Role of Radiation Therapy:

Protons for All, Some, or None?

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Penn Medicine

Disclosures

- **NIH SBIR Lignamed**

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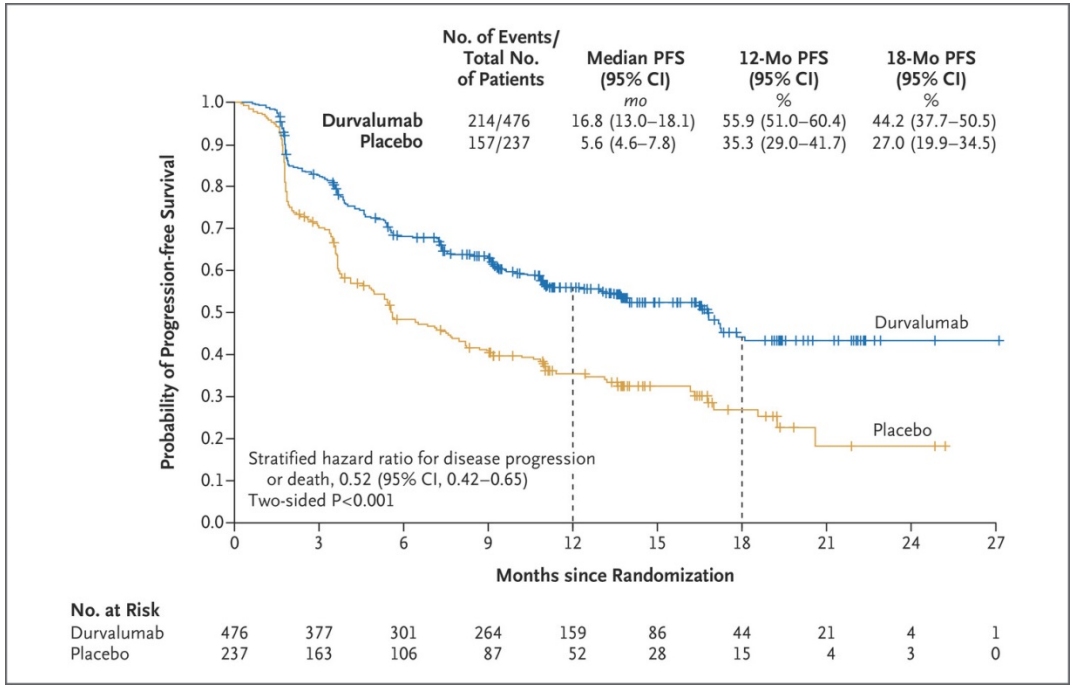
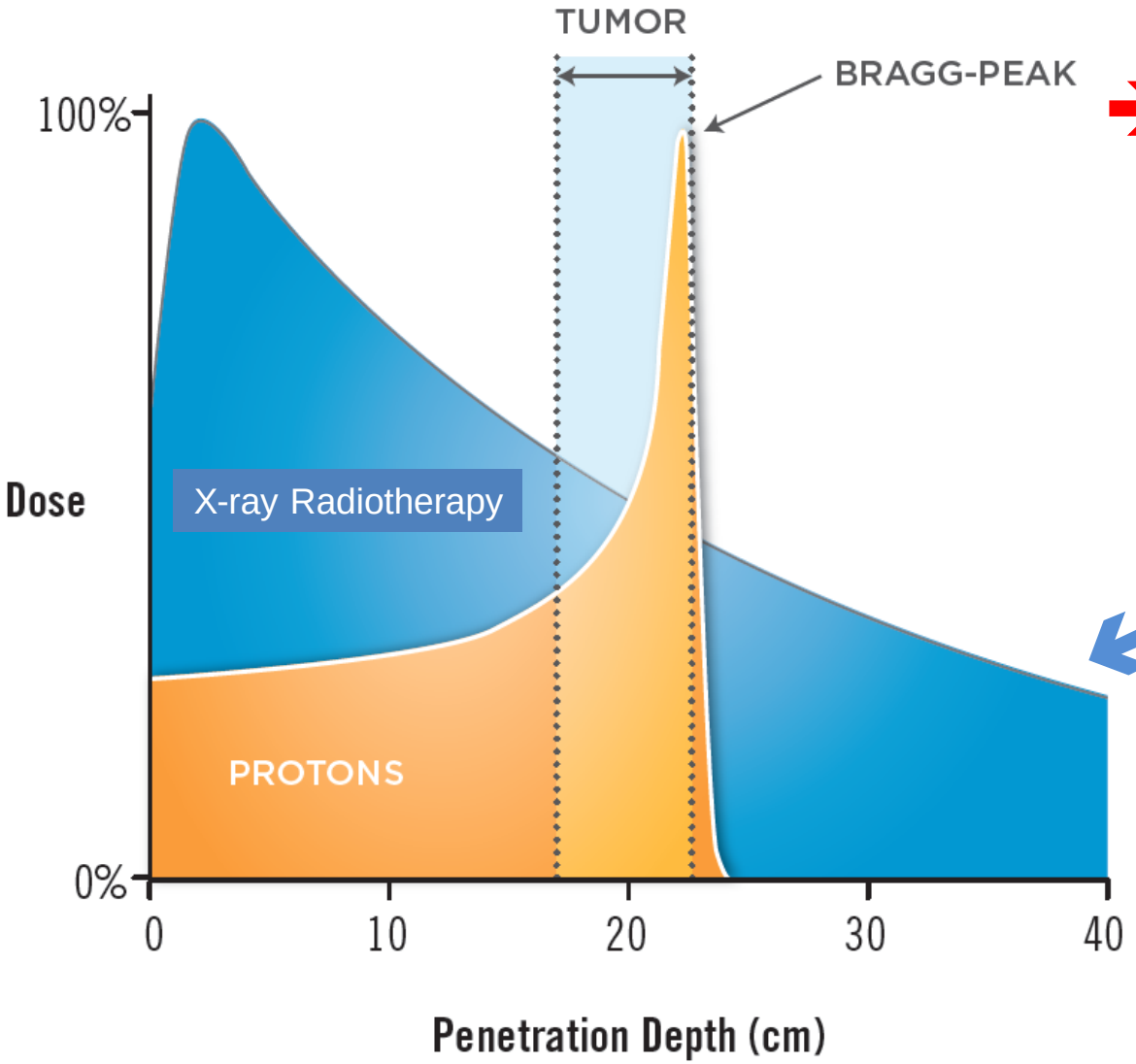
Radiation for LA-NSCLC

- **We are now- more than ever- concerned about the toxicity of radiation in LA-NSCLC:**
  - Patients are living longer
  - Controversy over the “best” radiation technique
  - We are giving MORE systemic therapy by the addition of IO



Antonia SJ et al. N Engl J Med 2017;377:1919-1929.

Can We Do Better?
Why Protons Can be Superior to Photons



Protons

X – Rays do not stop

- Excess radiation to healthy tissue results in potentially costly side effects and secondary tumors

LA-NSCLC Proton Therapy Studies: best endpoint?

overall survival →

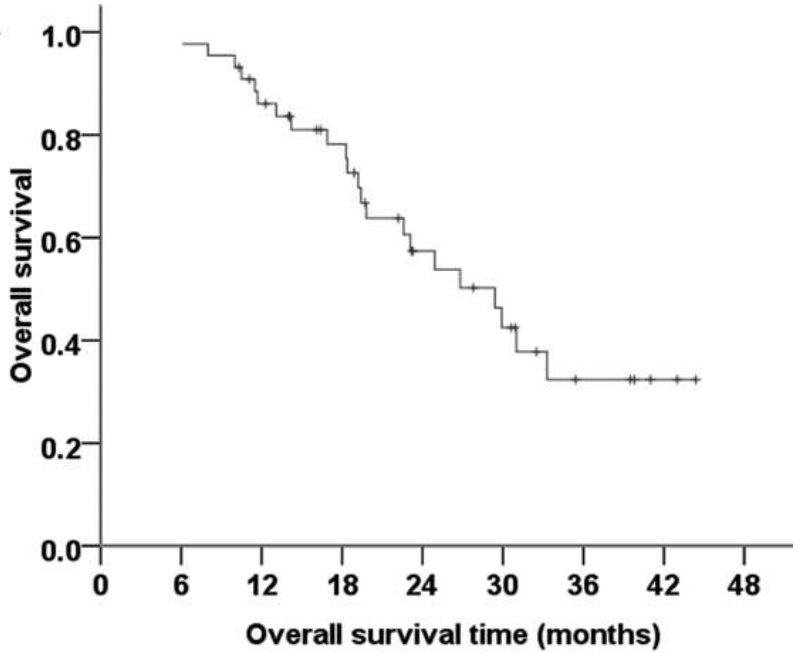
local control, grade ≥3 pneumonitis, esophagitis →

Locally advanced stage					
Terminated early	III	A Phase II Trial of 3 Dimensional Proton Radiotherapy With Concomitant Chemotherapy for Patients With Initially Unresectable Stage III Non-Small Cell Lung Cancer	NCT00881712	UF	2
Recruiting	II or III	Phase III Randomized Trial Comparing Overall Survival After Photon versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC	NCT01993810	NRG	3
Recruiting	II or III	A Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer	NCT01770418	PCG	1, 2
Recruiting	II or III	A Phase I Study of Radiation Dose Intensification With Accelerated Hypofractionated Proton Therapy and Chemotherapy for Non-Small Cell Lung Cancer	NCT02172846	WU	1
Recruiting	III	Phase I/II Trial of Image-Guided, Intensity-Modulated Photon (IMRT) or Scanning Beam Proton Therapy (IMPT) Both With Simultaneous Integrated Boost (SIB) Dose Escalation to the Gross Tumor Volume (GTV) With Concurrent Chemotherapy for Stage II/III Non-Small Cell Lung Cancer (NSCLC)	NCT01629498	MDA	1, 2
Recruiting	III	Feasibility and Phase I/II Trial of Preoperative Proton Beam Radiotherapy With Concurrent Chemotherapy for Resectable Stage IIIA or Superior Sulcus NSCLC	NCT01076231	UP	1, 2
Final result pending	II or III	A Bayesian Randomized Trial of Image-Guided Adaptive Conformal Photon versus Proton Therapy, With Concurrent Chemotherapy, for Locally Advanced Non-Small Cell Lung Carcinoma: Treatment Related Pneumonitis and Locoregional Recurrence	NCT00915005	MDA	2
Final result pending	III	Phase II Concurrent Proton and Chemotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Cancer (NSCLC)	NCT00495170	MDA	2
Completed	III	Phase I Dose Escalation Trial of Proton Beam Radiotherapy With Concurrent Chemotherapy and Nelfinavir for Inoperable Stage III NSCLC	NCT01108666	UP	1

Chang JY et al. IJROBP 2016

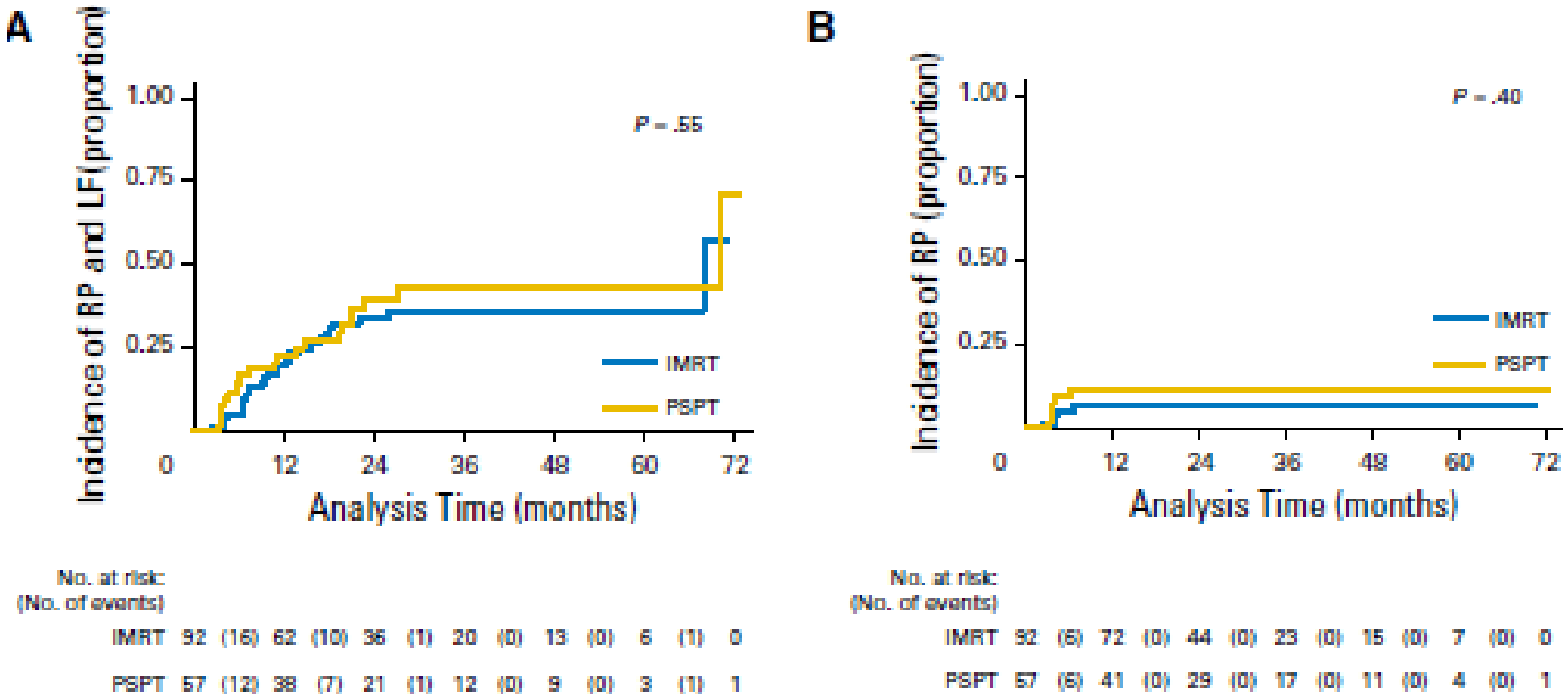
Conflicting Data on Protons: The Good

- MDACC phase II trial of 44 pts with stage III NSCLC
  - Protons to 74 CGE with concurrent carboplatin + paclitaxel
  - MS 29.4 mo
    - Best survival ever reported in a phase II or III chemorads trial for stage III NSCLC
  - 20.5% local failure
  - Toxicity: 1grade 3 pneumonitis 2%, no grade 4-5 toxicity



Chang JY, et al. *Cancer*. 2011;117(20):4707-13.

Conflicting Data on Protons: The Bad



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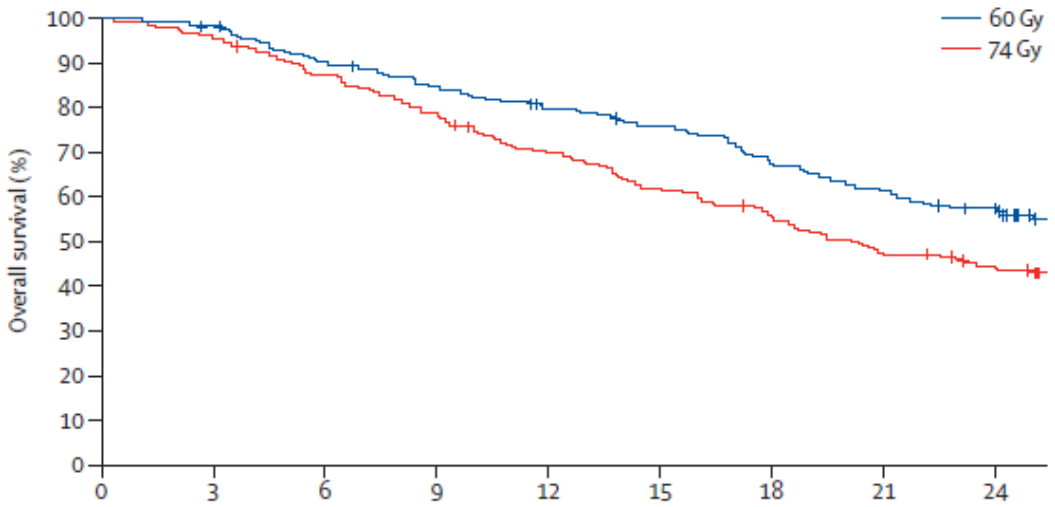
RADIATION THERAPY ONCOLOGY GROUP

RTOG 0617/NCCTG N0628/CALGB 30609

A RANDOMIZED PHASE III COMPARISON OF STANDARD- DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

	60 Gy	74 Gy	P Value
Grade ≥3 Pulmonary	20%	19%	0.71
Grade ≥3 Pneumonitis	7%	4%	0.25
Grade ≥3 Esophagitis	**7%**	**21%**	**<0.0001**
Grade ≥3 Any	76%	79%	NS
Grade 5 Toxicity	**N=3**	**N=8**	**<0.05**



Median OS: 28.7 months (60 Gy) vs. 20.3 months (74 Gy), p=0.0042
RTOG 9410 concurrent daily arm median overall survival: 17.0 months
ASTRO 2017 update: 5 y OS 32% vs 23%

Bradley JD, et al. *Lancet Oncol*. 2015;16(2):187-99.

RTOG 0617 Multivariate - Survival

Covariate	Comparison	Dead/Total RL	Dead/Total Group 2	HR (95% CI)	p-value*
Radiation Level	Standard Dose (RL) vs. High Dose	121/208	136/199	1.34 (1.04, 1.73)	0.0213
Maximum related esophagitis/dysphagia grade	Maximum grade < 3 (RL) vs. Maximum grade ≥ 3	210/349	47/58	1.54 (1.11, 2.15)	0.0102
Volume of PTV	Continuous	257/407		1.000 (1.000, 1.001)	0.0729
Heart V5	Continuous	257/407		1.007 (1.002, 1.011)	0.0035
Zubrod PS	0 (RL) vs. 1	151/240	106/167	1.14 (0.89, 1.47)	0.3045
PET Staging	No (RL) vs. Yes	30/39	227/368	0.77 (0.52, 1.13)	0.1766
Gender	Male (RL) vs. Female	153/240	104/167	0.97 (0.74, 1.26)	0.7975
Histology	Non-squamous (RL) vs. Squamous	146/228	111/179	1.01 (0.78, 1.31)	0.9380
Smoking History	Non-smoker/former light smoker (RL) vs.	39/60		--	--
	Former heavy/current smoker vs.	206/328		1.14 (0.80, 1.63)	0.4617
	Unknown	12/19		1.44 (0.74, 2.80)	0.2776

RL = reference level, HR = hazard ratio, CI = confidence interval
*Two-sided log-rank p-value

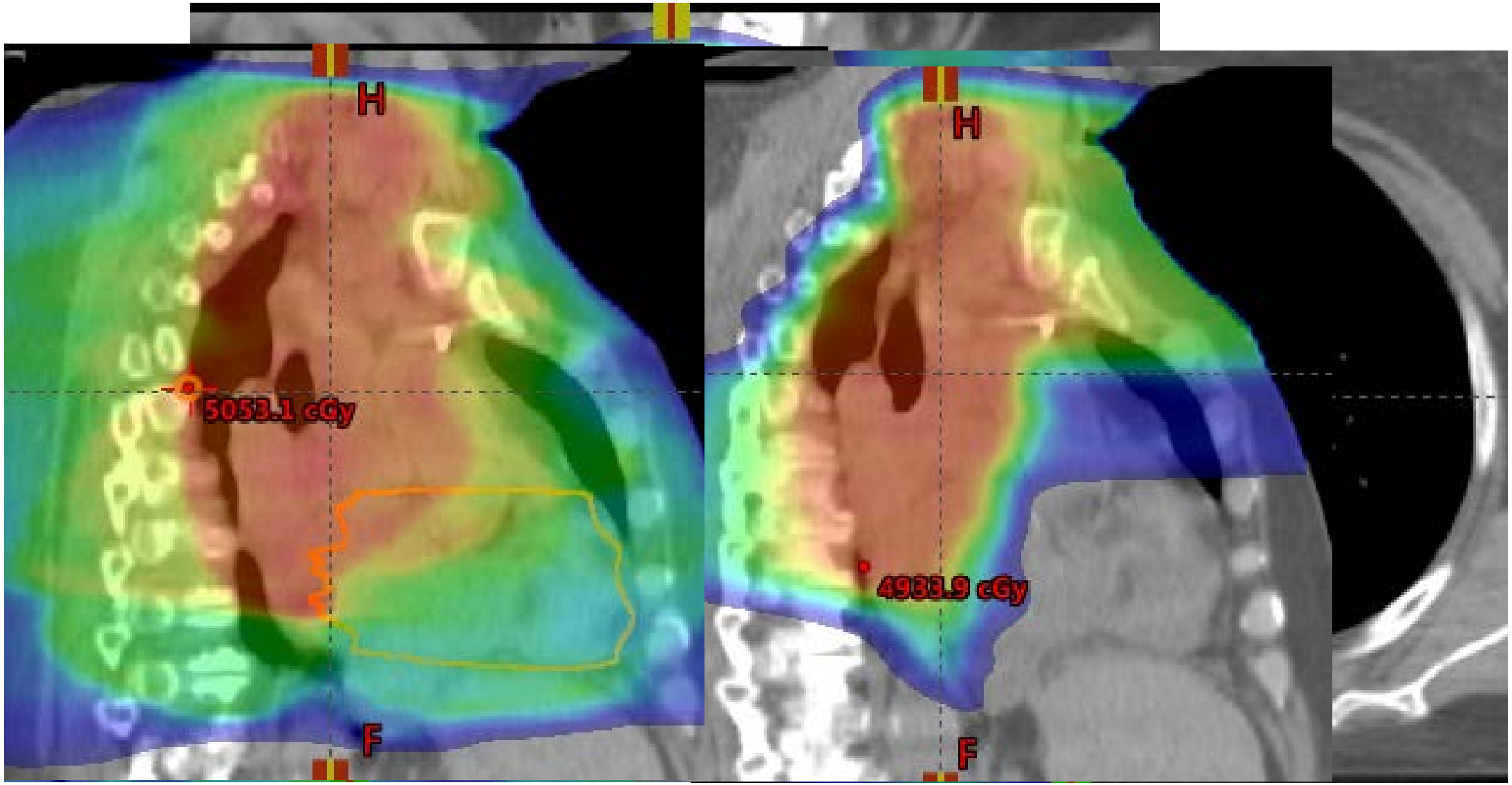
Authors: "heart dose might best explain why patients given 74 Gy did worse than patients given the 60 Gy"

- Did increased heart dose in the 74 Gy arm (V50 – 11% vs. 7%) lead to an increase in intercurrent cardiac deaths?

Pneumonitis or Radiation Pneumonitis

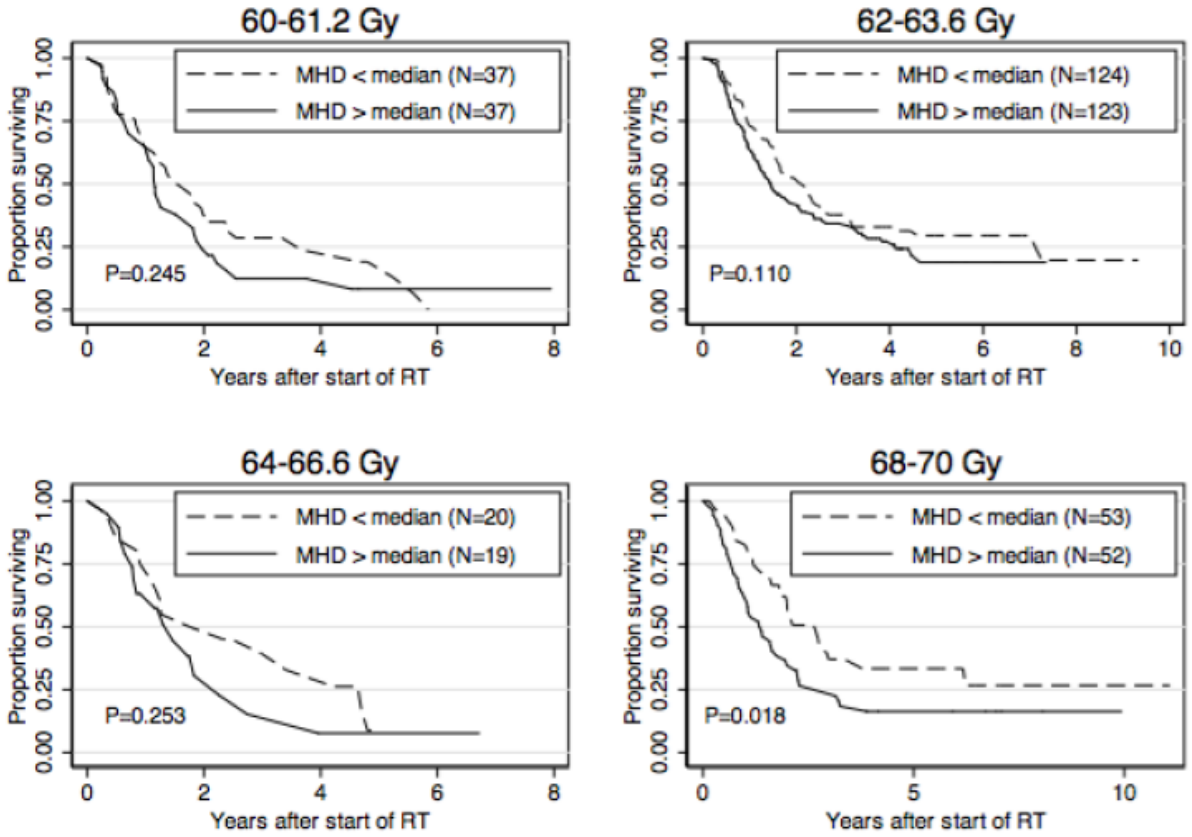
Pneumonitis (grouped terms) or radiation pneumonitis, n (%)*	Durvalumab (N=475)	Placebo (N=234)
Any grade	161 (33.9)	58 (24.8)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	5 (1.1)	4 (1.7)
Leading to discontinuation	30 (6.3)	10 (4.3)

Protons Can Improve Heart Dose



MDACC – Cardiac Toxicity

- **532 patients with NSCLC treated with concurrent chemoradiation**
  - Mean heart dose:
    - 22.3 Gy – 3DCRT
    - 15.1 Gy – IMRT
    - 6.5 Gy – PBT
- **Mean heart doses >25th percentile associated with increased risk of death (HR 1.4)**

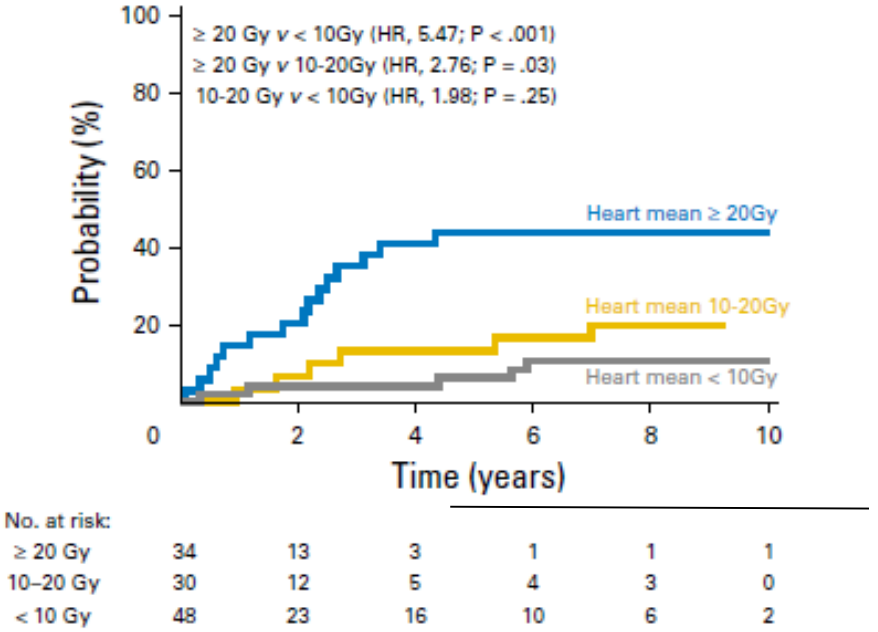


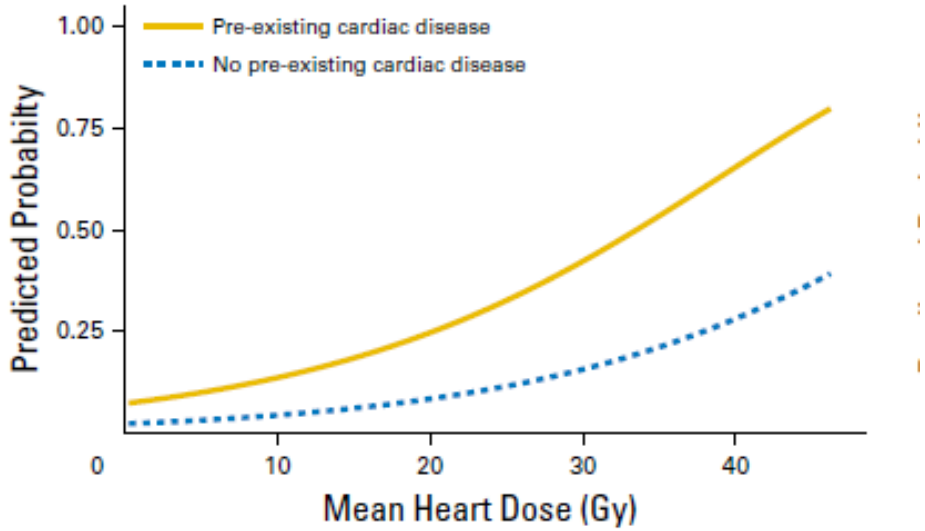
OS with mean heart dose above or below the median per RT dose subgroup

Liao Z, et al. ASTRO 2012.

Cardiac Dose

- **Endpoint – symptomatic cardiac events**





Considerations for LA-NSCLC Patient

- **Protons may be appropriate for consideration as a means to decrease toxicity**
- **Toxicity is a greater concern than ever with the addition of immunotherapy**
- **Total dose 60-72 Gy**
- **Grade 3 pneumonitis is increasingly rare**
- **Heart dose important predictor of survival and of symptomatic cardiac events**
- **Consider referral for proton therapy for LA-NSCLC**

Thank You

- **Patients!**
- **University of Pennsylvania Department of Radiation Oncology**
- **Cancer Service Line**

- **PCPM team**
  - David Roth, MD, PhD

@PennPrecisMed
@ATB_MD

When protons?

Table 1 Comparisons of and indications for VMAT-IMRT, PSPT, and IMPT

Technique	Pros	Cons	Clinical scenarios beneficial to proton therapy
IMRT-VMAT	High conformity between prescription isodose line and target Robust with respect to changes in motion or anatomy Lower cost and higher availability	Higher low to medium dose to normal tissues limiting the ability for dose escalation	
PSPT	Limited low or medium dose to normal tissues enabling target dose escalation	Possibly higher lung mean dose and volume receiving 20 Gy and higher for complicated anatomy, lack of proximate conformation to target	Centrally located stage I disease
	Can be made robust with respect to changes in motion or anatomy	Poor conformality of prescription isodose line to target due to 3D planning, lack of conformity in the proximal end of the target volume and range uncertainty	Stage II to III disease without contralateral hilar lymph node involvement
IMPT	High conformity between prescription isodose line and target	Because of range uncertainty, less robust with respect to motion and/or changes in anatomy, making the treatment of mobile targets difficult	Centrally located stage I disease
	Spares more normal tissues than IMRT or PSPT including the heart, cord, lung, esophagus, and so on	Complexity of motion management, plan optimization, and quality assurance	Stage II to III disease with adequate motion management, robustness optimization, and strict quality assurance

Chang et al. IJROBP 2016

Cardiac Toxicity-Jabbour