Risks of Cardiovascular Disease with Lung Cancer

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Disclosures

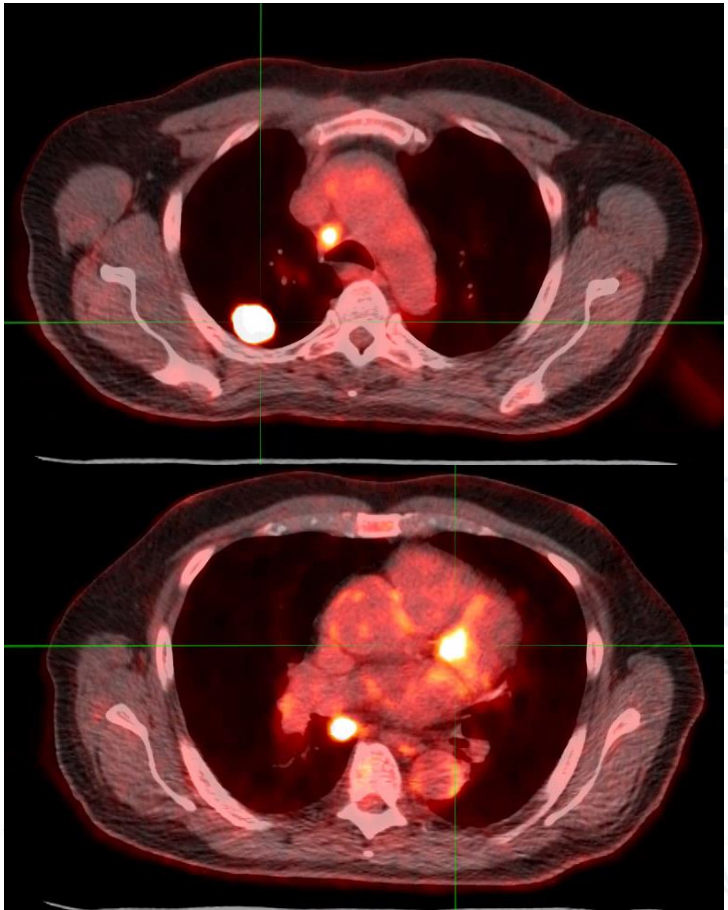
- LS:
  - Consulting: MJH Life Sciences, Regeneron, HMP Global
- RM:
  - Advisory Board: AstraZeneca, ViewRay
  - Research Grants: ViewRay

Outline

- Why does cardiovascular risk mitigation matter in lung cancer?
- Radiation-induced cardiac toxicity in lung cancer
- Chemotherapy-related cardiotoxicity in lung cancer
- Targeted Therapies/Immunotherapy

Case – Stage III NSCLC

- 68 year old man with 40-pk yr smoking history presents with progressive cough/dyspnea
- No prior cardiac history
- Bronch/EBUS reveals hilar and mediastinal lymph nodes involved with adenocarcinoma of lung origin (N2)



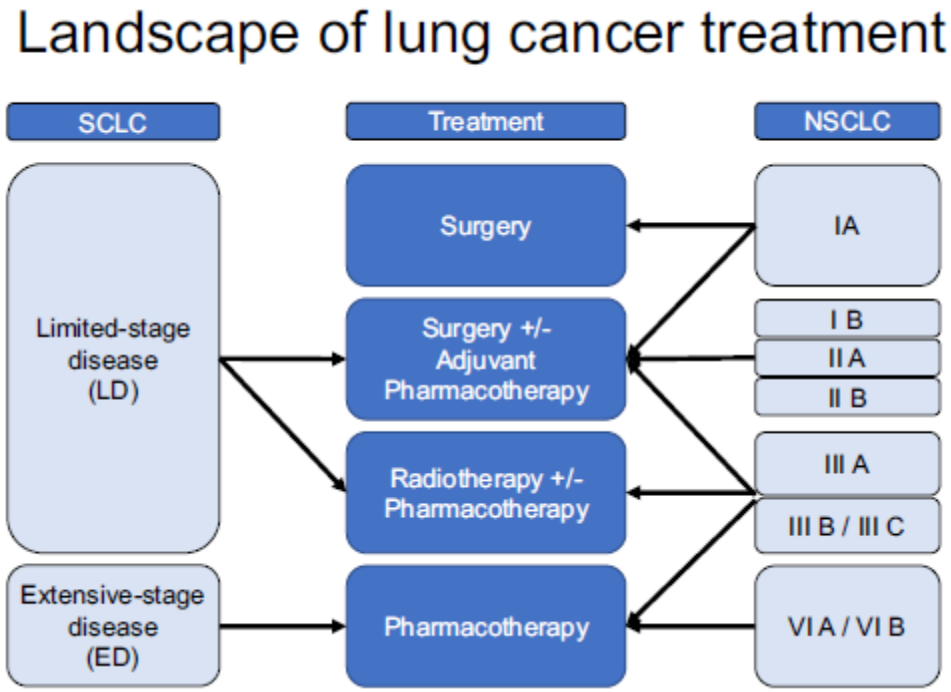
Patients with lung cancer often have underlying cardiovascular risk factors or disease

- Shared risk factors – smoking, age, systemic inflammation
- Patients with lung cancer have >60% increased risk of CVD[1]
- Smoking-related diseases (CVD, lung cancer) are leading causes of socioeconomic disparities in mortality[2]

[1]Yuan J Card Vasc Anes 2018 [2]Wong, NEJM 2002

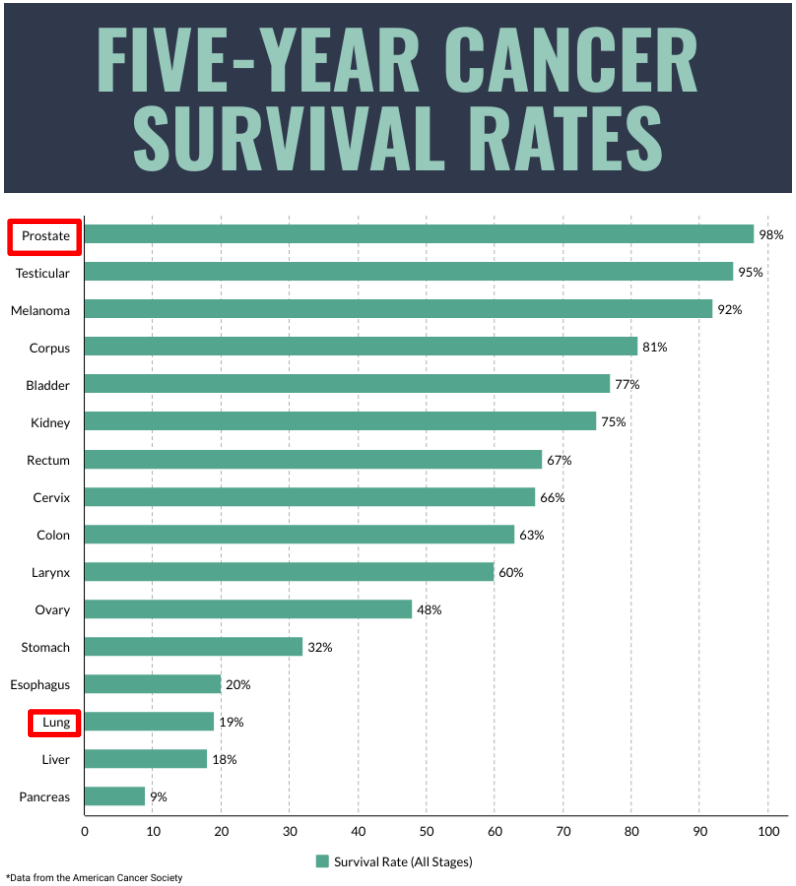
Lung cancer therapies can also increase CV risk

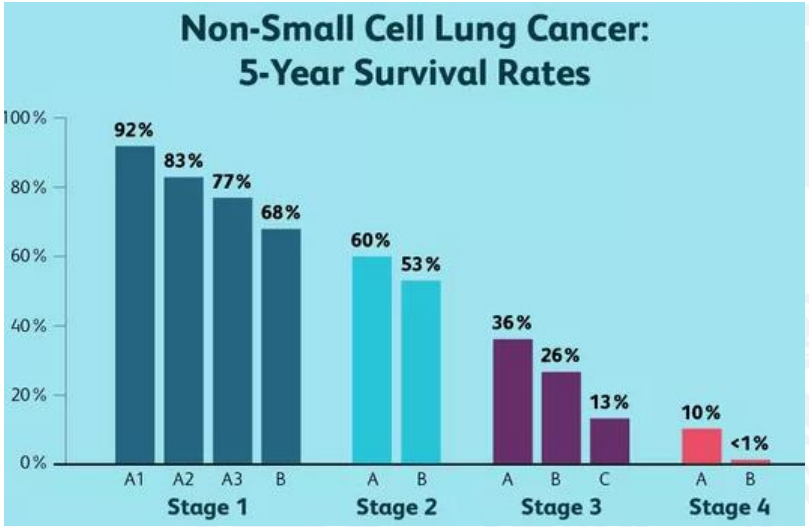
- Early stage
  - Surgery
  - RT
- Locally advanced
  - Chemoradiotherapy
- Metastatic
  - Chemotherapy
  - Immunotherapy
  - Targeted therapies



Sase Curr. Treat. Options in Oncol. (2021)

Importance of CV risk depends on cancer mortality: Concept of Competing Risks





American Cancer Society 2017

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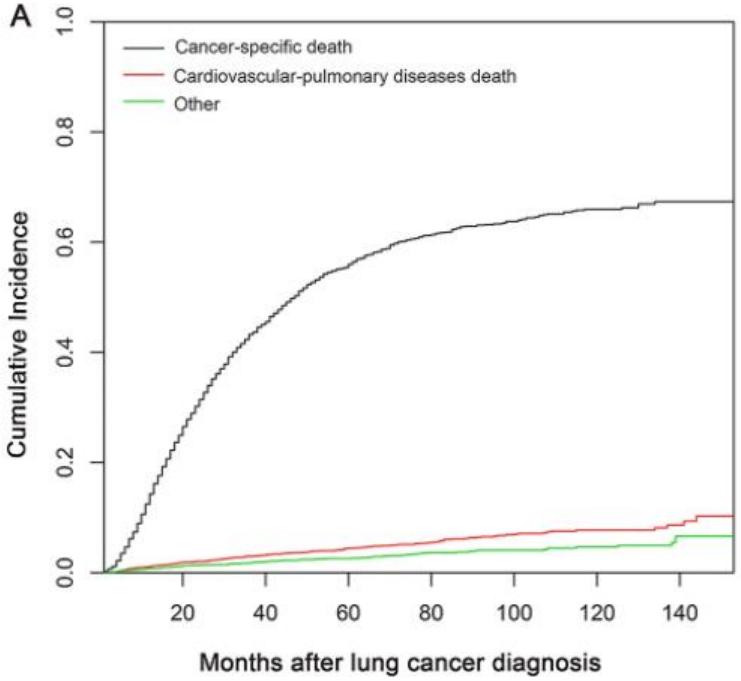
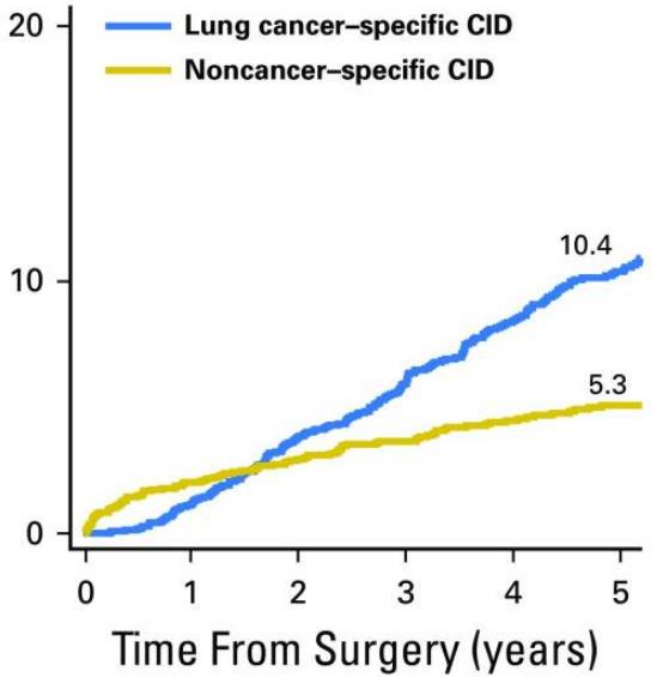
Cancer vs non-cancer mortality varies by disease stage

Stage IIIA disease (SEER database)
Wang et al Radiat Oncol 2021



Stage I disease (MSK)
Eguchi JCO 2017



- Focus CV risk mitigation strategies on earlier stage disease?

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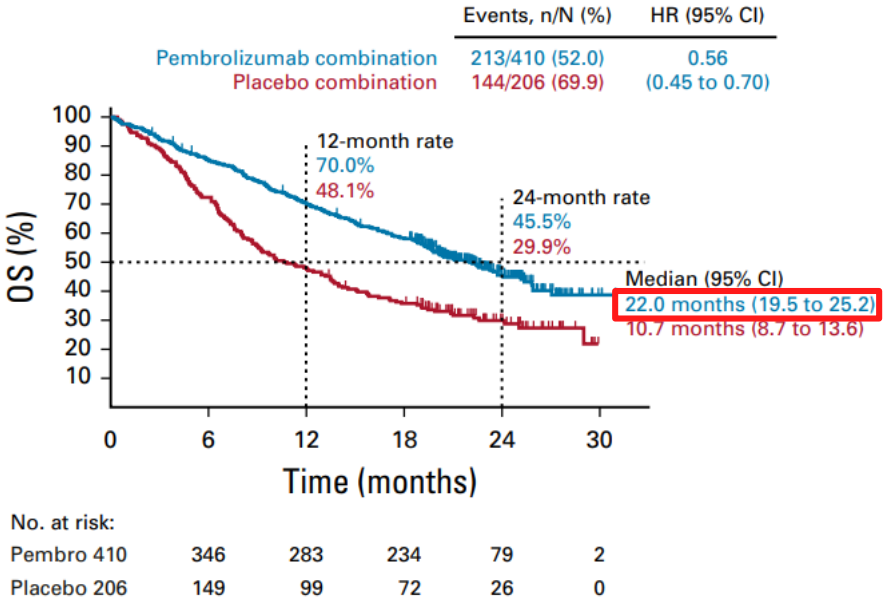
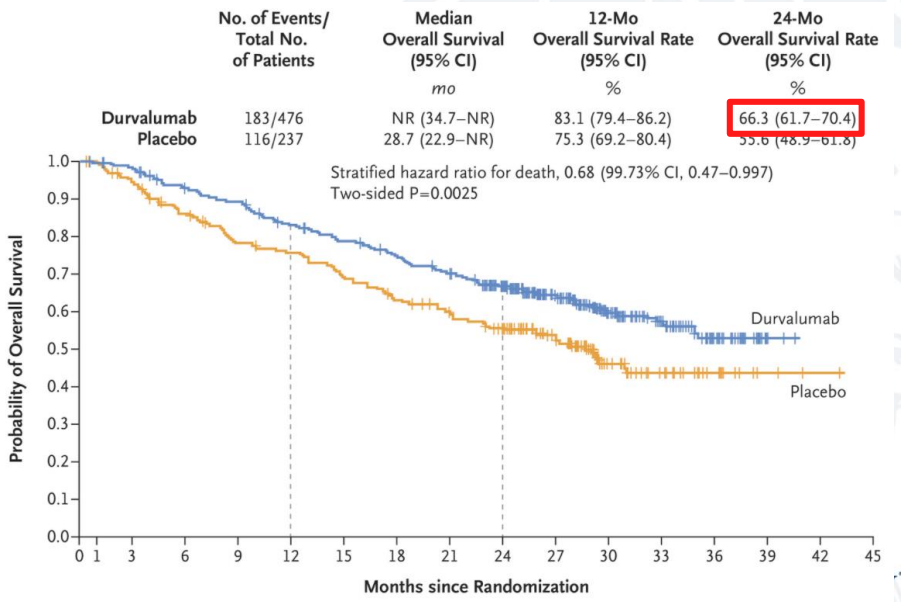
BUT: Patients with advanced/metastatic disease are now living longer with improvements in systemic therapy

KN189, Gadgeel JCO 2020 (Metastatic)



PACIFIC, Antonia, NEJM 2017 (Locally Advanced)



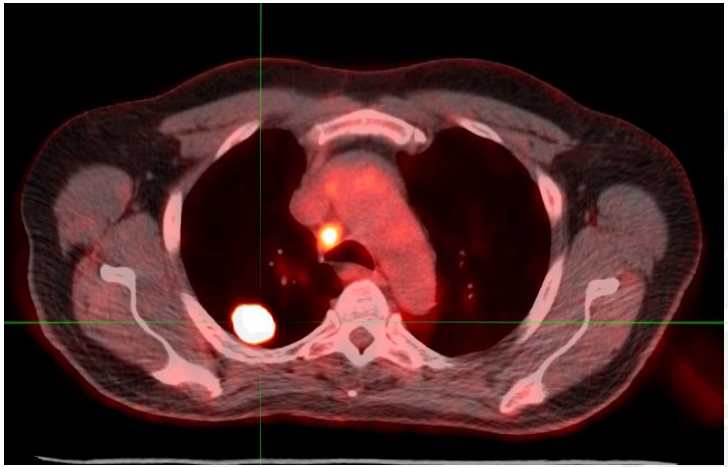
CV Risk Mitigation is an important goal in lung cancer management

- Lung cancer patients have a high burden of CV risk factors
- Early stage patients, but increasingly also advanced stage patients, may live long enough to experience cardiac toxicities from treatment
- Even if risk of cancer mortality >> cardiovascular mortality, CV events can have significant impact on quality of life
- CVD comorbidities are associated with decreased NSCLC survival[1]
  → Improving cardiovascular health may also improve cancer prognosis

Kravchenko Lung Cancer 2015

Back to the case

- Plan for RT + concurrent chemo



Radiation Therapy for Non-Small Cell Lung Cancer in 2022

Stage I Localized Lung Tumor

SURGERY
vs.

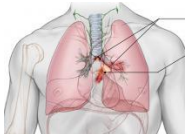
Stereotactic
Body Radiation Therapy

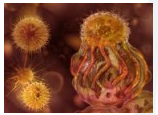
Stage II Localized Node+

SURGERY

CHEMO

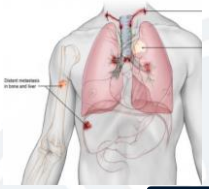
Stage IIIA/B Locally Advanced





COMBINED
MODALITY

Stage IV Metastatic



1st/2nd Line:
Immunotherapy,
Chemo, or Targeted
Therapy*

Palliative
Radiation Therapy
Or
Consolidative RT

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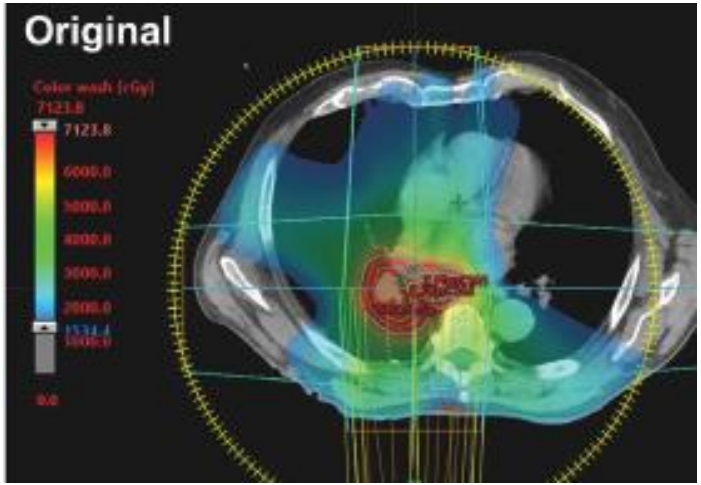
Introduction to Lung Cancer Radiation Therapy Planning

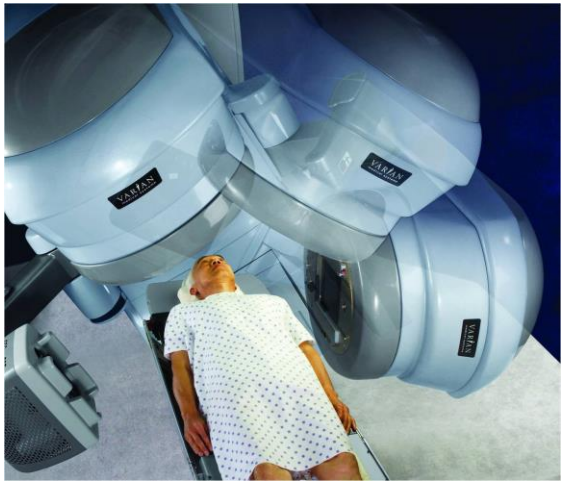


- Current RT planning techniques attempt to minimize radiation dose to the whole heart.
- Complete avoidance of the heart is often not feasible, due to tradeoffs with:
  - Adequate dose delivery to the tumor for **cure**
  - Dose reduction to other critical organs
    - Spinal cord, Lungs, Esophagus

1. Atkins KM, Chaunzwa TL, Lamba N, et al. Association of Left Anterior Descending Coronary Artery Radiation Dose with Major Adverse Cardiac Events and Mortality in Patients with Non-Small Cell Lung Cancer. *JAMA Oncol*. 2020;02115(2):206-219. doi:10.1001/jamaoncol.2020.6332

Modern Photon-Base Radiation Therapy Delivery :

The Linear Accelerator (“Linac”)



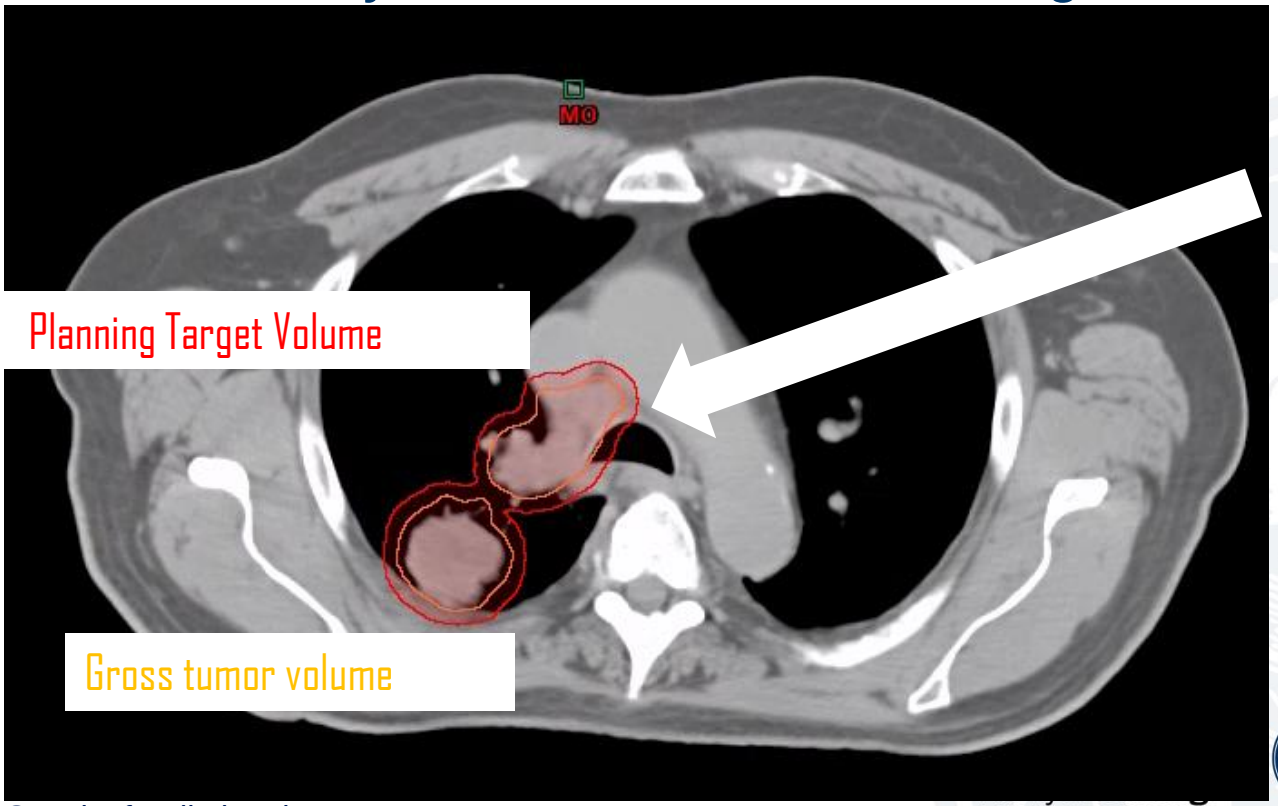
Treatment head on rotational gantry
Image-guided

Mobile couch to position patient

Beams shaped and modulated

Lung Cancer Target Volumes

Dose of ~60 Gray in 30 treatments for Stage III NSCLC



Tumor targets drawn slice-by-slice on planning CT scan

*Gray (Gy) is the SI unit of radiation dose

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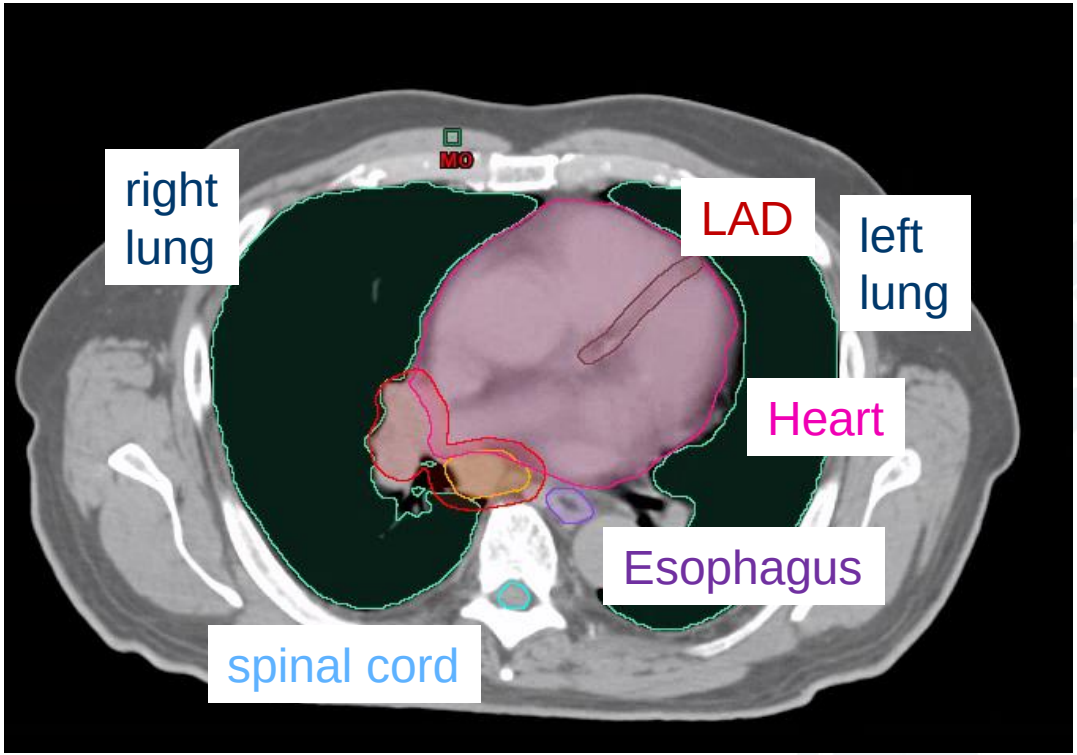
Critical Organs

Constraints need to be met

Organs drawn slice-by-slice on planning CT scan



Key point: If you don't draw it, you can't measure dose. *You can't avoid or protect it*

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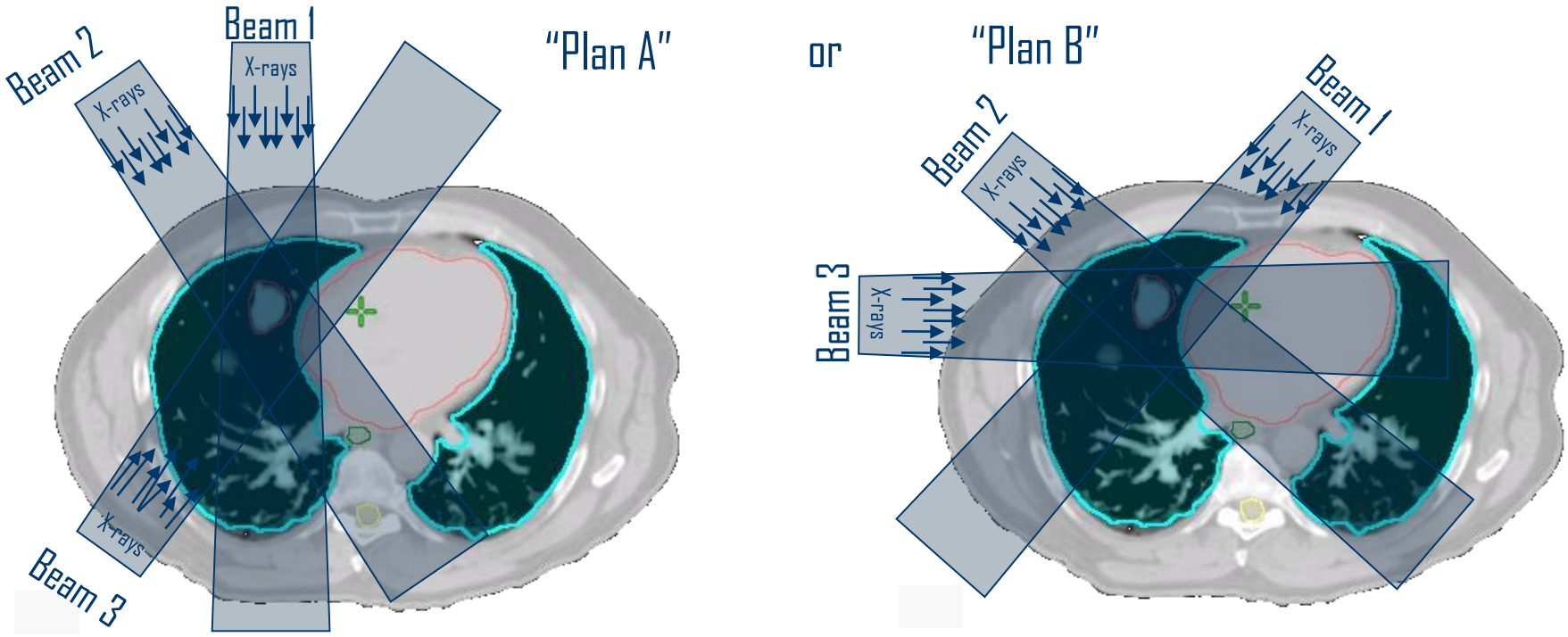
Radiation Treatment Planning: Placing Treatment Beams

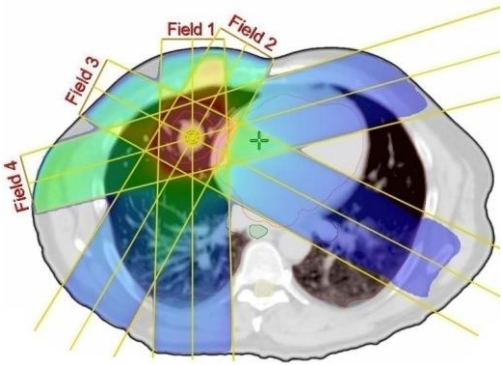


A radiation plan is composed of a set of X-ray 'Beams'
Each Beam directs radiation at the patient's tumor from a specific direction (angle).

Optimizing and Comparing Radiation Plans

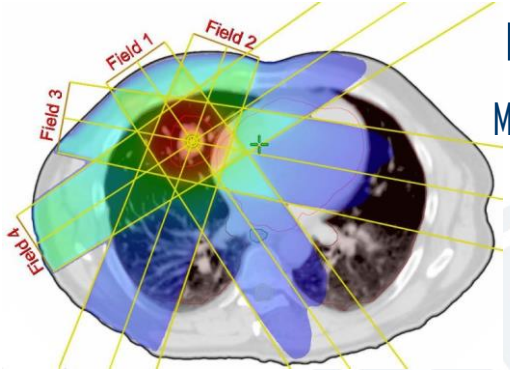
Plan A

Mean heart dose: 10 Gy



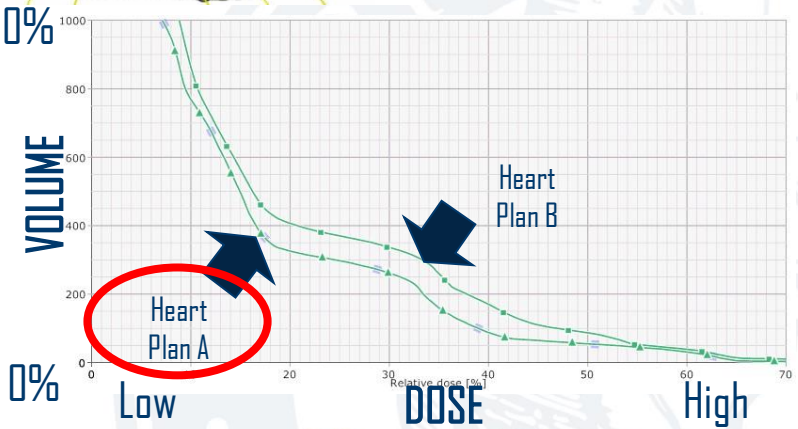
Plan B

Mean heart dose: 15 Gy



Blue: Low Dose
Green: Medium Dose
Red: High Dose

- Different plans may achieve different dose to a given volume of each organ
- In this case plan A is clearly better in terms of low-intermediate dose exposure to the heart.



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RT-Associated Cardiac Injury in NSCLC

- Clinical relevance historically **minimized** due to three assumptions:
  1. **High likelihood of competing risk of lung cancer death**
  2. **Prolonged latency of cardiac toxicity**
  3. **Cardiac dose exposure is less important than pulmonary dose**

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RT-Associated Cardiac Injury in NSCLC

- Recent studies have refuted all three claims
  1. **5 year survival for stage III NSCLC ~ 43% (PACIFIC trial)** [1]
  2. **Cardiac events** are **common** and occur early [2,3,6]
  3. **Heart dose** is an **independent predictor of mortality** [4-5] **and MACE**[5]

Dr. Katelyn Atkins

[1]Antonia et al. *N Engl J Med.* 2018;379:2342-50
[2]Wang, *J Clin Oncol* 2017;35:1387-1394
[3]Dess, *J Clin Oncol* 2017;35:1395-1402
[4]Bradley, *Lancet Oncol* 2015;16:187-99,
[5]Speirs, *J Thorac Oncol* 2017;12:293-301
[6]Atkins et al, *J Am Coll Cardiol.* 2019;73:2976-87

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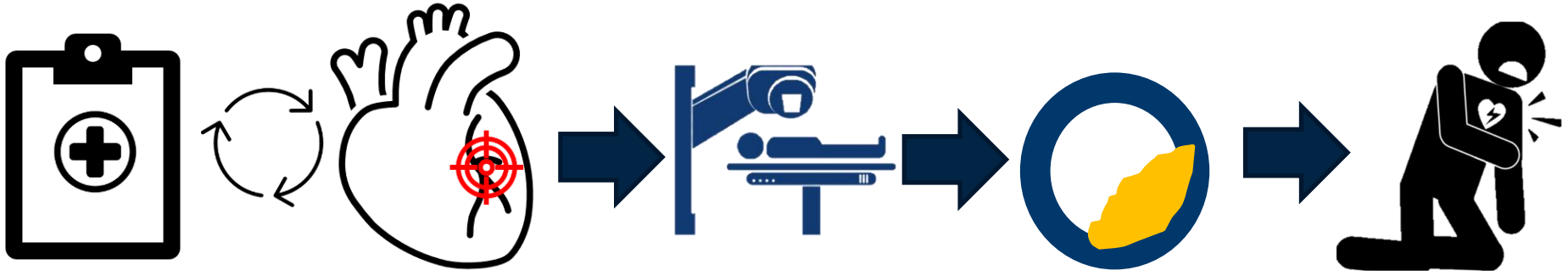
Guiding Principles to Understand Cardiac Injury after RT in Lung Cancer Patients

1) Impact of **pre-existing co-morbidities and cardiac health**
2) Radiation dose exposure to anatomic/functional cardiac sub-structures
3) A potential pathophysiological pathway of injury
4) An outcome that measures that injury



Our Approach to Study RT-Cardiac Injury

Data Set
- 748 patients with locally advanced NSCLC
- Treated with chemoradiation at BWH/DFCI in 1998-2014
- Median follow-up: 20.4 months

Detailed Radiation Dosimetric Data
- Whole heart manually re-segmented
- Coronaries and chambers segmented
- Dose exposure calculated

Baseline Cardiovascular Health
- Baseline cardiac risk factors and meds
- **Prior coronary heart disease (CHD)**
- Baseline **Framingham Risk** assessed
- Deep learning-based coronary artery calcium

Outcomes (Standardized Cardiac Clinical Trial Endpoints):
- Major adverse cardiovascular events (MACE):
  Myocardial infarction, Cardiac death, Coronary revascularization, Heart failure
- Detailed cardiac toxicity events by subtype (NCI CTCAE version 4.03)
- All cause mortality

American Heart Association.

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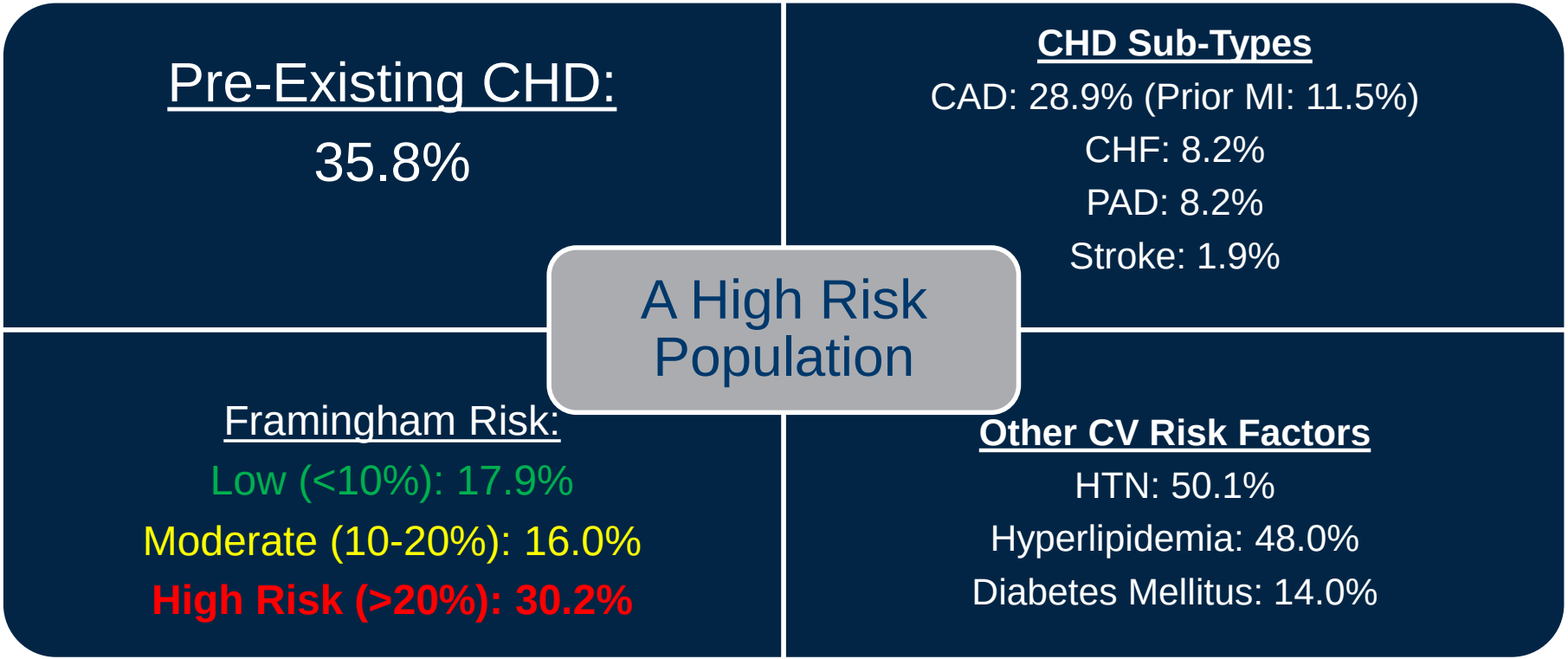
Cardiac Health ***Before*** RT for Lung Cancer



Atkins, *J Am Coll Cardiol*. 2019;73:2976-2987

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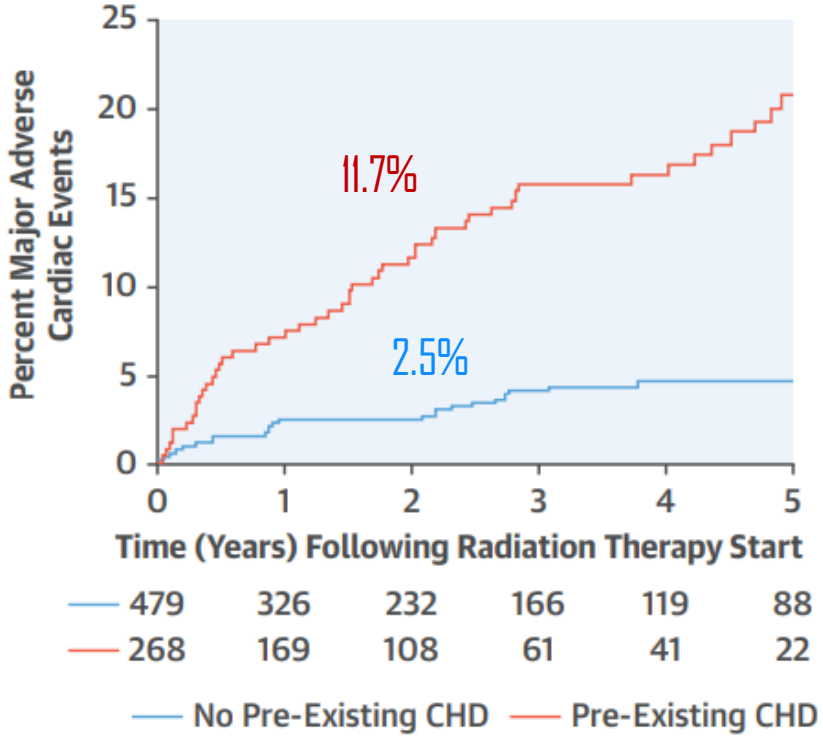
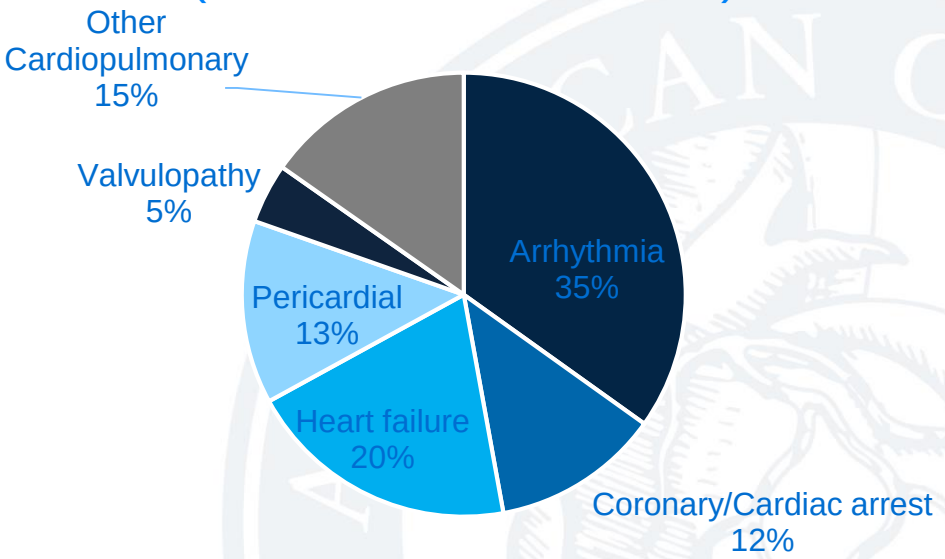
Cardiac Events After RT for Lung Cancer

MACE by CHD Status



Atkins, *J Am Coll Cardiol.* 2019;73:2976-2987

Grade ≥3 CTCAE Cardiac Toxicity (n=240; 32.1% of cohort)



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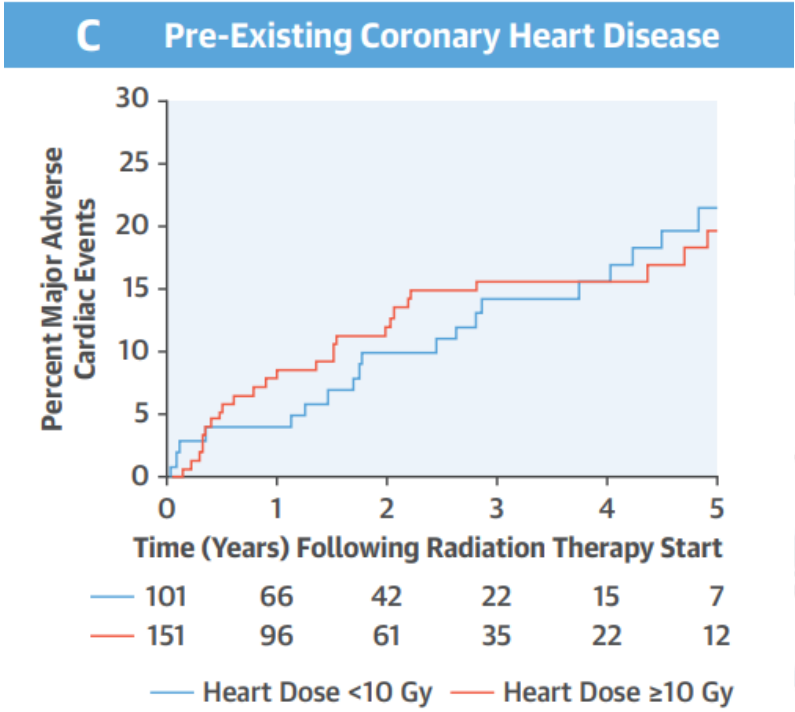
Mean Heart Dose, Major Adverse Cardiac Events and Mortality

- ↑ All-cause mortality: HR 1.02/Gy
- ↑ MACE: HR 1.05/Gy

- MHD ≥ vs.<10 Gy (**CHD-neg**):
  - ↑ MACE (HR 3.01, p=.025)
  - ↑ ACM (HR 1.34, p=.014)



Atkins, *J Am Coll Cardiol.* 2019;73:2976-2987

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Mean Heart Dose Summary

- Mean heart dose is associated with MACE and ACM
- CHD-negative patients may benefit most from minimization of mean heart dose to <10 Gy
- We should not assume that dose does not matter for CHD-positive patients
- Identifies high risk patients that may benefit from early cardiac intervention
- MHD is easily measurable and can be communicated

Atkins, *J Am Coll Cardiol.* 2019;73:2976-2987

Historical Trends in Recommended Heart Dose for Lung Cancer RT from National Guidelines

From Very, Very High To Very High

2011

Mean: No constraint

2013-2017

Mean ≤ 35 Gy

2018

Mean ≤ 26 Gy

2019-2022

Mean ≤ 20 Gy

Sanity Check Breast Cancer

Mean <1-2 Gy

Reference: NCCN

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Why Mean Heart Dose May Be Meaningless

Intersecting Dose, Pathophysiology and Endpoint

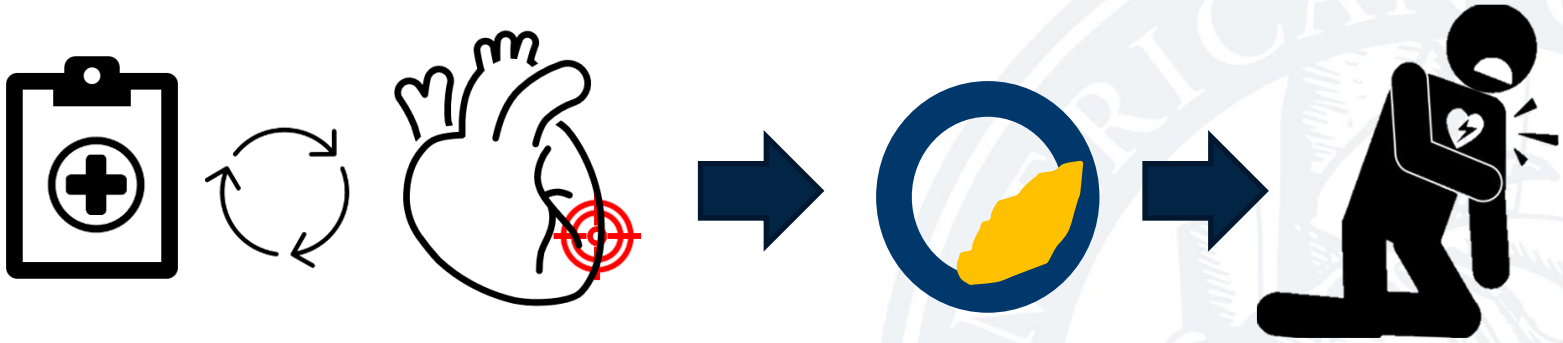
New Approach

Coronary Heart Disease History

Let's look at coronary dose!

Atherosclerosis?

MACE



Prior Approaches

~~Not captured~~

~~Mean Heart Dose~~

?

~~Pooled CTCAE Cardi Tox~~

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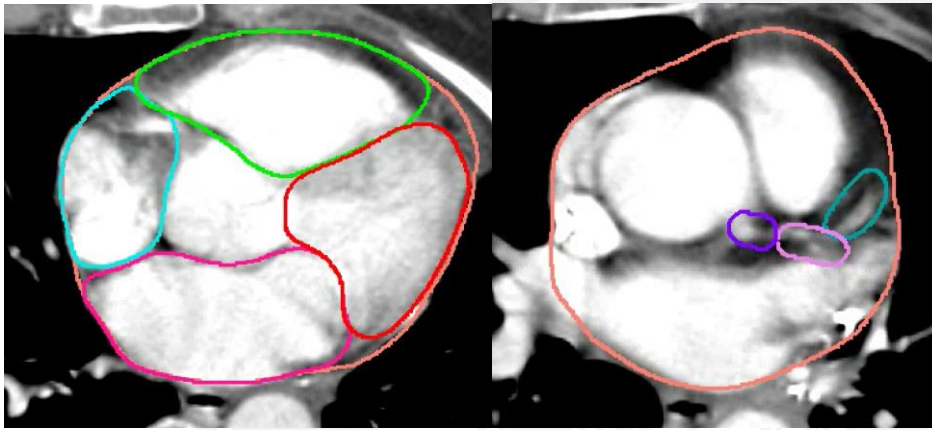
Coronary Dose and MACE

- Cardiac substructures **manually** delineated on planning CT using cardiac CT atlas[1]
  - Chambers (Atria and Ventricles)
  - Coronary artery spaces:
    - Left main (LM)
    - Left anterior descending (LAD)
    - Left circumflex (LCx)
    - Right (RCA)
    - Posterior descending (PDA)



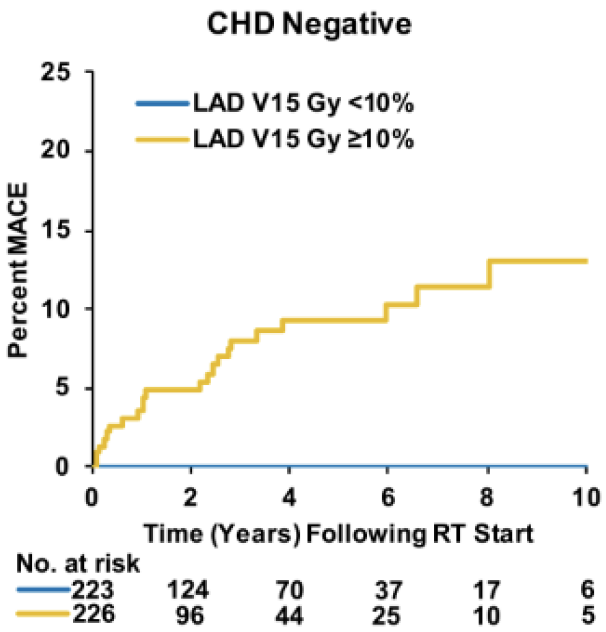
- Calculated radiation dose exposure to each substructure

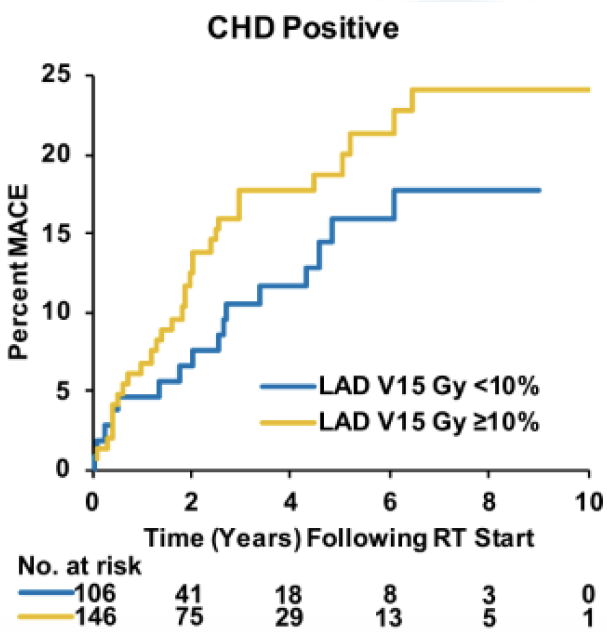
[1]Feng *Int J Radiat Oncol Biol Phys.* 2011;79:10-8,

Risk of MACE Associated with LAD Volume Receiving ≥15 Gy (V15)

1-year MACE Estimates Stratified by LAD V15 Gy

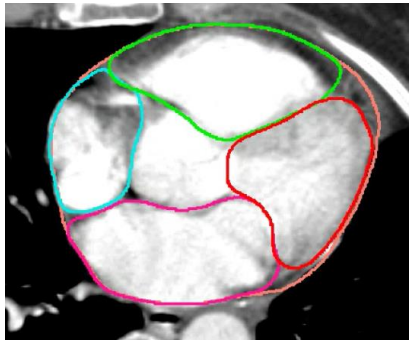
LAD V15	≥10%	<10%	*P*
Total	5.9%	1.5%	<.001
CHD−	**4.9%**	**0.0%**	**.001**
CHD+	7.6%	4.7%	.25

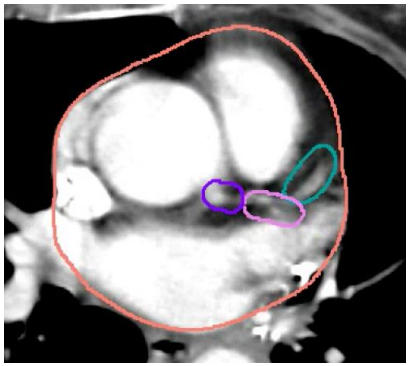




Atkins et al. *JAMA Oncol*. 2020;02115(2):206-219

Coronary Dose and MACE Summary





- Volume of left anterior descending (LAD) coronary artery receiving ≥15 Gy is associated with MACE
- Greatest increase in MACE risk in CHD-negative patients
- Left ventricular dose (V15 ≥ 1%) was associated with MACE risk for CHD-positive patients
- Radiation oncology guidelines and practice need to evolve to adopt coronary sparing planning approaches

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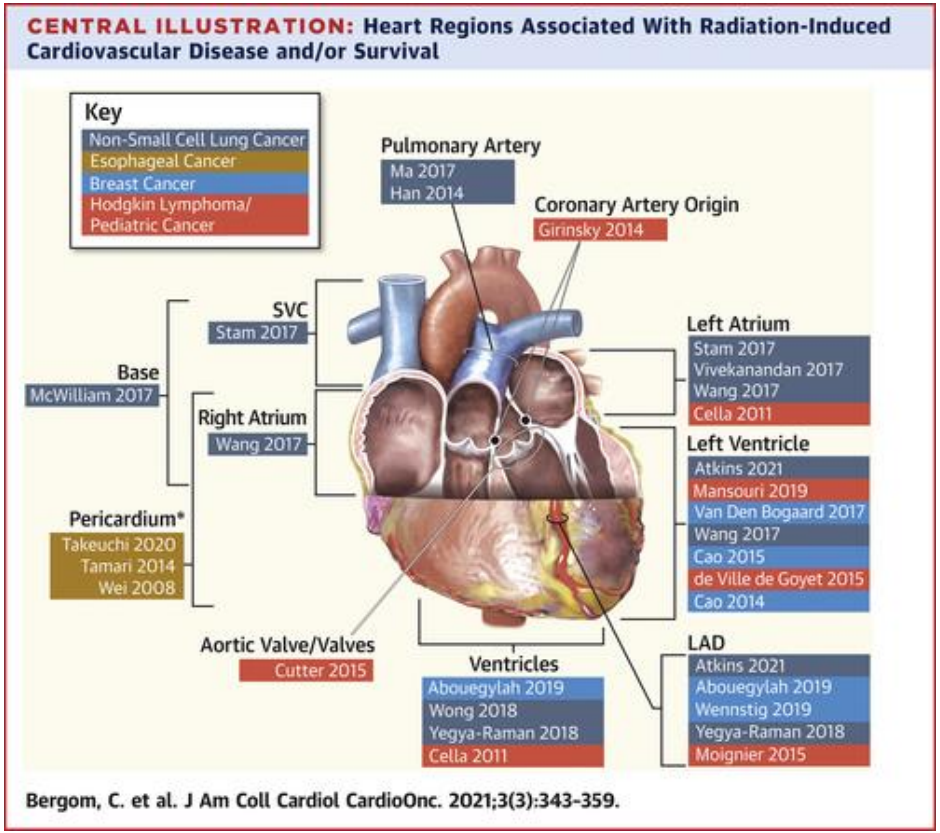
Atkins et al. *JAMA Oncol*. 2020;02115(2):206-219

Shifting Toward Sub-Structure Dose



- We will need to continue to improve our capture of cardiac endpoints too!

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Cardiac Toxicity Risk Mitigation

- Is it hopeless?
- No, it may be easier than we think…
  1. Medically optimizing lung cancer patients prior to cancer treatment
  2. Minimizing cardiac dose as a modifiable risk factor
  3. Screening for high risk patients

Cardiac Risk Optimization Pre-RT

- 66% of patients were **high cardiac risk** before RT
  (Framingham risk ≥20% or pre-existing CHD; n=496)
- Statin use in this subset was **51%**
- **Significant gap in application of guidelines-based cardiac risk modification**

Atkins et al. Pract Radiat Oncol 2021;11(5):e459-e467

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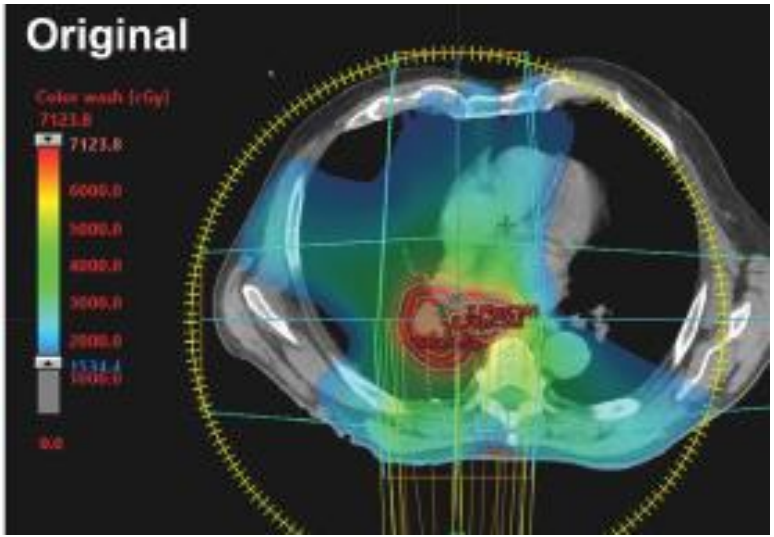
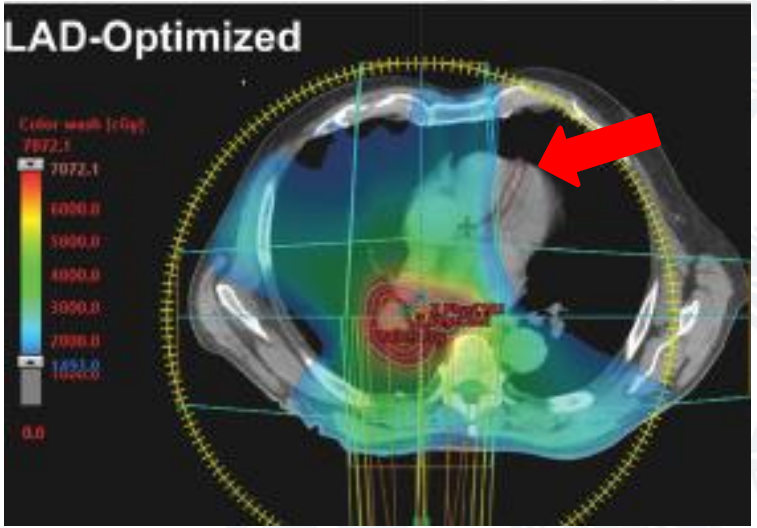
Lowering Mean Heart Dose and Coronary Sparing Radiation Plans

Machine Learning analysis revealed ~20% of prior RT plans could have a lower MHD[1]

Coronary Optimized to Low Dose (COLD-RT) radiation plan "library" for automated planning





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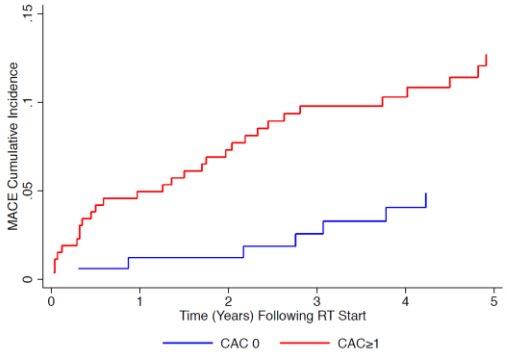
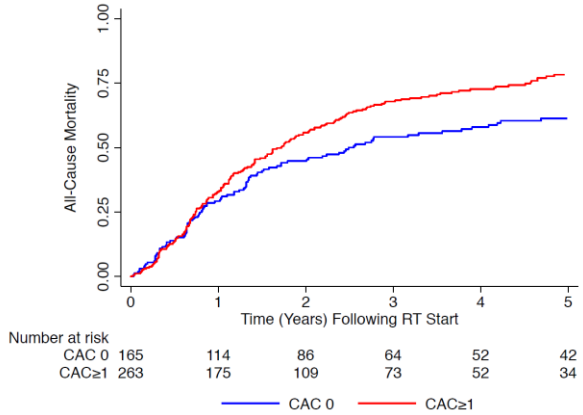
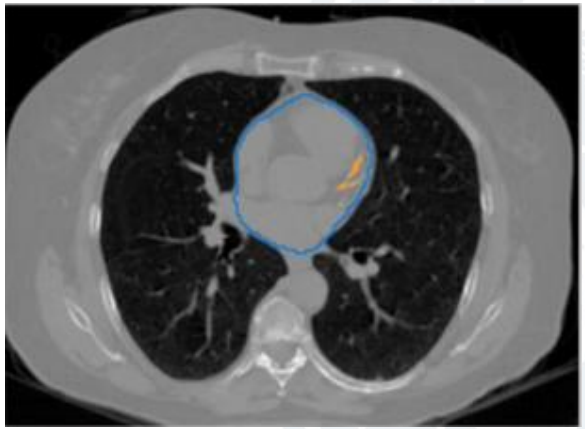
1. Bitterman et al. Int J Radiat Oncol Biol Phys. Accepted

Improving Cardiac Risk Screening at RadOnc Point of Care





- Deep learning algorithm for automated coronary artery calcium scoring[1]
- Proof-of-concept application to RT planning CT[2]
- Identifies patients at higher risk for MACE



1. Zeleznik et al. Nature Comm, 2021;12:715
2. Atkins et al. JCO Clin Cancer Inform. Accepted

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Where Do We Go From Here?
Short-Term – Building Bridges

Radiation Oncologists

- Refer lung cancer pts early to cardiologists
- Minimize heart dose
- Protect the coronaries
- Understand radiation dose as a **modifiable cardiac risk factor**

Cardiologists

- Ask your friendly radiation oncologist about MHD and coronary dose
- Risk stratify using cardiac dose and treat high risk lung cancer patients

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Where Do We Go From Here?
Long Term

- Communication and Training
- Shared Understanding of Risk and Prediction Tools
- Identifying Outcomes and Mitigation Approaches

Quantify baseline cardiac risk and mitigate

Focus on sub-structure dose

Cardiac-sparing RT plans

Understand pathophys mechanisms

Define and capture cardiac endpoints

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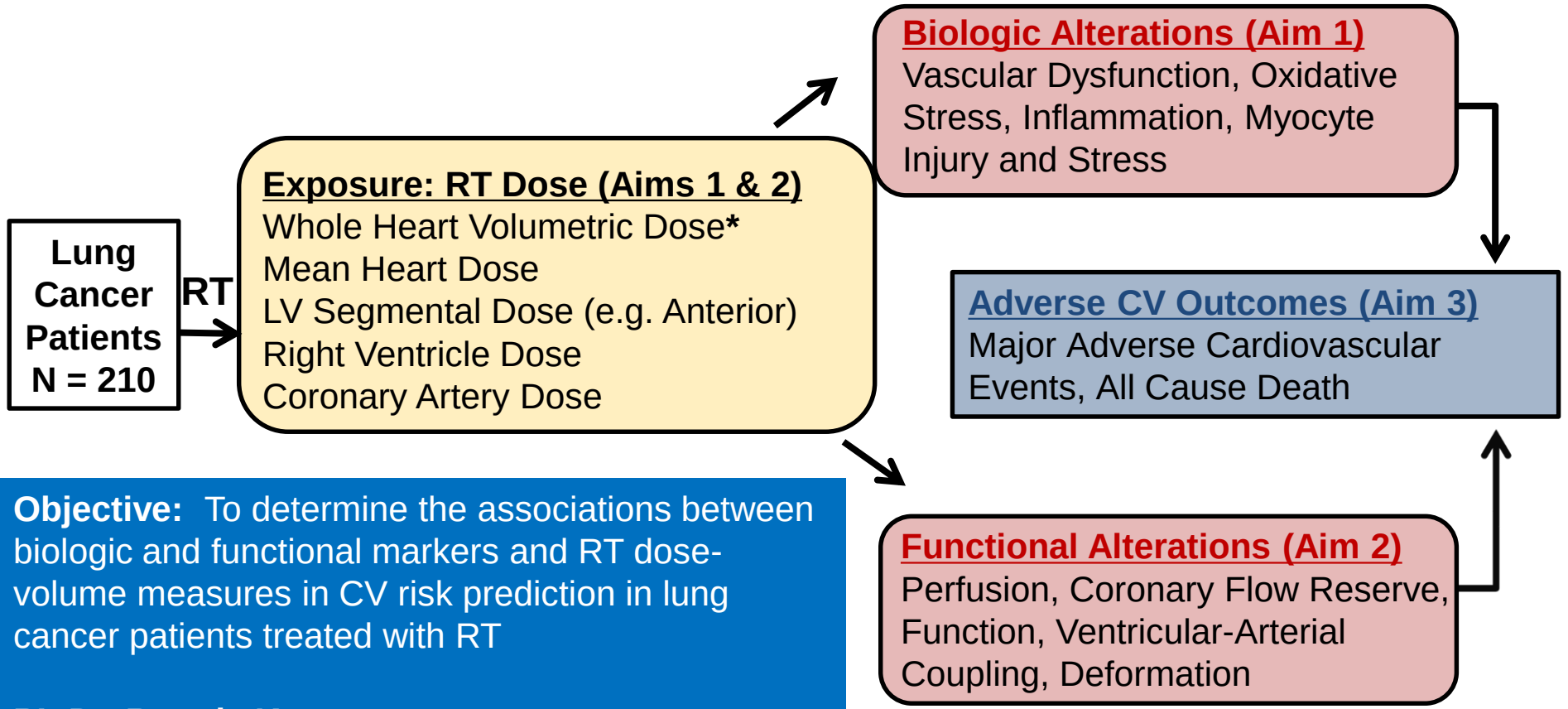
CLARITY: Cardiotoxicity in Locally Advanced Lung Cancer Patients Treated with Chemoradiation Therapy: A Prospective Longitudinal Cohort

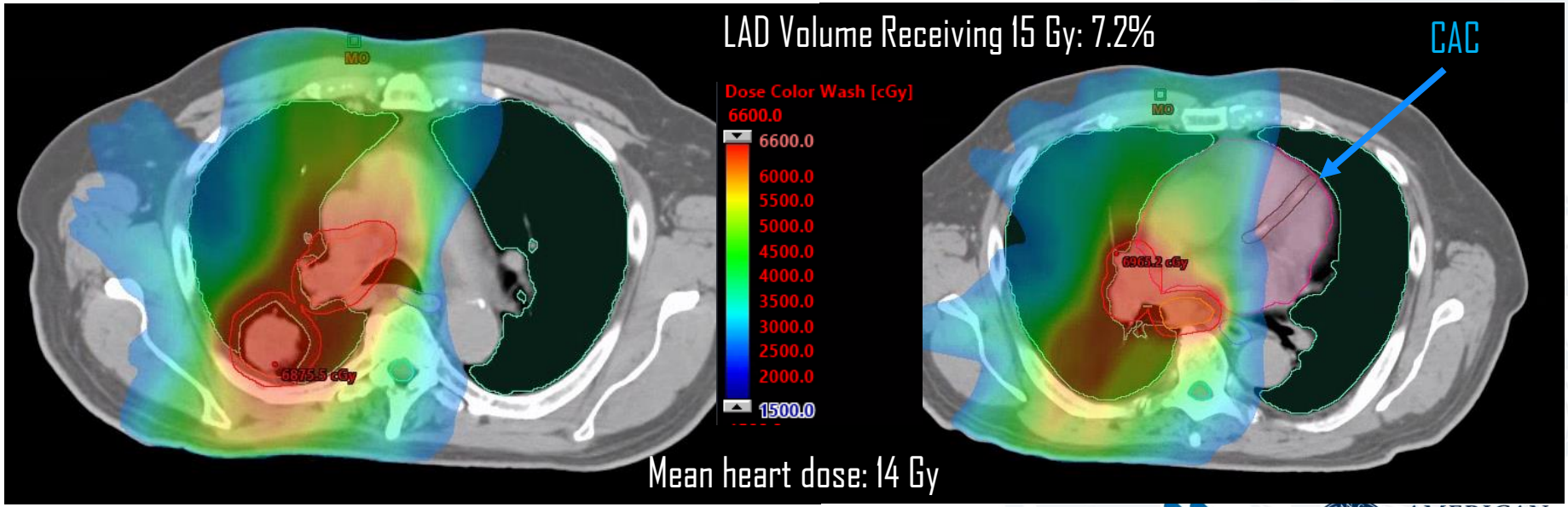


Objective: To determine the associations between biologic and functional markers and RT dose-volume measures in CV risk prediction in lung cancer patients treated with RT

PI: Dr. Bonnie Ky

Back to the Case

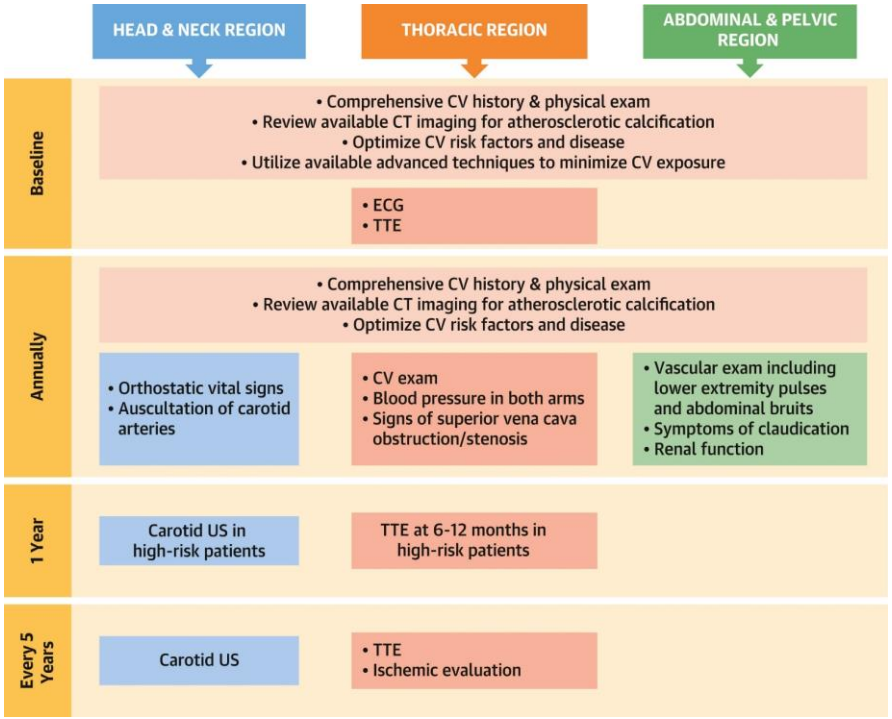
- IMRT plan to 66 Gy in 33 fractions with cisplatin/pemetrexed
- COLD-RT technique



- Follow-up?

International Cardio-Oncology Society

Recommendations for Treatment and Prevention of CV Disease During and After Thoracic RT



- Can be useful:
  - Baseline ECG/TTE if prior CV risk factors
  - Q5 yr screening with CAC, coronary CTA, or functional stress test
- Recommend:
  - Review available CT for coronary / aortic calcification
  - Screening TTE or cardiac MR after cancer therapy if ▲CM risk
  - Screening TTE within 5 years (6-12 mo in high risk) and q5 years to screen for valvular, pericardial disease

Mitchell et al. J Am Coll Cardiol CardioOnc. 2021;(3) 360–380

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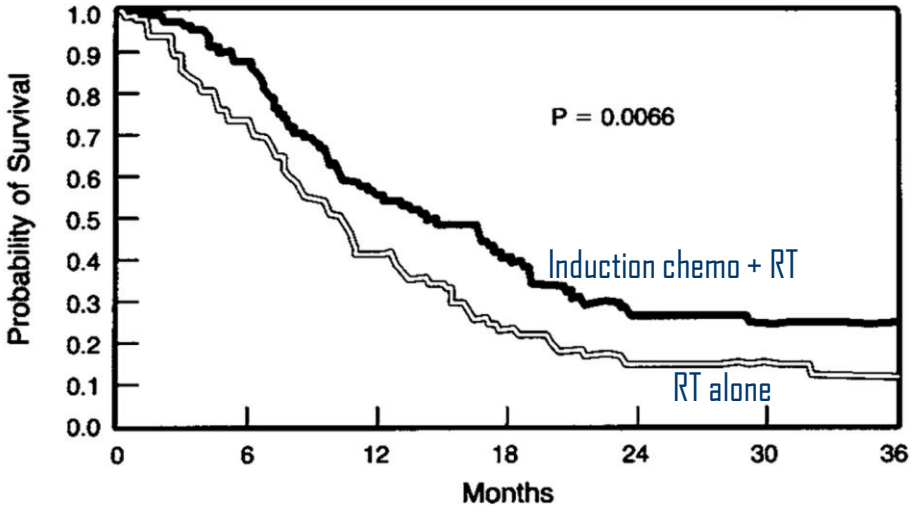
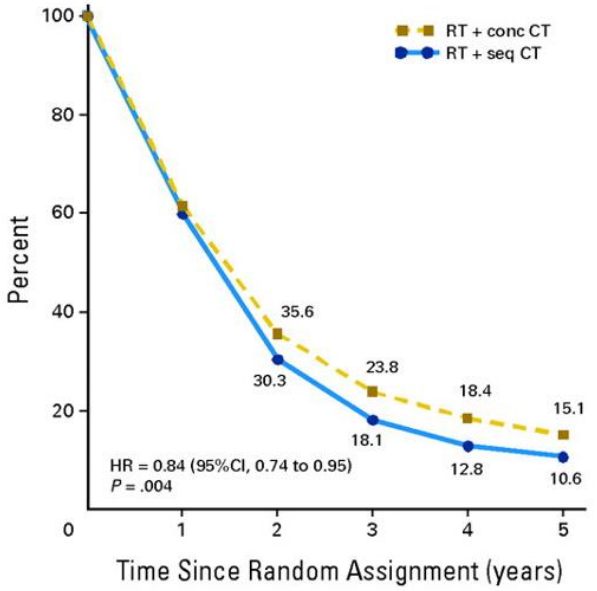
Back to the case:
We also add concurrent chemotherapy…



Group	Alive	Died	Total	Median Survival (mo)
1	20	58	78	13.8
2	9	68	77	9.7



	Deaths/Person-Years by Period				
	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/ 83	23/126

Dillman NEJM 1990
Auperin JCO 2010

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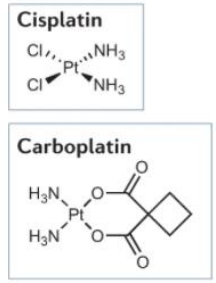
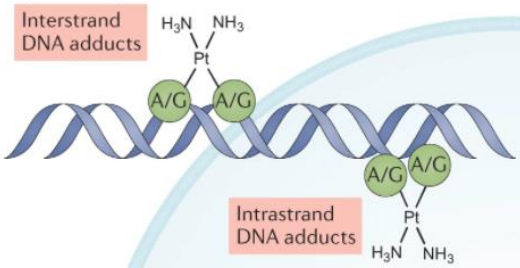
Cardiotoxicity from chemotherapy in lung cancer

- “Platinum doublet” is mainstay of therapy
- **Cisplatin** causes oxidative stress, vascular damage
  - Arrhythmias, EKG changes (SVT, bradycardia, BBB)
    - Also related to electrolyte abnormalities from renal dysfunction
  - Myocardial ischemia, myocarditis, cardiomyopathy
  - Long-term: HTN, Raynaud, CVA/cerebral ischemia[1]
- Microtubule agents: taxanes, vinca alkaloids
  - **Paclitaxel**, **docetaxel** – bradycardia, heart block[2]
  - **Vincristine, vinorelbine** – hypertension, MI
- Etoposide – MI, angina





[1]Meinardi JCO 2000 [2]Trimble JCO 1993 Yeh Circ 2004

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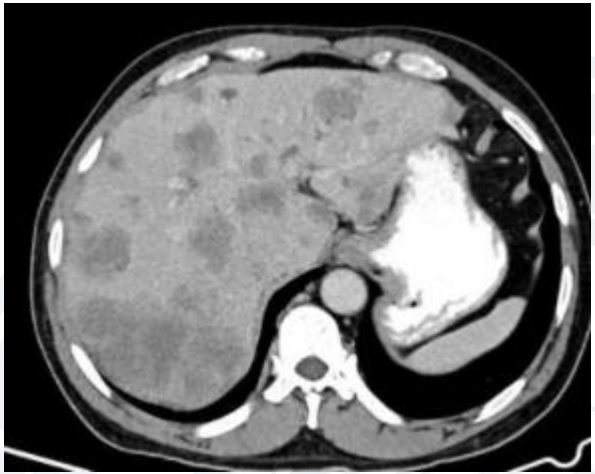
Cardiotoxicity from chemotherapy in lung cancer

- These agents are often not included in guideline statements on cardiotoxicity from cancer treatment
- Management / monitoring concepts
  - Primary/secondary CV risk mitigation
  - Choose the right agent (ex. carboplatin rather than cisplatin)
  - Routine clinical monitoring (electrolytes, BP)
  - Individualized risk-based LVEF monitoring
  - Investigational: cardiac blood biomarkers?[1]

[1]Demkow Resp Phys 2013

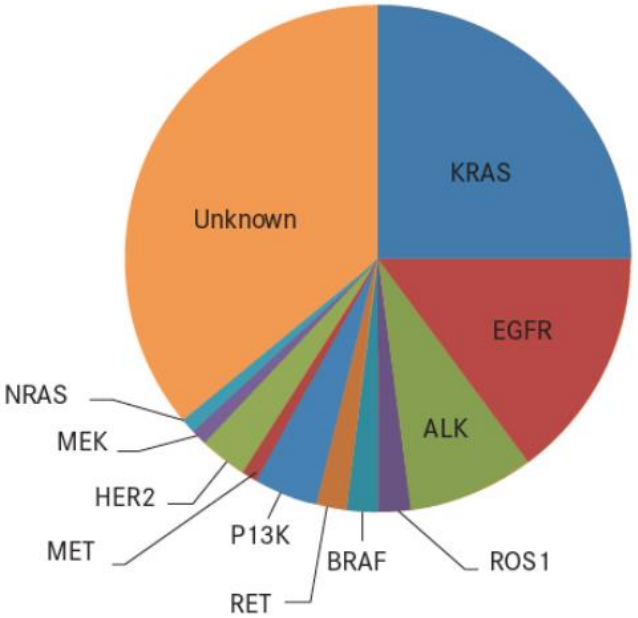
Back to case

- Soon after completion of chemoRT, scan shows new liver metastases
- Biopsy confirms metastatic lung adenocarcinoma, **PD-L1** 70%
- **Next generation sequencing** does not reveal actionable alterations
- **Both PD-L1 and molecular testing are essential for therapy selection in mNSCLC
- Starts immune checkpoint inhibitor monotherapy with good response



Precision Medicine: Immunotherapy and targeted therapies in aNSCLC

- 5-year survival rates for Stage IV NSCLC have increased from **<5% to >25%**
- There is improved understanding of the biology of disease and new therapies
- The question is no longer **who should** get immunotherapy or targeted therapy, but rather **who can *avoid*** chemotherapy



EGFR	ALK	ROS1	BRAF	MET	RET	TRK
Erlotinib	Crizotinib	Crizotinib	Dabrafenib	Crizotinib	Vandetanib	Larotrectinib
Gefitinib	Ceritinib	Entrectinib	Vemurafenib	Tepotinib	Cabozantinib	Entrectinib
Afatinib	Brigatinib		Trametinib	Capmatinib	Selpercatinib	
Osimertinib	Alectinib				Pralsetinib	
Dacomitinib	Lorlatinib					

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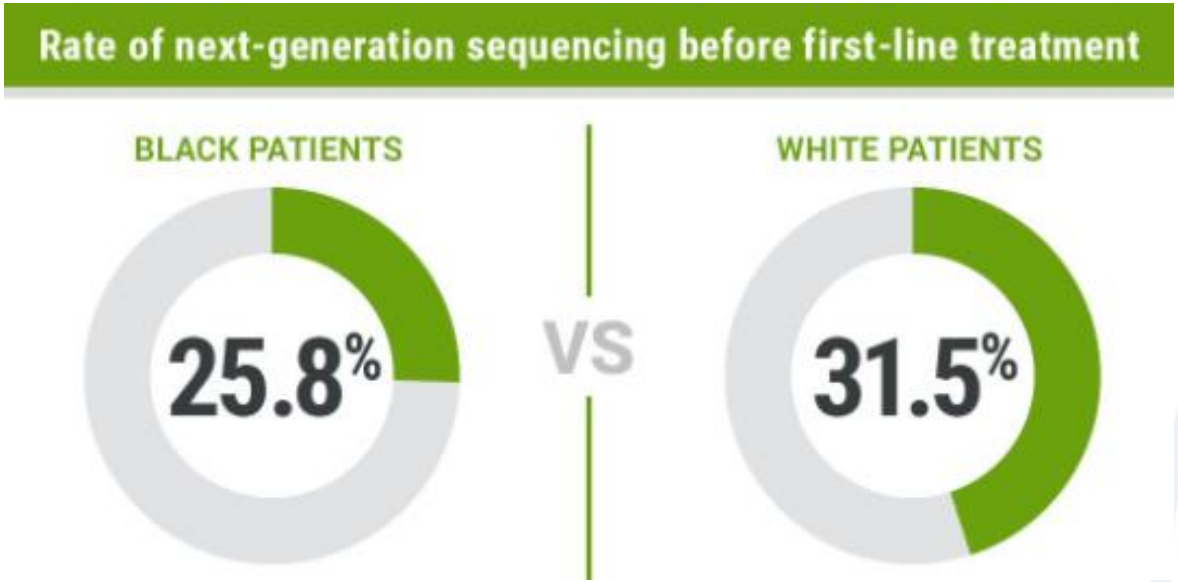
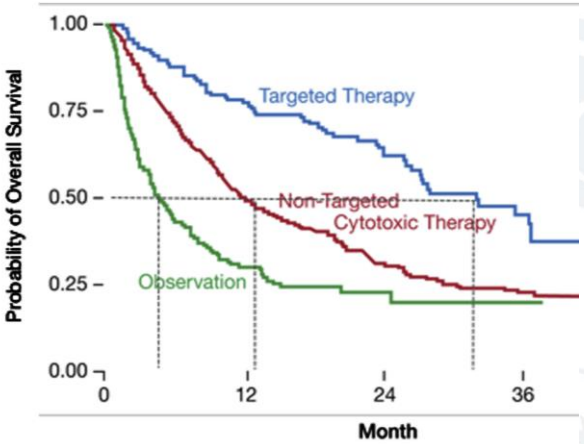
Disparities in molecular testing



Bruno et al ASCO 2021



Gutierrez Clin Lung Cancer 2017

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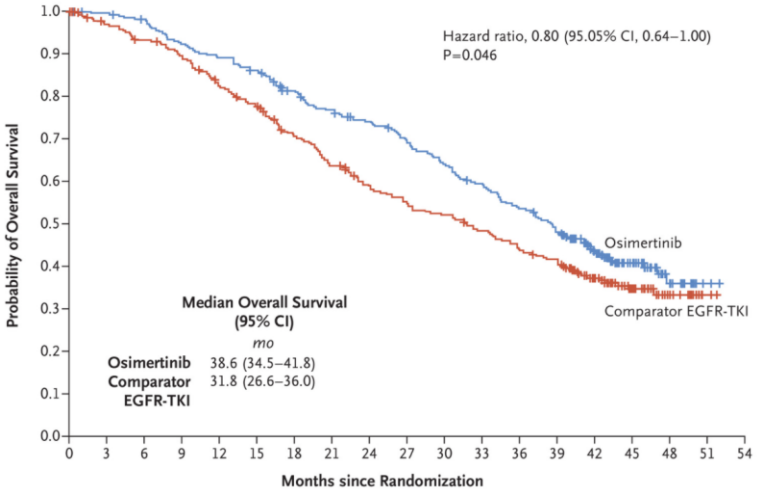
EGFR - Osimertinib

- QTc prolongation: 10% in FLAURA (2% grade 3-4)
- FAERS study: higher rate of HF, AF, QTc prolongation, MI, pericardial effusion compared to earlier generation TKIs[1]
- EF decline (>=10% decrease to EF<50%): 2-5%
  - Majority asymptomatic
  - Pre-existing CVRF may be more causal than osimertinib itself[2]

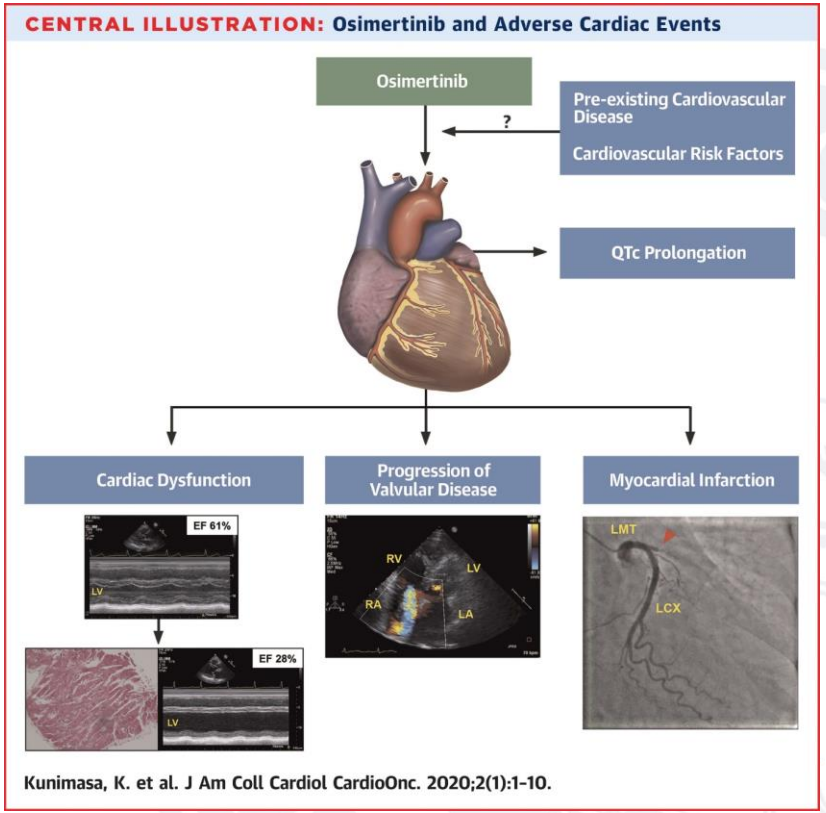


FLAURA, Ramalingam NEJM 2020

[1]Anand JACC CardioOncology 2019
[2]Ewer JCO 2021

Osimertinib in real world: Retrospective Japanese experience (n=123)

- 4.9% incidence of cardiac AE grade 3+ (MI, HF, valvular disease)
- Most patients had history of CVRF/CVD
- LVEF decline (69.4% → 63.4%) in 36 pts assessed serially



Monitoring/Management with Osimertinib

- EKG monitoring for QTc prolongation for high-risk patients (baseline long QT, concomitant meds, HF)
- Assessment of LVEF at baseline and q3mo in patients with cardiac risk factors or symptoms
- Clinical monitoring for signs/symptoms of heart failure
- More data to come – expanding indication to earlier stage settings (ADAURA[1], post-resection)

[1]Wu NEJM 2020

ALK inhibitors

ALK
Crizotinib
Ceritinib
Brigatinib
Alectinib
Lorlatinib

- ALK-rearranged NSCLC have higher incidence of VTE
- Class effects of ALK-TKI like **crizotinib**[1]
  - Prolonged QTc (4-6%)
  - Bradycardia (6-21%)
- **Alectinib** now 1st line SoC – better cardiac safety profile[2]
- **Brigatinib** – higher HTN rates (23% vs 7% with crizotinib[3])
- **Lorlatinib** – rare AV block and PR prolongation
- Recommendations
  - Avoid co-administration of medications with QTc prolongation, bradycardia, electrolyte abnormalities
  - Monitoring: BP, HR, ECG, electrolytes

[1]PROFILE, Shaw 2013/Solomon 2016/Blackhall 2017
[2]Marcos 2017, ALEX trial Peters NEJM 2017 [3]Camidge NEJM 2018

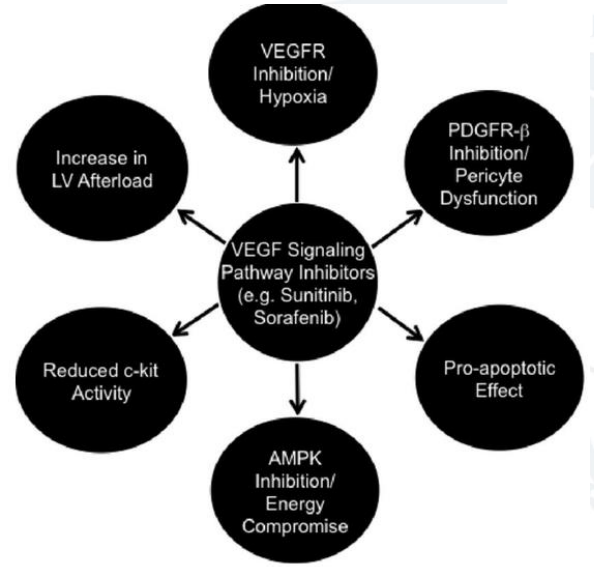
VEGF inhibition

Agents used in lung cancer

- Bevacizumab
  - First used in combination with chemo for mNSCLC[1]
  - Approved in combination with frontline chemo/immunotherapy[2]
- Ramucirumab – part of standard 2L therapy with docetaxel[3]

Toxicities

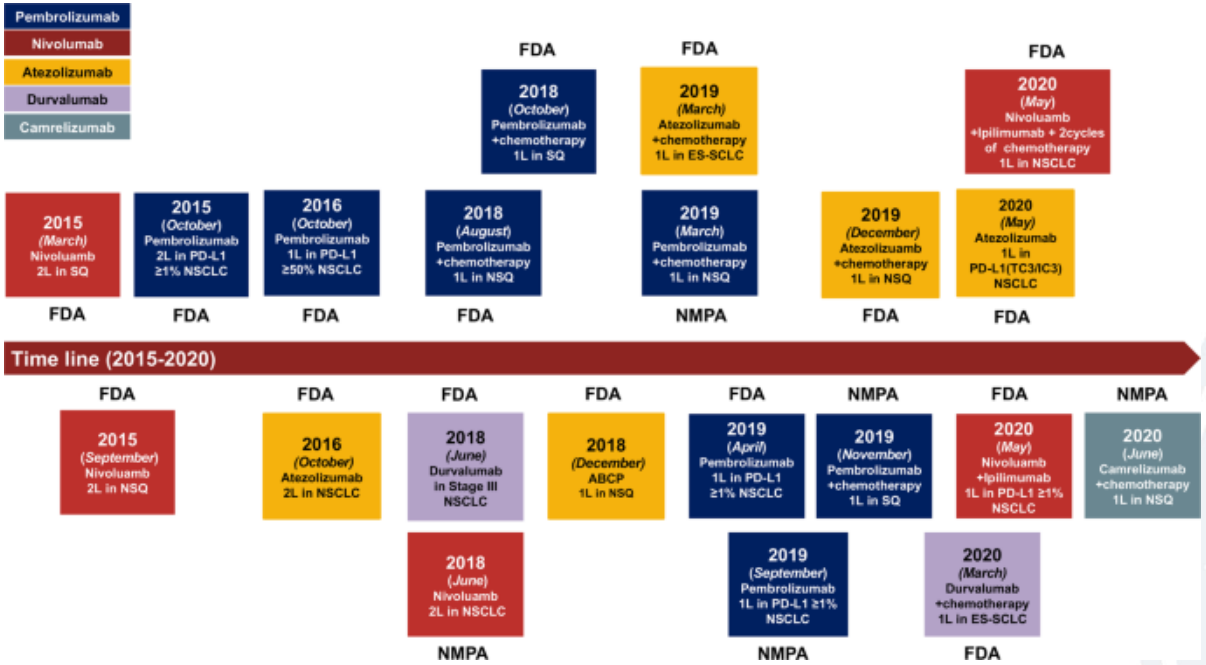
- HTN (4-35%) - may be associated with better response
  - Treat with standard antiHTN – ACEi, CCB
- CHF (2-4%)
- Thromboembolism / hemorrhage



Hahn JAHA 2014

[1]ECOG 4599, PointBreak JCO 2013
[2]IMPOWER 150 [3]REVEL

Immunotherapy: Indications in lung cancer



- Metastatic NSCLC
  - Pembrolizumab
  - Nivolumab
  - Atezolizumab
- Early stage NSCLC
  - Atezolizumab
  - Durvalumab
- Extensive stage small cell lung cancer
  - Atezolizumab
  - Durvalumab

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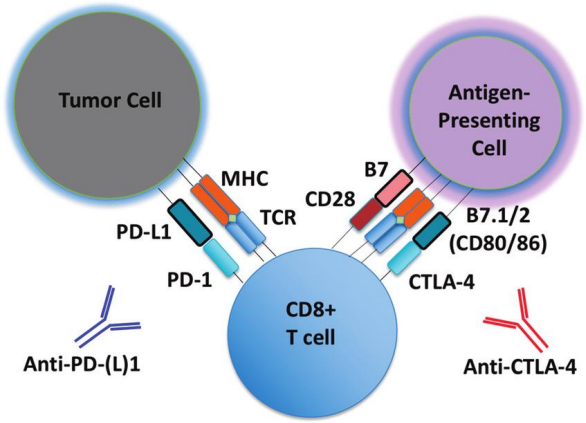
Cardiotoxicity from immune checkpoint inhibitors

- Cardiac immune-related adverse events (irAE)
  - Myocarditis, Pericardial effusion, Arrhythmia
- Reported incidence <1% but likely underrecognized
- High mortality rate
- Increasing concern in lung cancer:
  - ICIs now being used in earlier stage disease (consolidative durvalumab, adjuvant atezolizumab)
  - Combination with other treatment modalities including XRT



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Take-Home Points: Cardiotoxicity in lung cancer

- Cardiovascular risk mitigation is increasingly important in lung ca:
  - Improving outcomes and survival
  - Increasing array of systemic therapies with specific cardiac risk profiles
- Treatment modalities are associated with different cardiac risks, and patients often undergo multiple types of treatment
  - XRT (IMRT, proton therapy)
  - Chemotherapy
  - Targeted therapy
  - Immunotherapy
- Consensus guidelines around monitoring and management are sparse; data/evidence continuing to develop
- Multidisciplinary collaboration is key

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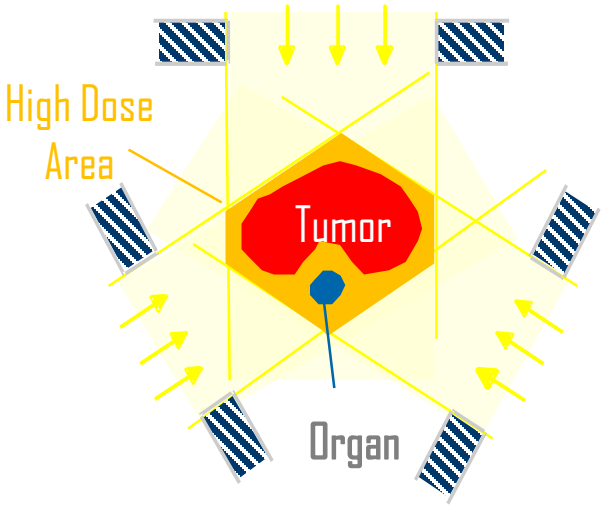
Radiation for Lung Cancer

- Radiation therapy is a key part of lung cancer treatment
- ~50% of lung cancer patients will receive RT
- Curative or palliative treatment

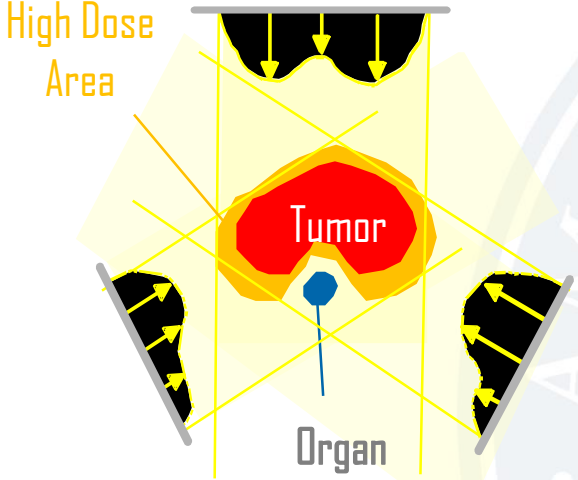
Liu et al. Transl Lung Cancer Res 2019;8(Suppl 2):S163-S171

Modern Radiation Planning Techniques:

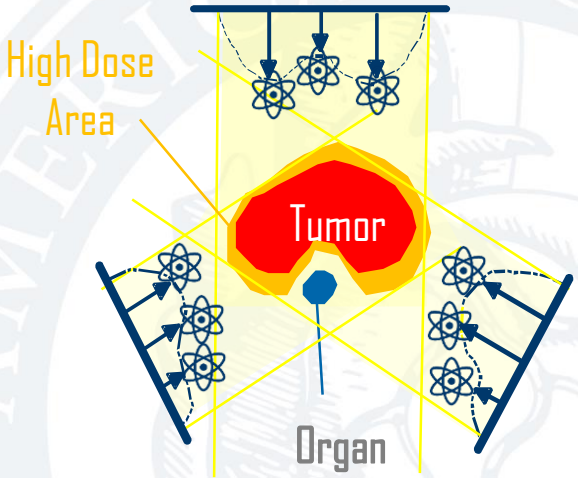
3D Conformal Radiation Therapy (3DCRT)



Intensity Modulated Radiation Therapy (IMRT)



Intensity Modulated Proton Therapy (IMPT)



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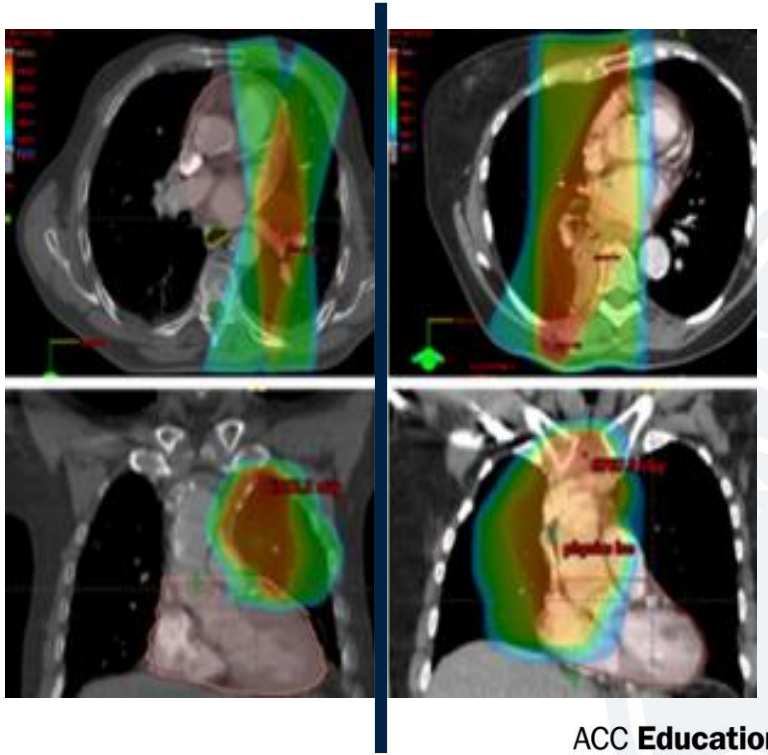
Mean Heart Dose (MHD) Is an Inadequate Surrogate for Coronary Artery Dose

MHD and LAD Discordance in 23.1% of patients

Low MHD (5 Gy)
and
High LAD V15 Gy (35%)

2-year MACE Estimate:
13.0%



High MHD (26 Gy)
and
Low LAD V15 Gy (2%)

2-year MACE Estimate:
4.2%

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Atkins et al. Int J Radiat Oncol Biol Phys. 2021;110(5):1473-1479