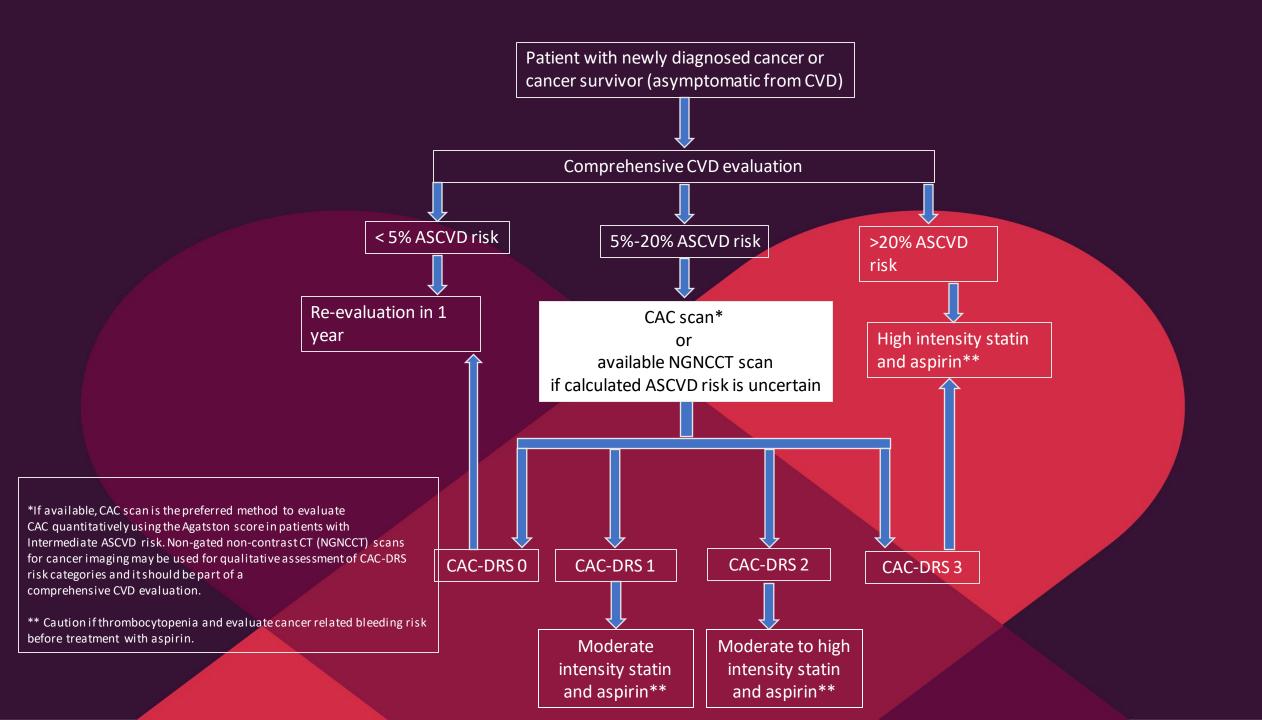
Juan Lopez-Mattei ^{a,1,*}, Eric H. Yang ^{b,1}, Lauren A. Baldassarre ^{c,1}, Ali Agha ^{d,1}, Ron Blankstein ^{e,1}, Andrew D. Choi ^{f,1}, Marcus Y. Chen ^{g,1}, Nandini Meyersohn ^{h,1}, Ryan Daly ^{i,1}, Ahmad Slim ^{j,1}, Carlos Rochitte ^{k,1}, Michael Blaha ^{l,1}, Seamus Whelton ^{l,1}, Omar Dzaye ^{l,1}, Susan Dent ^{m,1}, Sarah Milgrom ^{n,1}, Bonnie Ky ^{o,1}, Cezar Iliescu ^{a,1}, Mamas A. Mamas ^{p,1}, Maros Ferencik ^{q,1}

Comprehensive Cardiovascular evaluation (CVD) evaluation for cancer patients and survivors



Imaging for ischemia





a. Agatston Score					
Categories	CAC score	Cardiovascular Risk	<u>Possible</u> Treatment Recommendation		
CAC-DRS 0	0	Very low	Statin not recommended*		
CAC-DRS 1	1-99	Mildlyincreased	Moderate intensity statin		
CAC-DRS 2	100-299	Moderately increased	Moderate to high intensity statin + aspirin 81 mg [#]		
CAC-DRS 3	≥300	Moderately-Severely increased	High intensity statin + aspirin 81 mg [#]		
a. Visual Score					
Categories	CAC Score	Cardiovascular Risk	Treatment Recommendation		
CAC-DRS 0	0	Very low	Statin not recommended*		
CAC-DRS 1	1	Mildlyincreased	Moderate intensity statin		
CAC-DRS 2	2	Moderatelyincreased	Moderate to high intensity statin + aspirin 81 mg [#]		
CAC-DRS 3	3	Moderately-Severely increased	High intensity statin + aspirin 81 mg [#]		

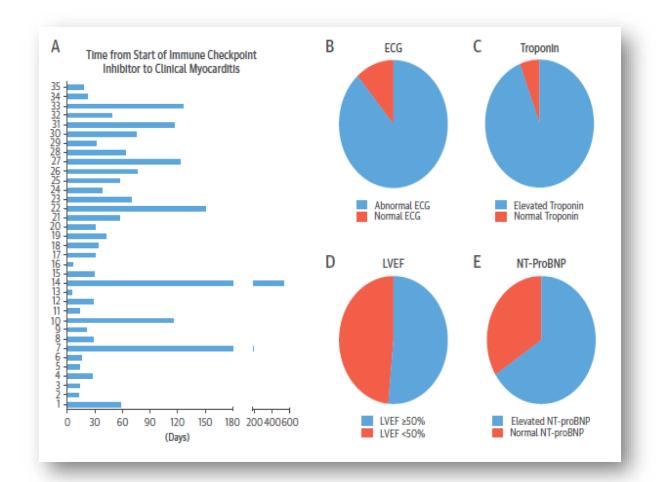
<u>Oncologic</u> Therapy Type	Examples	Common Cardiovascular Side Effects	<u>Possible Roles</u> of Cardiovascular CT
Anthracyclines ¹⁸⁴⁻¹⁸⁷	Doxorubicin Daunorubicin Idarubicin Mitoxantrone	Cardiomyopathy (toxicity increases in a cumulative, dose-dependent fashion) Myopericarditis Arrhythmia Pericardial effusion	 CCTA to rule out obstructive CAD as the etiology of decreased left ventricular systolic function/cardiomyopathy CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely CAC assessment on non-cardiac CT scans for baseline risk assessment
Alkylating Agents ¹⁸⁸	Cyclophosphamide	Hemorrhagic myopericarditis	 Cardiac CT to evaluate pericardial effusion (HU measurements for characterization of the <u>effusion if</u> <u>clinically relevant</u>) CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely (e.g. myopericarditis) CAC assessment on non-cardiac CT scans for baseline risk assessment
Fluoropyrimidines ¹⁸⁹ , ¹⁹⁰⁻¹⁹⁵	5-fluorouracil Capecitabine	Anginal chest pain (incidence up to 18%) Coronary vasos pasm Myocardial infarction	 CCTA to rule out obstructive CAD <u>in patients presenting with symptoms of chest pain suspected to</u> <u>be coronary vasospasm to exclude other concomitant processes that could account for an acute</u> <u>coronary event.</u> Coronary CTA to evaluate coronary atherosclerosis prior to therapy CAC assessment on non-cardiac CT scans for baseline risk assessment
HER2/neu Receptor Inhibitors ¹⁹⁶⁻¹⁹⁸	Trastuzumab Pertuzumab	Cardiomyopathy	Same as anthracyclines
Taxanes ^{190, 195, 199, 200}	Paclitaxel Docetaxel	Myocardial ischemia <u>Coronary vasospasm</u> Cardiomyopathy Arrhythmias	 CCTA to rule out obstructive CAD as the etiology of decreased left ventricular systolic function/cardiomyopathy CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely Coronary artery calcium assessment on non-cardiac CT scans for baseline risk assessment
Vascular Endothelial Growth Factor (VEGF) Inhibitors ²⁰¹⁻²⁰⁵	Bevacizumab Sunitinib Sorafenib Pozapanib	Arterial hypertension Acute thromboembolic events, including ACS	 CCTA to rule out ACS <u>CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis</u> for myocardial injury other than coronary thrombosis is more likely
Immune Checkpoint Inhibitors ²⁰⁶⁻²¹⁶	Pembrolizumab Nivolumab Ipilimumab Atezolizumab	Myocarditis Increased risk of coronary atherosclerosis	 CCTA to rule out obstructive CAD when myocarditis is suspected (e.g. elevated troponin) CCTA to evaluate coronary atherosclerosis prior to therapy CAC assessment on non-cardiac CT scans
CAR-T Therapy ²¹⁷		Cytokine release syndrome Elevated troponin Cardiomyopathy Arrhythmias	 CCTA to rule out obstructive CAD with elevated troponin CCTA to rule out obstructive CAD as the etiology of decreased left ventricular systolic function/cardiomyopathy CCTA to rule out obstructive CAD in patients with troponin elevation, when an alternative diagnosis for myocardial injury other than coronary thrombosis is more likely
Hematopoietic Stem Cell Transplantation ^{218, 219}	Autologous Allogenic	Population with an increased prevalence of CV risk factors	 Coronary artery calcium assessment on non-cardiac CT scans or CAC scan for baseline risk assessment CCTA to rule out obstructive CAD in patients with symptoms suggestive of obstructive CAD

The Non-Ischemic Complications



Check Point Inhibitors

- Conditions CPI used for:
 - Reports of fulminant myocarditis with rapid deterioration, need to anticipate and have a system in place for biopsy and potential VAD support in advanced cases





NEJM 2012;366:2517-2519 Curr Cardiol Rep 2017;19:21 JACC 2018;71:1755-64

Cardiotoxicity beyond cardiac dysfunction

			Oncological Use
Agent	Incidence	Manifestations	oute myeloid leukemia, acute myelogenous leukemia, chroni lymphocytic leukemia, Hodgkin and non-Hodgkin transiti sarcoma, mycosis fungoides, thyroid
thracyclines Doxorubicin	3%-26%	Myopericarditis, cardiac arthythmia, ECO abnormalities	lymphocyoc textury and the same of the sam
Epirubicin Idarubicin Mitoxantrone	0.9%-33% 5%-18% 0.2%-30.0%	Cardiac anhythmia, ECG abnormalities, arcono embolism ECG abnormalities	Cancer, wing con- Breast, esophageal, and gastric cancer Acute myeloid leukemia Acute nonlymphocytic leukemias, prostate cancer (multip scienosis) Bone marrow transplant, bladder cancer, lung cancer, word cancer, myeloproliferative disorders,
kylating agents Cyclophosphamide (high dose)	7%-28%	Pericarditis/myocarditis, cardiac tamponade, arrhythmia	sarcomas, anal cances leukemias chronic myelogenous leukemias cenoical cancer, Hodgkin and non-Ho
Ifosfamide	17%	Arrhythmia, cardiac arrest, myocardial hemorrhage myocardial infarction	sarcoma
Busulfan	Rare	Endomyocardial fibrosis, pericardial effusion and tamponade, ECG changes, chest pain, thrombosis, anhythmia	thrombocythemia Stomach or pancreas adenocarcinoma, anal carcinom
Mitomycin	10%	-	

numetaboutes			
Clofarabine	27%	Arrhythmias, hypotension/hypertension, pericarditis/pericardial effusion	Acute lymphocytic leukemia
5-Fluorouracil	2%-20%	Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes including ventricular ectopy, hypotension	Advanced colon cancer, anal cancer, gastrointestinal cancer pancreatic cancer, hepatobiliary cancers, breast cancer, bladder cancer, head and neck cancers, and as a radiatio sensitizer in several tumors
Capecitabine	2%-7%	Coronary vasospasm, myocardial ischemia and infarction, arrhythmias, ECG changes, thrombosis	Breast cancer, advanced colon cancer, anal cancer, gastrointestinal cancers, pancreatic cancer, hepatobiliary cancers
Cytarabine	Undefined	Pericarditis, chest pain (including angina)	Hodgkin and non-Hodgkin lymphoma, acute leukemia (myelo and lymphocytic)
latinum agents			
Cisplatin	Rare	Arterial vasospasm, amhythmia	Lung cancer, bladder cancer, sarcomas, testicular cancer, ovarian cancer, head and neck cancer, metastatic breast cancer, cancer of unknown origin, esophageal cancer
ntimicrotubule agents			
Vincristine	25%	Myocardial ischemia and infarction, arrhythmia	Acute lymphocytic leukemia, central nervous system tumors Hodgkin and non-Hodgkin lymphoma, multiple myeloma Ewing sarcoma, ovarian cancer, small cell lung cancer, thymoma
Ionocional antibody-based	tyrosine kinase inhibitor	5	
Bevacizumab	1.7%-3.0%	Arterial and venous thromboembolism	Renal cancer, colorectal cancer, lung cancer
Trastuzumab	2%-28%	Arrhythmia, vascular thrombosis	HER2+ breast cancer, HER2+ gastric cancer
Pertuzumab	3%-7%	-	HER2+ breast cancer
Alemtuzumab	Rare	Arrhythmia	Chronic lymphocytic leukemia, cutaneous T-cell lymphoma, bone marrow transplant

Cardiotoxicity beyond cardiomyopathy

				Drug	HTN	Ischemia	Arterial embolic	QT prolongation	CHF
				Sorafenib	11.3%	3.8%	1.7%	40.5%	11%
				Sunitinib	34.3%	-	-	-	5-10%
Chemotherapeutic	Cardiotoxicity			Dasatinib		-	-	<1%	2%
Agent	Incidence	Manifestations	Oncological Use	Imatinib	24.2%	-	-	18%	<2%
mall-molecule tyrosine kinase i				Axitinib	43%	<1%	-	<1%	21%
Dasatinib	2%-4%	Pericardial effusion, hypertension, arrhythmia, ECG changes	Philadelphia chromosome-positive chronic myeloid leukemia and acute lymphoblastic leukemia	Regorafenib	38.3%	-	-	-/~	6%
Imatinib mesylate	0.5%-1.7%	Pericardial effusion and tamponade, arrhythmia	Philadelphia chromosome-positive chronic myeloid leukemia	Vatalanib	22.7%	-	-	\sim	22.6%
			and acute lymphoblastic leukemia, gastrointestinal stromal tumors, dermatofibrosarcoma protuberans, hypereosinophilic syndrome	Nintedanib	15.4%	-	Rare	-	8.7%
Lapatinib	1.5%-2.2%	QTc interval prolongation, myocardial ischemia (Prinzmetal angina)	HER2+ breast cancer						8.7%
Sunitinib	3%-15%	Arterial and venous thrombosis, aortic dissection, ECG changes	Renal cell cancer, pancreatic neuroendocrine tumors, gastrointestinal stromal tumors						
Sorafenib	4%-28%	Thrombosis, coronary vasospasm, myocardial ischemia/infarction	Renal cell cancer, hepatocellular carcinoma, differentiated thyroid carcinoma						
Pazopanib	7%-13%	Thrombosis, myocardial ischemia/infarction, bradycardia, ECG changes	Renal cell cancer, soft tissue sarcoma						
roteasome inhibitor									
Bortezomib	2%-5%	Ischemia, bradycardia	Multiple myeloma, mantle cell lymphoma						
mmune checkpoint inhibitor									
Pembrolizumab	Unknown	Myocarditis	PD-L1+ tumors						
liscellaneous									
All-transretinoic acid	6%	Pericardial effusion	Acute myeloid leukemia (promyelocytic leukemia)						
Pentostatin	3%-10%	Myocardial ischemia and infarction, arrhythmia	Hairy cell lymphoma, chronic lymphocytic leukemia, cutaneous T-cell lymphoma						
Interferon alpha-2b	25%	Myocardial ischemia and infarction, ECG changes, sudden cardiac death	Metastatic melanoma, renal cell carcinoma						
Aflibercept	1.0%-6.8%	Myocardial ischemia/infarction, stroke	Metastatic colorectal cancer						
			and the second						

JACC 2018;72:202-27 Expert Opin Drug Safety 2015;14:253-267 Cardiovasc Toxicol 2012;12:191-207 Myocardial ischemia/infarction, stroke

ocardial subjemus and infraction. ECG changes

Metastatic colorectal cancer

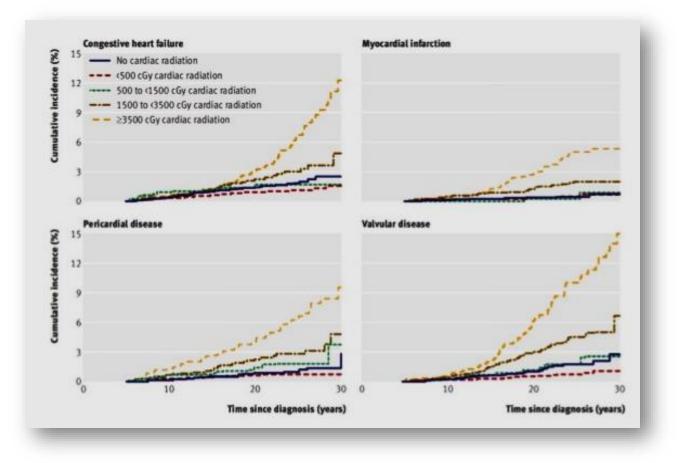
Sastatic melanoma, renal cell cercenena.

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Radiation Therapy

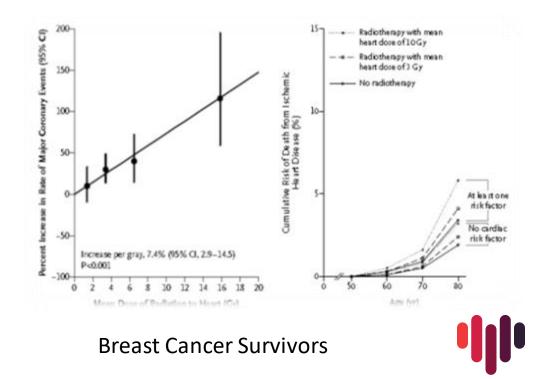


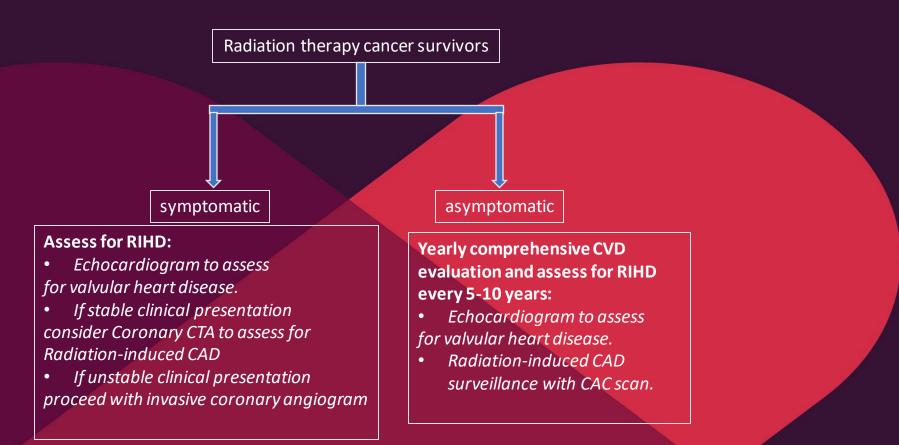
Radiation therapy



Childhood Cancer Experience

Mulrooney et al, BMJ 2009 Darby et al, NEJM 2013





Nuclear Imaging In Cardio-Oncology



Equilibrium Radionuclide Ventriculography (ERNV)

- ➤Can calculate systolic function
- ➤Can evaluate for diastolic dysfunction
- ➤Can assess RV function
- Most validated for screening and follow up for chemotherapeutic
 - agents



Guidelines for Monitoring Doxorubicin (Adriamycin) Therapy with Serial Resting RNA

LVEF > 50% at baseline:

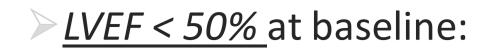
- Baseline MUGA within <u>first 100 mg/m²</u> in all patients
- Next MUGA at <u>250 300 mg/m²</u>
- \rightarrow Next MUGA at <u>450 mg/m²</u> or <u>400 mg/m²</u> if high risk: cyclophosphamide,

heart disease, mediastinal radiation, abnormal ECG

- > Next MUGA prior to <u>each dose > 450 mg/m²</u>
- Discontinue therapy if <u>LVEF decreases > 10%</u> from baseline <u>AND</u> reaches <</p>



Guidelines for Monitoring Doxorubicin (Adriamycin) Therapy with Serial Resting RNA



> Baseline MUGA within first <u>100 mg/m²</u> in all patients

Serial MUGA prior to each subsequent dose

Discontinue therapy if LVEF <u>decreases > 10% from baseline</u>

OR reaches LVEF < 30%





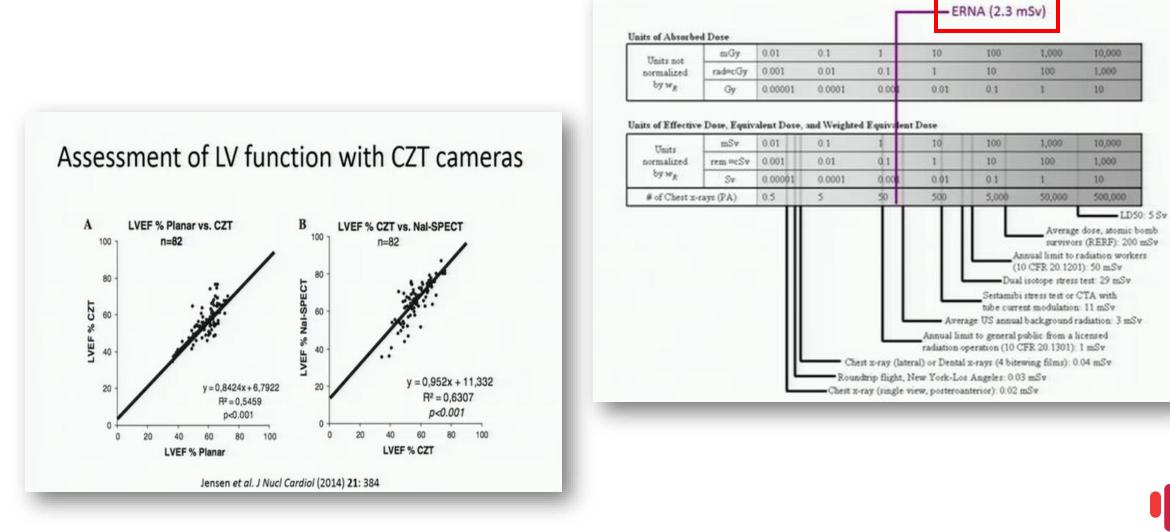
Reliability and accuracy of ERNA (MUGA)

- Diagnostic Accuracy of ERNV
 - Excellent correlation with LVG with calculated LVEF (r = 0.93)
 - Point-by-point LV volume curve
 - Excellent LVEF precision
 - Robust automated computer processing (90% correlation with manual analysis)
 - repeat acquisitions (3.7% variability)
 - repeat processing (2% variability)
 - Excellent intra-observer agreement (1.4% variability)

Excellent inter-observer agreement (1.6% variability)



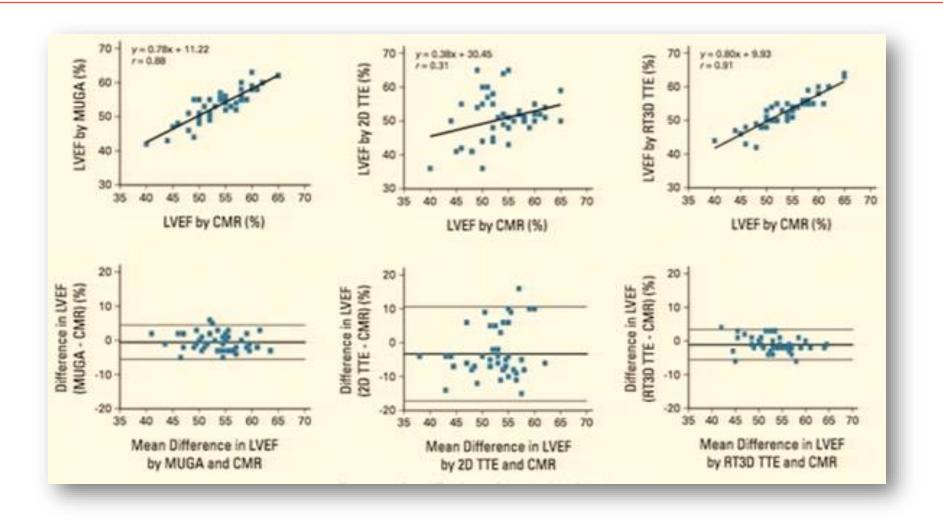
Can We Decrease Radiation Exposure?



ALTERNATIVES TO NUCLEAR IMAGING

Echocardiography with 3D EF and Global Longitudinal Strain

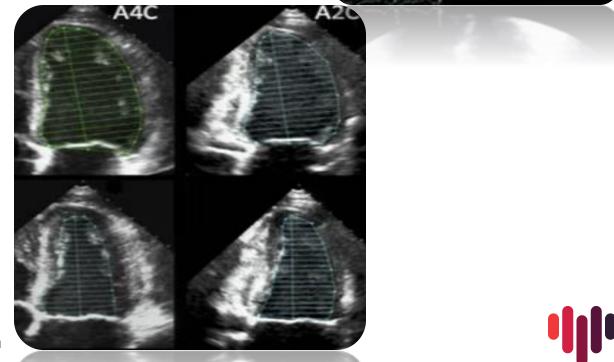
Multi-Imaging Modality Correlation



Early Detection and Screening With Echocardiography

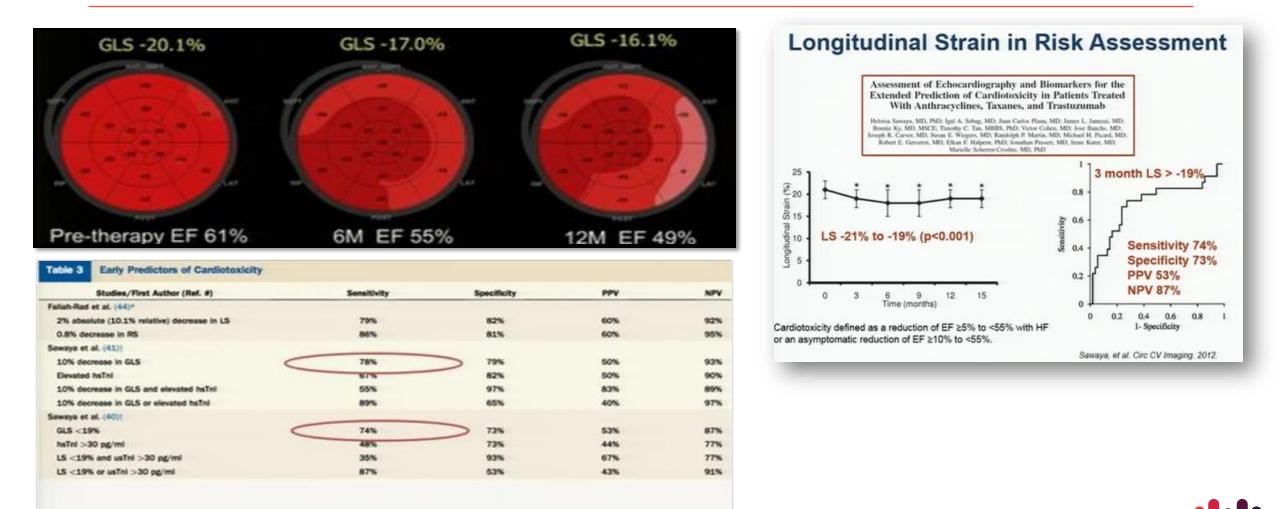
- LV Assessment 2D vs. 3D echocardiography:
- Modified Biplane Simpson's Technique:
 - Range 53% 73% with wide variation
 - Inter- & Intra-observer variability of 8-9%
- 3D EF: automated and reproducible with <u>0.6% variability</u>





Tha vendirana than P, et al. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: Application to patients undergoing cancer chemotherapy. J Am CollCardiol. 2013;61:77–84

Early Detection and Screening With Echocardiography



Thavendiranathan P, et al. JACC: 63:2751-68

Independent and Incremental Value of Deformation Indices for Prediction of Trastuzumab-Induced Cardiotoxicity

Kazuaki Negishi, MD, PhD, Tomoko Negishi, MD, James L. Hare, MBBS, PhD, Beian A. Haluaka, PhD, Juan Carlos Plana, MD, and Thomas H. Marwick, MBBS, PhD, MPH, Cleveland, Obio; Brishane and Hobart, Australia

- 81 breast cancer patients with at least 3 echocardiograms
- GLS and systolic and diastolic strain rate of incremental utility
 11% reduction in GLS had sensitivity 65%; specificity 94%
- Table 3 Percent changes in echocardiographic parameters in 6 months within the groups

11.4 ± 9.8

 12.8 ± 19.4

-11.9 ± 14.5

 -17.0 ± 23.9

 -10.0 ± 28.7

 -10.0 ± 39.3

 9.3 ± 27.4

 02 ± 86

 -0.2 ± 16.8

5.1 ± 21.2

 3.5 ± 37.1

 -1.0 ± 29.7

83 ± 485

 -5.0 ± 18.9

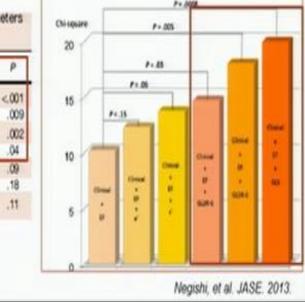
GLS

GLSR-S

GLSR-E

0CS

GRS

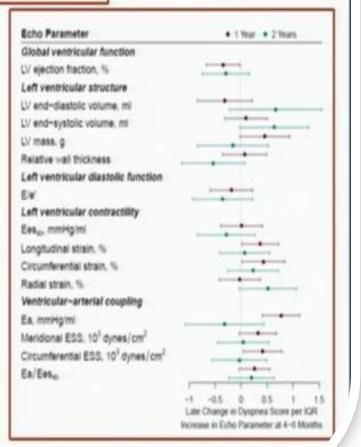


INAL RESEARCH ARTICLE

Detailed Echocardiographic Phenotyping in Breast Cancer Patients

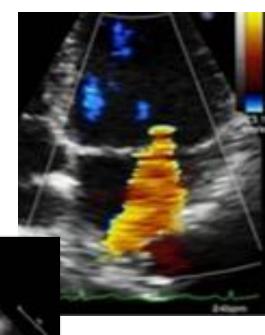
Associations With Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up

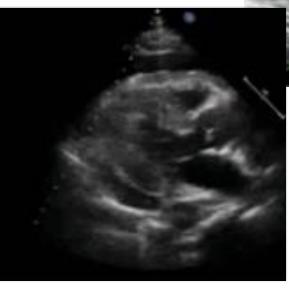
- 277 participants with breast cancer, treated with doxorubicin and/or trastuzumab
- Early changes in volumes, longitudinal & circumferential strain, arterial load (Ea), and Ea/Ees_{sb} are associated with subsequent LVEF declines and with cardiac symptoms



Structural Heart Disease in Echocardiography

- Valvular pathology with stenosis or regurgitation (aortic and mitral) from remodeling or radiation
- Tumor expansion :
 - Metastatic tumors >Primary (Lung, renal Cell, Melanoma and Mesothelioma)
 - Pericarditis/Pericardial effusion : Mets vs. radiation
- Pulmonary hypertension with RV dysfunction
 - Dasatinib, carfilzomib
 - Malignancies





Chemotherapy related cardiac dysfunction (CTRCD): Definition

	Definition	Modality of Measurement	Che motherapy Agents	Comments
Alexander et al.		Multigated acquisition (MUGA) s can	Anthra cycline	
Schwartz et al.	<u>Decline in LVEF > 10% to final</u> LVEF < 50%	MUGAscan	Anthra cycline	
Cardiac Review and Evaluation Committee		MUGA s ca n and e chocardiogram	Trastuzumab+/- Anthracycline	
Common Terminology Criteria for Advers e Events, version 4.03 (HF, left ventricular dysfunction)		Not de fined	N/A	Other definitions included such as troponin and clinical HF
American Society of Echocardiography and European As sociation of Cardiovascular Imaging	<pre>< 53% (suggests repeat i maging)</pre>	Echocardiography; two- dimensional (2D) and three- dimensional (3D) contrast, cardiac magnetic resonance imaging, MUGA scan		<u>First guideline to include</u> global longitudinal strain > -15%

Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 1979;300:278-83.

23. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med 1987 82:1109-18.

24. Seidman A, Hudis C, Pierri NK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215-21.

Common Terminology Criteria for Adverse Events (CTCAE) (U.S Department of Health and Human Services website). 2010. Available at: http://evs.nci.nih.gov/ftpt/CTCAE, Accessed February 2016.

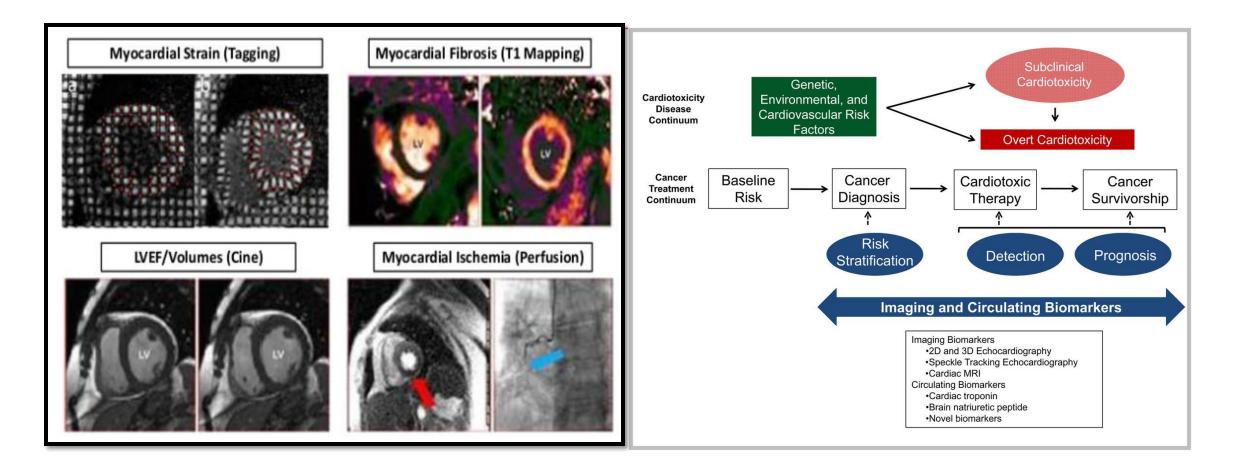
Routine Surveillance, How Often & For How Long?

Guideline	Who?	How Often
ASE Plana, et al. JASE. 2014.	 Anthracyclines Anti-HER2 therapies VEGF Inhibitors Proteasome inhibitors 	 Repeat 2-3 weeks after abnormal study 6 months after therapy completed Annual assessment with imaging as per provider
ESC Zamorano,	 Cardiotoxic therapies (Broadly defined)[†] 	LVEF before and periodically during Repeat 2-3 weeks after abnormal study
et al. EHJ. 2016.	Survivors	Periodic screening
ASCO Armenian,	 Asymptomatic, high risk DURING treatment* 	 Routine surveillance, frequency determined by provider
et al. JCO. 2016.	 Those with signs/symptoms concerning for dysfunction 	
ASCO Armenian,	 Asymptomatic, high risk AFTER treatment 	6 to 12 months after therapy completion
et al. JCO. 2016.	 Those with signs/symptoms concerning for dysfunction 	

* High risk = high dose anthracyclines, high dose radiotherapy; multiple CV risk factors, older age, compromised CV function; sequential therapy (anthracyclines + radiation or trastuzumab) † Cardiotoxic therapies = anthracyclines, alkylating agents, antimetabolites, antimicrotubules, monoclonal antibodies. TKIs, proteasome inhibitors, misc.

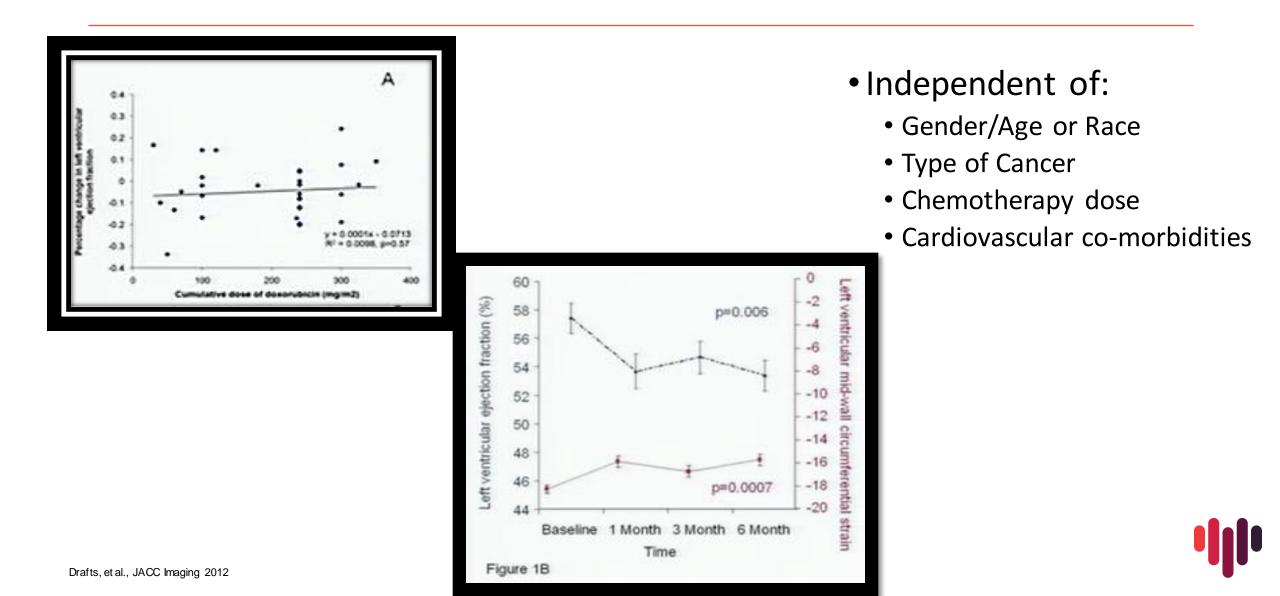
Cardiac Magnetic Resonance Imaging

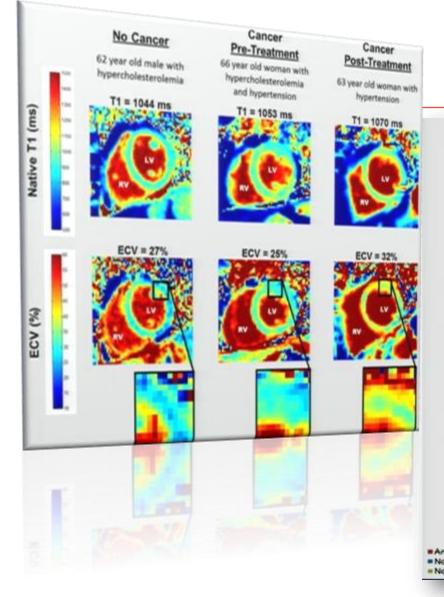
Chemotherapy and CMR

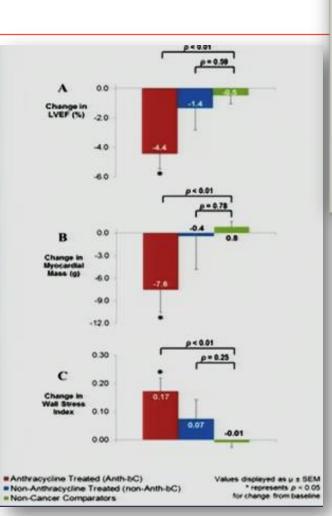


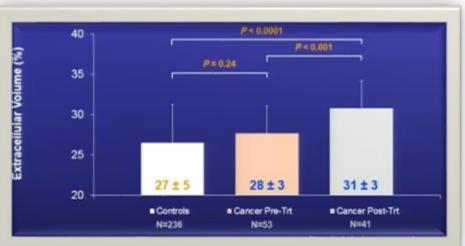
Hundley, et al J Cardiovasc MR 2013 Drafts, et al., JACC Imaging 2012

Anthracyclines Based Chemotherapy and Strain on CMR









Questions