Best Practices for the Continuum of Care: Difficult Cases

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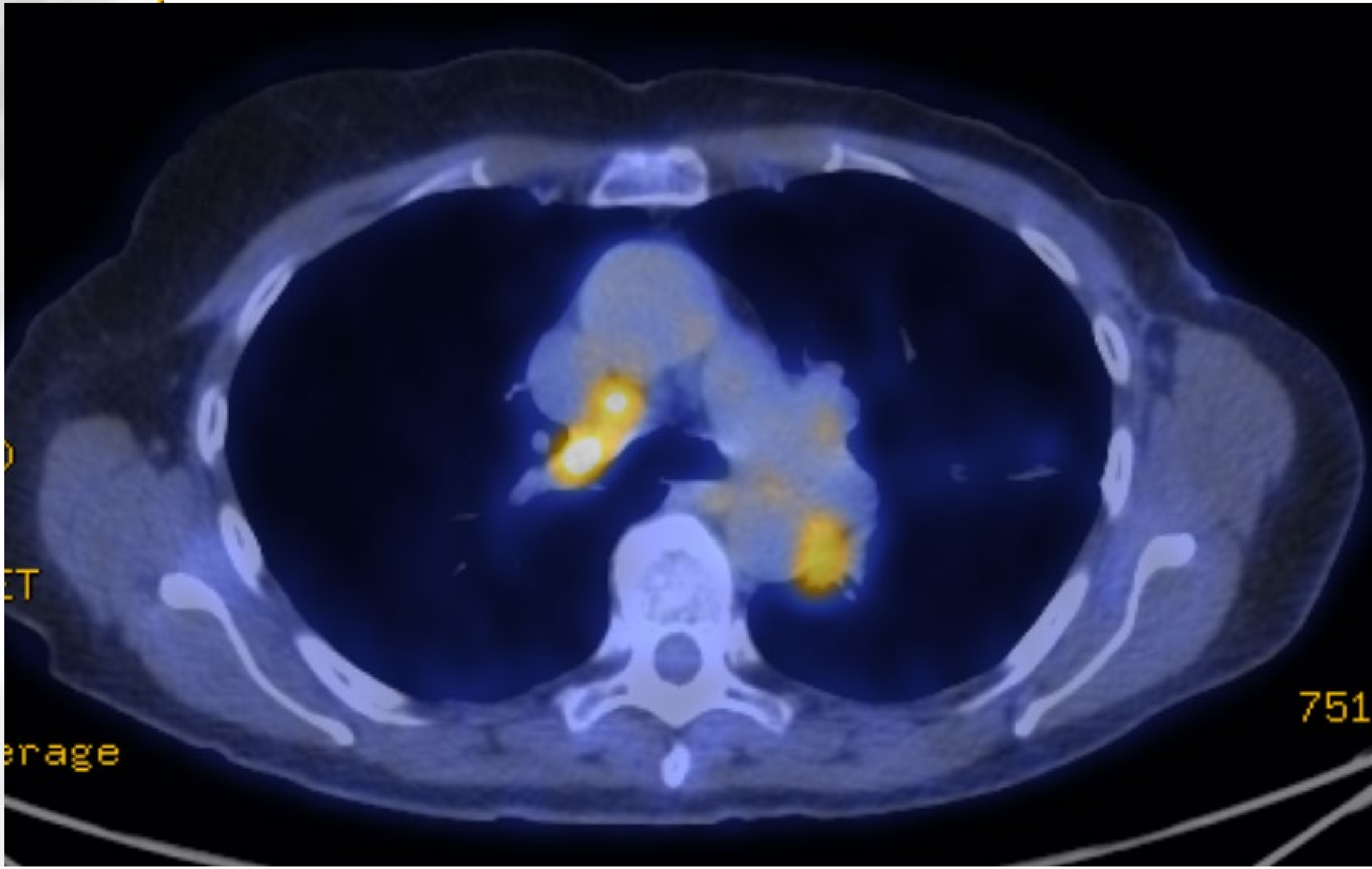
OUTLINE FOR WEBINAR 3

- Discussion of difficult cases
  - N3 disease – the conundrum of long and/or wide radiation fields
  - Bulky disease ?role for induction systemic therapy
  - Treatment of patients with ILD
  - Role of SBRT for large peripheral N0 disease if patient is not a candidate for CRT
  - Role of hypofractionation in patients who are not CRT candidates for central N0 disease

Case 1: Bilateral Hilar N3 disease

- 82 year-old woman in otherwise good health presents with dyspnea
- Found to have a 2.2 cm spiculated RUL tumor and a 1 cm RML tumor with associated mediastinal and hilar adenopathy
- Mediastinoscopy revealed adenocarcinoma in levels 2R and 4R (2L, 4L and 7 were uninvolved)
- PET/CT revealed RUL tumor 2.5 cm, RML tumor 0.9 cm, multiple R mediastinal nodes, and a left hilar node measuring 1.9 cm with SUV 5.7.
- Brain MRI negative
- T4N3M0 adenocarcinoma of the right lung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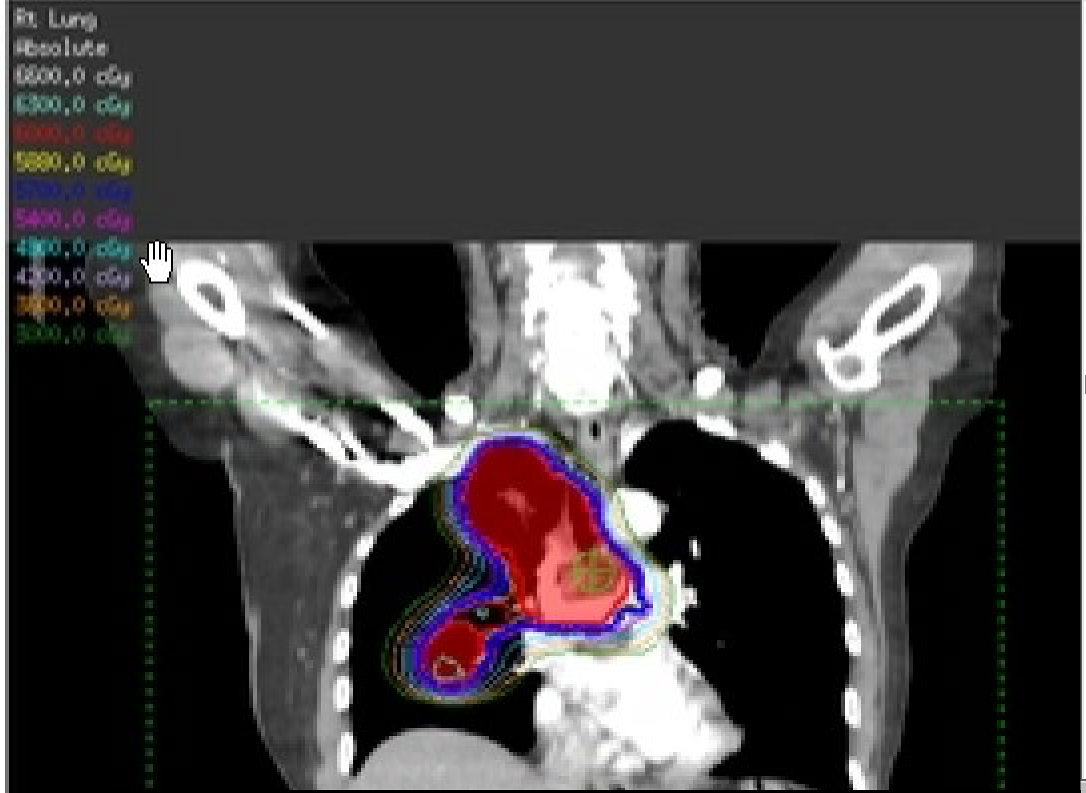
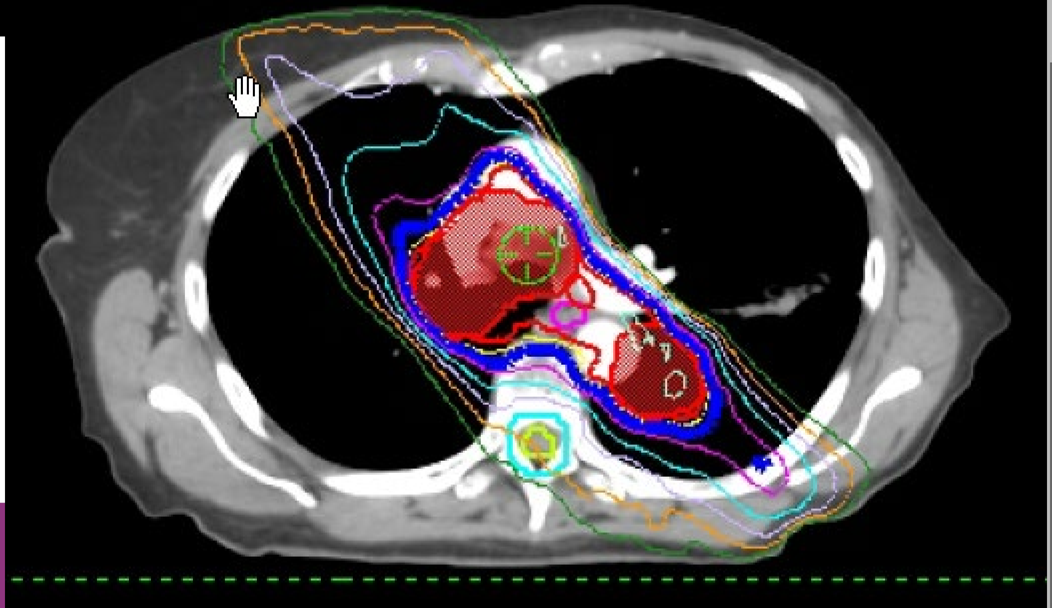
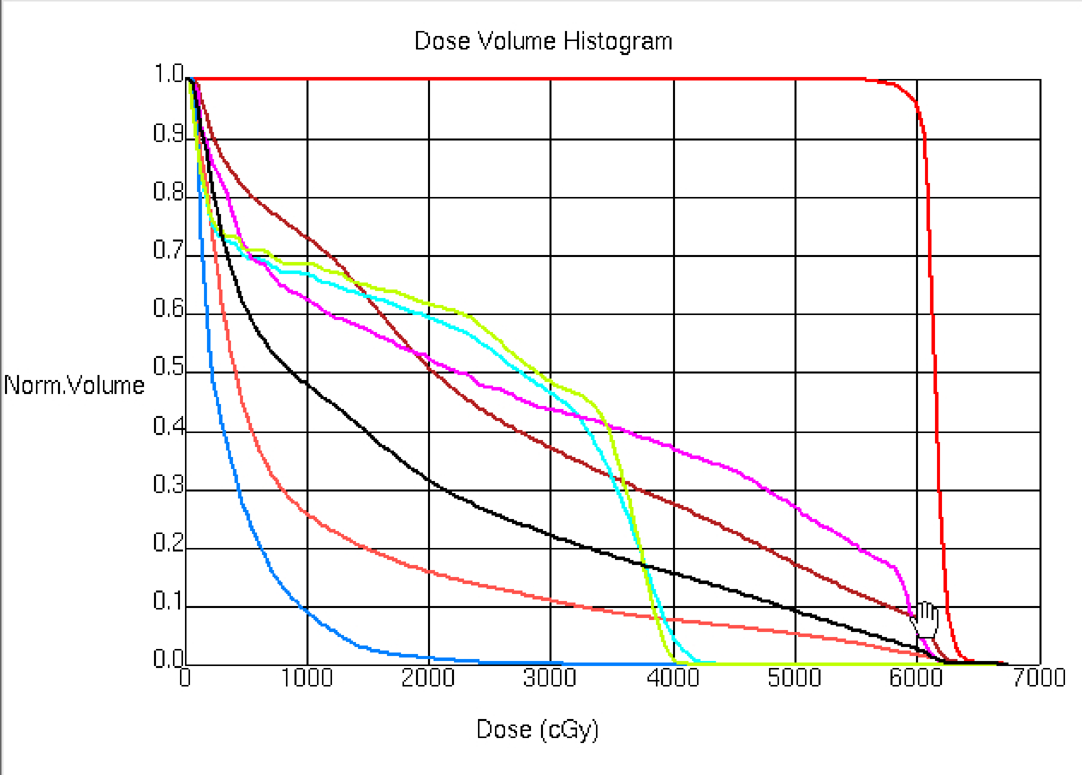






DVH Calculation

- Cumulative
- Differential

Dose Axis Display

- Normalized Dose
- Absolute Dose

- Auto-Compute Max
- Specify Max Dose

Volume Axis Display

- Normalized Volume
- Absolute Volume

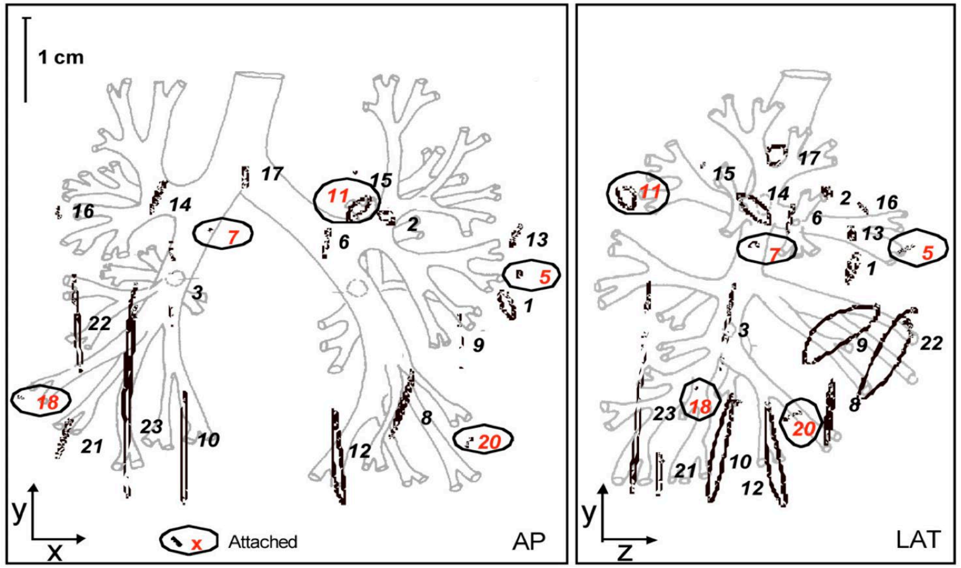
Tabular DVH...

ROI Statistics

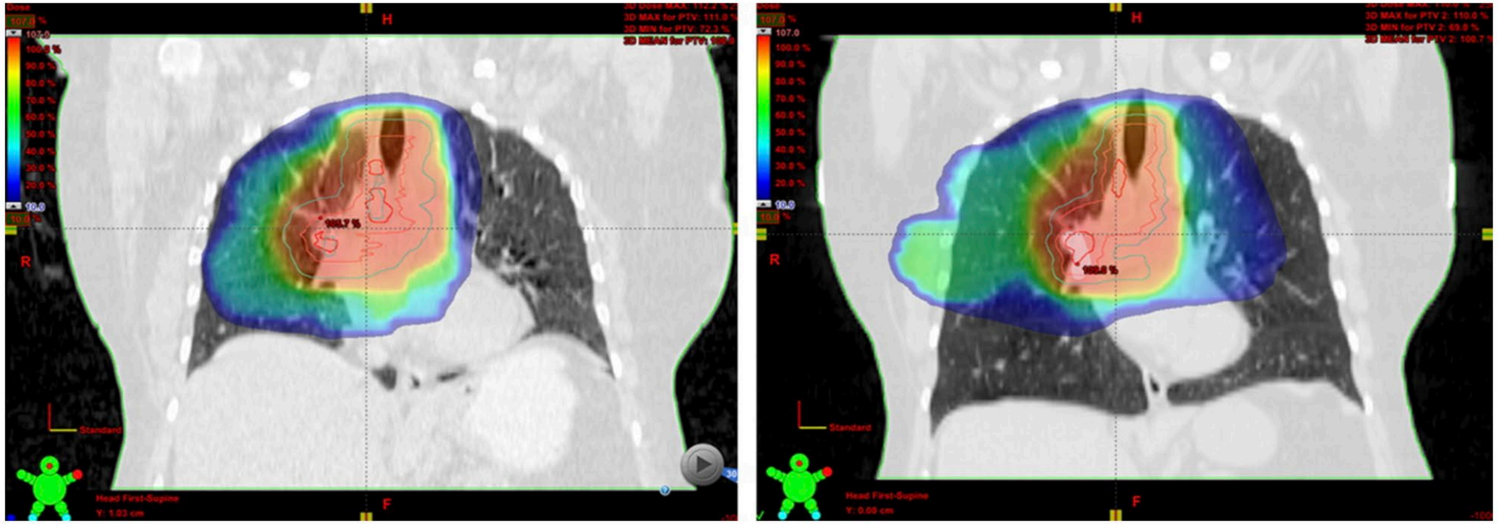
Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max
	Lung_L1	Rt Lung	55.5	6406.7	1040.1	1461.4	0.00 %	0.00 %
	Lung_R1	Rt Lung	63.0	6695.9	2567.6	1964.6	0.00 %	0.00 %
	PTV_MED	Rt Lung	5162.1	6695.9	6141.0	99.9	0.00 %	0.00 %
	cord + 5mm	Rt Lung	50.0	4369.6	2000.1	1608.6	8.92 %	0.00 %
	esophagus	Rt Lung	92.2	6241.4	2582.5	2299.6	5.50 %	0.00 %
	heart	Rt Lung	63.0	3096.0	397.6	405.0	0.00 %	0.00 %
	spinal cord	Rt Lung	54.7	4111.9	2147.3	1586.8	5.42 %	0.00 %
	total lung - ctv	Rt Lung	54.1	6690.9	1694.9	1794.8	0.01 %	0.00 %

Motion Management

- Motion assessment is recommended in locally advanced NSCLC, but when to employ motion management depends on several factors including
  - Extent of tumor motion
  - Lung size and function
  - Dosimetric benefit of a motion management technique



Seppenwoolde et al IJROBP 2002



Josipovic et at Acta Oncol 2014

Use of PET in Treatment Planning

- Fusion can be challenging due to differences in breath hold (PET could be gated or free breathing and CT from PET/CT is typically just a random capture)
- Deformable registration should be used with care
- Many factors can affect the use of thresholded volumes. RTOG1106 used a threshold of 1.5 x aortic arch intensity. Nuclear Medicine can be consulted with questions.

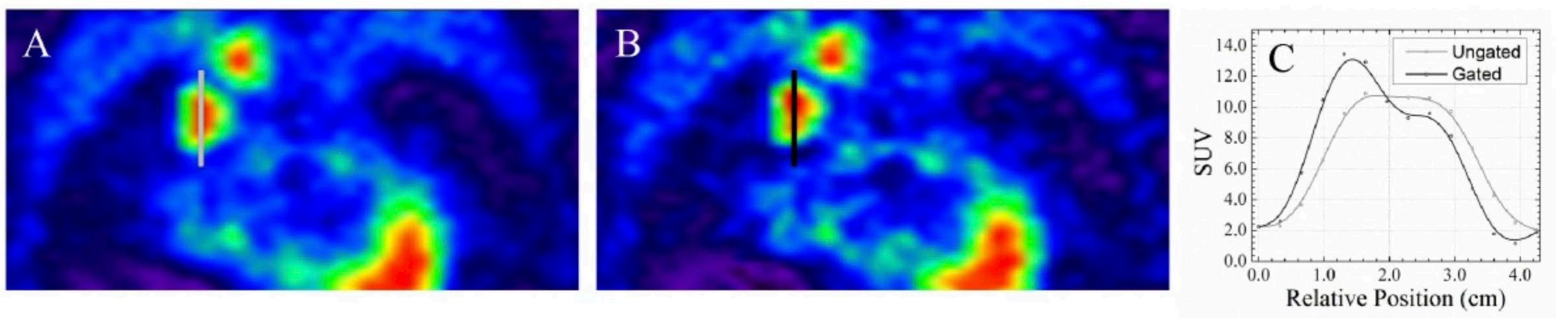
ELSEVIER

Radiotherapy and Oncology
Volume 116, Issue 1, July 2015, Pages 27-34

IAEA consensus report

PET/CT imaging for target volume delineation in curative intent radiotherapy of non-small cell lung cancer: IAEA consensus report 2014

Tom Konert[a, b], Wouter Vogel[a, b], Michael P. MacManus[c], Ursula Nestle[d], José Belderbos[b], Vincent Grégoire[e], Daniela Thorwarth[f], Elena Fidarova[g], Diana Paez[g], Arturo Chiti[h], Gerard G. Hanna[i]



Bowen et al

Image Guidance

- Soft tissue image guidance is essential for lung radiotherapy especially when there is not other surrogate available (such as markers)
- Monitoring with CBCT can identify changes that may require adaptation
- Dosimetric evaluation can be performed prior to making a plan change

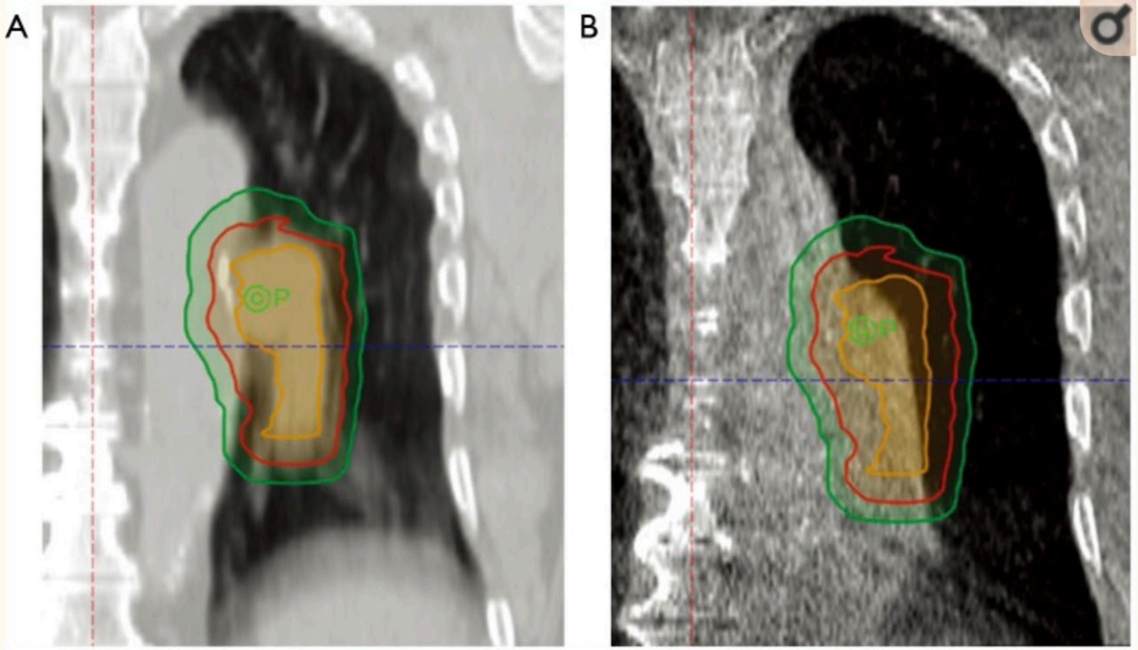


Figure 1

Coronal CT images of a patient with newly diagnosed LA-NSCLC planned for concurrent chemoradiotherapy. (A) CT simulation with delineation of ITV (orange), CTV (red), and PTV (green); (B) CBCT performed at the time of first treatment with overlaid target volumes from simulation with interval lung collapse and associated shifting of the target volumes.

Molitoris et at J Thor Dis 2018

Non-resectable NSCLC Planning Techniques and Considerations

Kate Aldridge, B.S., R.T.T., CMD
Henry Ford Cancer Institute
Detroit, MI

Planning Considerations

- Tumor volumes for these types of cases may have bilateral disease, supraclav/mediastinal nodal involvement and potentially long radiation fields
- PTV expansions can differ depending on availability/ability of patients to use breath hold or compression techniques to reduce motion.
- OAR dose constraints may be difficult to achieve with the prescribed dose needed to provide local tumor control.

RTOG 0617 CHEMO-RT OAR DOSE CONSTRAINTS

Standard dosing regiment is

60Gy (2Gy x 30 fractions)

LUNG (Lung-GTV):

- Mean<20Gy
- V20<35%
- V5<65%, V10<45%

(Mean dose and V20 are biggest predictors of radiation pneumonitis)

ESOPHAGUS:

- Mean<34Gy
- V60<33%

HEART:

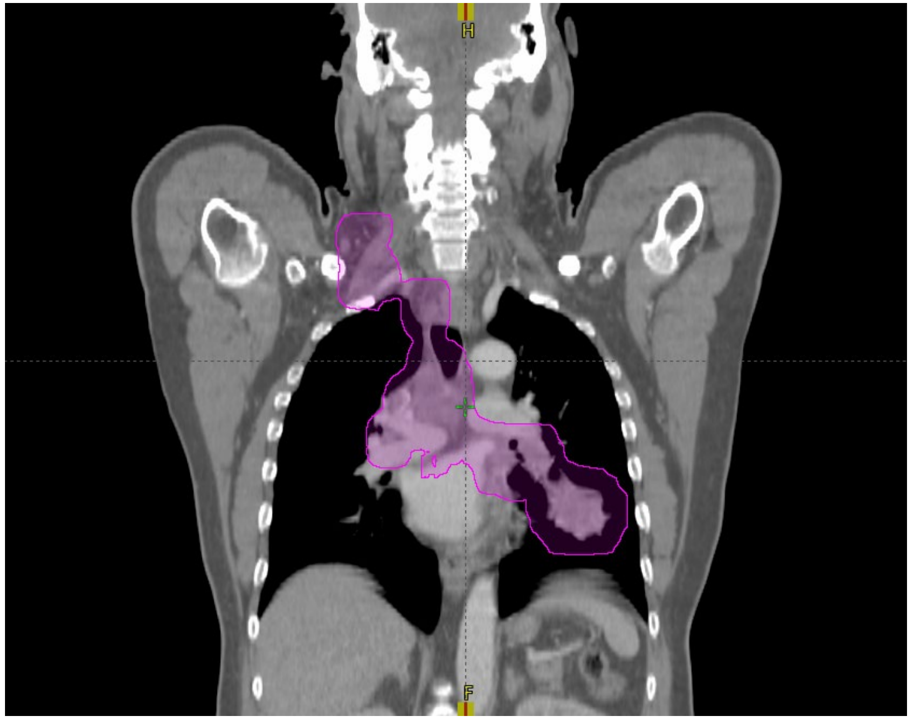
- V40<100%
- V45<66%
- V60<33%

SPINAL CORD:

MAX 45Gy

Planning Techniques

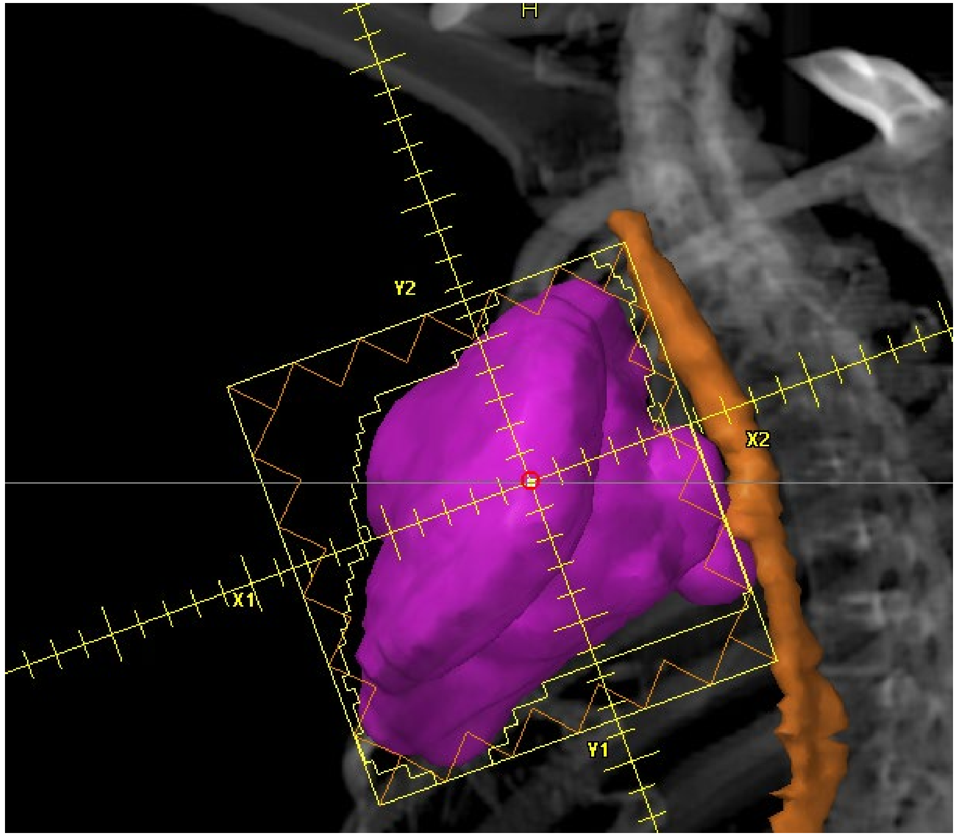
- A recent AAMD plan study on a large NSCLC Thorax field showed the majority of photon cases were being planned utilizing VMAT or static IMRT techniques to better spare organs at risk.
- Other planning strategies include using multiple isocenters to break up the planning volume and help spare OARs, combining VMAT/IMRT techniques, using non-coplanar arcs & utilizing partial arcs or avoidance sectors.
- Beam energies can also be manipulated as a means of sparing OARs. The most common photon energy used is 6X but alternate options would be to use 6/10X mixed beams or 6X FFF and/or 10X FFF beams



Fellows Z. 2021 AAMD Plan Study: Thorax, Sponsored by Elekta. Oral Presentation. AAMD Annual Meeting 2021. 2021, June 6.

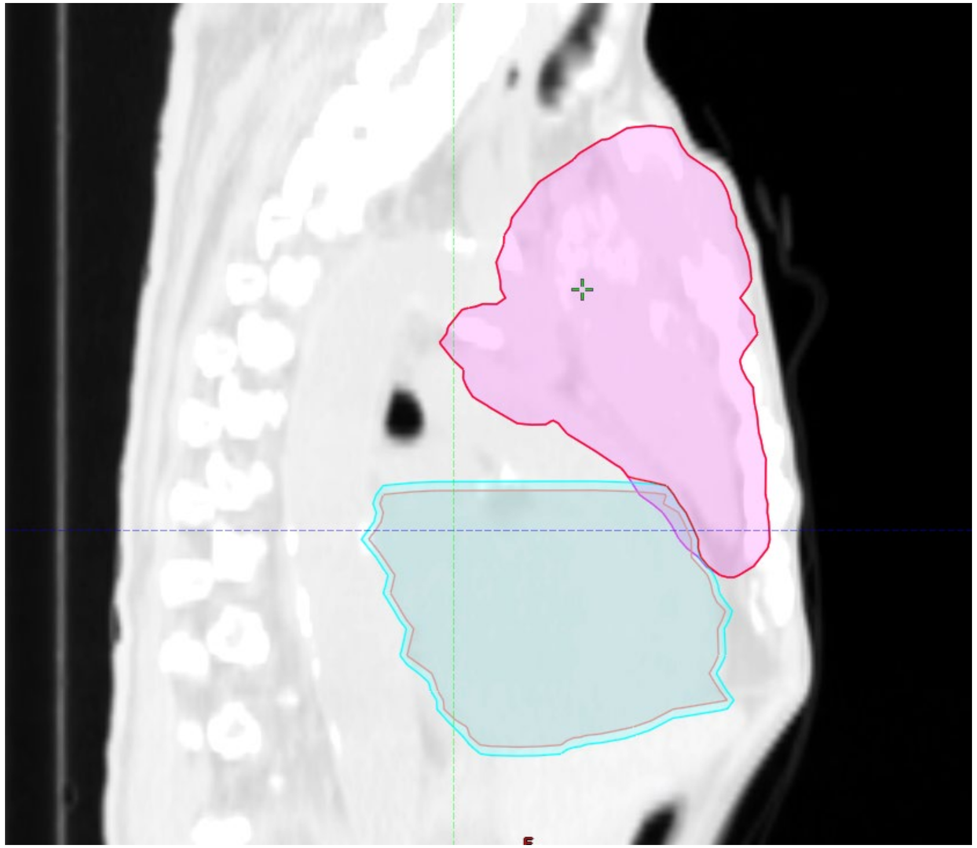
Beam Optimization

- The selection of beam angles and arcs is also a valuable tool to consider when planning these types of cases. Some planning systems also have a feature that can automatically optimize beam angles that will help achieve planning goals.
- Collimator angles can be optimized to block OARs and jaw sizes can be limited for this purpose as well.



Beam Optimization

- Using PRVs (margins around organs) to optimize the OARs and cropping target structures away from OARs can help achieve goals during the planning process as well.



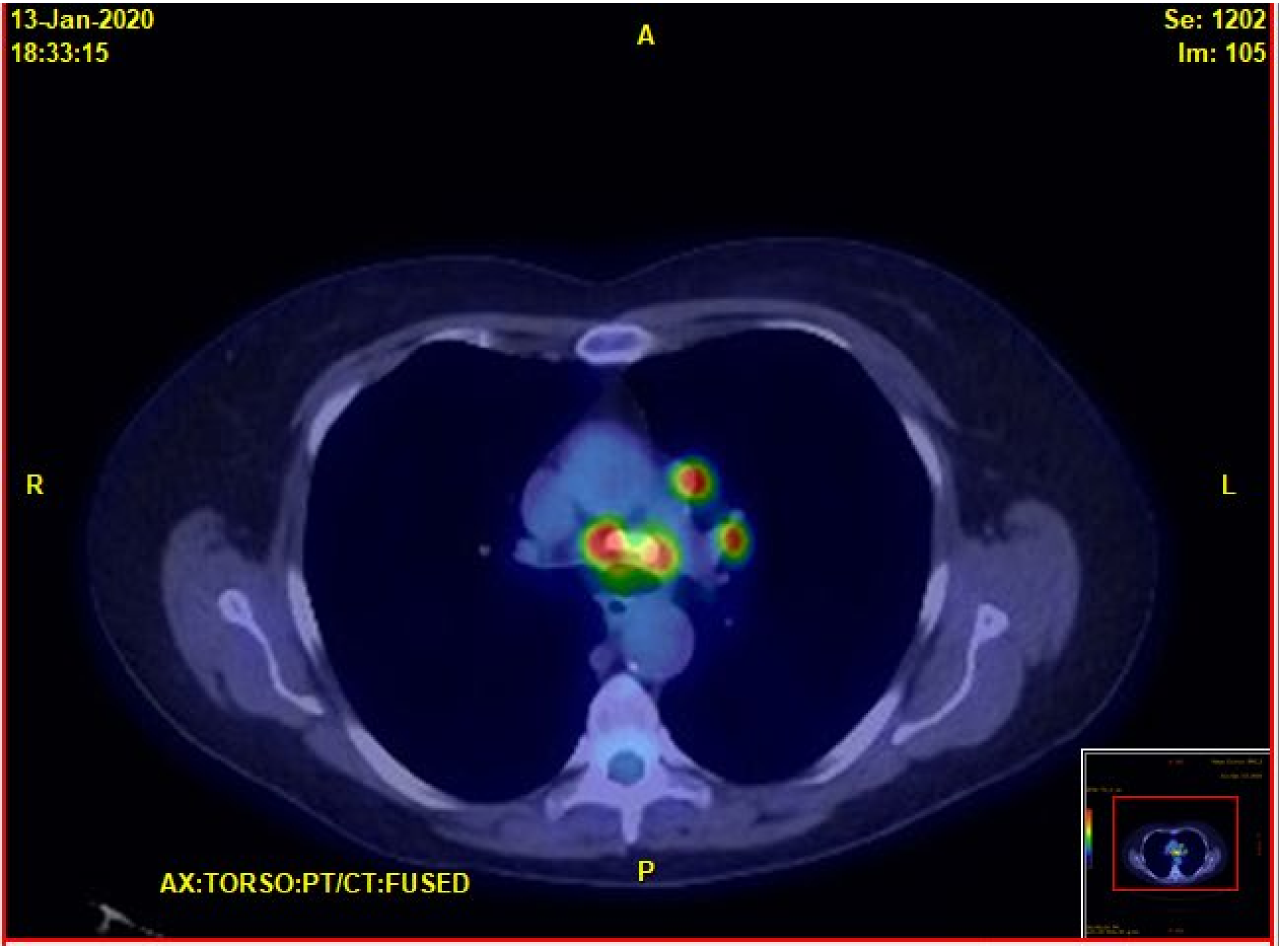
Achieving Planning Goals

So what can we do if we try all of these methods and still can’t meet the planning goals?

- Option to reduce PTV margin
- Option to resim the patient at a certain point during the treatment to try and reduce the planning volume for the remainder of the treatment
- Consider breath hold/compression technique if not already utilized, possibly combined with resim if patient was unable to comply for the initial plan but may be able to do so later in the treatment.
- Option to do an adaptive planning process with several target revisions throughout the treatment

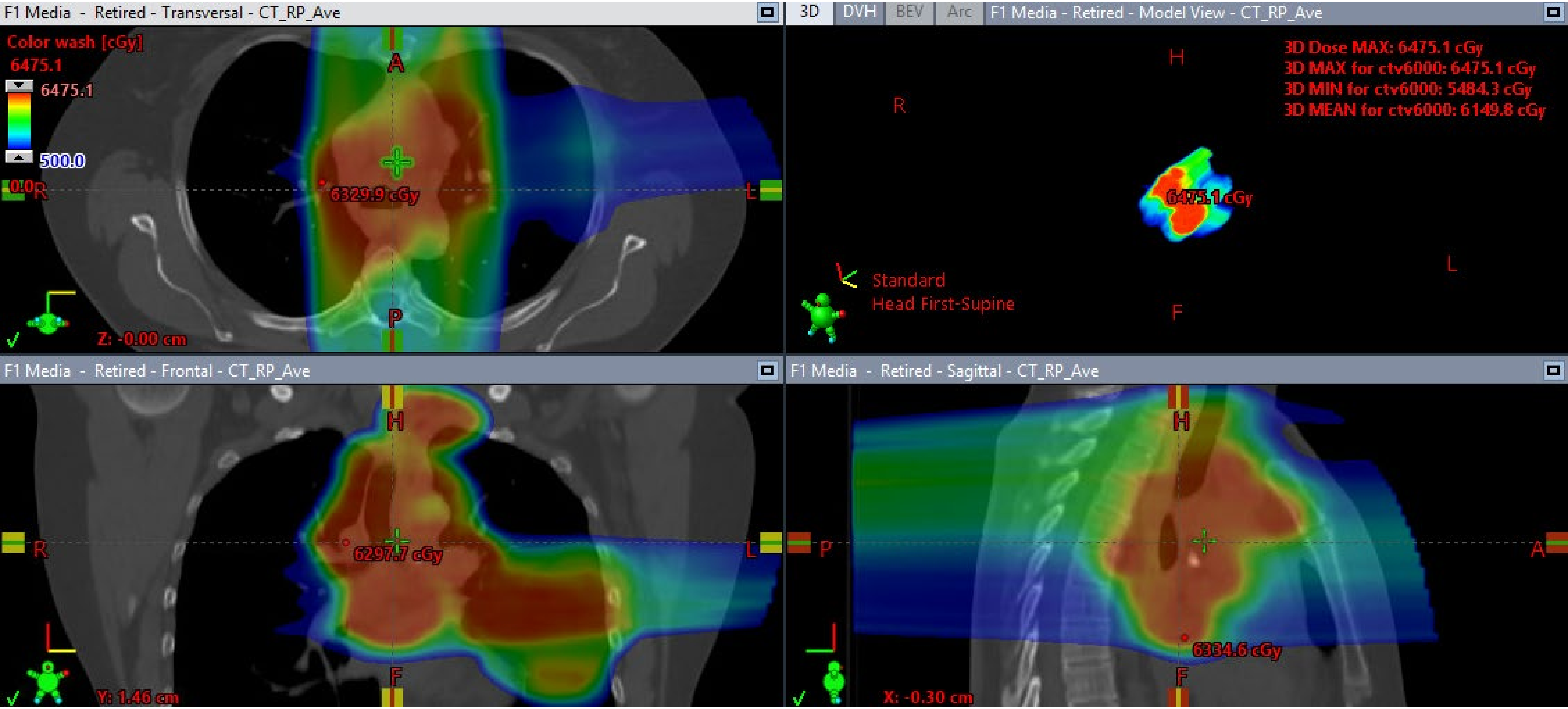
Case 2: Supraclav N3 + long RT field

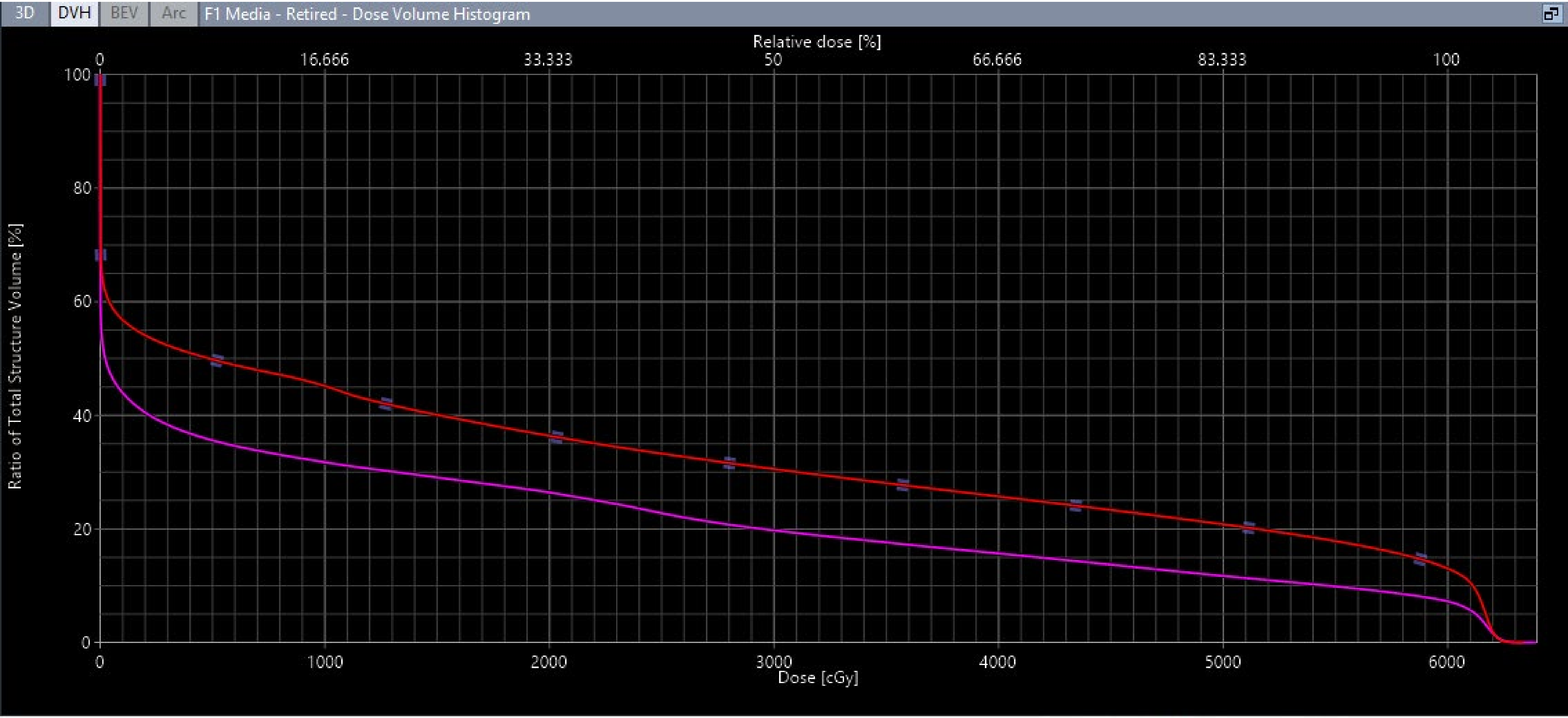
- 62 year old female
- Presented with shortness of breath and escalating cough
- CT chest shows 4.3 cm LUL nodule
- PET-CT shows FDG avid left supraclavicular, hilar, and paratracheal nodes in addition to the FDG avid primary
- MR brain is negative for metastasis
- EBUS shows station 4L, 7 positive for adenocarcinoma, TTF1 positive, tumor cells 1% PDL1 expressing
- NGS shows no actionable mutations



13-Jan-2020
18:33:15
A
Se: 1202
Im: 105
R
L
P
AX:TORSO:PT/CT:FUSED

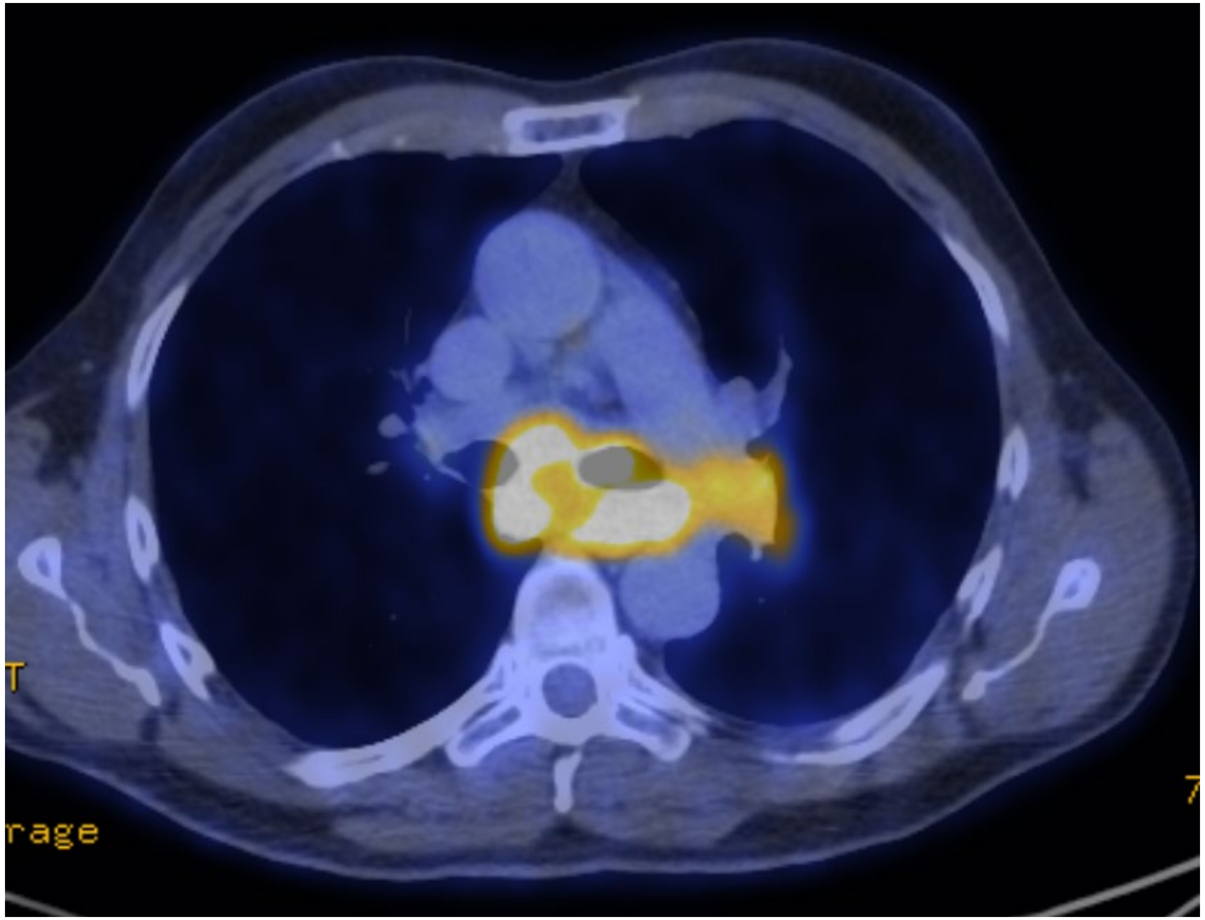
13-Jan-2020
18:33:15
S
Se: 1201
Im: 64
R
L
I
COR:TORSO:PT/CT:FUSED

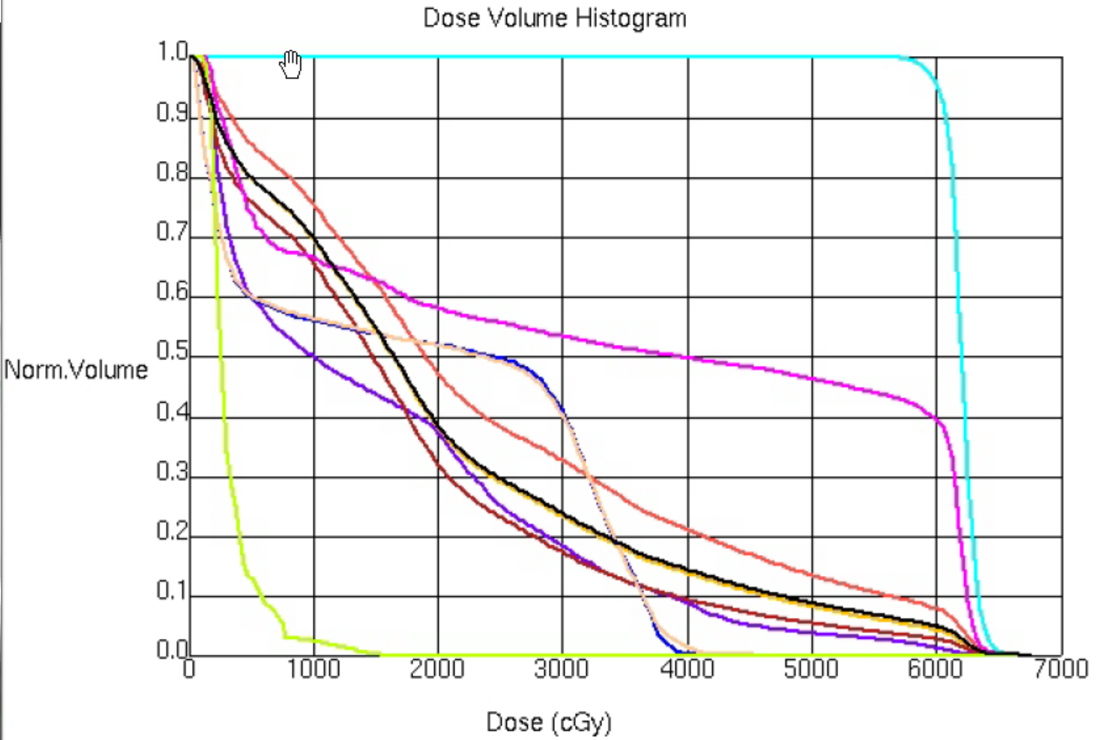

F1 Media - Retired - Transversal - CT_RP_Ave
Color wash [cGy]
6475.1
6475.1
500.0
0.0
A
R
L
P
6329.9 cGy
Z: -0.00 cm
3D
DVH
BEV
Arc
F1 Media - Retired - Model View - CT_RP_Ave
3D Dose MAX: 6475.1 cGy
3D MAX for ctv6000: 6475.1 cGy
3D MIN for ctv6000: 5484.3 cGy
3D MEAN for ctv6000: 6149.8 cGy
H
R
6475.1 cGy
L
F
Standard
Head First-Supine
F1 Media - Retired - Frontal - CT_RP_Ave
H
R
L
6297.7 cGy
F
Y: 1.46 cm
F1 Media - Retired - Sagittal - CT_RP_Ave
H
P
A
6334.6 cGy
F
X: -0.30 cm


3D
DVH
BEV
Arc
F1 Media - Retired - Dose Volume Histogram
Relative dose [%]
0
16.666
33.333
50
66.666
83.333
100
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
1000
2000
3000
4000
5000
6000
Dose [cGy]

Case 3: Bulky disease

- 66 year-old man developed persistent cough
- Chest x-ray demonstrated left lower lobe consolidation and findings suspicious for hilar adenopathy.
- CT of the chest with contrast performed demonstrated multiple large mediastinal lymph nodes including a right lower paratracheal lymph node measuring 2.2 cm with a necrotic-appearing hypodense center, and a left lower paratracheal lymph node measuring 1.9 cm with a necrotic-appearing hypodense center, along with a mass-like confluence of the subcarinal lymph nodes. There was a large left hilar mass encasing the left inferior lobar pulmonary artery and inferior pulmonary vein. There was endobronchial invasion of the left lower lobe bronchus with partial obstruction of the superior segmental bronchus and complete obstruction of the basilar segmental bronchi with postobstructive pneumonitis
- PET/CT confirmed CT findings with no evidence of metastatic disease
- Brain MRI negative
- EBUS with biopsy demonstrated SCC

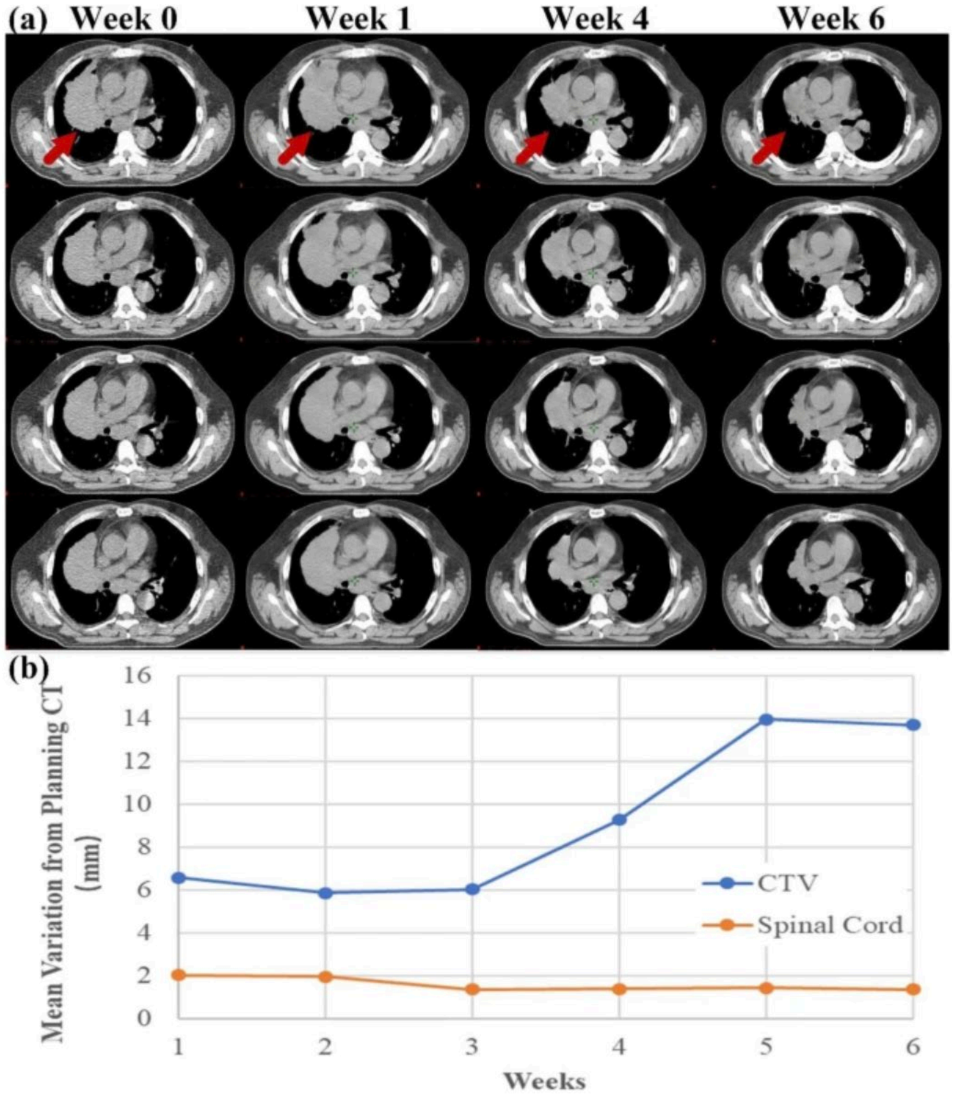




Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max
	Lung_L1	Left Lung	31.3	6662.1	2424.3	1829.5	0.00 %	0.00 %
	Lung_R1	Left Lung	42.0	6679.5	1755.1	1490.8	0.00 %	0.00 %
	PTV	Left Lung	5347.0	6679.5	6199.4	115.6	0.00 %	0.00 %
	cord	Left Lung	54.8	4148.8	1061.9	1467.9	42.69 %	0.00 %
	cord +2mm	Left Lung	53.6	4545.4	1078.8	1475.1	41.89 %	0.00 %
	esophagus	Left Lung	152.4	6612.2	3473.2	2627.3	0.00 %	0.00 %
	left bp	Left Lung	124.5	1538.4	280.0	224.2	14.22 %	0.00 %
	total lung	Left Lung	31.3	6679.5	2039.5	1676.6	0.00 %	0.00 %

Adaptation

- Within common photon techniques, the dose distribution is fairly robust to changes during treatment
- Larger geometric or density shift and the use of protons may necessitate adaptive planning
- At the physician's discretion, adaptive planning can also be used to reduce volumes and better meet dosimetric objectives
- Dose accumulation can be challenging with major geometric changes. IGRT is essential and plans can be evaluated using dose projected out to full dose when deformable dose accumulation is not available or accurate



Chen et at 2020

Case 3: no validated role of induction therapy

- No validated role in the PACIFIC era
- Prior studies of induction platinum-based therapy failed to show benefit prior to cCRT in lung cancer:
  - Similar survival
  - Increased toxicity
  - Attrition prior to cCRT
- Also, unclear benefit in other solid tumors

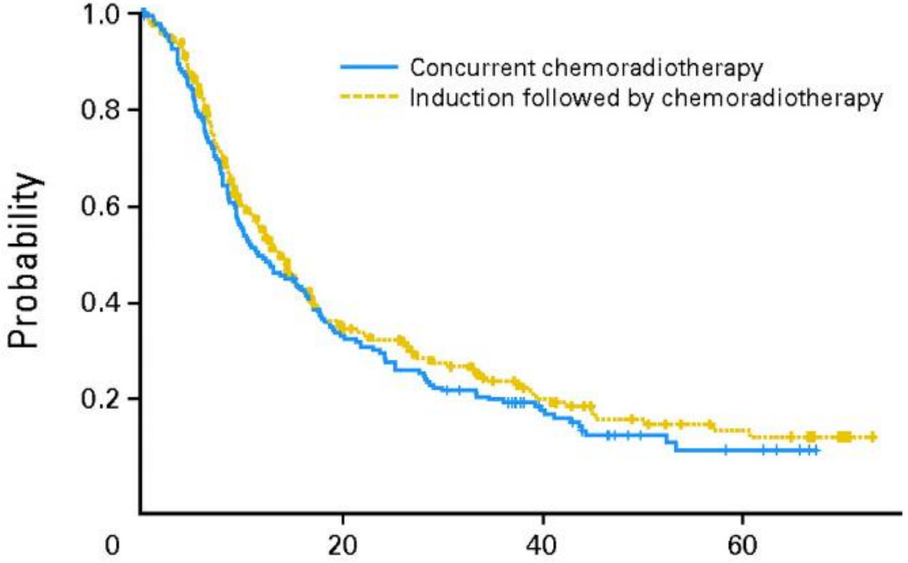


Table 3. CALGB 39801 Adverse Events (Concurrent CT/X)

	Arm A (CT/X)		Arm B (Ind Followed by CT/X)	
Variable	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
ANC	11	4	24	7*
WBC	32	4	38	6
HgB	5	0	12	0
Lymphopenia	55	8	47	9
Febrile neutropenia	2	0	4	0
Fatigue	19	1	17	4
Anorexia	15	5	11	8
Dysphagia-esophageal	30	2	28	8
Dyspnea	11	3	15	4
Pneumonitis	3	1	8	2†
Maximum toxicity	58	26	55	30‡

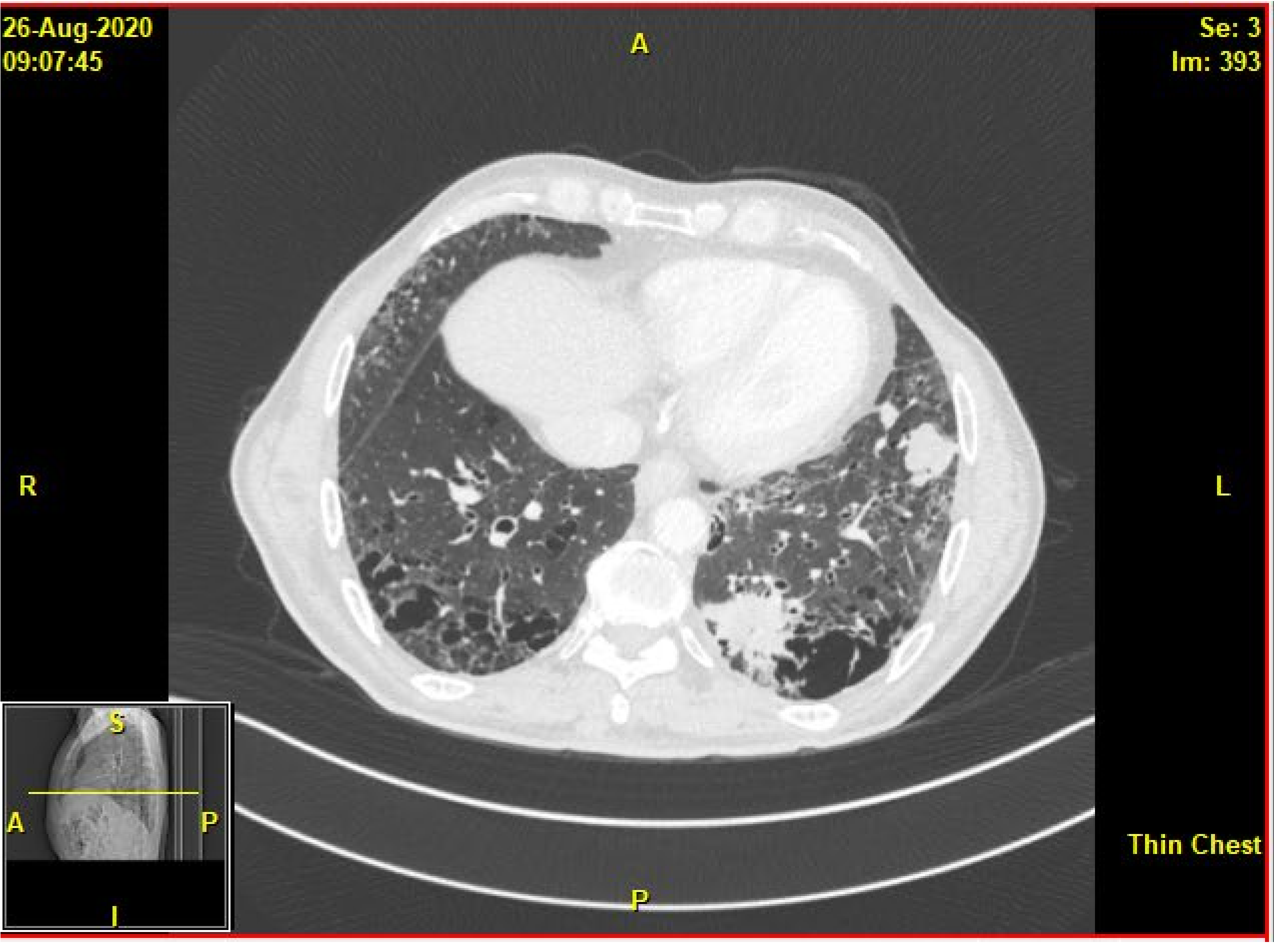
Vokes E, J Clin Oncol 2007; Liu S, Nat Commun 2021; Zhang L, Sci Rep 2015

Case 3: “induction” therapy

- In a patient with bulky disease where we are unable to proceed with standard cCRT consider utility of treating with a metastatic paradigm and, pending response, “consolidate”
- Role/risk of KN189 regimen unclear.
  - In proper setting we consider 2-4 cycles and then, if RT reasonable, holding the pembrolizumab during the RT and adding back maintenance afterwards
- Similar paradigm considered in unique situations for oligometastatic disease

Case 4: Interstitial Lung Disease

- 62 year old man
- Presents with persistent cough for which CXR shows a LUL nodule
- CT chest shows lung scarring concerning for ILD 4.3 cm mass in LUL and a smaller lesion in the lingula
- PET-CT shows FDG avidity in both these lesions, no adenopathy; EBUS is negative for any nodal involvement
- MR brain negative for metastasis
- EBUS biopsy of LUL nodule shows squamous cell carcinoma, PDL1 tumor cells 0%, NGS shows no actionable mutations
- PFTs show FEV1 1.63 L (50% predicted), FVC 2.33 L (55% predicted), DLCO 24%


26-Aug-2020
09:07:45
Se: 3
Im: 393
A
R
L
Thin Chest
S
A
P
I
P


26-Aug-2020
09:07:44
Se: 4
Im: 76
SR
RA
LP
Cor Chest
S
A
P
I
IL

Thoracic Radiation and Interstitial Lung Disease

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- **WHAT IS ILD?**
  - Diffuse parenchymal lung disease – more than 200 different causes that affect the lung parenchyma
  - Associated with increased morbidity and mortality

- **PRESENTATION**
  - Non-specific symptoms including impaired exercise tolerance, cough, progressive shortness of breath
  - Pulmonary function tests: restrictive pattern (decreased FVC and TLC), decreased DLCO

- **CLASSIFICATION**
  - Fibrotic
  - Non-fibrotic

Goodman, Christopher D., et al. "A Primer on Interstitial Lung Disease and Thoracic Radiation." *Journal of Thoracic Oncology* 15.6 (2020): 902-913.

- **FIBROTIC ILD**
  - Sub-classified as either IPF or non-IPF ILD
  - Radiological pattern: traction bronchiectasis, reticulation, +/- honeycombing

- **NON-FIBROTIC ILD**
  - Include a variety of inflammatory, multinodular, and cystic lung diseases
  - Better prognosis and response to therapy than fibrotic ILD

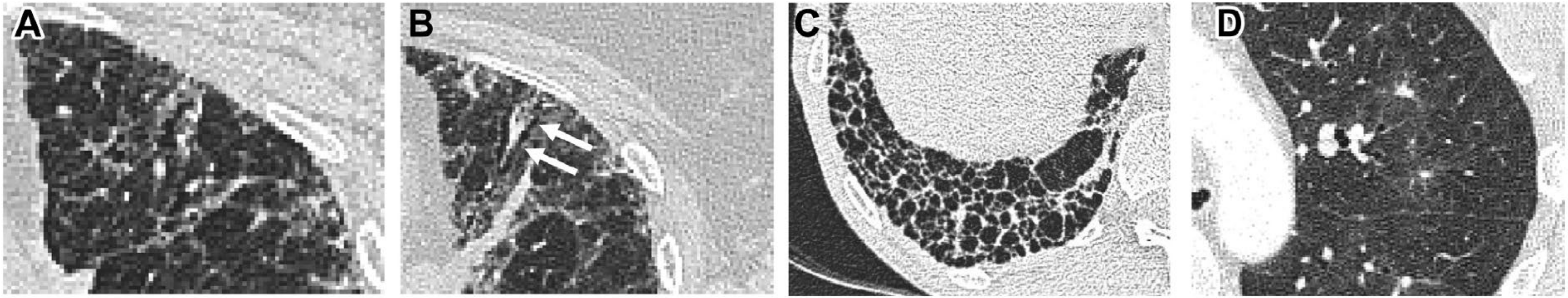
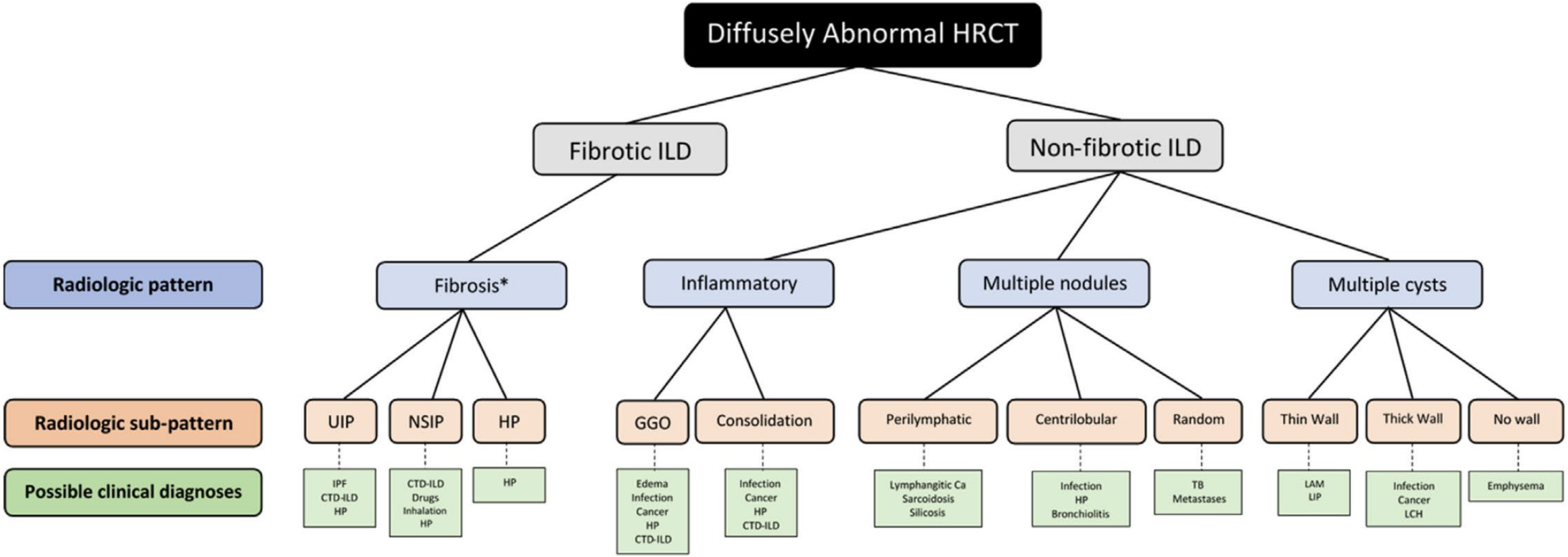


Figure 1. Computed tomography images of dense fibrosis with reticulation (*A*), traction bronchiectasis (*B*), honeycombing (*C*), and patchy ground-glass opacity (*D*).

Goodman, Christopher D., et al. "A Primer on Interstitial Lung Disease and Thoracic Radiation." *Journal of Thoracic Oncology* 15.6 (2020): 902-913.



Goodman, Christopher D., et al. "A Primer on Interstitial Lung Disease and Thoracic Radiation." *Journal of Thoracic Oncology* 15.6 (2020): 902-913.

ILD & RT

- Incidence of lung cancer in ILD about 10-20%

- Individuals with pre-existing ILD are at higher risk of SABR-related complications
  - Treatment-related mortality about 15%
  - Treatment-related toxicity (grade ≥3 radiation pneumonitis or acute ILD flare) about 25%

- Pre-existing IPF are at even HIGHER RISK
  - SABR-related mortality with IPF about 33%
  - SABR-related toxicity rates with IPF about 71%

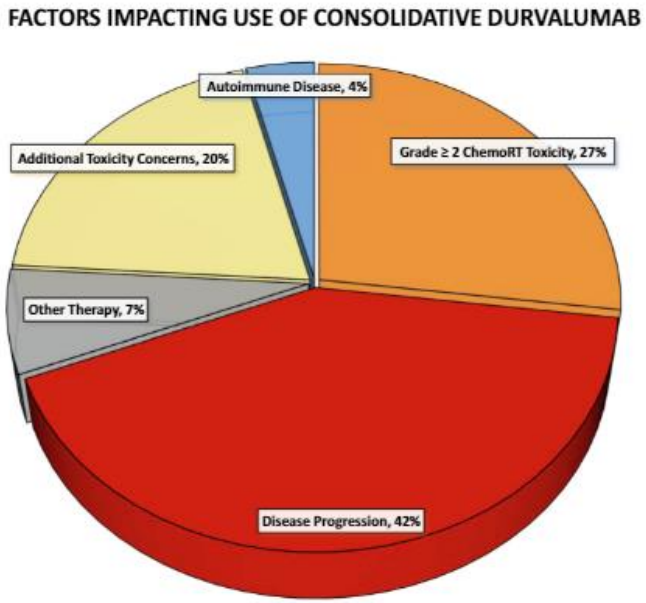
Goodman, Christopher D., et al. "A Primer on Interstitial Lung Disease and Thoracic Radiation." *Journal of Thoracic Oncology* 15.6 (2020): 902-913.

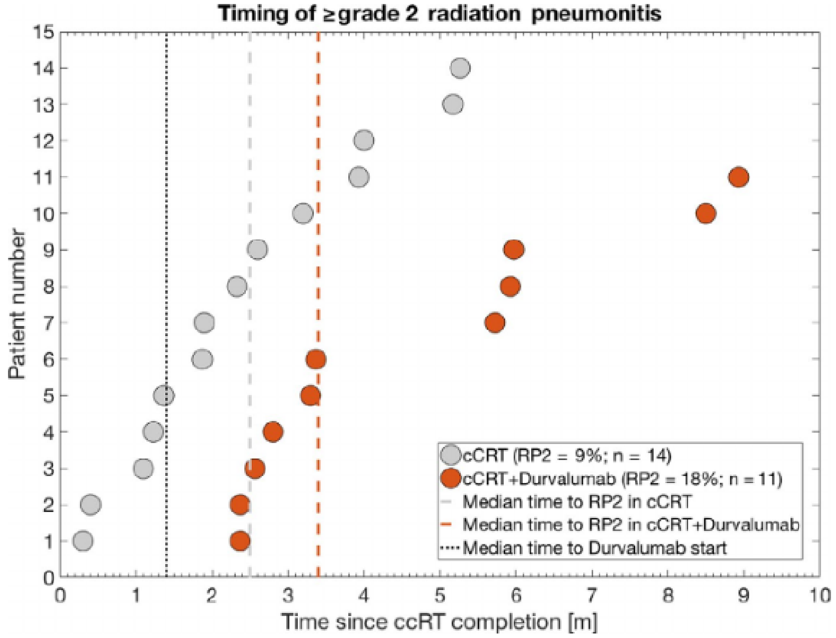
Case 4: durvalumab and ILD

- ICIs have known rate of pneumonitis with potentially higher rates (irAE +/- radiation) after cCRT
- ILD was an exclusion criteria on prospective trials evaluating safety of ICIs in the advanced and locally advanced setting
- Understanding severity of the ILD (prior biologic therapies, oxygen dependence, exacerbations, etc), PFT assessment, and close collaboration with pulmonology are warranted
- Ensuring no worsening symptoms or radiographic findings after cCRT
- Shared decision making with the patient of potential risk

Case 4: Utilization factors for durvalumab

- Real world setting: 27% did not start durvalumab
- Multiple factors preclude start of durvalumab in the real world
    - Progression of disease
    - KPS/toxicity from concurrent therapy
    - Radiation pneumonitis
    - Autoimmune disease
- More patients who get durva developed ≥ grade 2 radiation pneumonitis and with a longer latency from RT than cCRT alone

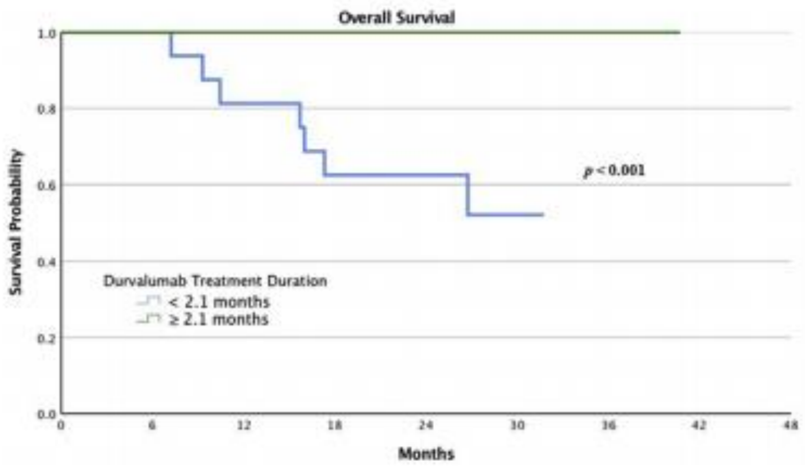


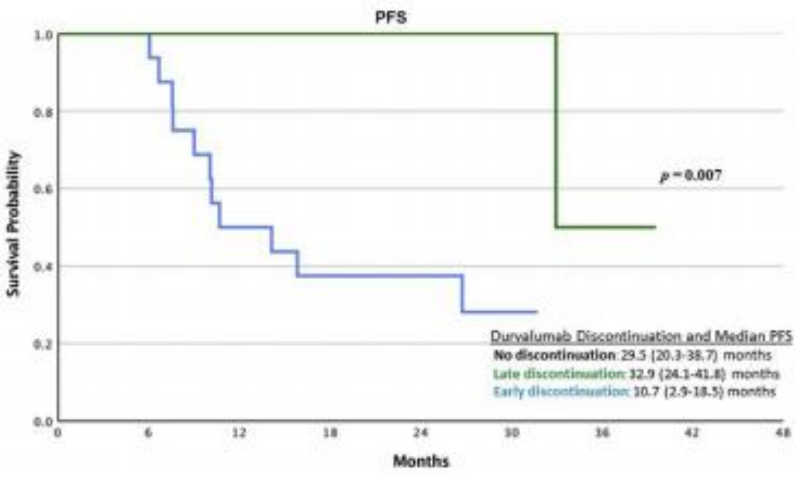


Shaverdian N, Radiotherapy and Oncology 2019; Shaverdian N, Cancer Med 2020

Case 4: Durvalumab discontinuation and effect on outcomes

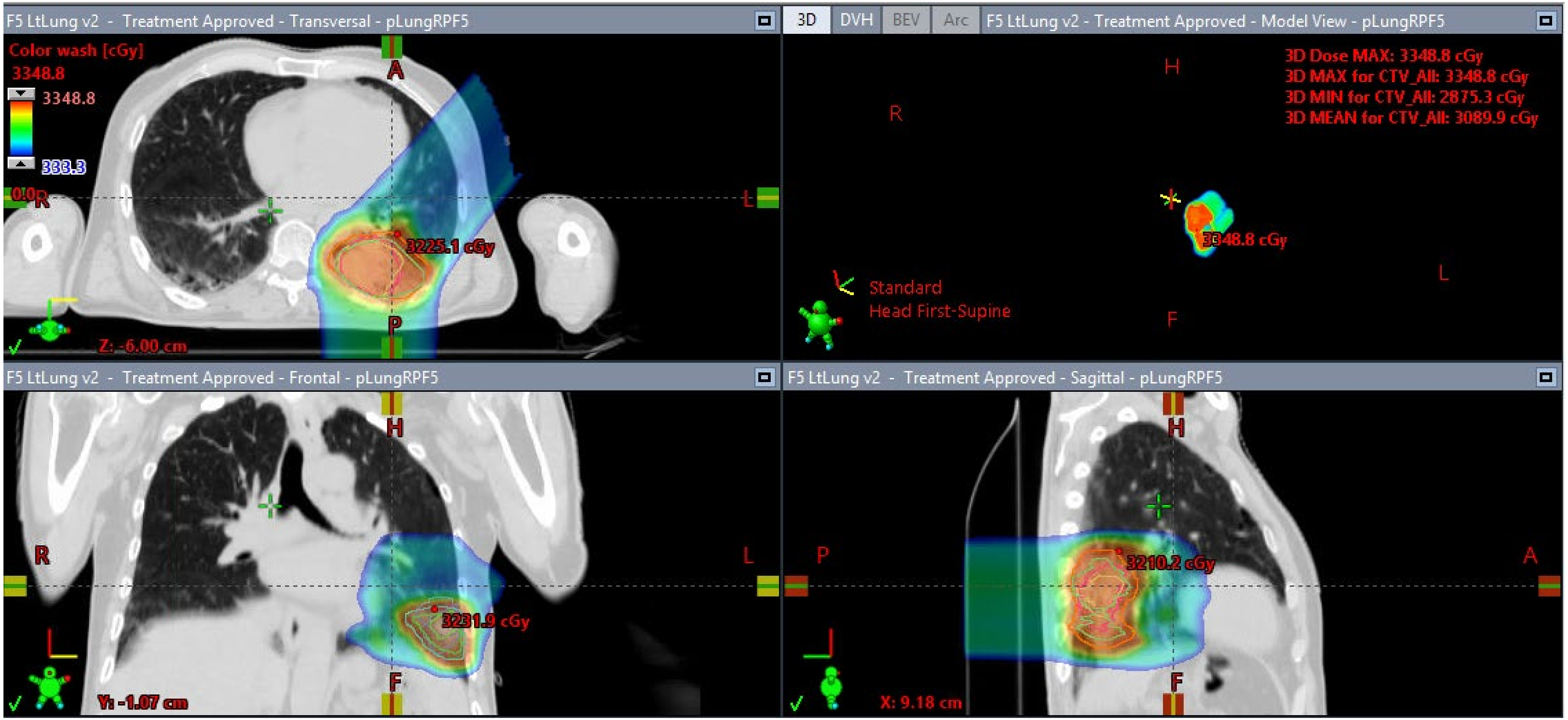
- Duration of durvalumab among patients who discontinued for irAEs impacts survival
- Seems to have somewhat of a threshold where ~4 months or more prior to discontinuation did similarly to those that did not discontinue

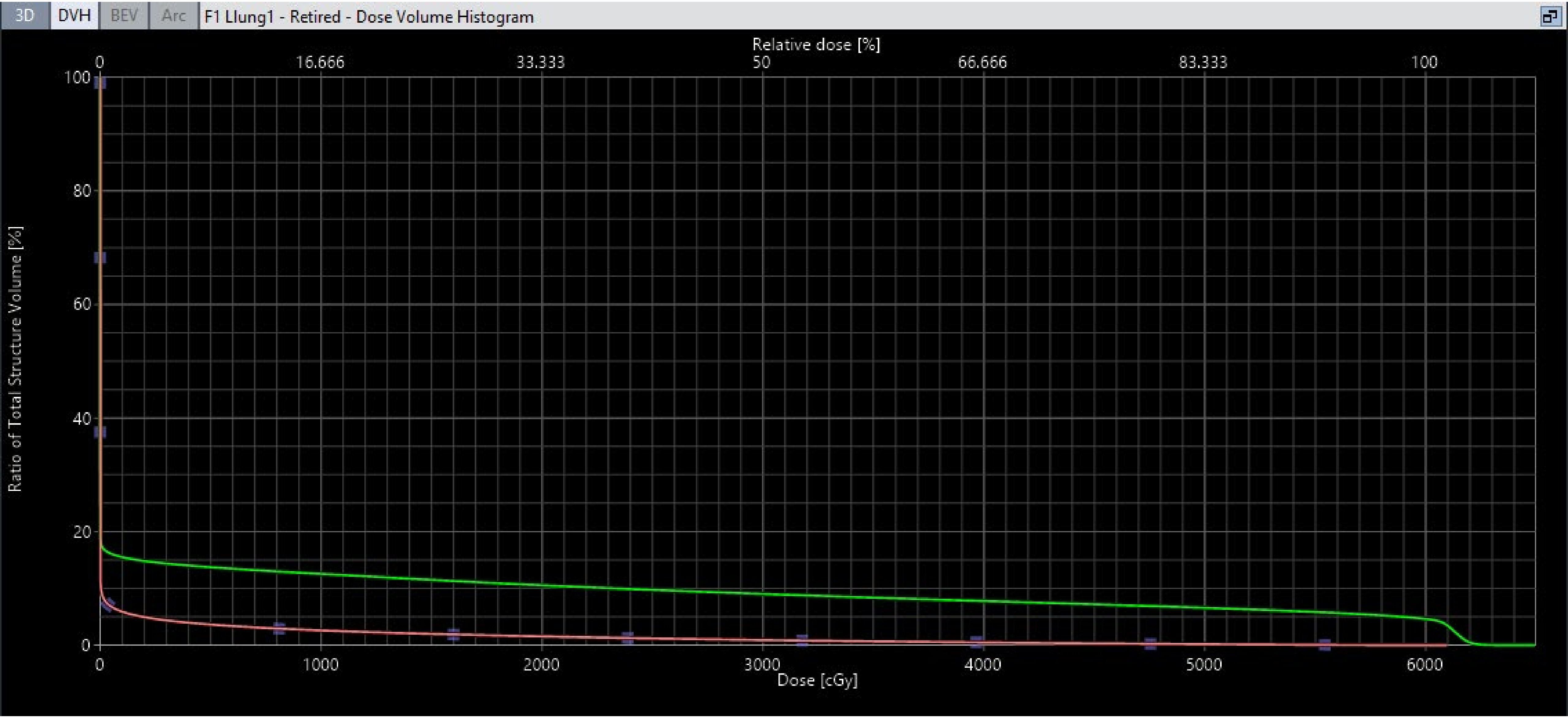


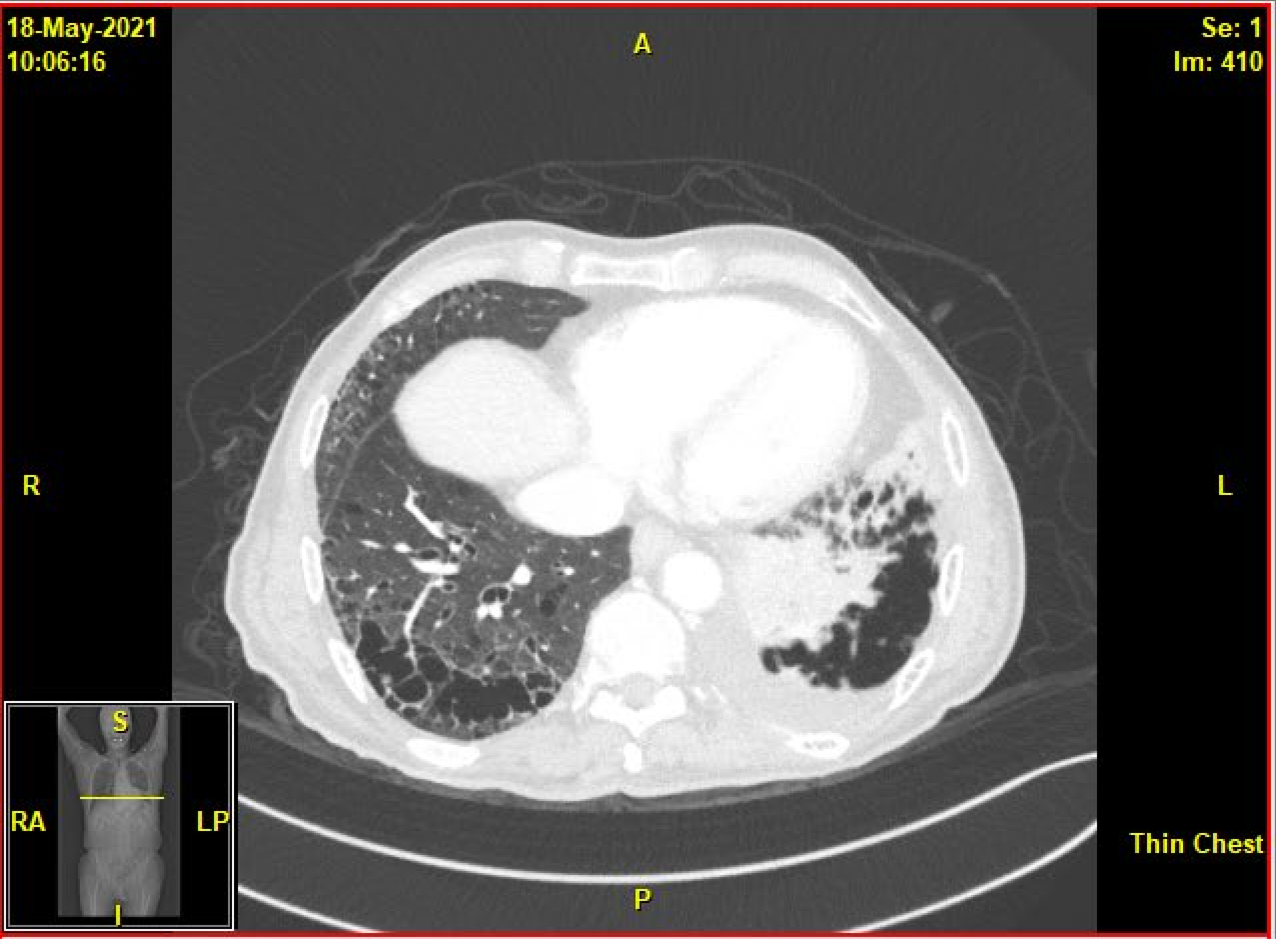


Characteristics	All Patients (N = 113)
Time to durvalumab start[a]	
Median, IQR (mo)	1.5 (1.1-2)
Durvalumab treatment duration	
Median, IQR (mo)	8.5 (2.3-11.8)
Durvalumab discontinuation reason	
Radiation pneumonitis	20 (66)
ICI pneumonitis	3 (10)
Colitis	2 (7)
Dermatitis	2 (7)
Myositis 3 (10)	2 (13)

Shaverdian N, JTO Clinical and Research Report 2021


F5 LtLung v2 - Treatment Approved - Transversal - pLungRPF5
Color wash [cGy]
3348.8
3348.8
333.3
A
R
L
P
3225.1 cGy
Z: -6.00 cm
3D
DVH
BEV
Arc
F5 LtLung v2 - Treatment Approved - Model View - pLungRPF5
3D Dose MAX: 3348.8 cGy
3D MAX for CTV_All: 3348.8 cGy
3D MIN for CTV_All: 2875.3 cGy
3D MEAN for CTV_All: 3089.9 cGy
H
R
3348.8 cGy
L
F
Standard
Head First-Supine
F5 LtLung v2 - Treatment Approved - Frontal - pLungRPF5
H
R
L
3231.9 cGy
F
Y: -1.07 cm
F5 LtLung v2 - Treatment Approved - Sagittal - pLungRPF5
H
P
A
3210.2 cGy
F
X: 9.18 cm


3D
DVH
BEV
Arc
F1 Llung1 - Retired - Dose Volume Histogram
Relative dose [%]
0
16.666
33.333
50
66.666
83.333
100
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
1000
2000
3000
4000
5000
6000
Dose [cGy]


18-May-2021
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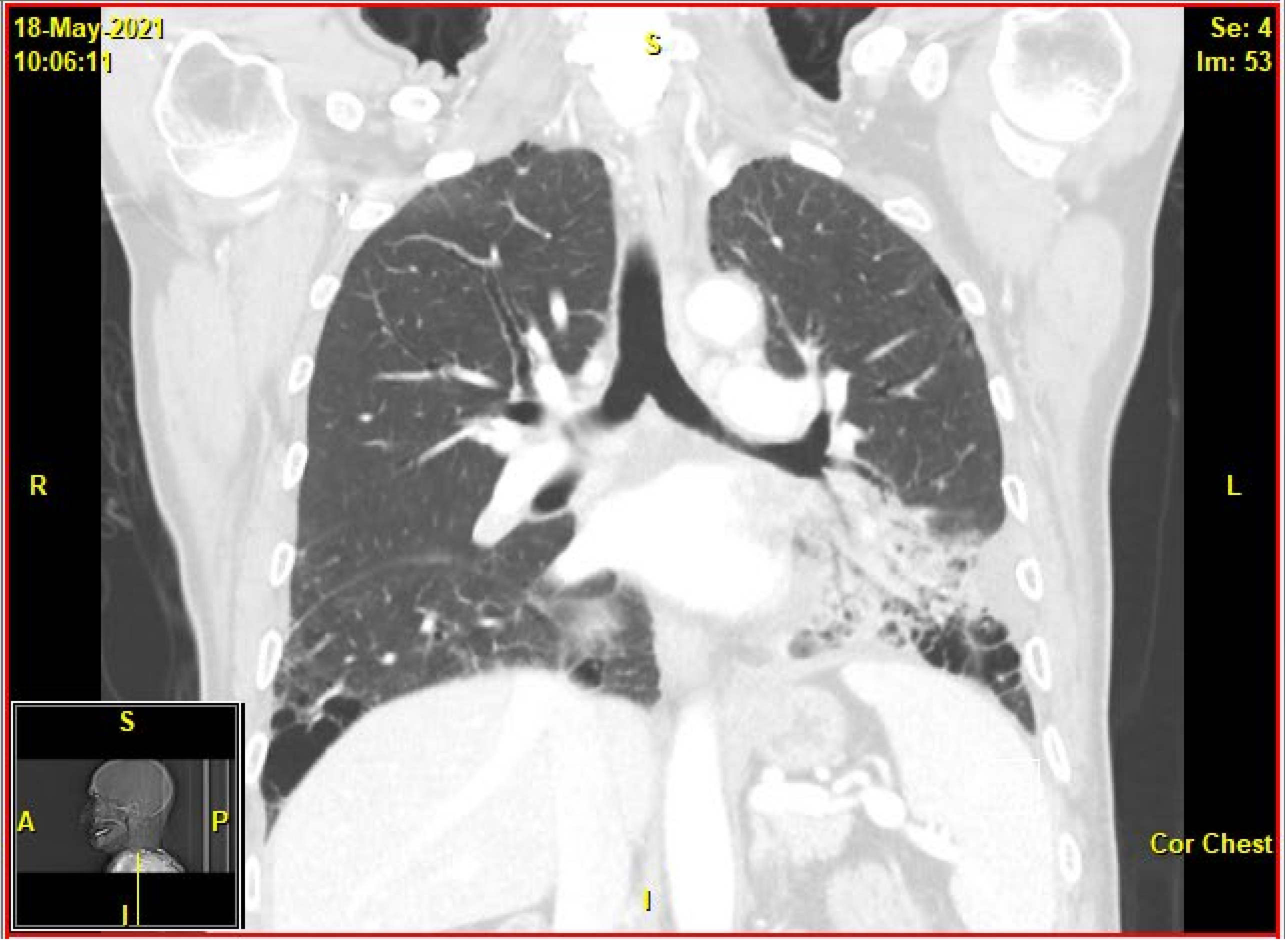
A
Se: 1
Im: 410
R
L
S
RA
LP
I
Thin Chest
P


18-May-2021
10:06:11
S
Se: 4
Im: 53
R
L
S
A
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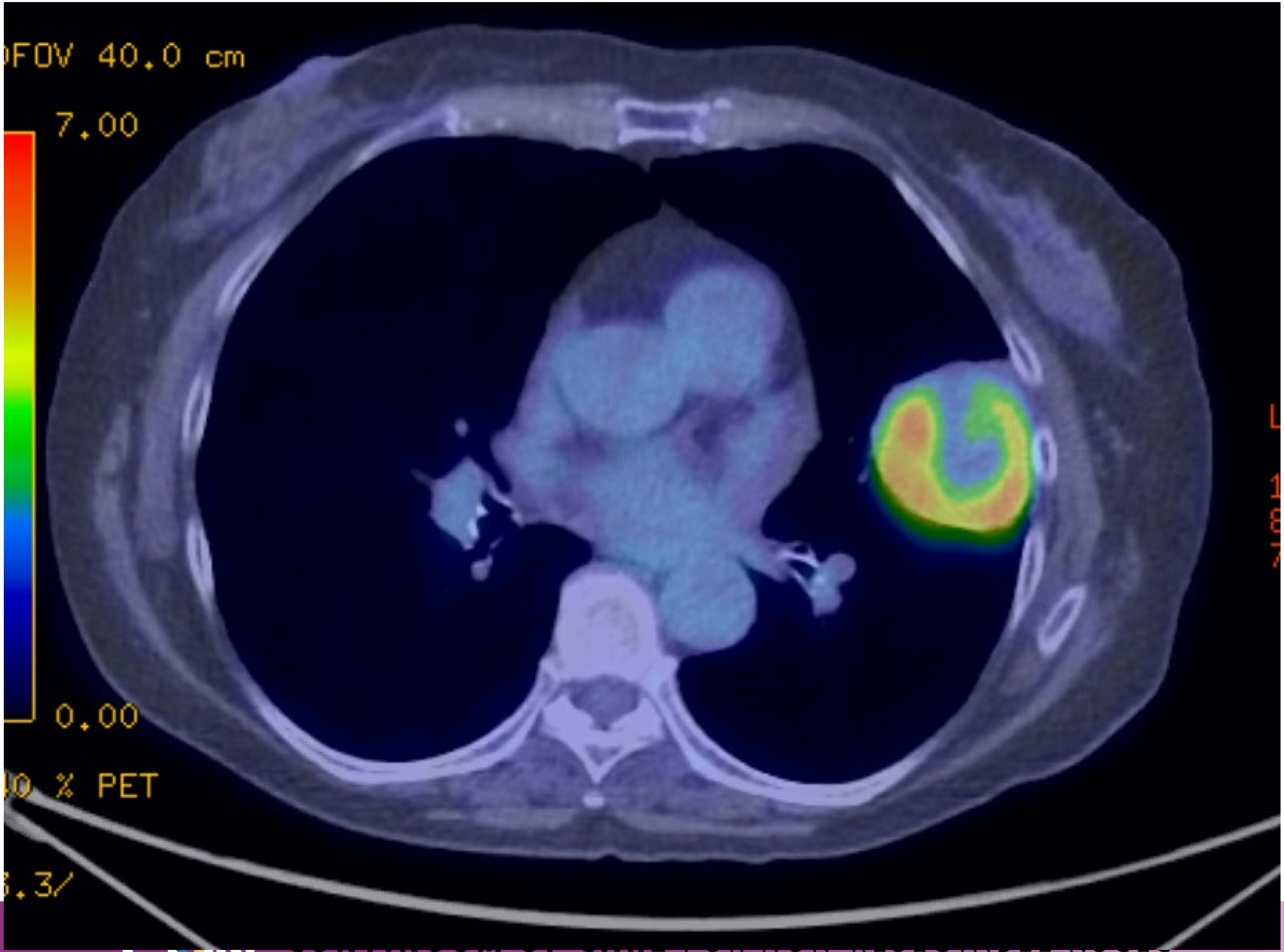
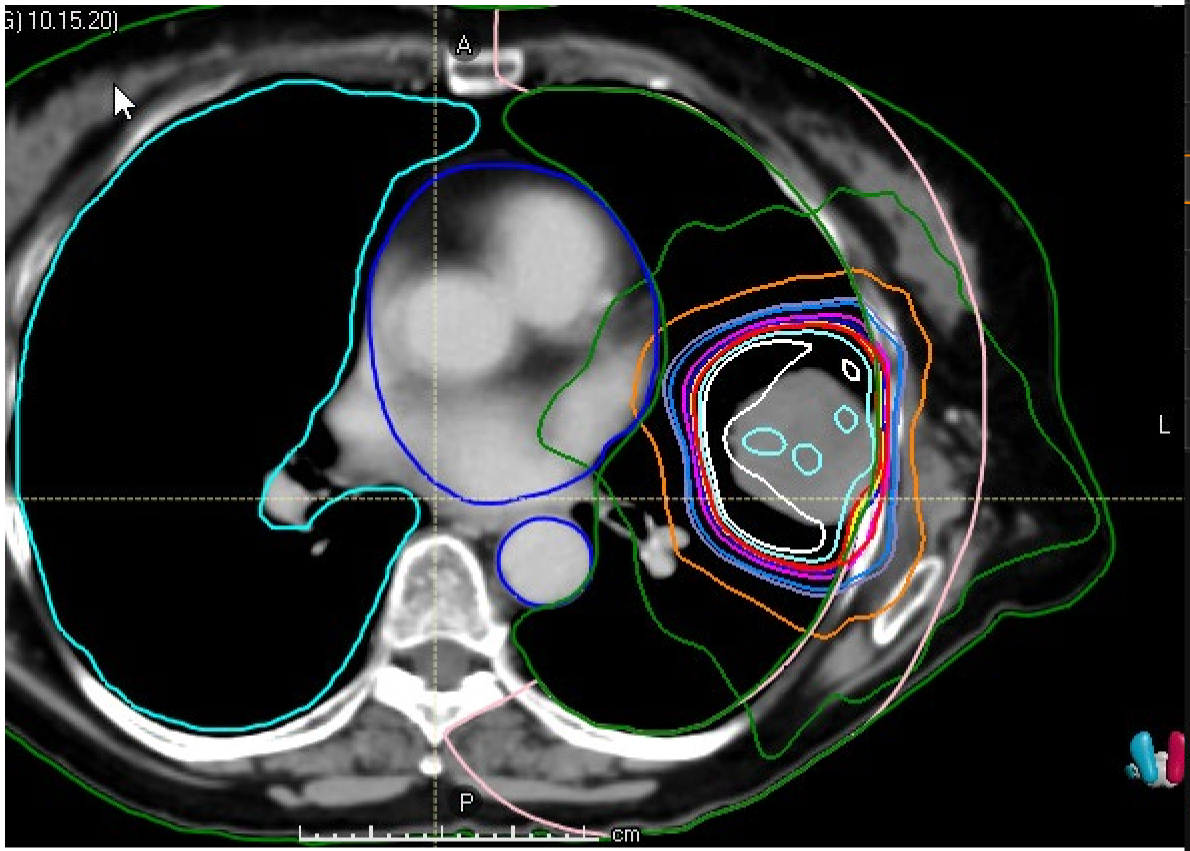
I
Cor Chest
I

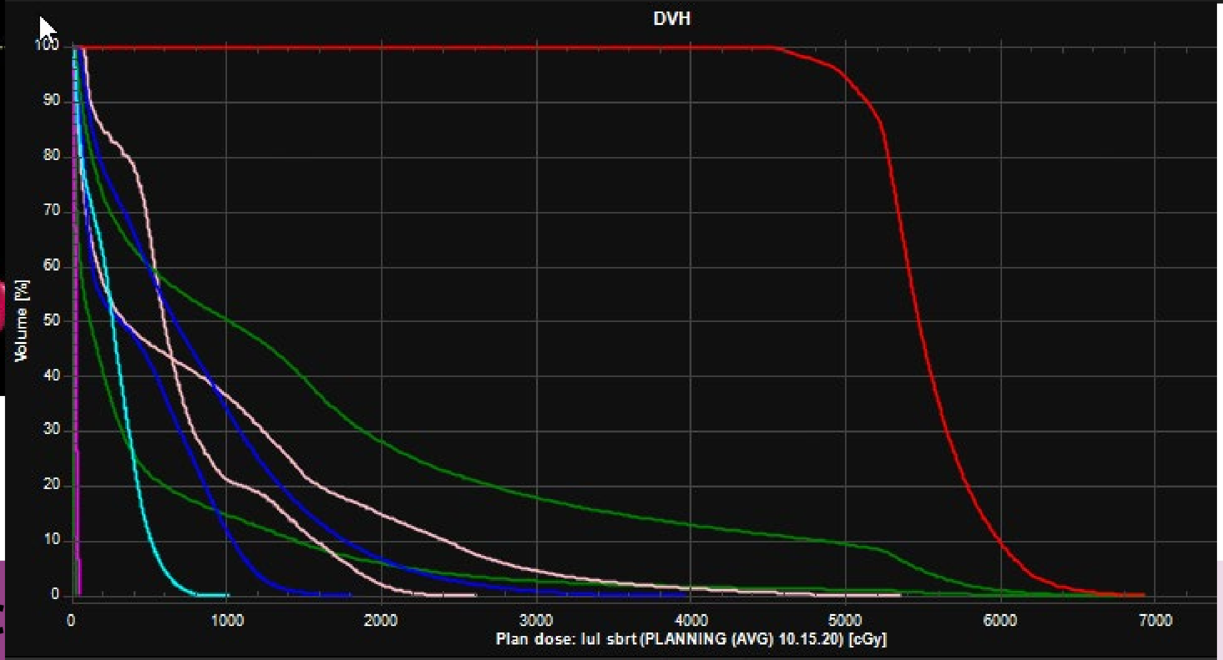
Case 5: Large peripheral tumor for SBRT

- 72 year old woman with COPD and 45 PY smoking history
- Screening CT revealed a 5.2 cm LUL mass
- Biopsy revealed adenocarcinoma
- PET/CT showed 5.4 cm hypermetabolic LUL mass with no evidence of mediastinal or hilar adenopathy
- PFTs:
  - FEV1 1.34 L (59% predicted)
  - DLCO 7.51 ml/mmHG/min (29% predicted)
- EBUS negative for nodal involvement


FOV 40.0 cm
7.00
0.00
% PET



ROI	ROI vol. [cm³]	Dose [cGy] D99	D98	D95	Average	D50	D2	D1	% outs
BrachialPlexus_L	6.53	4	5	15	30	30	50	51	0 %
BrachialPlexus_R	4.78	3	4	7	18	18	28	29	0 %
Bronchus	22.79	87	90	101	732	599	2005	2109	0 %
Chestwall	2148.56	19	22	28	867	345	3652	4163	0 %
External	16740.64	2	5	10	471	121	3488	5074	0 %
GreatVes	175.45	19	23	33	452	315	1303	1398	0 %
Heart	835.26	57	63	78	825	672	2609	2898	0 %
Lung_L	1841.33	30	34	45	1572	1018	5774	5984	0 %
Lung_R	2189.05	20	22	27	272	268	680	731	0 %
PTV_10Gyx5	176.91	4653	4766	4981	5521	5475	6348	6479	0 %



SBRT for T3 Tumors

Megan E. Daly MD

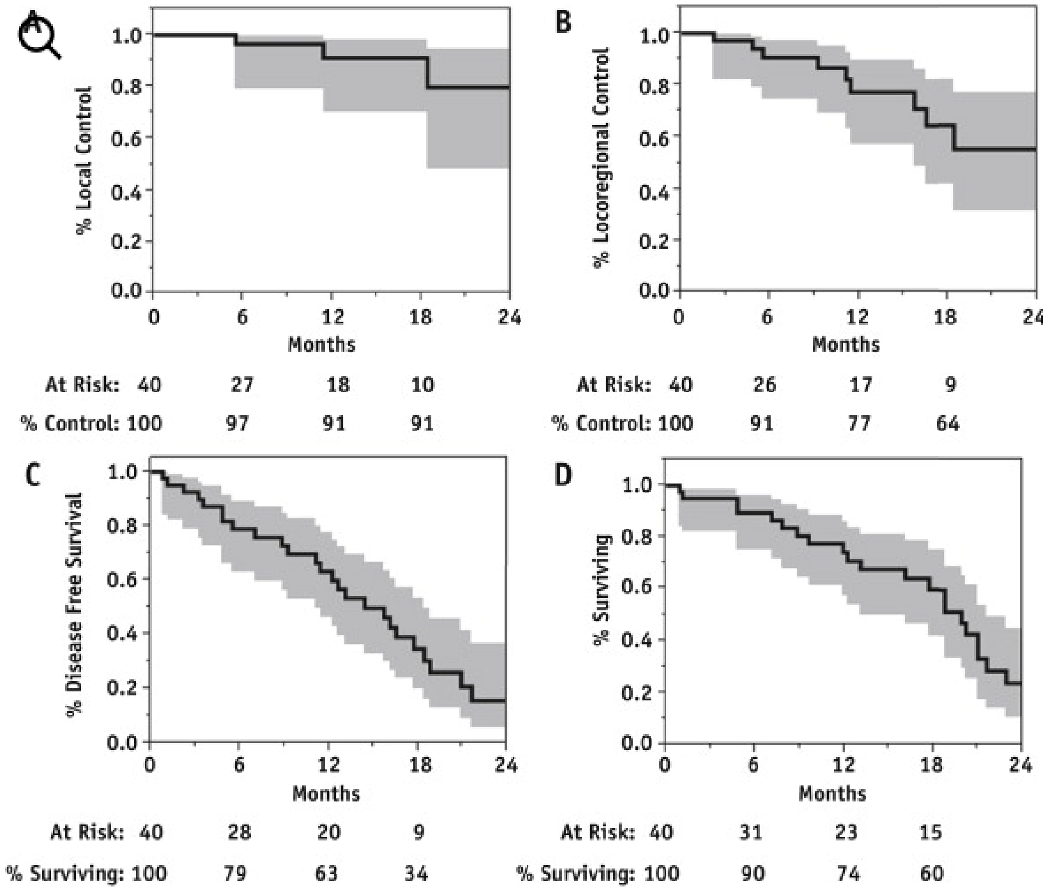
Cooperative Group SBRT Eligibility

Trial	Eligibility
RTOG 0236	T1-3 tumors ≤5 cm, peripheral (no T3 enrolled)
RTOG 0618	T1-3 tumors ≤5 cm, peripheral, operable (no T3 enrolled)
RTOG 0813	T1-2 tumors ≤5 cm, central
RTOG 0915	T1-3 tumors ≤5 cm, peripheral

- Early US-based cooperative group trials generally limited enrollment to patients with tumors <5 cm diameter. Trials that allowed T3 tumors (RTOG 0236 and 0618) did not enroll any
- However, retrospective studies suggest modest toxicity when standard dose volume constraints on normal tissues are respected
- Predominant failure pattern for large tumors is distant
- Several current SBRT protocols testing addition of immunotherapy allow T3 tumors

Cleveland Clinic Experience: >5 cm tumors

- 40 patients with tumors >5 cm treated with SBRT
- Median 5.6 cm (range 5.1-10 cm)
- Median SBRT dose 50 Gy (range 30-60 Gy) in 5 fractions (range 3-10) – Most patients receive 50/5 or 60/8



Woody NM et al. Stereotactic Body Radiation Therapy for Non-Small Cell Lung Cancer Tumors Greater Than 5 cm: Safety and Efficacy. IJROBP 2015

Cleveland Clinic Experience: Toxicity

Table 3 Treatment toxicities with patient and tumor characteristics

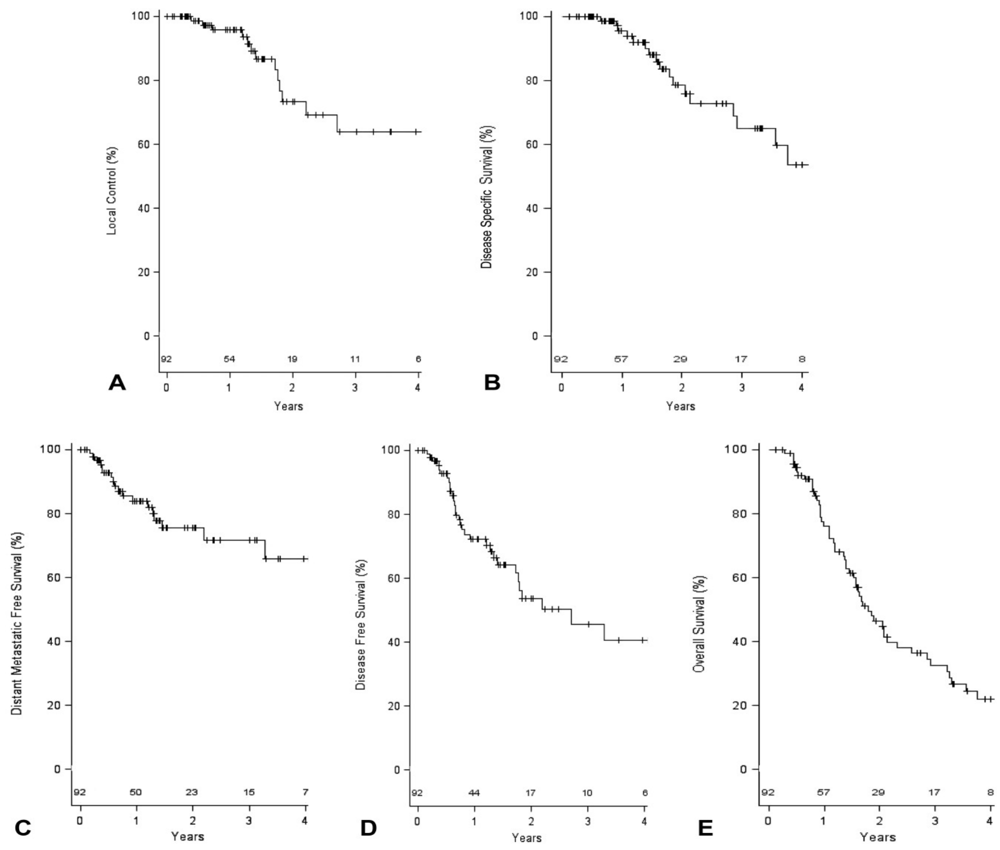
Toxicity	Toxicity grade	Time to toxicity (mo)	Patient comorbidities	FEV1 (L)/DLCO%	Central location	Tumor diameter (cm)
Chest wall pain	I	10.5	COPD, hypertension	0.96/NA	Yes	7.5
Chest wall pain	I	8.4	Diabetes, hypertension	N/A	Yes	5.4
Chest wall pain	I	4.4	Renal insufficiency, peripheral vascular disease	1.41/51%	Yes	6.7
Pneumonitis	II	0.5	COPD, hypertension	1.24/67%	No	6.4
Pneumonitis	II	7.8	COPD	2.3/49%	Yes	5.1
Lobar collapse	III	3.5	COPD, congestive heart failure	2.24/53%	Yes	7.2
Pleural effusion	III	10.3	Dementia, hypertension	0.97/35%	Yes	7.2
Pneumonitis	IV	0.2	COPD, hypertension, previous stroke	1.34/60%	Yes	5.4

Abbreviations: **COPD = chronic obstructive pulmonary disease; DLCO = diffusion capacity; FEV1 = forced expiratory volume in 1 second; L = liter; NA = not available.**

Woody NM et al. Stereotactic Body Radiation Therapy for Non-Small Cell Lung Cancer Tumors Greater Than 5 cm: Safety and Efficacy. IJROBP 2015

Multi-institution pooled analysis tumors ≥5 cm

- 92 patients from 12 institutions with tumors ≥5 cm
- Median size 5.4 cm (range 5.0-7.5 cm)
- Most patients (92%) received 50-60/5, 48/4, or 54/3



Verma V et al. Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non–small cell lung tumors*. Cancer 2016*

Multi-institution report: Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Entire cohort					
Pulmonary	9	8	4	0	1
RP	4	5	4	0	1
Cough/SOB	5	2	0	0	0
Pleural effusion	0	1	0	0	0
CW pain	2	7	0	0	0
Dermatitis	3	1	1	0	0
Rib fracture	2	0	0	0	0
Fatigue	2	1	0	0	0
Anorexia	1	0	0	0	0
Total	19	17	5	0	1

Verma V et al. Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non–small cell lung tumors*. Cancer 2016*

SBRT with Chest wall invasion: Cleveland Clinic Experience

- Single institution analysis, 13 patients
- Most (11) received 50 Gy in 5 daily fractions
- Median diameter 4.0 cm
- Median FU 10.5 months
- Of 9 patients with CW pain at presentation, 7 improved with SBRT and 2 worsened
- No patient without CW pain at baseline developed new pain
- No grade 3-4 toxicity

Barriochao C et al. Steotactic Body Radiotherapy for T3N0 Lung Cancer with Chest wall Invasion. Clinical Lung Cancer 2016

Current SBRT Phase III Trial Eligibility

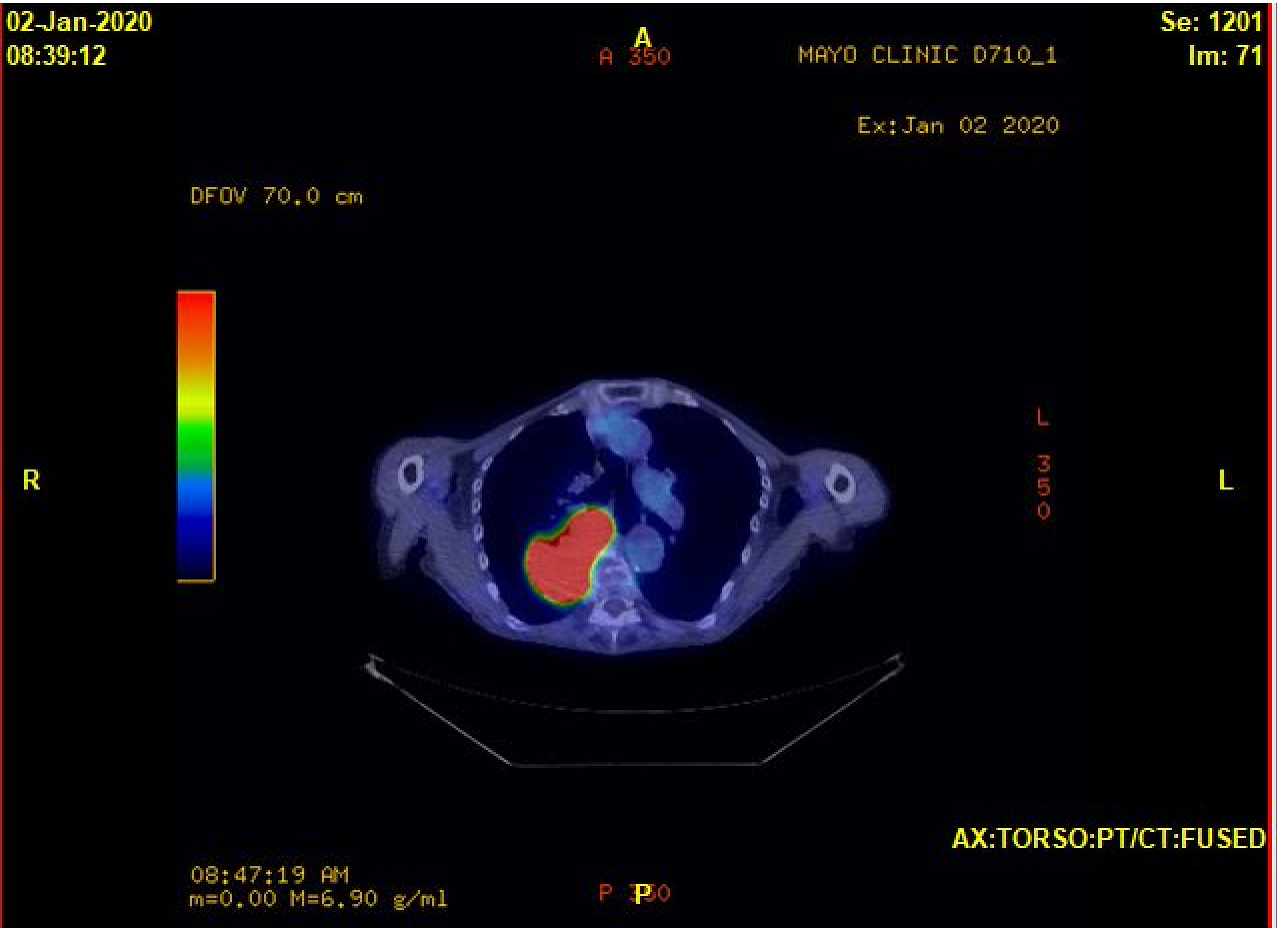
Study	Drug	Eligibility	Length of IO	Primary Endpoint	n
PACIFIC 4	Durvalumab	**T1-3** NSCLC	Adjuvant Up to 24 months	PFS	630
SWOG/NRG S1914	Atezolizumab	**T1-3** NSCLC CW invasion allowed but not separate nodules	Neoadjuvant, concurrent and adjuvant Up to 6 months	OS	480
KEYNOTE 867	Pembrolizumab	T1-2 NSCLC	Concurrent and Adjuvant Up to 12 months	OS and EFS	530

Summary: SBRT for T3 tumors

- Retrospective studies suggest modest toxicity and good local disease control when standard dose volume constraints on normal tissues are respected for T3 tumors treated with SBRT
- Predominant failure pattern for large tumors is distant
- Several current SBRT protocols testing addition of immunotherapy allow T3 tumors

Case 6 – RT Alone Ultracentral LA-NSCLC

- 85 year old female
- Presented with shortness of breath and escalating cough
- CT chest shows RLL mass with mediastinal involvement
- PET-CT shows no adenopathy but highly FDG avid mass
- MR brain is negative for metastasis
- EBUS shows bronchial involvement, adenocarcinoma 95% PDL1 expressing, no nodes involved
- NGS shows no actionable mutations
- Pt is not a chemotherapy candidate due to multiple comorbidities and age


02-Jan-2020
08:39:12
A
A 350
MAYO CLINIC D710_1
Se: 1201
Im: 71
Ex:Jan 02 2020
DFOV 70.0 cm
R
L
L
350
AX:TORSO:PT/CT:FUSED
08:47:19 AM
m=0.00 M=6.90 g/ml
P


02-Jan-2020
08:39:12
S
S 167
MAYO CLINIC D710_1
Se: 1202
Im: 94
Ex:Jan 02 2020
DFOV 93.3 cm
R
L
L
467
COR:TORSO:PT/CT:FUSED
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m=0.00 M=6.90 g/ml

Hypofractionation for Ultracentral LA-NSCLC

Dawn Owen, MD, PhD

DOSE AND FRACTIONATION FOR DEFINITIVE DOSE?

- Multiple phase II trials looking at 50-60 Gy/15 fractions, small series and single institution in patients who are not candidates for CRT
- Appears to be feasible but toxicity is not well understood
- Suggested dose constraints are all over the place
- EQD2 of 60 Gy/15 fractions is 70 Gy

Phase II Study of Accelerated Hypofractionated Three-Dimensional Conformal Radiotherapy for Stage T1-3 N0 M0 Non–Small Cell Lung Cancer: NCIC CTG BR.25

Patrick Cheung, Sergio Faria, Shahida Ahmed, Pierre Chabot, Jonathan Greenland, Elizabeth Kurien, Islam Mohamed, James R. Wright, Helmut Hollenhorst, Catherine de Metz, Holly Campbell, Thi Toni Vu, Anand Karvat, Elaine S. Wai, Yee C. Ung, Glenwood Goss, Frances A. Shepherd, Patti O'Brien, Keyue Ding, Chris O'Callaghan

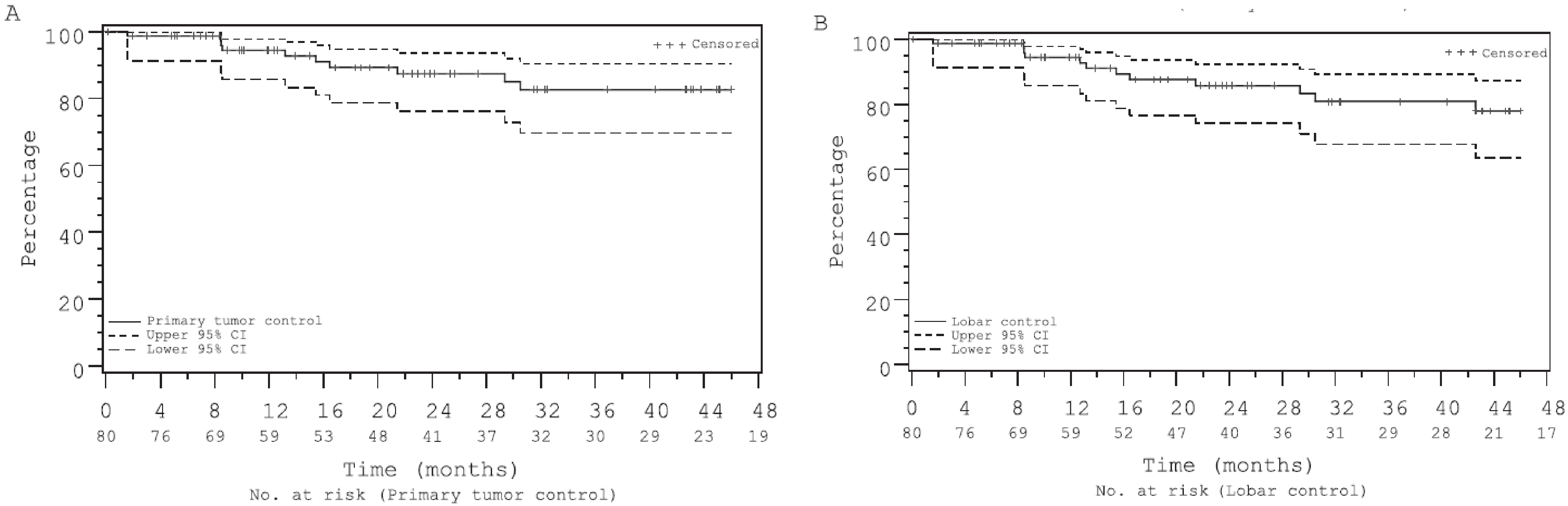


Table 3. Sites and time of failure

Site	0–12 mo	12–24 mo	24–36 mo	>36 mo	Total
Lobar failure	2	4	1	1	8
Lobar + distant failure	1	0	1	0	2
Lobar + regional + distant failure	1	1	0	0	2
Regional failure	2	0	0	0	2
Regional + distant failure	2	1	1	1	5
Distant failure	8	1	3	1	13
Total	16	7	6	3	32

Table 4. Adverse events (worst grade over the study period)

	Grade				
Adverse event	**1**	**2**	**3**	**4**	**5**
Fatigue, No. (%)	28 (35.0)	24 (30.0)	4 (5.0)	1 (1.3)	0 (0.0)
Radiation dermatitis, No. (%)	18 (22.5)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia, No. (%)	9 (11.3)	4 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophagitis/heart burn, No. (%)	11 (13.8)	5 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary hemorrhage, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Chest pain, No. (%)	8 (10.0)	3 (3.8)	1 (1.3)	0 (0.0)	0 (0.0)
Cough, No. (%)	39 (48.8)	3 (3.8)	6 (7.5)	0 (0.0)	0 (0.0)
Dyspnea, No. (%)	24 (30.0)	21 (26.3)	8 (10.0)	3 (3.8)	0 (0.0)
Pneumonitis, No. (%)	5 (6.3)	4 (5.0)	7 (8.8)	1 (1.3)	0 (0.0)

Precision Hypofractionated Radiation Therapy in Poor Performing Patients With Non-Small Cell Lung Cancer: Phase 1 Dose Escalation Trial

Kenneth D. Westover, MD, PhD,[*] Billy W. Loo, Jr, MD, PhD,[†] David E. Gerber, MD,[‡] Puneeth Iyengar, MD, PhD,[*] Hak Choy, MD,[*] Maximilian Diehn, MD, PhD,[†] Randy Hughes, MD,[‡] Joan Schiller, MD,[‡] Jonathan Dowell, MD,[‡] Zabi Wardak, MD,[*] David Sher, MD, MPH,[§] Alana Christie, MS,[||] Xian-Jin Xie, PhD,[||] Irma Corona,[*] Akanksha Sharma,[¶] Margaret E. Wadsworth, MD,[#] and Robert Timmerman, MD[*]

**Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas; [†]Department of Radiation Oncology, Stanford University, Stanford, California; [‡]Division of Hematology-Oncology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; [§]Department of Radiation Oncology, Rush University Medical Center, Chicago, Illinois; [||]Department of Clinical Science, Southwestern Medical Center, Dallas, Texas; [¶]School of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; and [#]Radiation Oncology of Mississippi, Jackson, Mississippi*

60 Gy/15 fractions – should we use it?

Table 5 Dose-volume statistics for patients experiencing >G2 toxicity

>G2 toxicity	Relevant dose constraint	Average	±SD	Minimum	Maximum
Dyspnea	Mean lung dose (Gy)	15	3	8	18
	V18 (%)	31	4	27	38
Esophagitis	Maximum (Gy)	63	6	59	68
	D5cc (Gy)	61	6	57	65

Abbreviation: D5cc = Maximum dose to 5 cc of the organ.

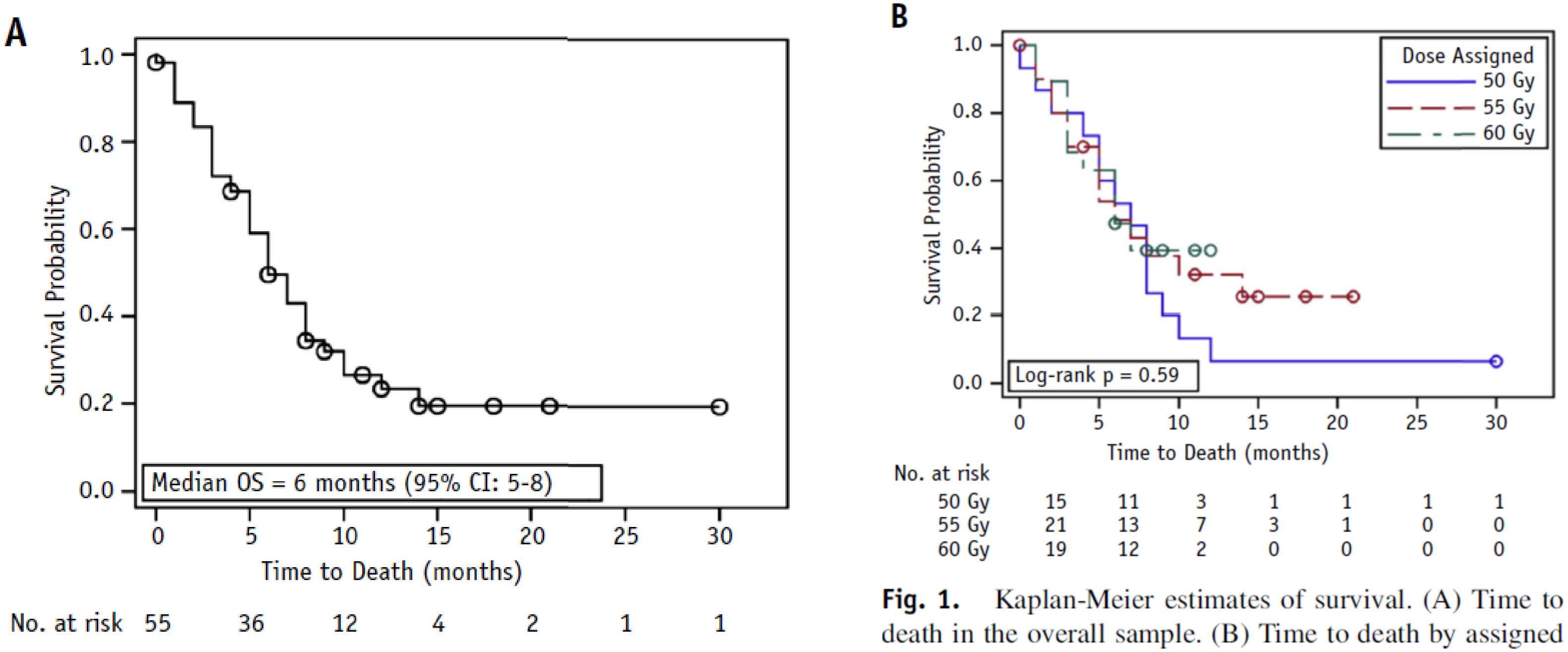


Fig. 1. Kaplan-Meier estimates of survival. (A) Time to death in the overall sample. (B) Time to death by assigned dose level.

Westover et al., IJROBP, 2015

Basic Original Report

Outcomes and toxicity following high-dose radiation therapy in 15 fractions for non-small cell lung cancer

Penny Fang MD [a, 1], Cameron W. Swanick MD [a, 1], Todd A. Pezzi BS [b], Zhongxing Liao MD [a], James Welsh MD [a], Steven H. Lin MD, PhD [a,*, 2], Daniel R. Gomez MD [a, 2]

[a] *Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas*
[b] *Baylor College of Medicine, One Baylor Plaza, Houston, Texas*

60 Gy/15 fractions – should we use it?

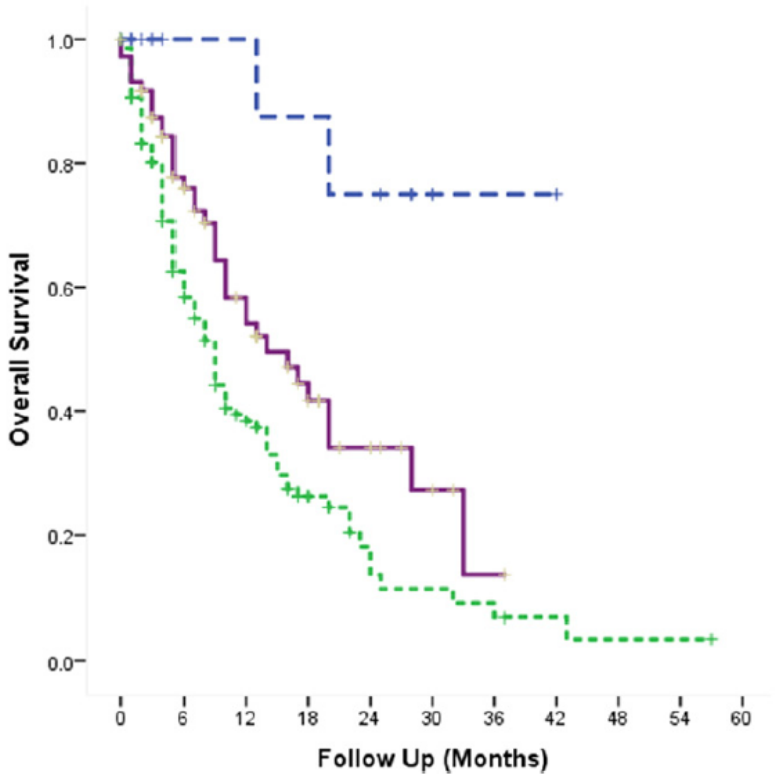


Figure 1 Overall survival for all patients by stage. Stage I: long dashed line, stages II and III: solid line, stage IV: short dashed line (n = 229).

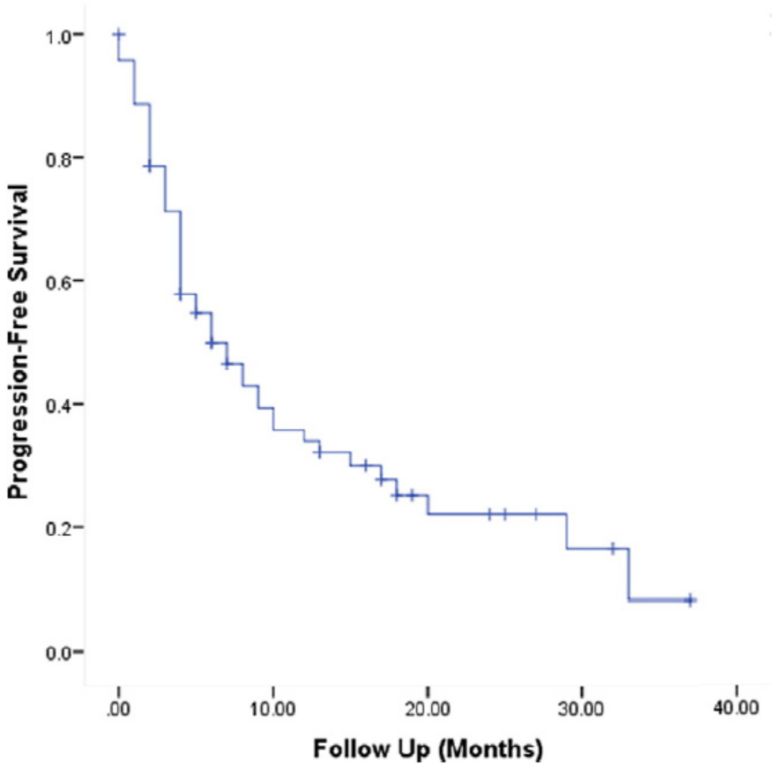


Figure 2 Progression-free survival for stage II-III patients (n = 73).

Fang et al., PRO, 2017

60 Gy/15 fractions – should we use it?

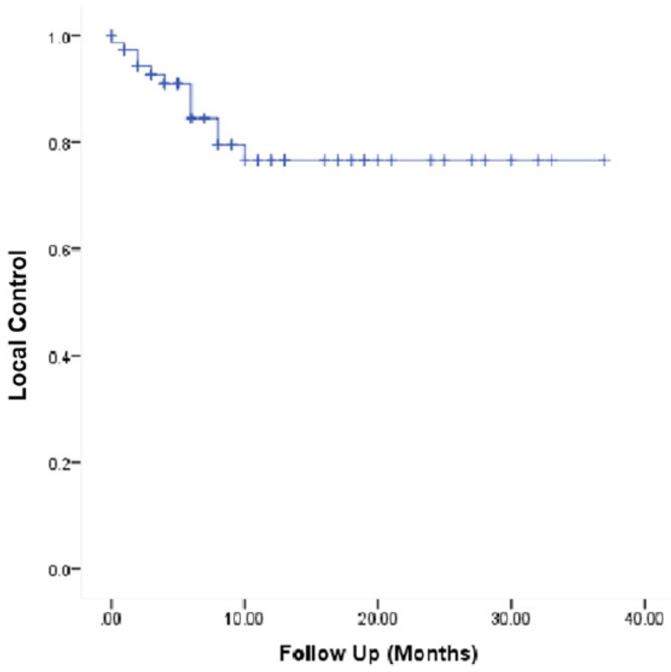


Figure 3 Local control for stage II-III patients (n = 73).

Table 2 Radiation-related toxicity in our cohort (n = 229)

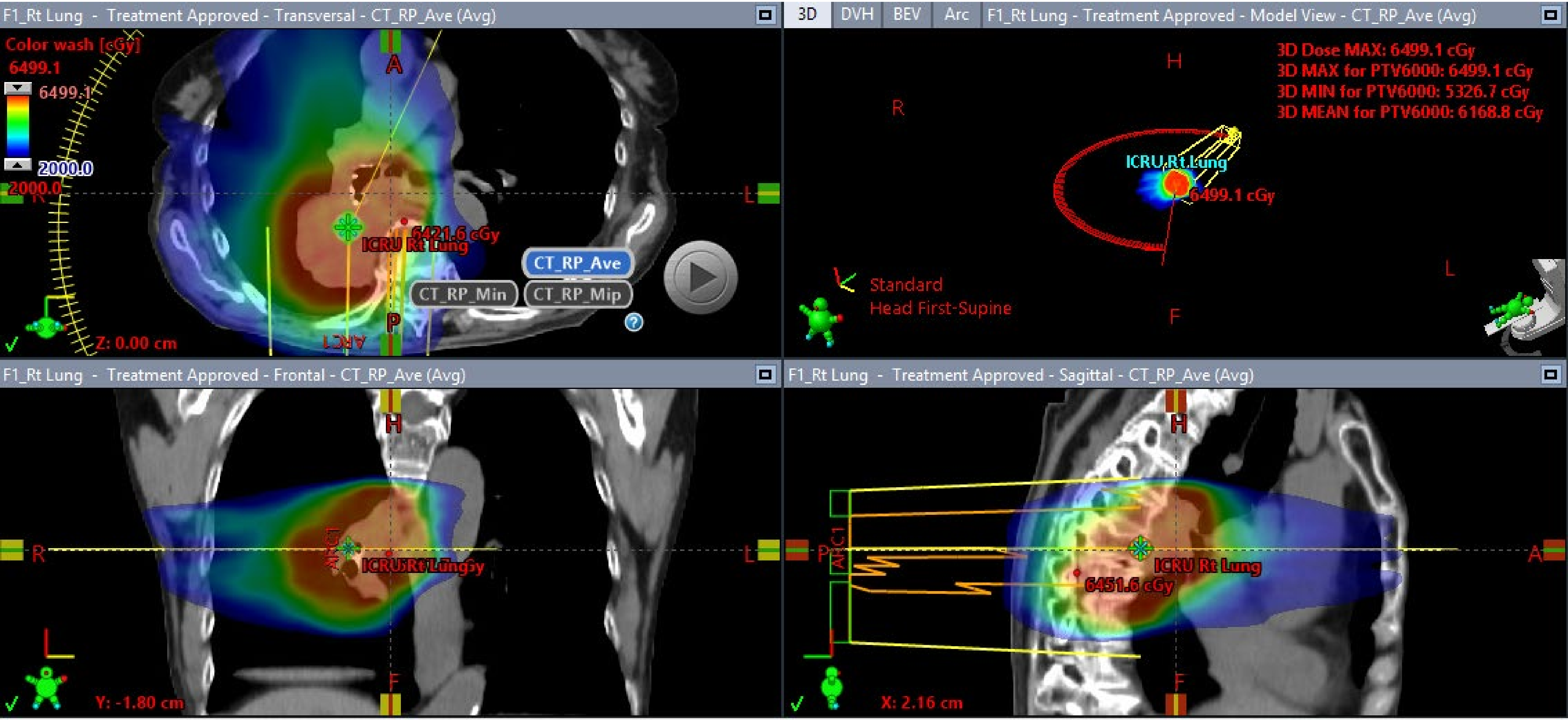
Toxicity	No. of patients (%)
Esophagitis grade	
0	135 (59)
1	4 (2)
2	81 (35)
3	8 (3)
5	1 (0.4)
Pneumonitis grade	
0	175 (76)
1	12 (5)
2	34 (15)
3	6 (3)
4	2 (1)
Brachial plexopathy	0 (0)

Fang et al., PRO, 2017

- Suggest V20 < 22%, V40 < 4%, max esophagus dose < 55Gy, mean esophageal dose < 17 Gy

Summary: Hypofractionated RT Alone for Bulky ultracentral tumors

- Most prospective data is for peripheral lesions but some ultracentral lesions included
- Moderate risk of radiation pneumonitis with RT alone (8-15%)
- Limited long term follow up on risk of bronchial stenosis or esophageal stricture/fistula
- Can consider for select cases but need to pay attention to dose to ultracentral structures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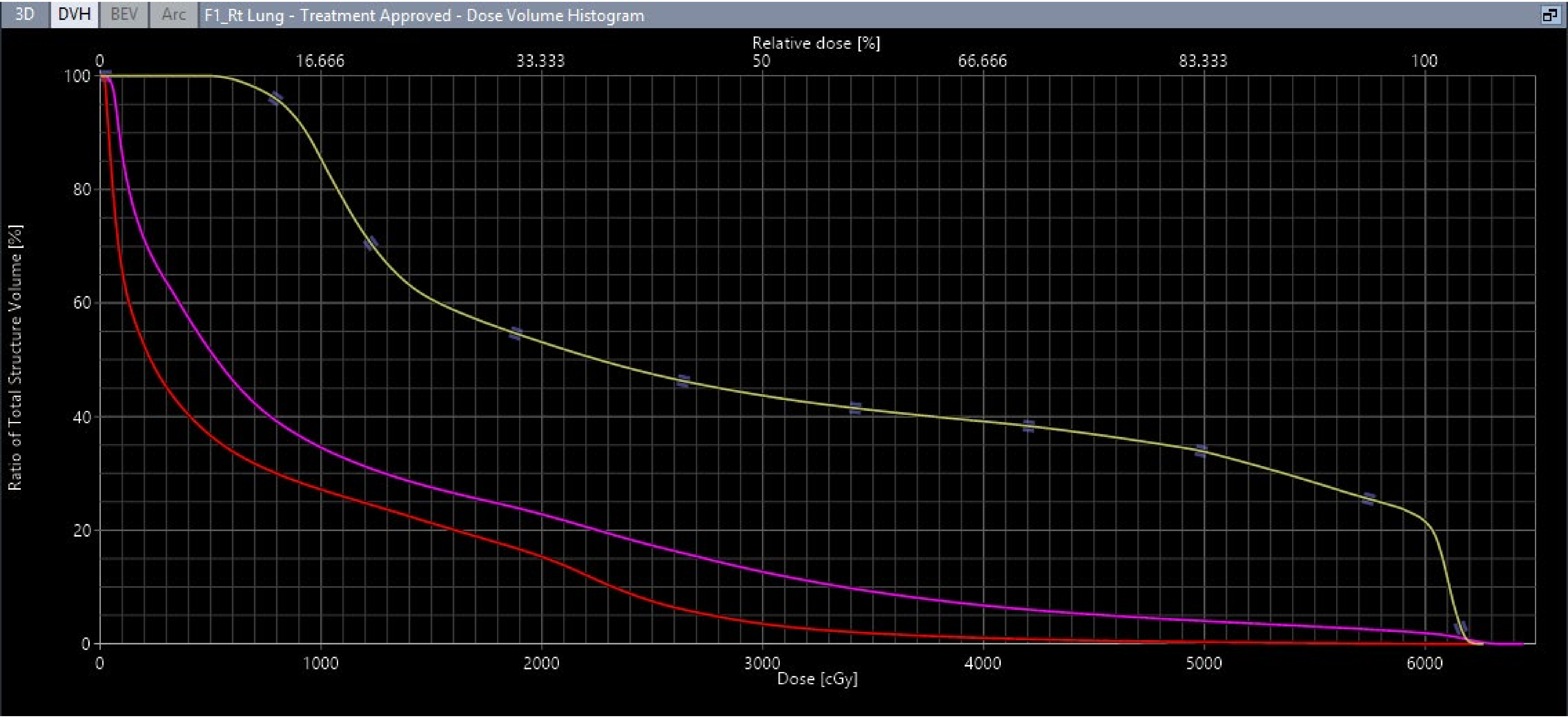
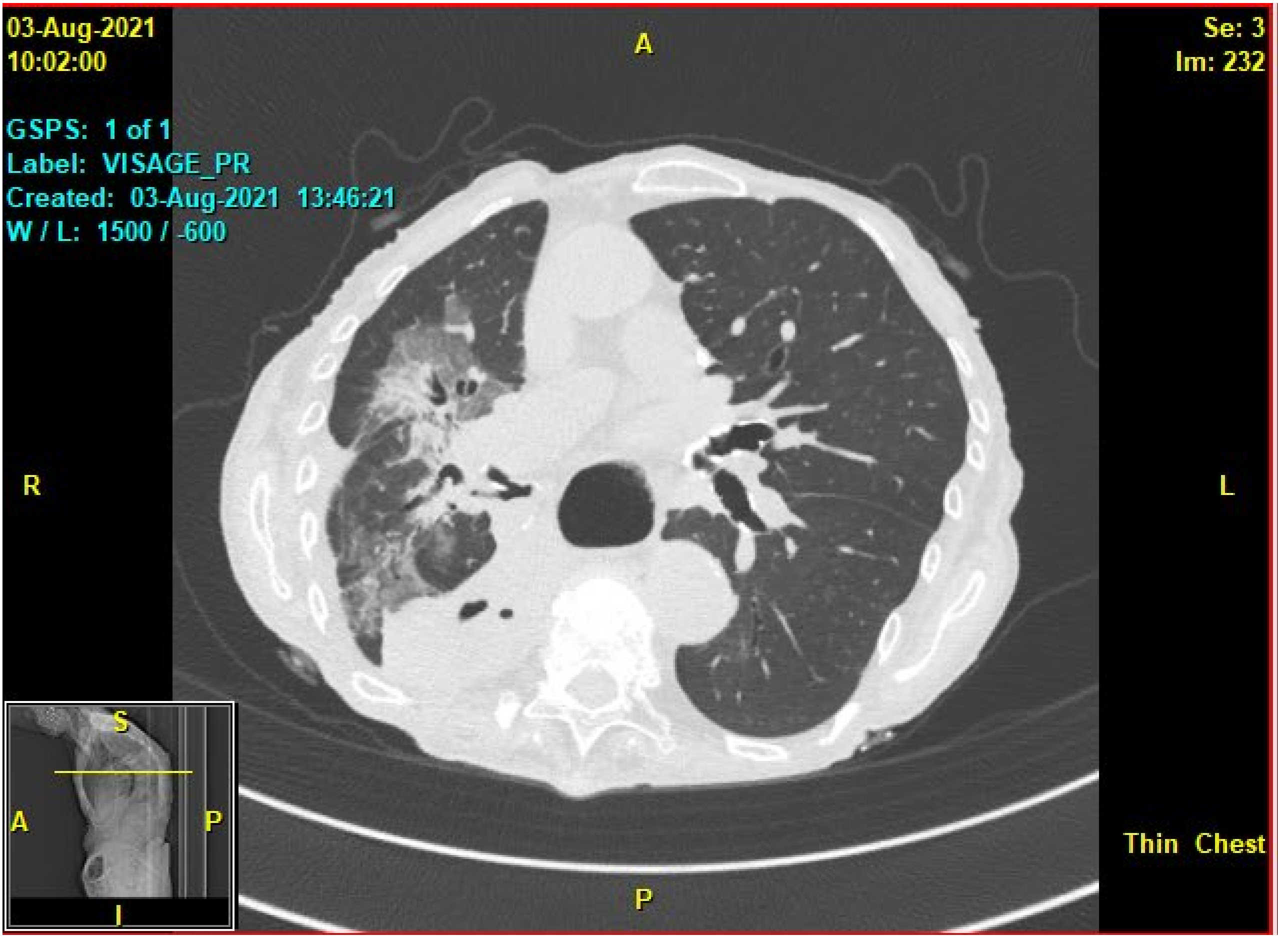
6499.1
2000.0
6421.6 cGy
ICRU Rt Lung
CT_RP_Ave
CT_RP_Min
CT_RP_Mip
Z: 0.00 cm
3D
DVH
BEV
Arc
F1_Rt Lung - Treatment Approved - Model View - CT_RP_Ave (Avg)
3D Dose MAX: 6499.1 cGy
3D MAX for PTV6000: 6499.1 cGy
3D MIN for PTV6000: 5326.7 cGy
3D MEAN for PTV6000: 6168.8 cGy
ICRU Rt Lung
6499.1 cGy
Standard
Head First-Supine
F1_Rt Lung - Treatment Approved - Frontal - CT_RP_Ave (Avg)
Y: -1.80 cm
F1_Rt Lung - Treatment Approved - Sagittal - CT_RP_Ave (Avg)
ICRU Rt Lung
6451.6 cGy
X: 2.16 cm



3D
DVH
BEV
Arc
F1_Rt Lung - Treatment Approved - Dose Volume Histogram
Relative dose [%]
0
16.666
33.333
50
66.666
83.333
100
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
1000
2000
3000
4000
5000
6000
Dose [cGy]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W / L: 1500 / -600
R
L
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A
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I
P
Thin Chest


03-Aug-2021
10:02:00
S
Se: 5
Im: 60
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A
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L
P
I
Cor Chest