

Regional Functional Avoidance in Lung Radiotherapy

Using Ventilation Mapping: Results of phase II trial

Yevgeniy (Jenia) Vinogradskiy, PhD
Associate Professor
Vice-Chair and Director of Medical Physics
Thomas Jefferson University



Disclosures

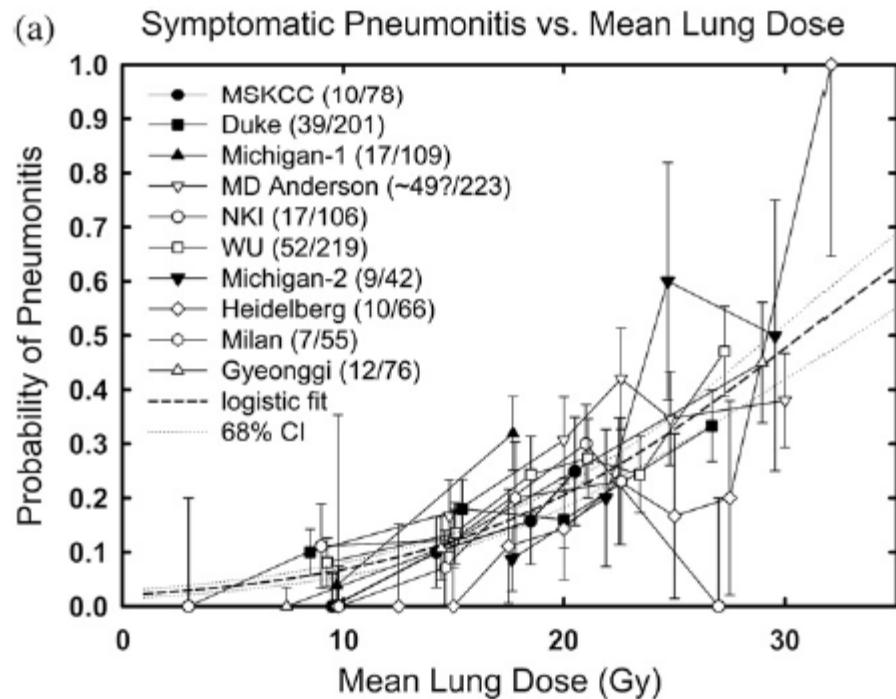
Funding: R01CA200817, R01CA236857, UG3CA247605,

Cancer Center: CU Cancer Center

Vendor funding: MIM Software

Pulmonary Toxicity in Lung Cancer Treatment

QUANTEC



Palma et al, pneumonitis review

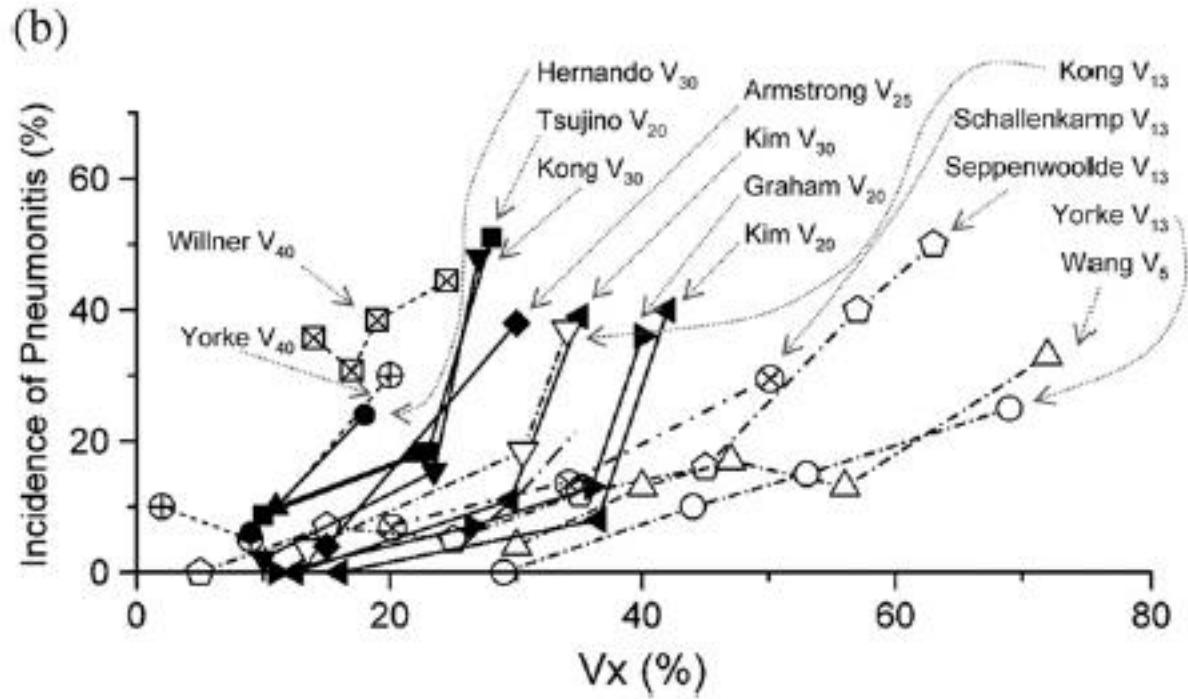
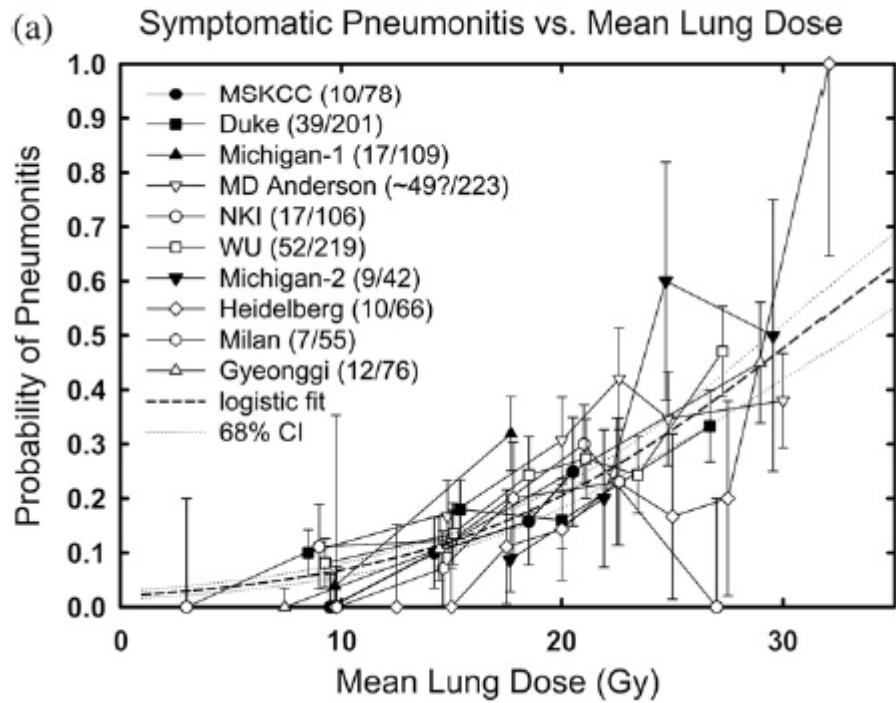
Results—The median radiotherapy dose was 60 Gy, and median follow-up was 2.3 years. Most patients received concurrent cisplatin/etoposide (38%) or carboplatin/paclitaxel (26%). The overall rate of symptomatic pneumonitis was 29.8% (n=249), with fatal pneumonitis in 1.9%

RTOG 0617

	60 Gy (acute n=151; late n=131)					74 Gy (acute n=107; late n=93)					60 Gy plus cetuximab (acute n=137; late n=112)					74 Gy plus cetuximab (acute n=100; late n=86)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
(Continued from previous page)																				
Nausea	47 (31%)	12 (8%)	8 (5%)	0 (0%)	0 (0%)	35 (33%)	7 (7%)	3 (3%)	0 (0%)	0 (0%)	33 (24%)	21 (15%)	6 (4%)	0 (0%)	0 (0%)	26 (26%)	13 (13%)	9 (9%)	0 (0%)	0 (0%)
Neutrophil count decreased	7 (5%)	18 (12%)	20 (13%)	16 (11%)	0 (0%)	8 (7%)	14 (13%)	14 (13%)	14 (13%)	0 (0%)	6 (4%)	13 (9%)	26 (19%)	30 (22%)	0 (0%)	2 (2%)	11 (11%)	24 (24%)	22 (22%)	0 (0%)
Peripheral sensory neuropathy	33 (22%)	12 (8%)	2 (1%)	0 (0%)	0 (0%)	26 (24%)	9 (8%)	3 (3%)	0 (0%)	0 (0%)	25 (18%)	17 (12%)	5 (4%)	0 (0%)	0 (0%)	23 (23%)	8 (8%)	4 (4%)	0 (0%)	0 (0%)
Platelet count decreased	38 (25%)	9 (6%)	8 (5%)	2 (1%)	0 (0%)	24 (22%)	12 (11%)	4 (4%)	4 (4%)	0 (0%)	27 (20%)	11 (8%)	8 (6%)	3 (2%)	0 (0%)	20 (20%)	8 (8%)	10 (10%)	6 (6%)	0 (0%)
Pneumonitis	2 (1%)	6 (4%)	6 (4%)	1 (<1%)	0 (0%)	2 (2%)	10 (9%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	7 (5%)	9 (7%)	0 (0%)	1 (<1%)	1 (1%)	10 (10%)	5 (5%)	1 (1%)	0 (0%)

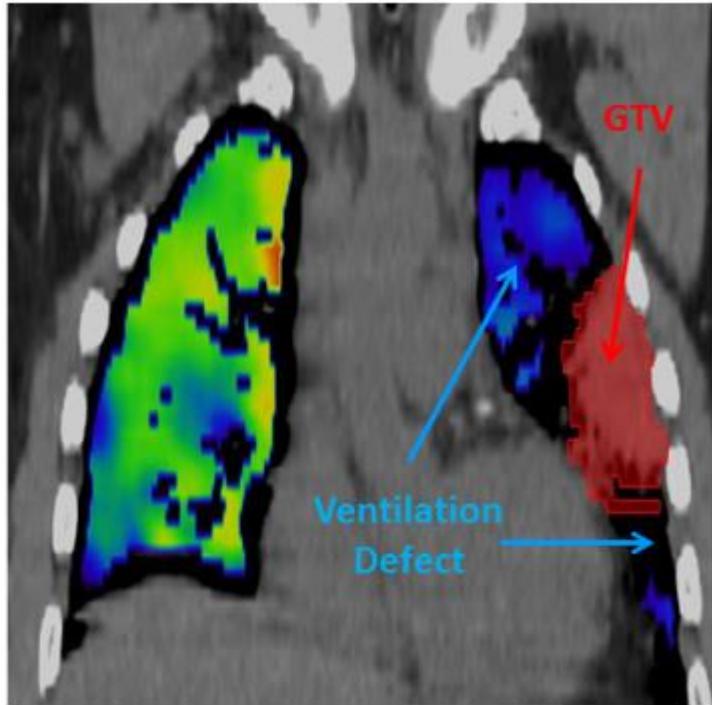
Typical dose metrics (MLD, V20) assume homogenous lung function

QUANTEC Lung

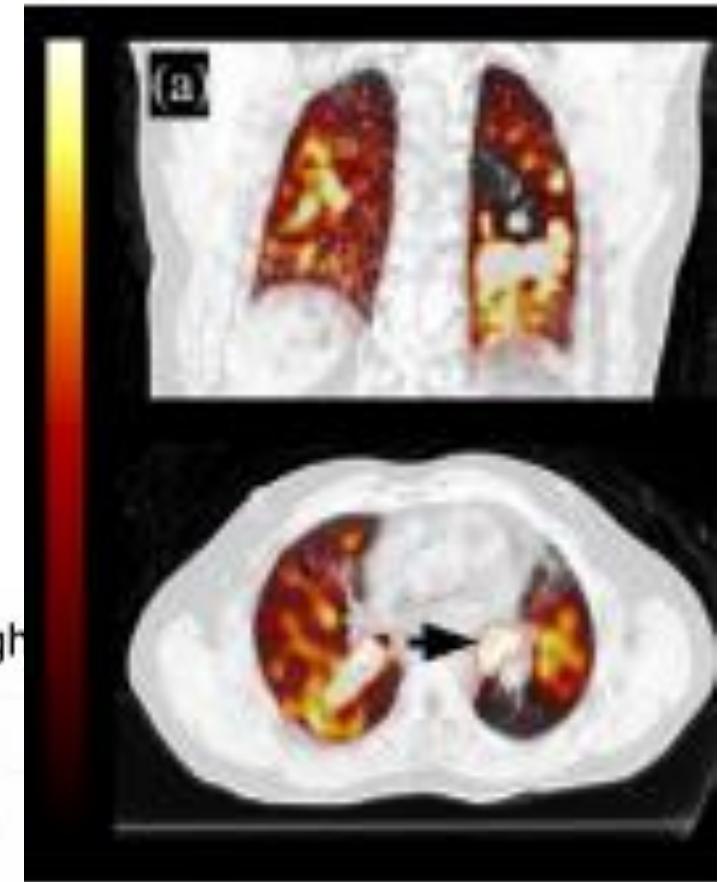


Lung function is not homogenous

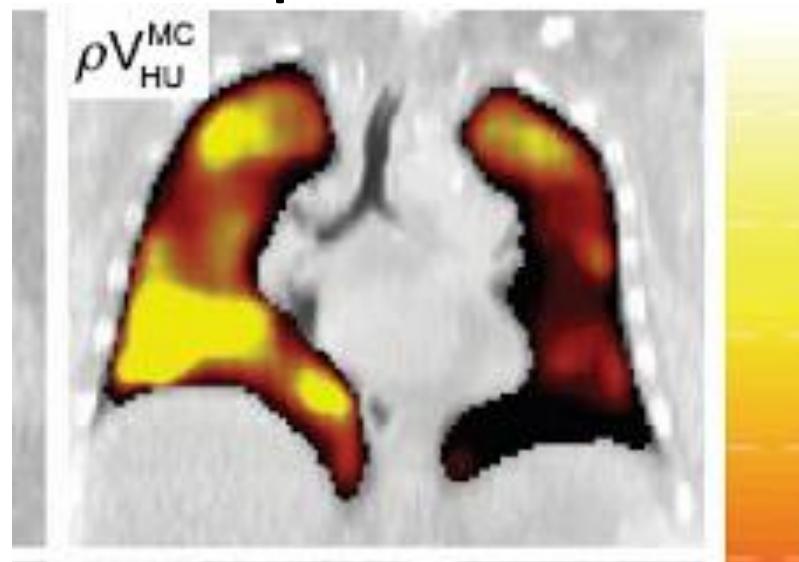
Vinogradskiy et al



Castillo et al



Kipritidis et al



Conformal Avoidance For Lung Cancer



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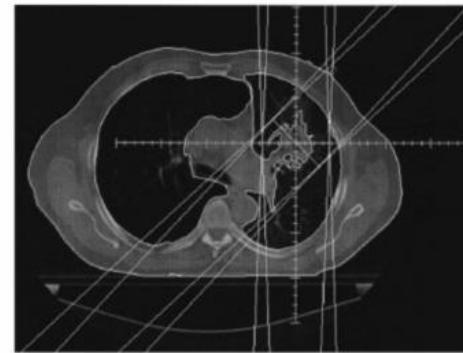
Volume 33, Issue 1, 30 August 1995, Pages 65–75



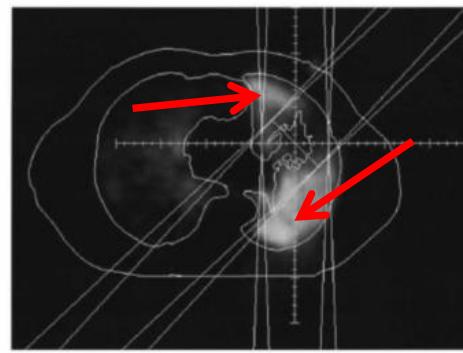
Clinical original contribution

The role of three dimensional functional lung imaging in radiation treatment planning: The functional dose-volume histogram

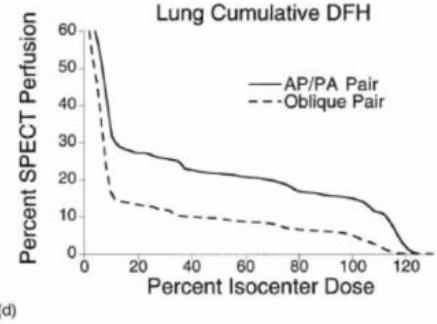
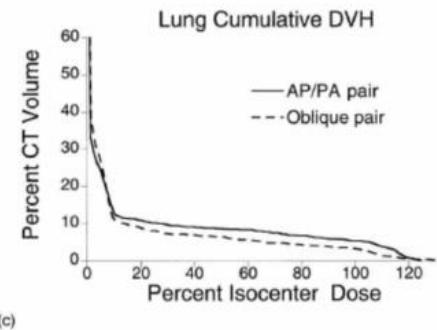
Lawrence B. Marks, M.D. *, , David P. Spencer, Ph.D.* , George W. Sherouse, Ph.D.* , Gunilla Bentel, R.N., R.T.T.* , Robert Clough*, Karen Vann, R.N.* , Ronald Jaszczak, Ph.D.† , R. Edward Coleman, M.D.† , Leonard R. Prosnitz, M.D.*



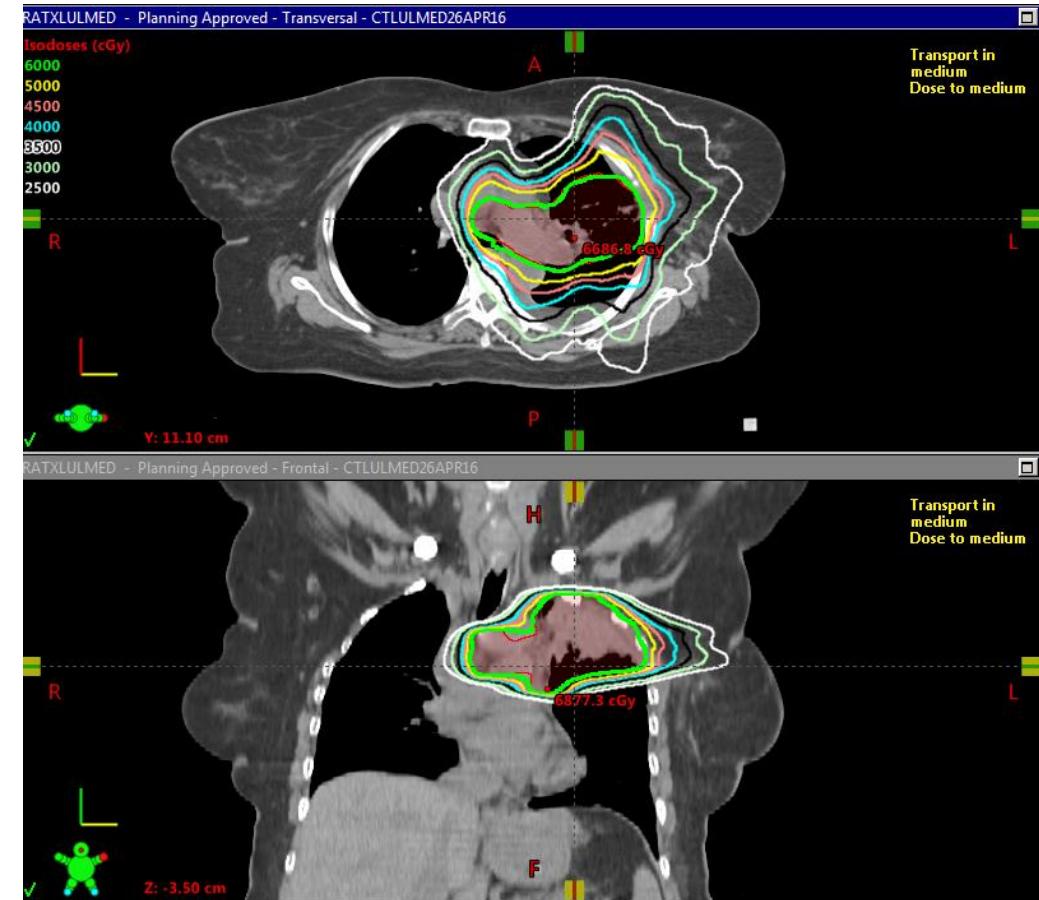
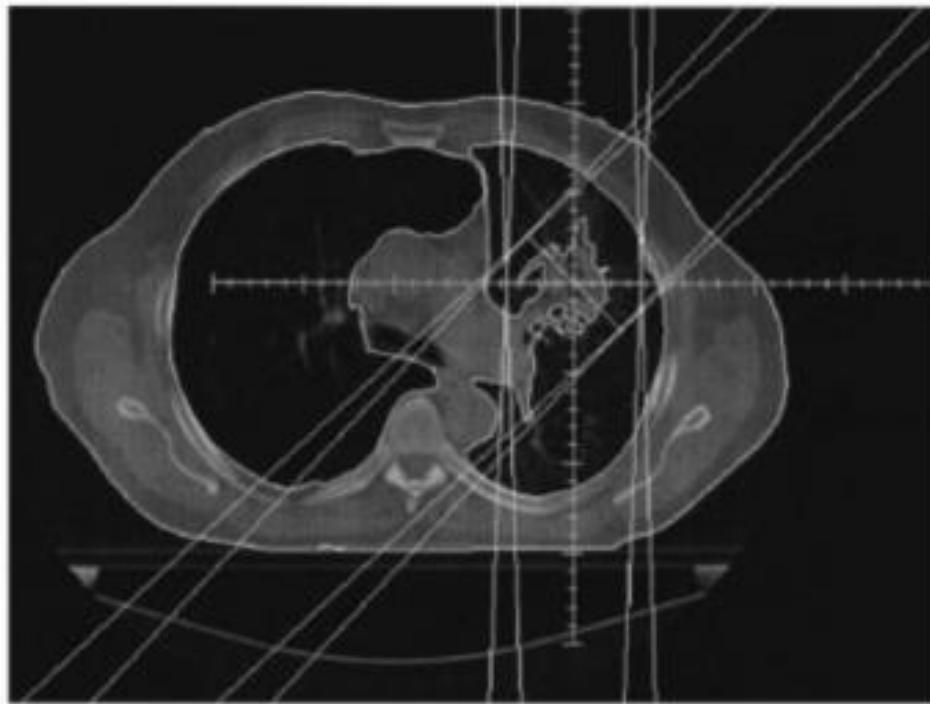
(a)



(b)

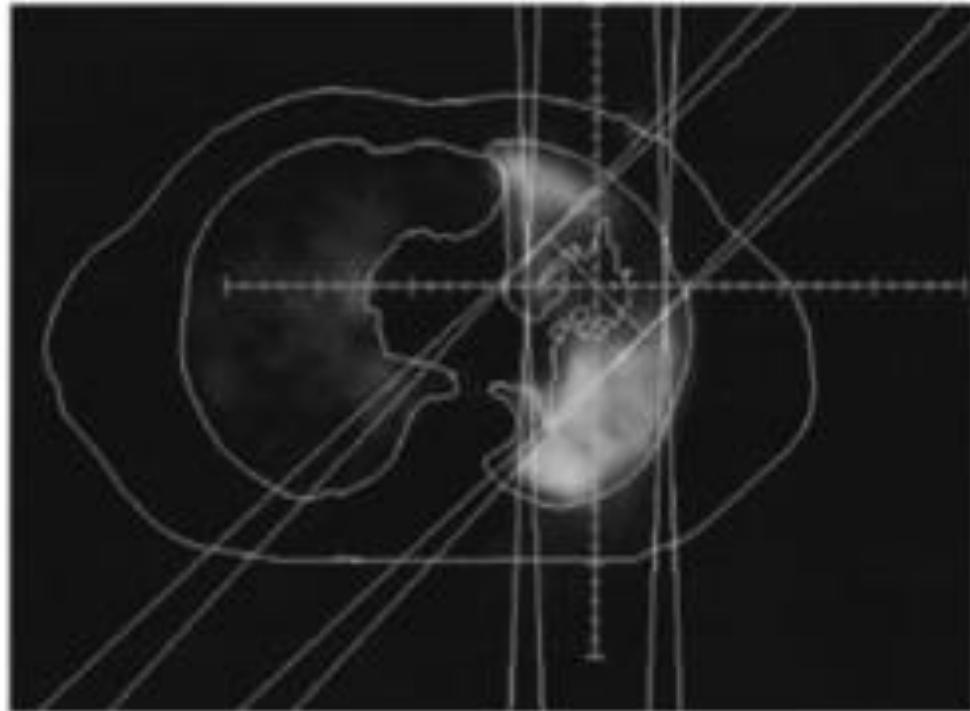


Conformal Avoidance For Lung Cancer

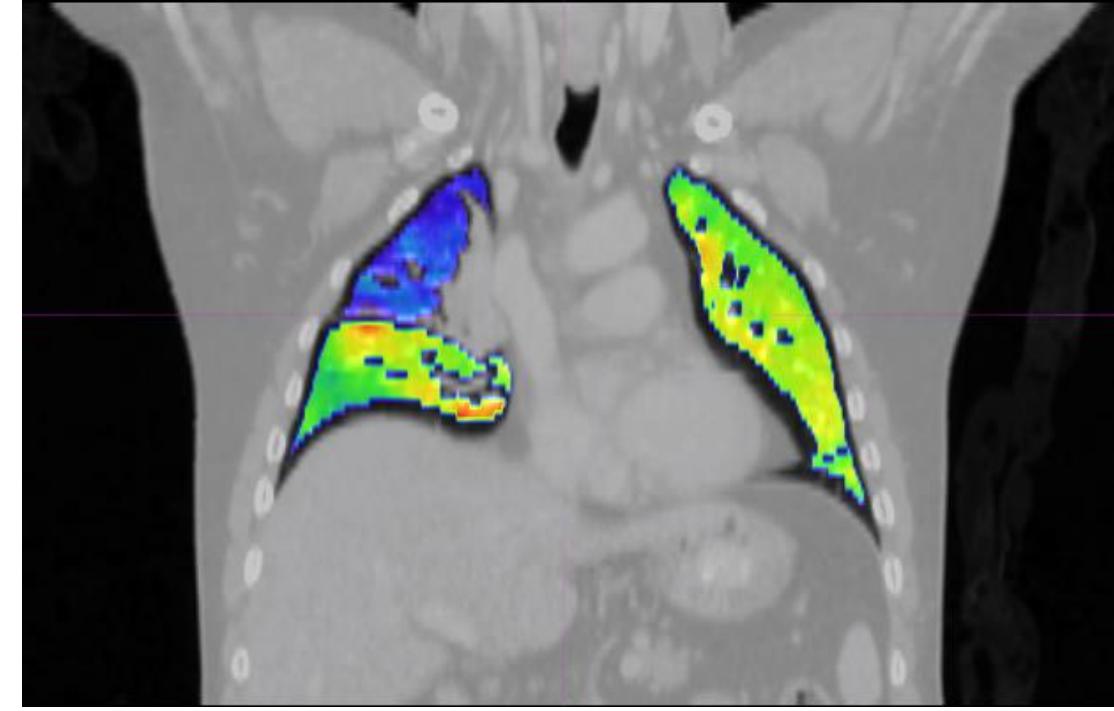


Conformal Avoidance For Lung Cancer

SPECT



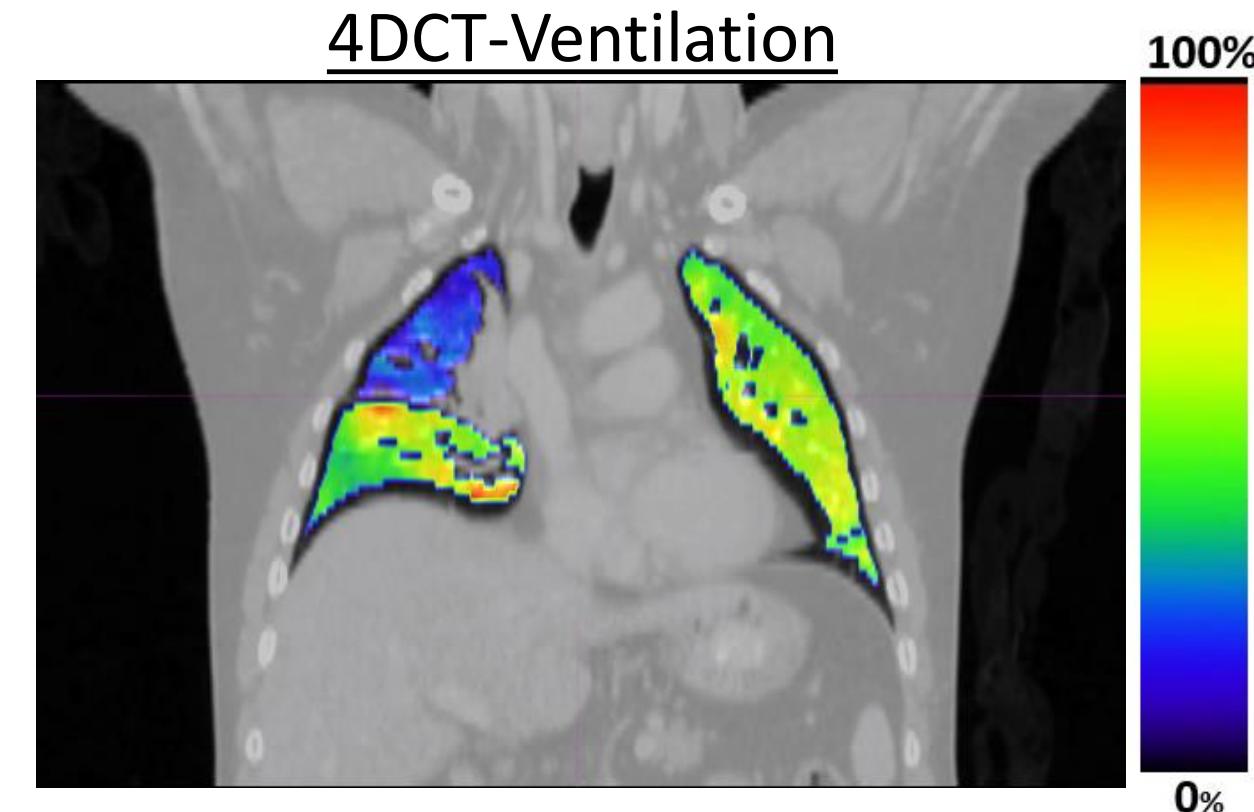
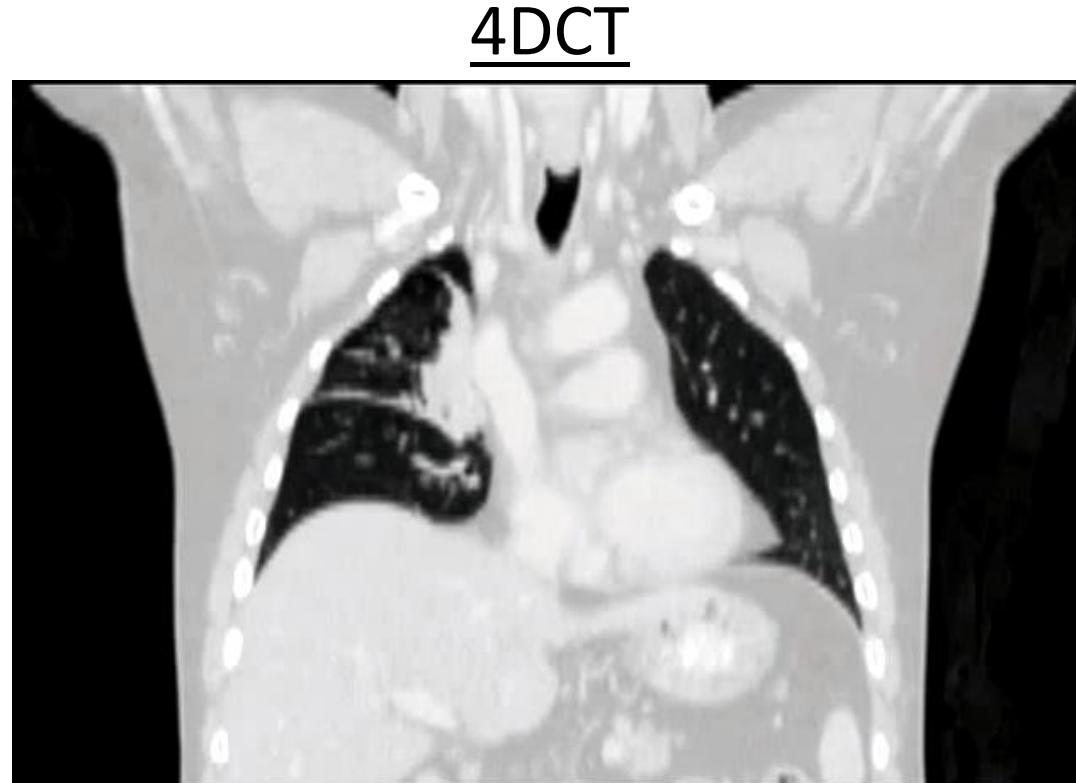
4DCT-Ventilation



Functional Radiotherapy For Lung Cancer

4DCT-Ventilation

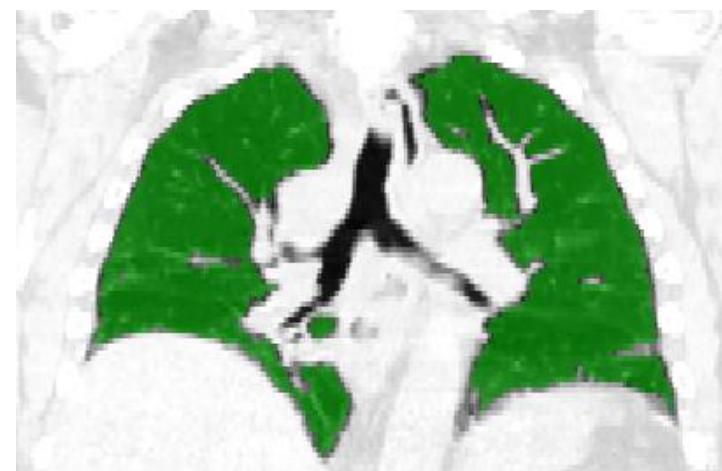
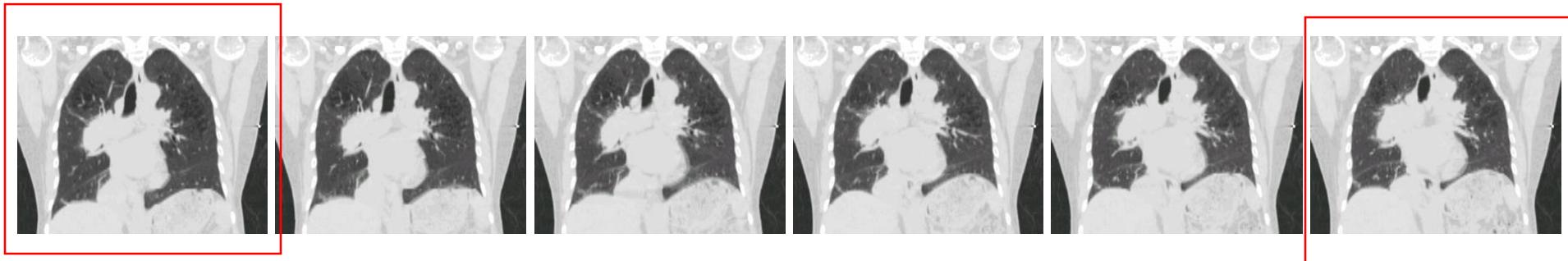
- 4DCT acquired for simulation (reduced time, cost, dose)
- Anatomical + Functional information
- Good spatial resolution



Calculating Ventilation Images

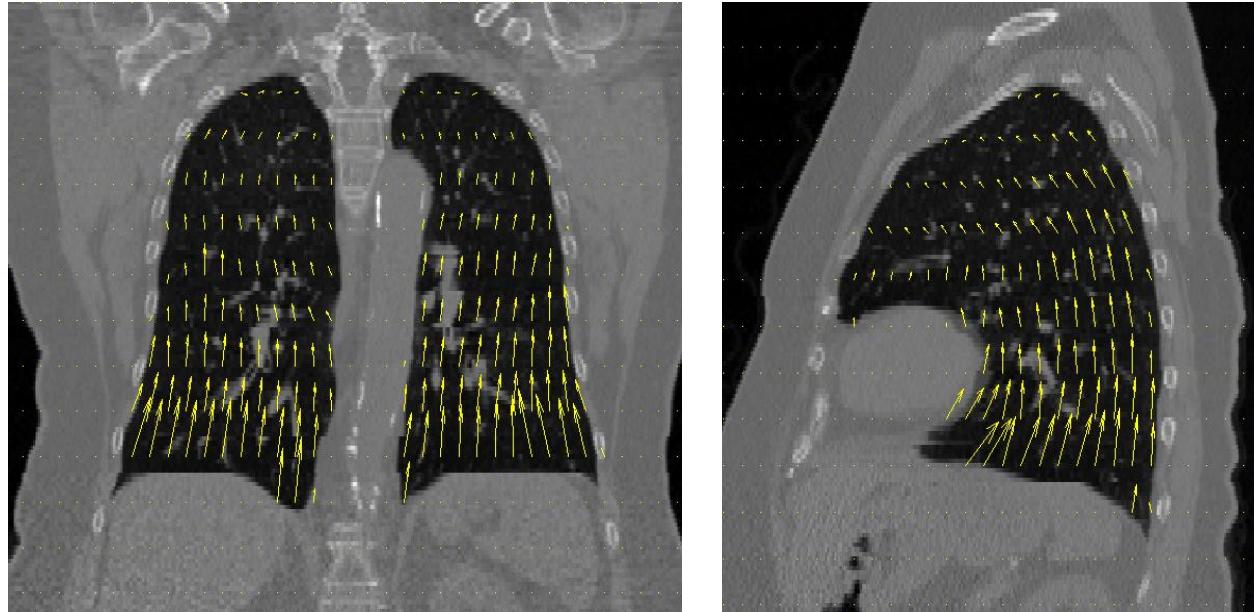
Calculating ventilation maps

4DCT – 10 phases



Calculating Ventilation Images

Link lung voxel elements from inhale to exhale using deformable registration

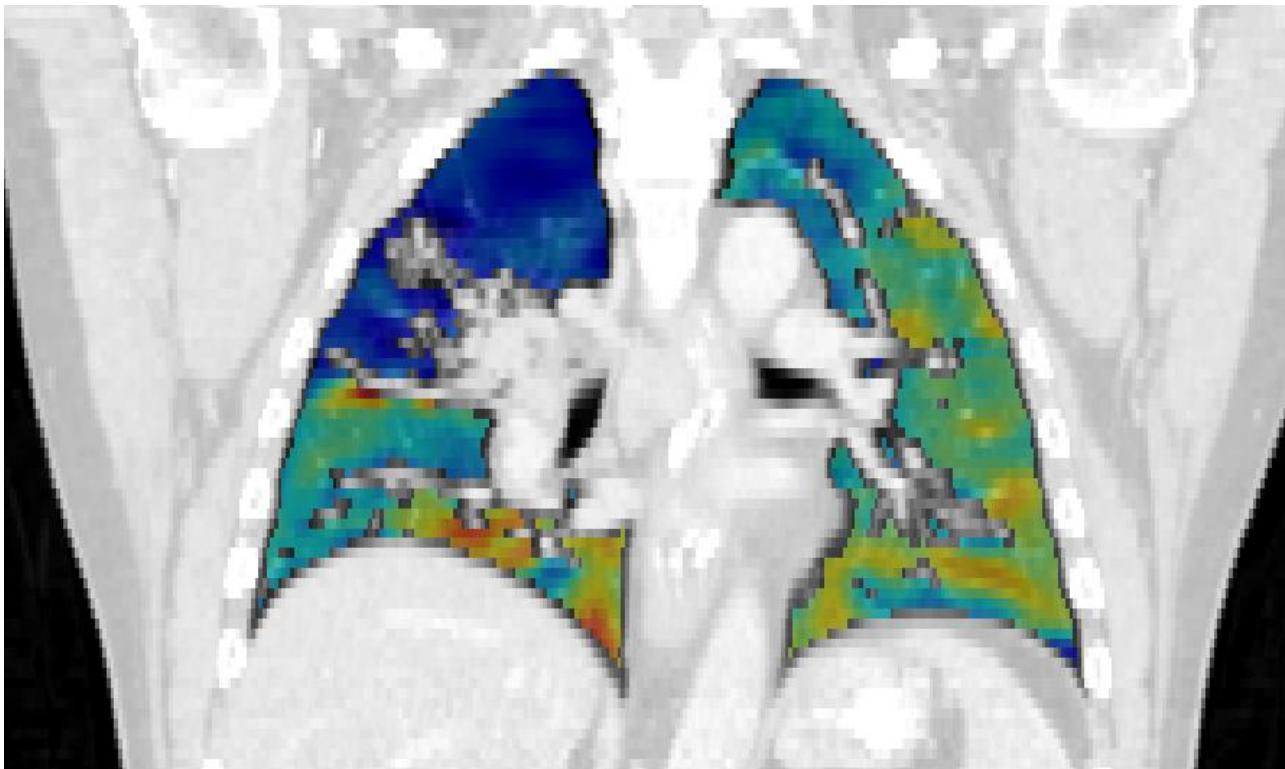
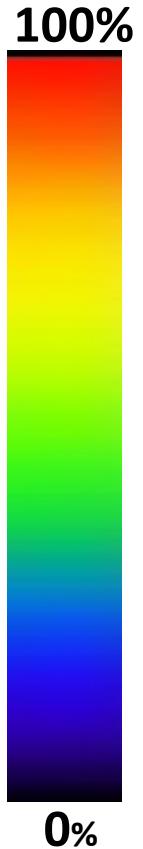


(Castillo et al., 2010)

Apply density-change-based equation

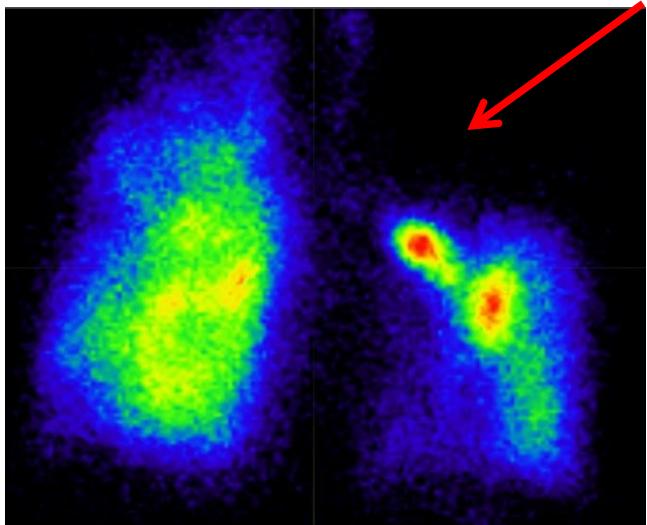
$$\frac{V_{in} - V_{ex}}{V_{ex}} = 1000 \frac{\overline{HU}_{voi}^{voi} - HU_{ex}}{HU_{ex}(1000 + \overline{HU}_{in}^{voi})}^{1,2}$$

Calculating Ventilation Images

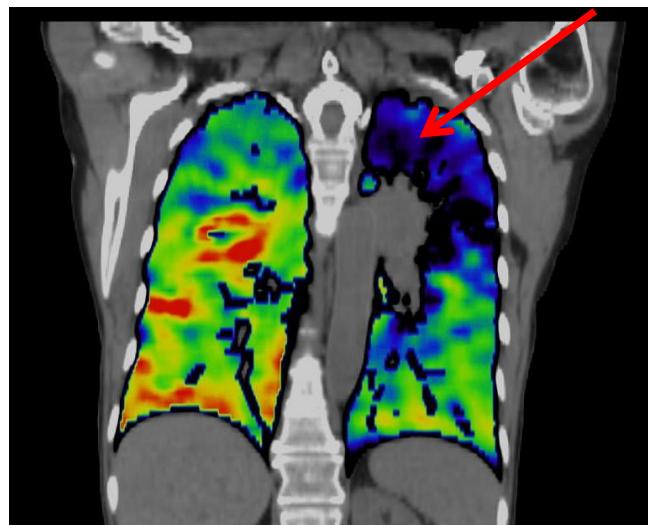


Functional Imaging to Conformal Avoidance RT: Validation

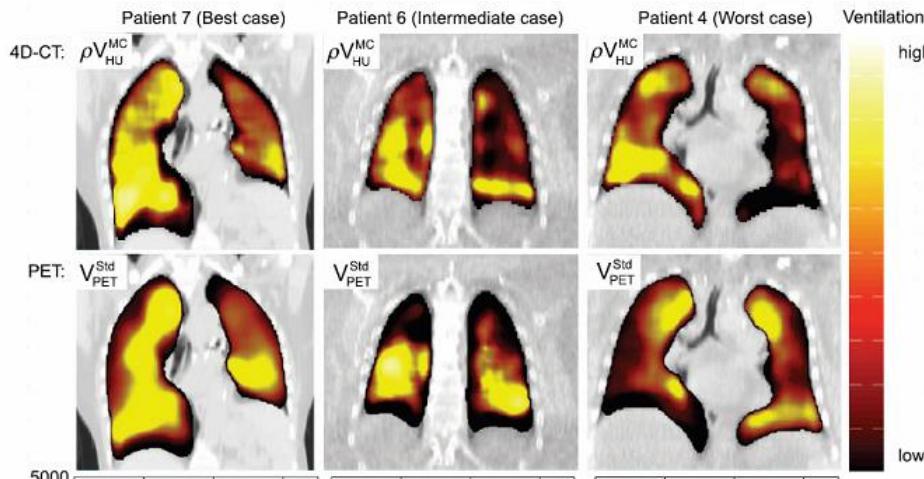
VQ Ventilation Scan



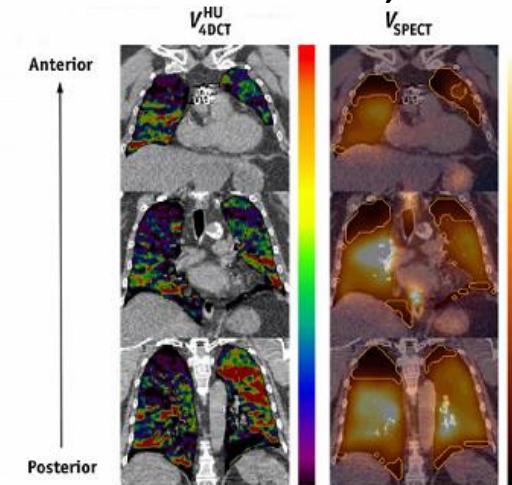
4DCT Ventilation Map



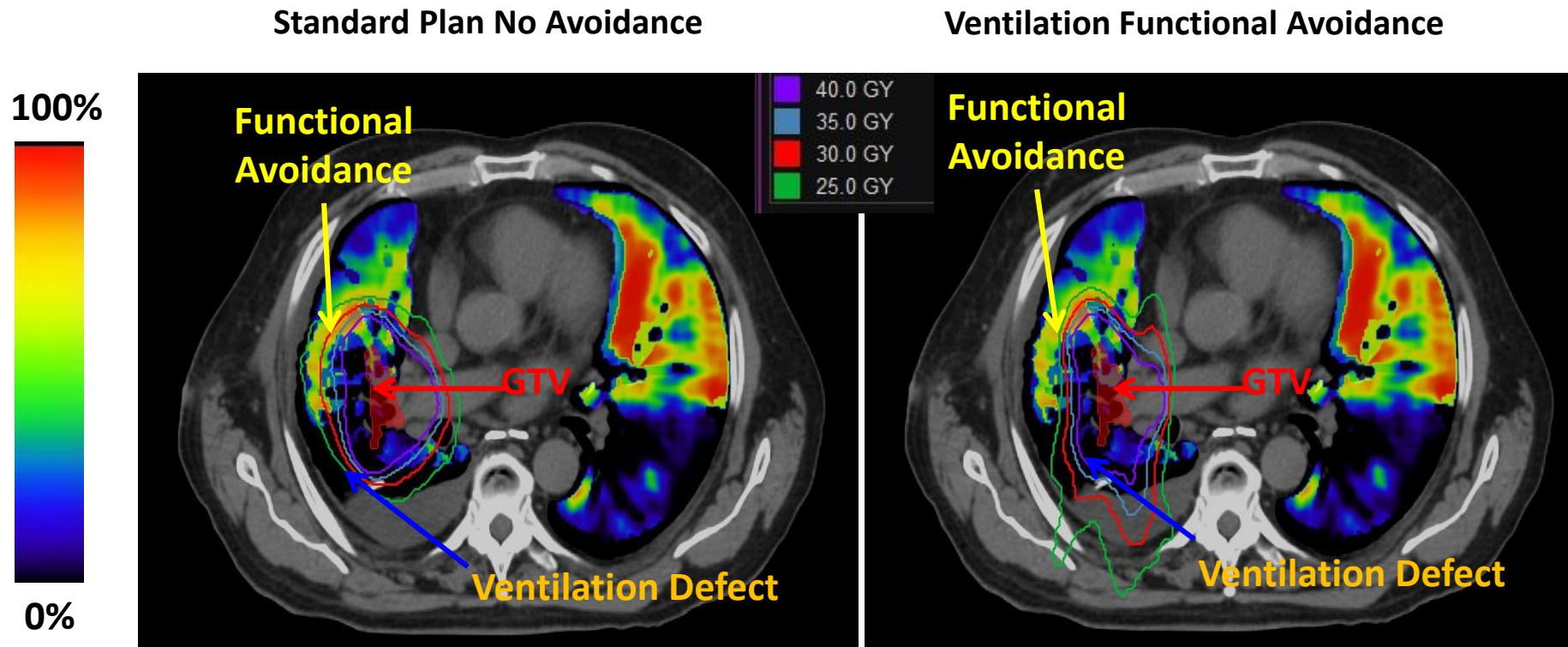
Kipritidis et al – PET 68Ga, University of Sydney



Yamamoto et al – SPECT, UC Davis



Functional radiotherapy with CT Ventilation



Functional radiotherapy objective: reduce pneumonitis rates

Predicting pneumonitis: dose + function > dose ???

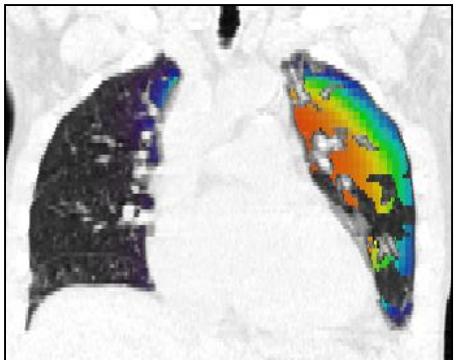
- 96 NSCLC patients
- Radiation pneumonitis toxicity information using CTCAE grading
- Calculated dose metrics
 - Mean lung dose
 - V20 Gy = Volume of lung receiving 20 Gy or higher
- Calculated dose + function metrics
 - Functionally weighted mean lung dose
 - FV20 Gy = Amount of functioning lung getting 20 Gy or higher

Functional planning

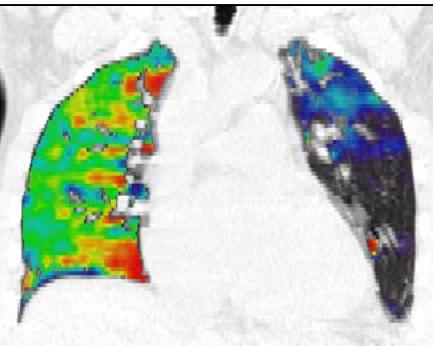
MLD = 22.9 Gy

No pneumonitis

Dose



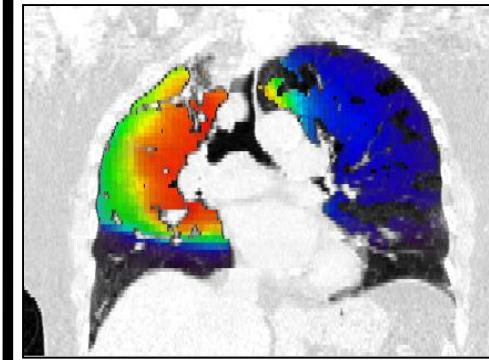
Ventilation



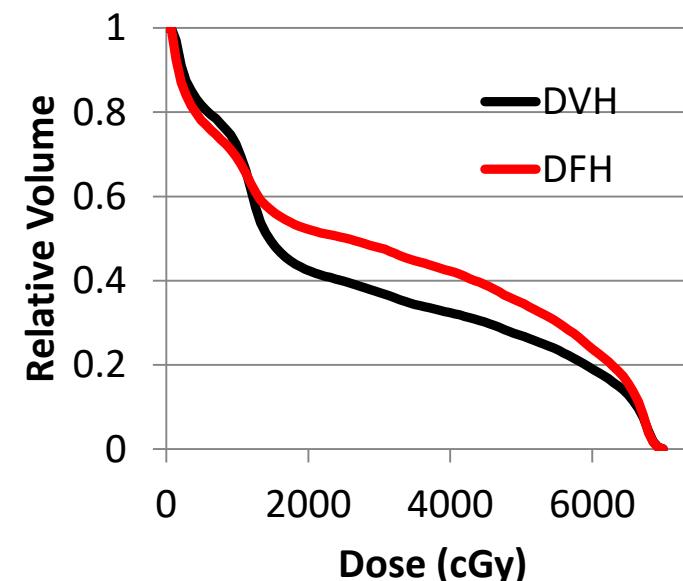
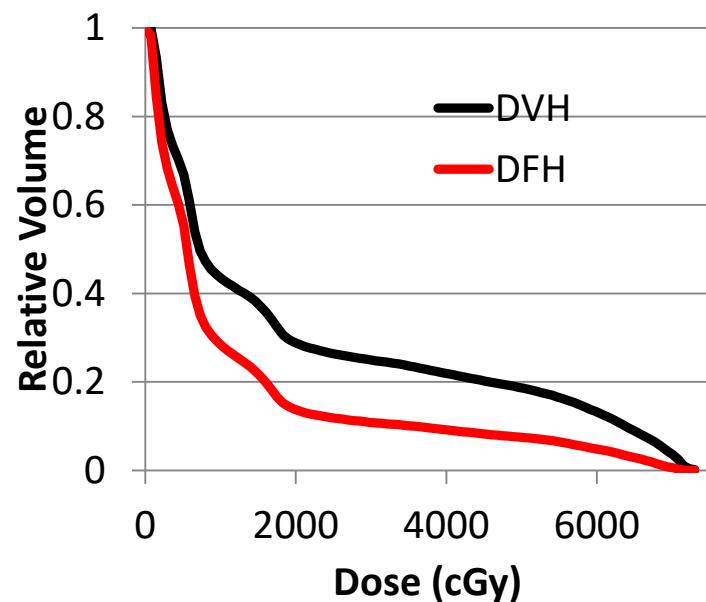
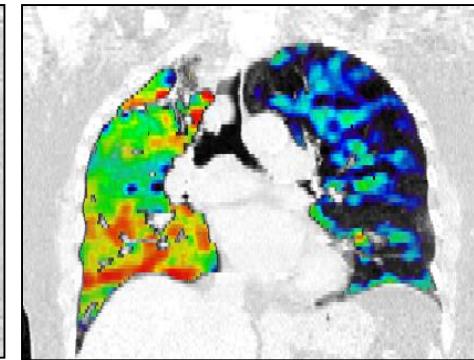
MLD = 23.2 Gy

Grade 3 pneumonitis

Dose

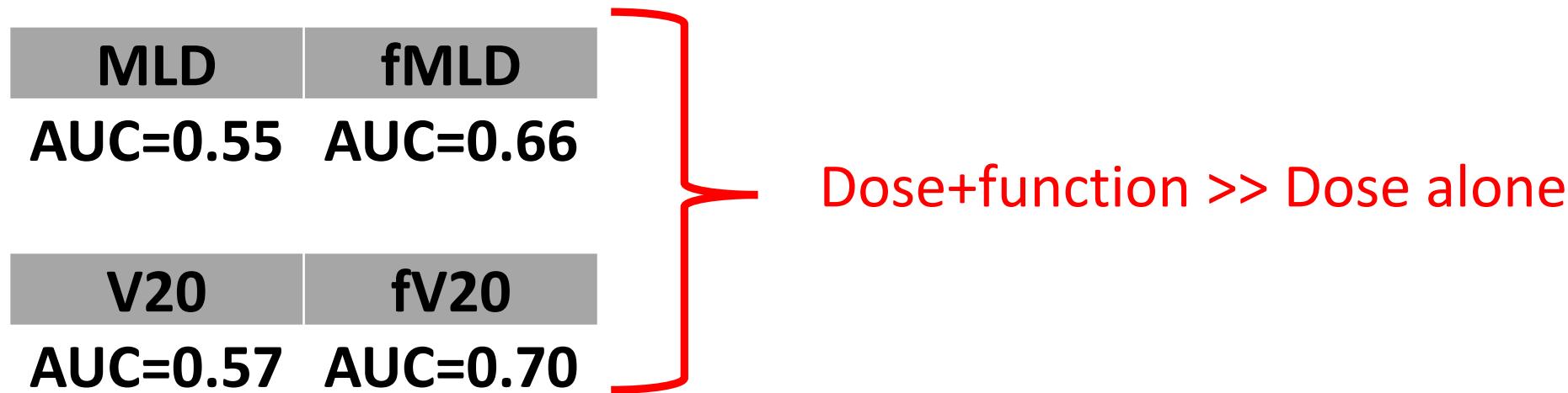


Ventilation



4DCT-ventilation conformal avoidance – Will it work?

Ability of dose and dose + function metrics to predict for grade 3+ radiation pneumonitis: area under the curve (AUC) and logistic regression (Vinogradskiy et al 2013, Faught et al 2017)



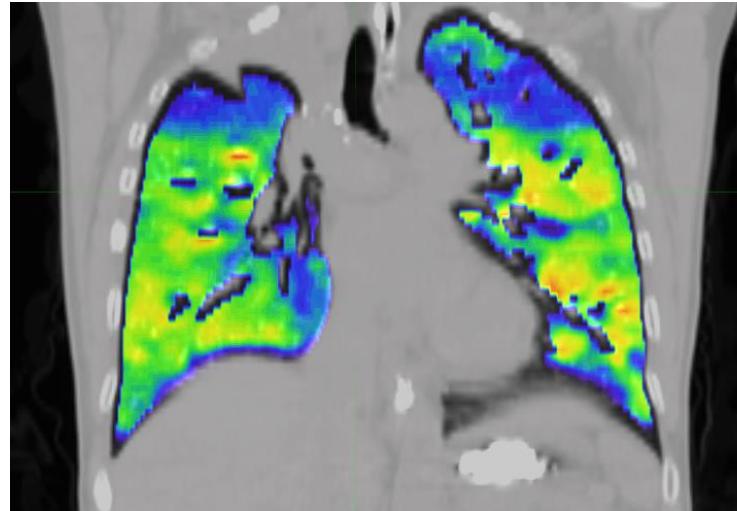
CT Ventilation Functional Radiotherapy Clinical Trial

- 67 lung cancer patients at University of Colorado + William Beaumont (NCT02528942)
- Use 4DCT to calculate ventilation imaging
- Use 4DCT-ventilation to design functional radiation plans
- Reduce functional dose metrics using favorable arc geometry + optimization
- Single-arm, early phase trial looking at feasibility, safety, toxicity rates to be compared to current standard of care techniques

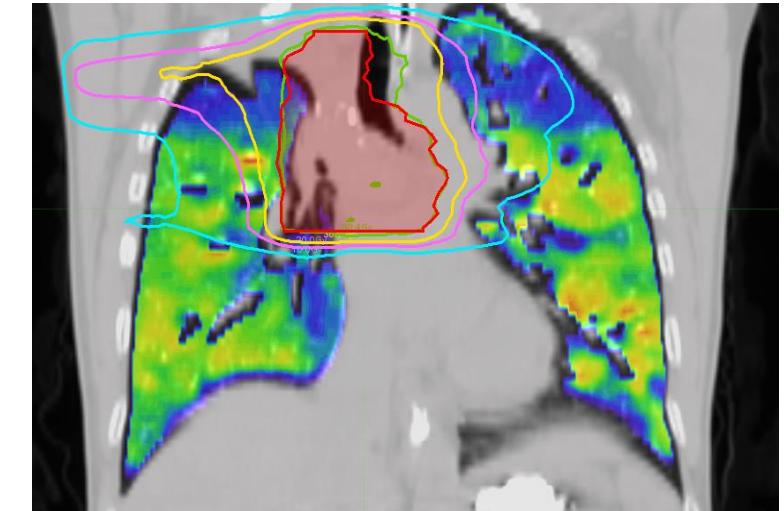
4DCT



4DCT-Ventilation

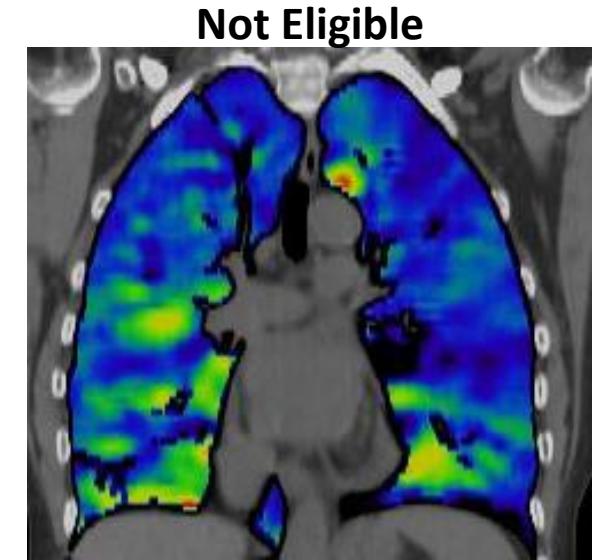
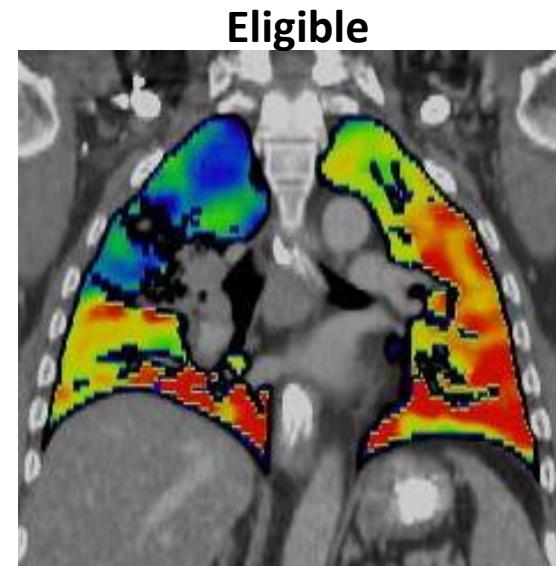


Functional Plan



Inclusion/Exclusion Criteria

- Trial inclusion/exclusion criteria
 - No SBRT, No palliative RT
 - Curative intent Rx dose $\geq 45\text{Gy}$
 - Planned curative intent (concurrent) chemotherapy regimen
 - Image heterogeneity criteria



Trial Design

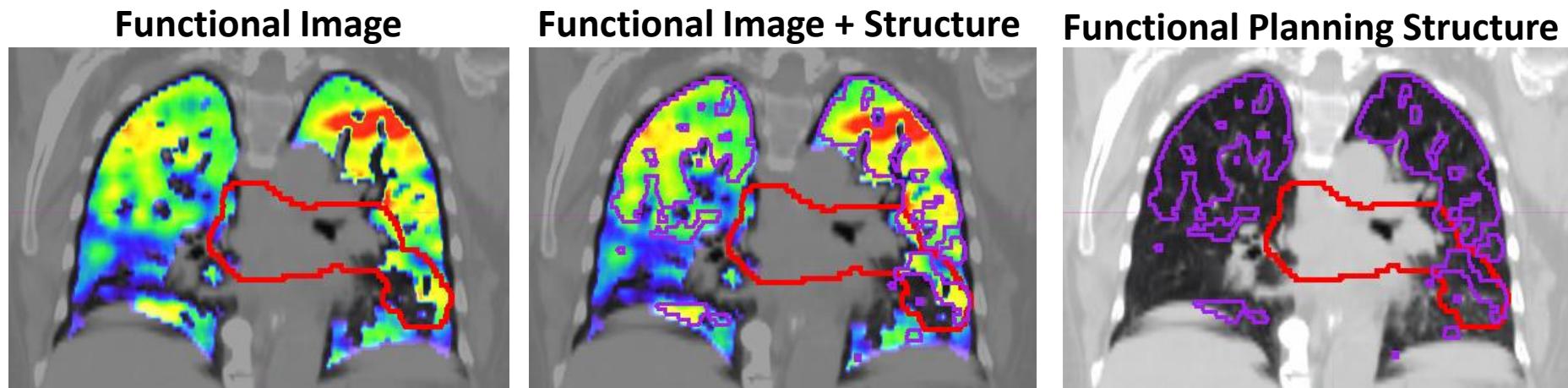
- Study phase: II
- Primary endpoint: grade \geq 2 Radiation Pneumonitis
- Hypothesis: Rate of grade \geq 2 Radiation Pneumonitis can be reduced to 12% with functional radiotherapy compared to 25% rate of grade \geq 2 Radiation Pneumonitis with historical control
- Historical control pneumonitis rate of 25%: QUANTEC Lung, Pneumonitis review by Palma et al (IJORBP, 2013), single institutional experiences published at the time of study design (MSKCC, MDA)
- Trial design: Simon's Two-Stage, futility analysis at 17 patients
- Stats: Using one-sided alpha=0.05, power = 0.8, trial would be positive if \leq 11 ($11/67 = 16.4\%$) patient experience \geq grade 2 radiation pneumonitis

Outcome assessments

- **Assess lung function in a variety of ways**
 - **CTCAE Toxicity (Pulmonary toxicity, pneumonitis, esophagitis)**
 - **PFTs**
 - **QOL Questionnaires**
 - **Imaging: CT, 4DCT-Ventilation, PET, VQ/SPECT**

Implementation: Treatment planning

- **Structure-based treatment planning**
- **Start with standard lung plan (has to be clinically approved), proceed to functional avoidance plan using favorable arc geometry/optimization**
- **Priorities 1) Target coverage, 2) Standard OAR constraints, 3) Functional dose reduction**



Futility analysis

- Trial met futility criteria, progressed with accrual



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Volume 102, Issue 4, 15 November 2018, Pages 1357-1365



Imaging to Prevent Radiation Sequelae

Interim Analysis of a Two-Institution, Prospective
Clinical Trial of 4DCT-Ventilation-based
Functional Avoidance Radiation Therapy

Yevgeniy Vinogradskiy PhD *  , Chad G. Rusthoven MD *, Leah Schubert PhD *, Bernard Jones PhD *, Austin
Faught PhD †, Richard Castillo PhD ‡, Edward Castillo PhD §, Laurie E. Gaspar MD, MBA *, Jennifer Kwak MD ||,
Timothy Waxweiler MD *, Michele Dougherty PhD ¶, Dexiang Gao PhD #, Craig Stevens MD, PhD ||, Moyed Miften
PhD *, Brian Kavanagh MD, MPH *, Thomas Guerrero MD, PhD §, Inga Grills MD §

Results

Patient, clinical, and treatment parameters for the study cohort

- 101 consented patients, 67 patients (\geq 3 month f/u)
- 60% Female
- KPS: 90 (range 60 – 100)
- 55% with COPD
- 93% smokers or former smokers
- 79% NSCLC
- 76% stage III disease
- 16% had surgery (lobectomy, pneumonectomy)
- Rx: 60 Gy (range 45 – 66 Gy), in 30 fractions (range 15 to 33 fractions)
- 25% treated with I/O
- Median f/u 312 days (range 78 to 427 days)

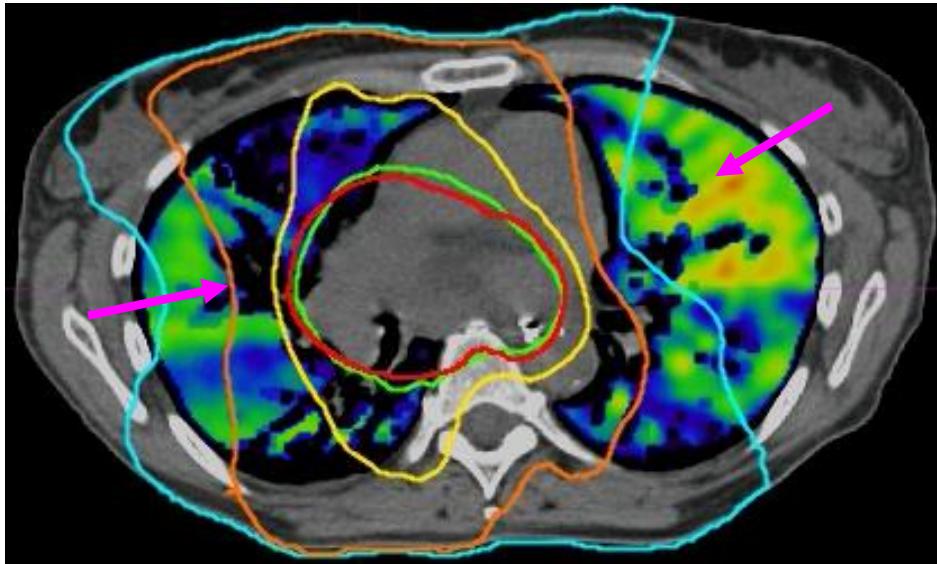
Results: Toxicity

- 10 patients experienced \geq grade 2 radiation pneumonitis (10/67, 14.9%, upper 95% CI of 24.0%)
- Trial outcome positive

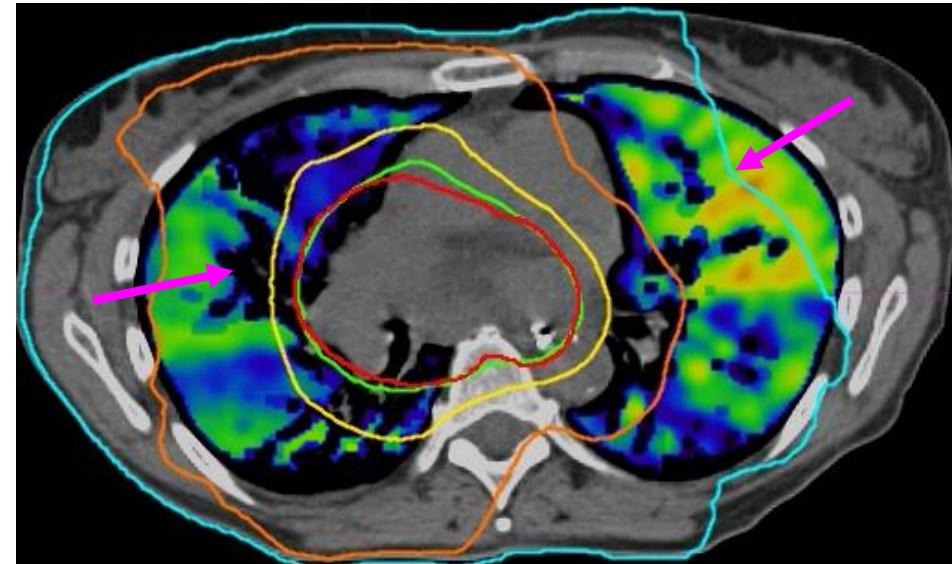
Adverse Event	Grade 0 Number (%)	Grade 1 Number (%)	Grade 2 Number (%)	Grade 3 Number (%)
Pneumonitis	42 (62.7)	15 (22.4)	7 (10.4)	3 (4.5)
Esophagitis	7 (10.4)	27 (40.3)	28 (41.8)	5 (7.5)
Dyspnea	15 (22.4)	38 (56.7)	10 (14.9)	4 (6.0)
Cough	7 (10.4)	47 (70.1)	13 (19.4)	0 (0.0)
Fatigue	5 (7.5)	48 (71.6)	12 (17.9)	2 (3.0)

Patient plan example

Functional avoidance plan



Standard lung plan



■	54.00 (Gy)
■	40.00 (Gy)
■	20.00 (Gy)
■	10.00 (Gy)

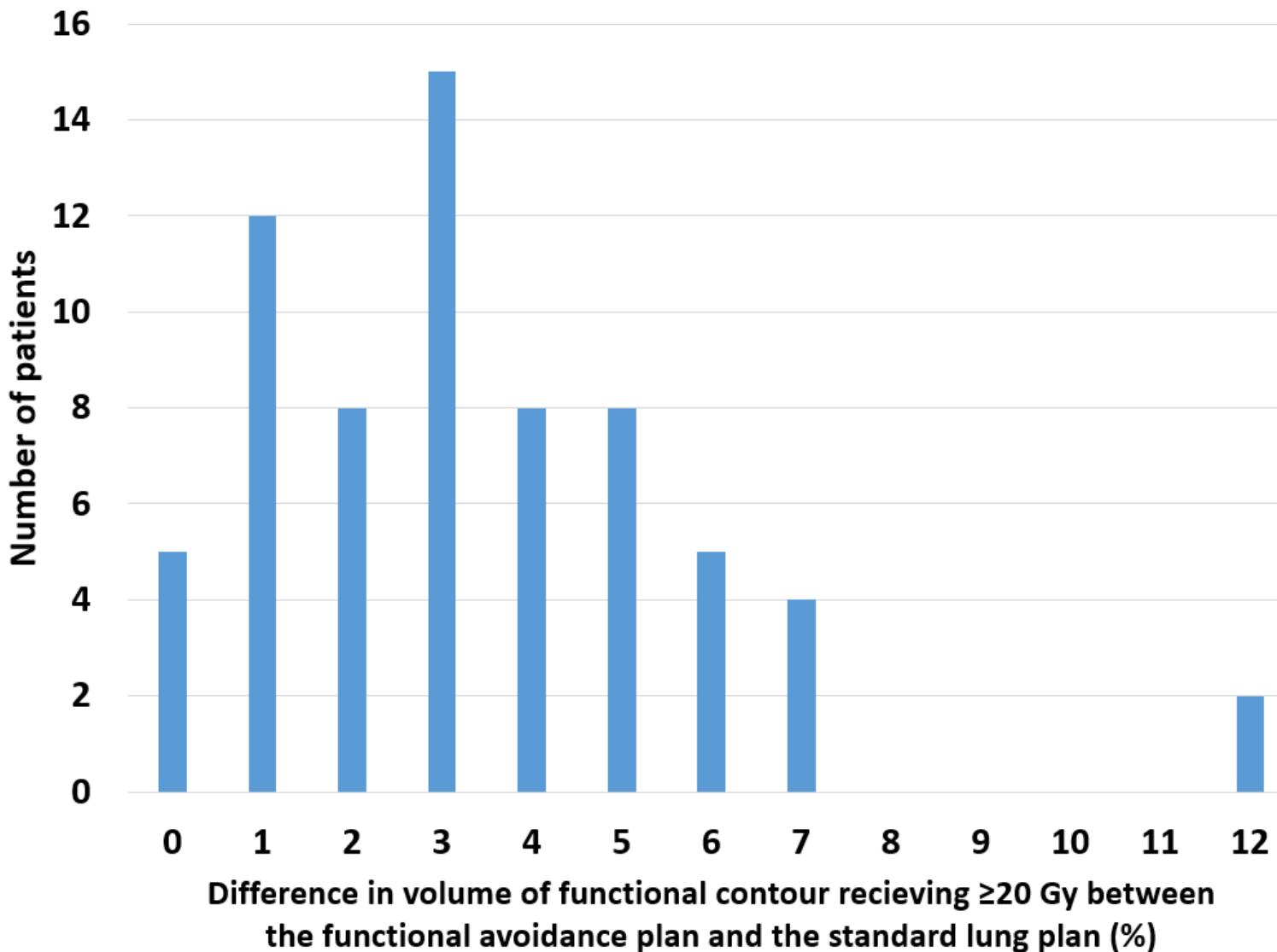
Functional and Standard Dosimetry

- Standard, non-lung metrics get worse, differences are not clinically significant
- Functional dosimetry improved with functional avoidance

Parameter	Functional Avoidance Plan: mean ± sd	Non-functional Plan: mean ± sd	t test p value
PTV Coverage of Rx dose (%)	94.7 ± 3.5	95.5 ± 3.7	0.002
PTV Hotspot (%)	21.7 ± 10.0	21.0 ± 10.4	0.043
Mean Lung Dose (Gy)	14.2 ± 3.8	14.9 ± 3.8	<0.001
Lung V20 (%)	24.3 ± 8.6	26.3 ± 9.0	<0.001
Max Spinal Cord Dose (Gy)	33.5 ± 8.7	32.1 ± 9.1	<0.001
Mean Esophagus Dose (Gy)	22.0 ± 8.3	22.7 ± 8.2	<0.001
Heart V40 (%)	5.2 ± 6.3	5.3 ± 6.0	0.646
Functional Avoidance Structure			
Mean (Gy)	13.5 ± 3.8	14.9 ± 3.8	<0.001
fV5 (%)	67.7 ± 14.2	71.1 ± 13.0	<0.001
fV10 (%)	42.2 ± 13.5	48.6 ± 14.5	<0.001
fV20 (%)	21.6 ± 8.9	25.1 ± 9.4	<0.001
fV30 (%)	12.9 ± 6.8	14.7 ± 7.5	<0.001

Functional and Standard Dosimetry

Average reduction in fV20 = 3.5% (range 0% – 12%)



Discussion

- More recent comparison: RTOG 0617: 21.6% ≥ grade 2 radiation pneumonitis, 20% ≥ grade 3 pulmonary events in 60 Gy arm
- IMRT/3D
- Performance status/PFT requirement
- Surgery allowed
- I/O
 - I/O: 24% ≥ grade 2 radiation pneumonitis
 - No I/O: 12% ≥ grade 2 radiation pneumonitis
- Lung function heterogeneity requirement
- Next steps: secondary outcomes, phase III?, is a phase III needed?

Summary

- **4DCT-based ventilation provides a way to generate lung function images with no extra imaging procedure**
- **Phase II study positive: Functional avoidance reduces rates of side-effects for lung cancer patients**
- **Future work to include robustness, QA, IO**