Understanding Radiation Pneumonitis: Causes, Symptoms and Treatment

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Midwest Thoracic and GI Oncology 9/7/2023

No conflict of interest to disclose

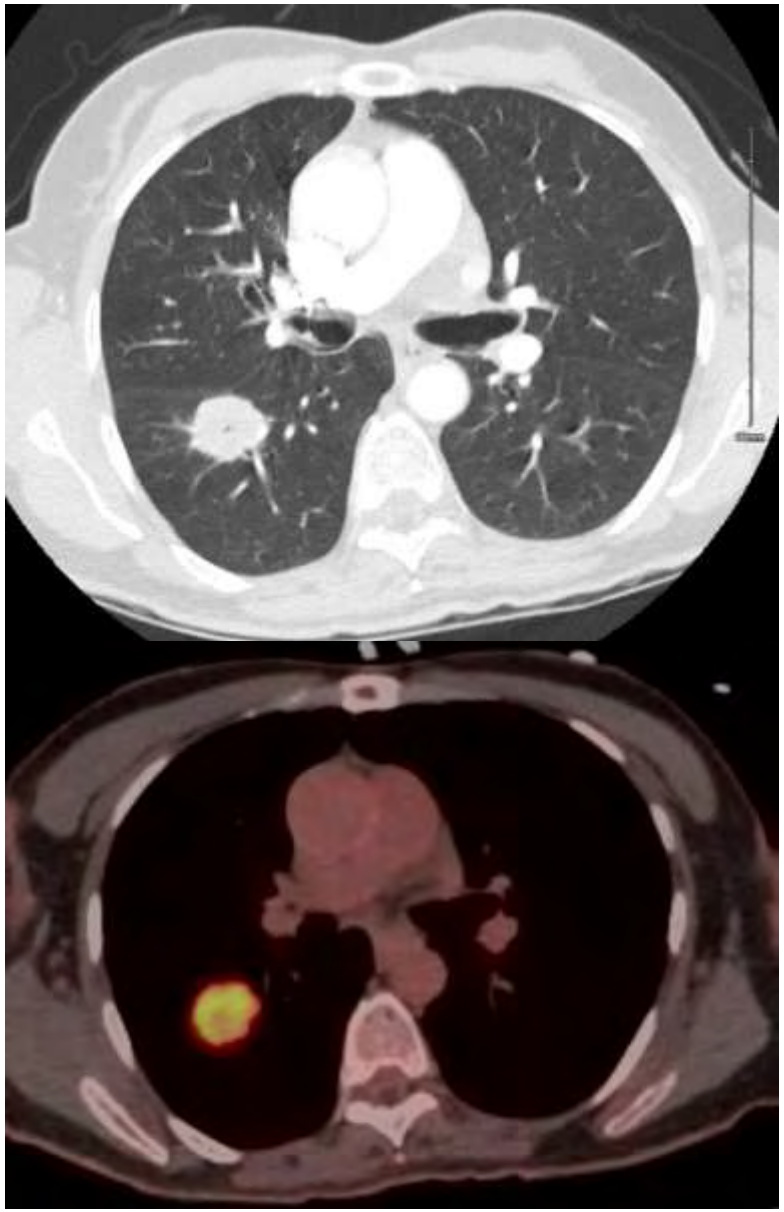
University of Nebraska Medical Center

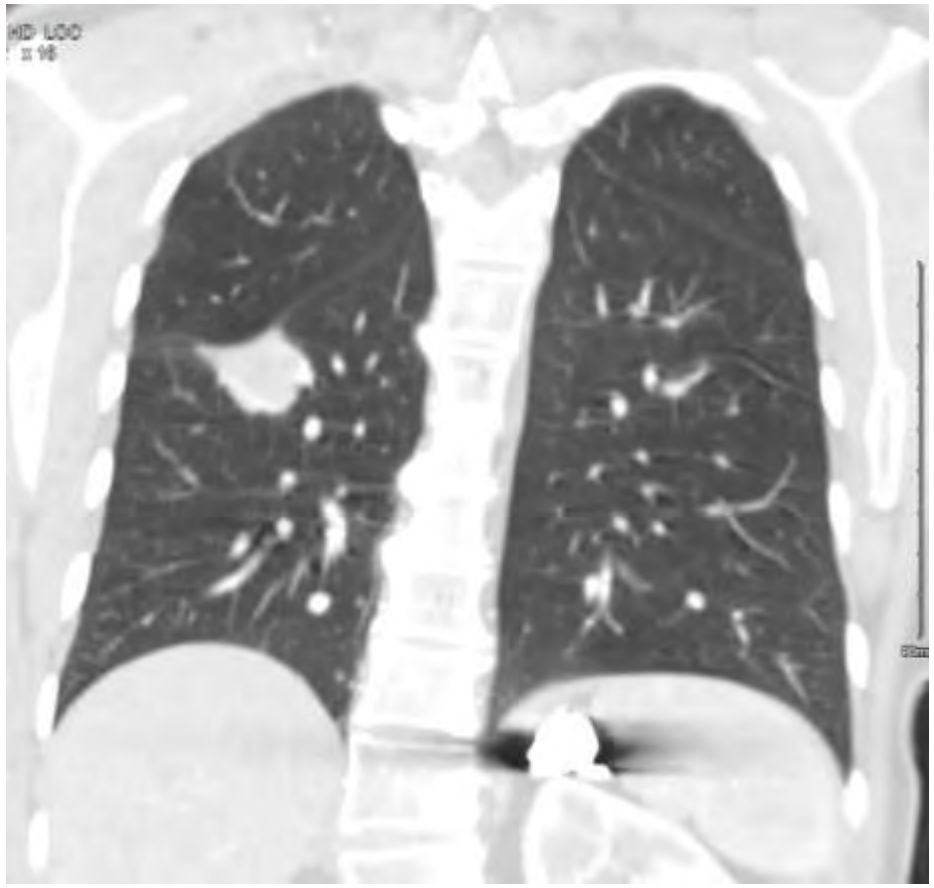
Objectives:

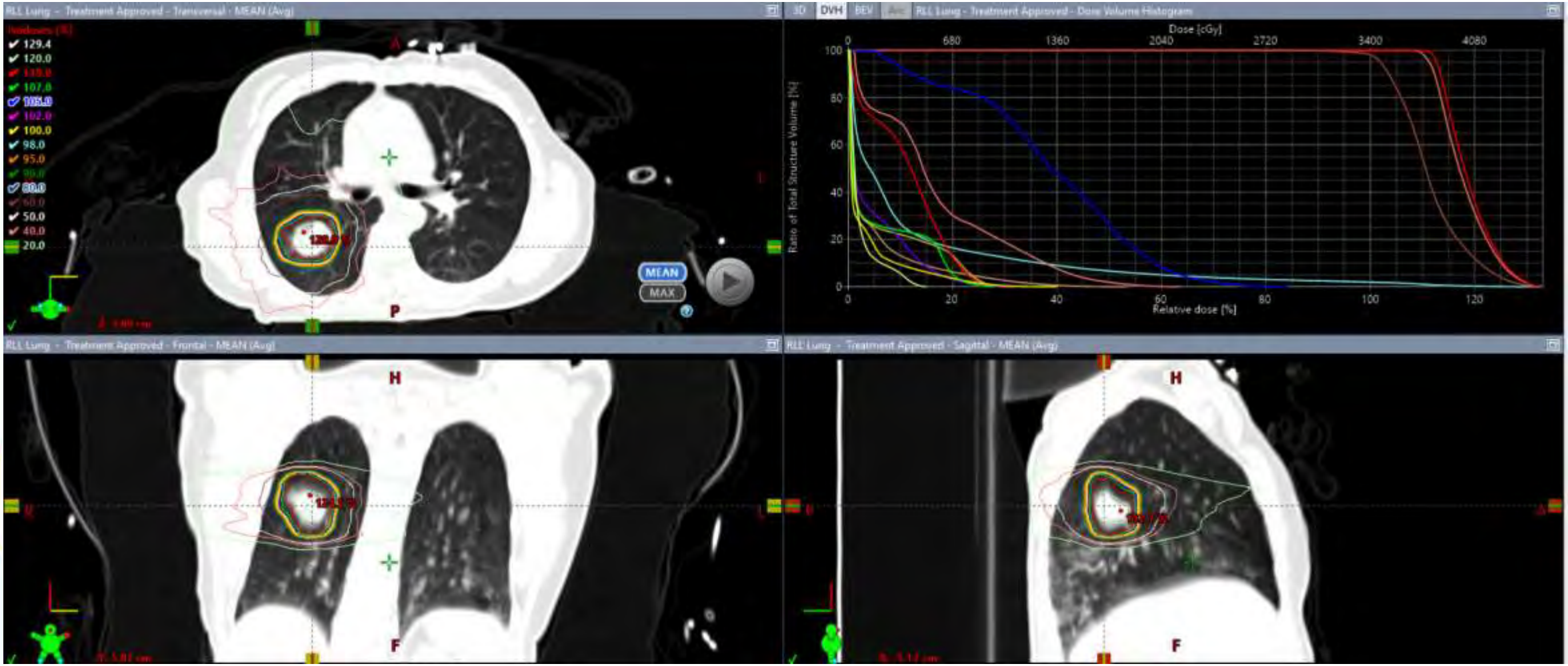
- To review clinical syndrome of radiation lung injury
- To discuss mitigation and management
- To discuss the challenges in follow up post lung RT

A 62 y.o. patient with past medical history significant for severe mental handicap who presents with T1cN0M0 adenocarcinoma of the right lower lobe lung.

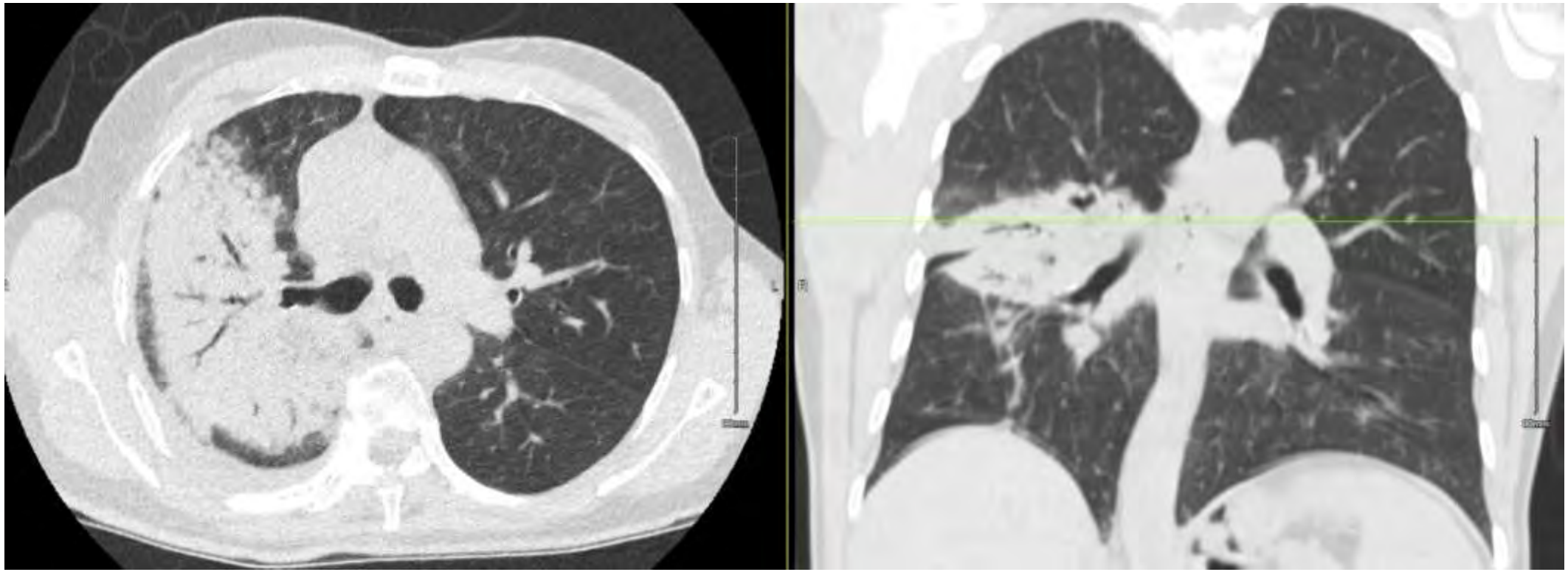
The patient required general anesthesia for all imaging and treatment.
The patient received 34Gy in a single fraction according to RTOG 0915.






RLL Lung - Treatment Approved - Transversal - MEAN (Avg)
129.4
120.0
107.0
100.0
98.0
95.0
50.0
40.0
20.0
MEAN
MAX
A
P
3D
DVH
BEV
RLL Lung - Treatment Approved - Dose Volume Histogram
Dose [cGy]
0
680
1360
2040
2720
3400
4080
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
20
40
60
80
100
120
Relative dose [%]
RLL Lung - Treatment Approved - Frontal - MEAN (Avg)
H
F
RLL Lung - Treatment Approved - Sagittal - MEAN (Avg)
H
F

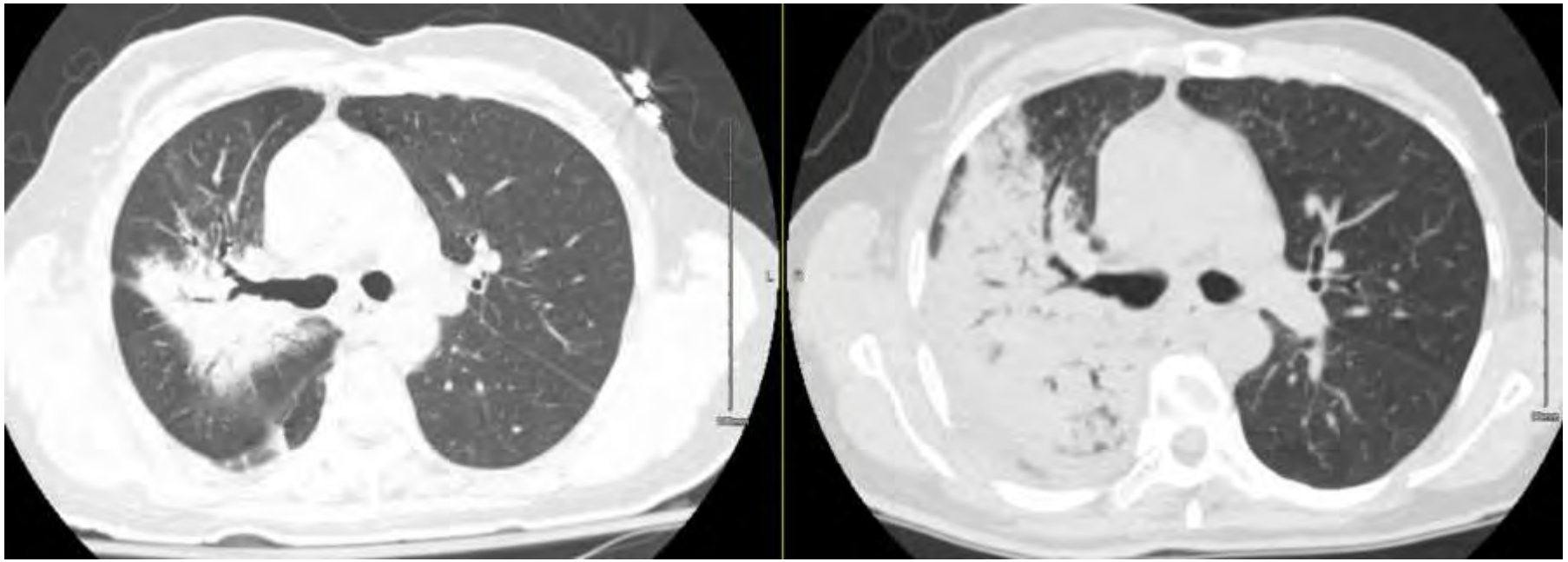
3 months post SBRT, the patient developed severe cough.

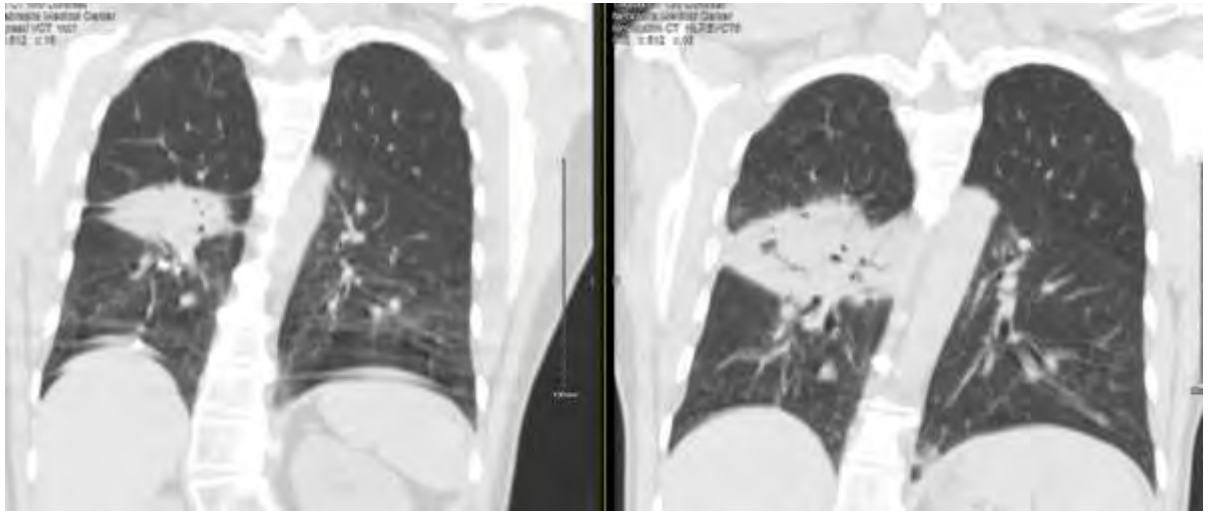


850cGy line


RLL Lung - Treatment Approved - CT_DIA
Isodoses [cGy]
4400.0
4080.0
3740.0
3638.0
3570.0
3468.0
3400.0
3332.0
3060.0
2720.0
2040.0
1700.0
1360.0
850.0
680.0
Showing dose from image MEAN
MEAN
MAX
H
F
P

8 months post SBRT





Prednisone 20 mg bid x 2 weeks, then 10 mg bid x 2 weeks, then 10 mg one daily for a week followed by 5 mg once daily for a week

Radiation pneumonitis (RP) is a common side effect of thoracic radiation therapy, with rates of grade (G) 2 or higher (G2+) RP near 20%

- RILI is a severe complication of thoracic RT and embraces radiation pneumonitis (RP) and radiation fibrosis

- It is caused by direct cytotoxic effect, oxidative stress, and immune-mediated injury.

- It encompasses two phases:
  - ✓ Early phase known as Radiation Pneumonitis (RP), characterized by acute lung tissue inflammation as a result of exposure to radiation; and a
  - ✓ Late phase called Radiation Fibrosis (RF), a clinical syndrome that results from chronic pulmonary tissue damage

Radiation induced lung injury

- Clinical syndrome
- Pathophysiology
- Prevention/mitigation
- Treatment
- NTCP/QUANTEC/prediction models

	Parameters	Risk increase
Patients characteristics	Age	over 65
	Gender	female
	Smoking	non-smokers
	Pre-existing lung diseases	ECOG performance 3–4
	Genetic predisposition	SNPs in various genes
	Tumor location	Base, the upper half of the lung, the region adjacent to the pleura
	Low KPS	Radiation pneumonitis
Dosimetric parameters	Chemotherapy	Most chemotherapies
	Chemo-XRT schedule:	Sequential > concurrent fraction size >2.67 Gy
	Targeted therapies	TKI monotherapy and with RT
	Mean Lung Dose (MLD)	Higher MLD
	Dose to the heart	Undetermined

Front. Oncol., 06 September 2019
Sec. Radiation Oncology
Volume 9 - 2019 | https://doi.org/10.3389/fonc.2019.00877

Clinical RILI

Acute (pneumonitis) < 6 months

Constellation of pulmonary symptoms of varying severity, dependent on the degree of pulmonary involvement.

Usually occurs within weeks to 3 months of RT, but may present sooner

Mild symptoms:
Cough
Low grade fever
Chest congestion/fullness

More severe symptoms:
Dyspnea
Pleuritic pain
Blood stained sputum

In the worst cases can lead to ARDS and acute cor pulmonale

Physical examination usually benign, but may have signs of consolidation, friction rub or pleural effusion

Chronic (fibrosis) > 6 months

Clinically presents as varying degrees of pulmonary impairment. May not be associated with acute injury.

Characterized by progressive fibrosis of alveolar septa which can be detected by medical imaging

Typically follows area of high dose radiation, but with continued evolution may become distorted

Commonly used grading system for radiation induced lung toxicity

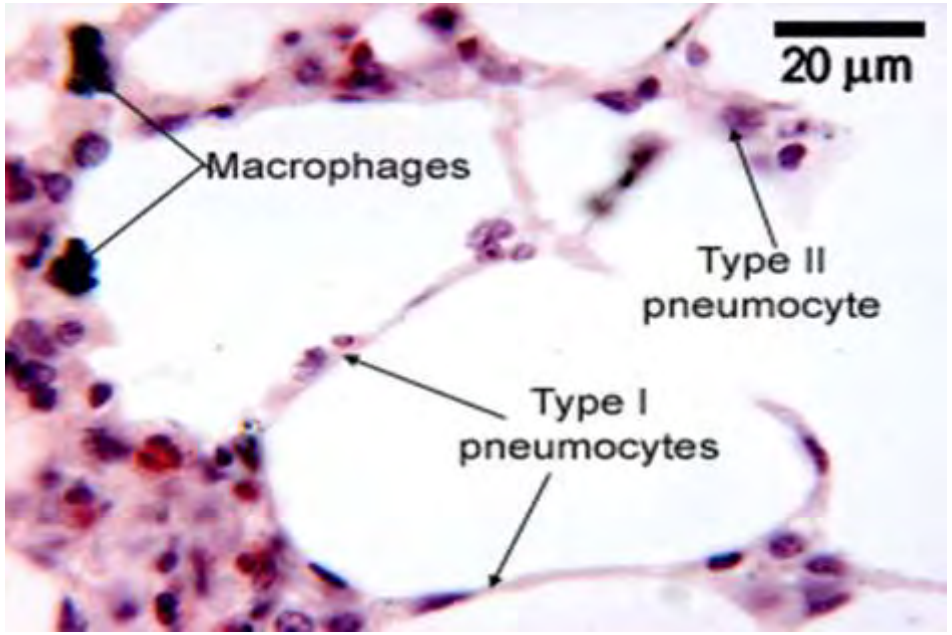
Criteria	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE v4.0	Asymptomatic	Symptomatic; Required medical intervention; Limits ADLs	Severe symptoms; Oxygen indicated; Impairs ADLs	Life threatening respiratory dysfunction	Death
RTOG	Mild symptoms	Persistent symptoms requiring symptomatic treatment	Severe symptoms, possibly requiring intermittent O_2 or steroids	Severe symptoms requiring continuous O_2 or assisted ventilation	-
EORTC (LENT-SOMA)	Asymptomatic or mild symptoms; slight imaging changes	Moderate symptoms; patchy imaging changes	Severe symptoms; increased density imaging changes	Severe symptoms requiring continuous O_2 or assisted ventilation	Death
SWOG	Imaging changes; mild symptoms without steroids	Symptoms requiring steroids or tap for effusion	Symptoms requiring oxygen	Symptoms requiring assisted ventilation	Death

CTCAE 4.0, common terminology criteria for adverse events, version 4.0; RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; LENT-SOMA, late effects in normal tissue-subjective objective management analysis; SWOG, Southwest Oncology Group; ADL, activities of daily living.

Normal alveoli

Pulmonary epithelium consists of two types of cells;

- Type I pneumocytes are involved in gas exchange and cover ~ 97 % of the alveolar surface
- Type II pneumocytes produce surfactant and can replicate and/or differentiate to replace damaged type I cells.

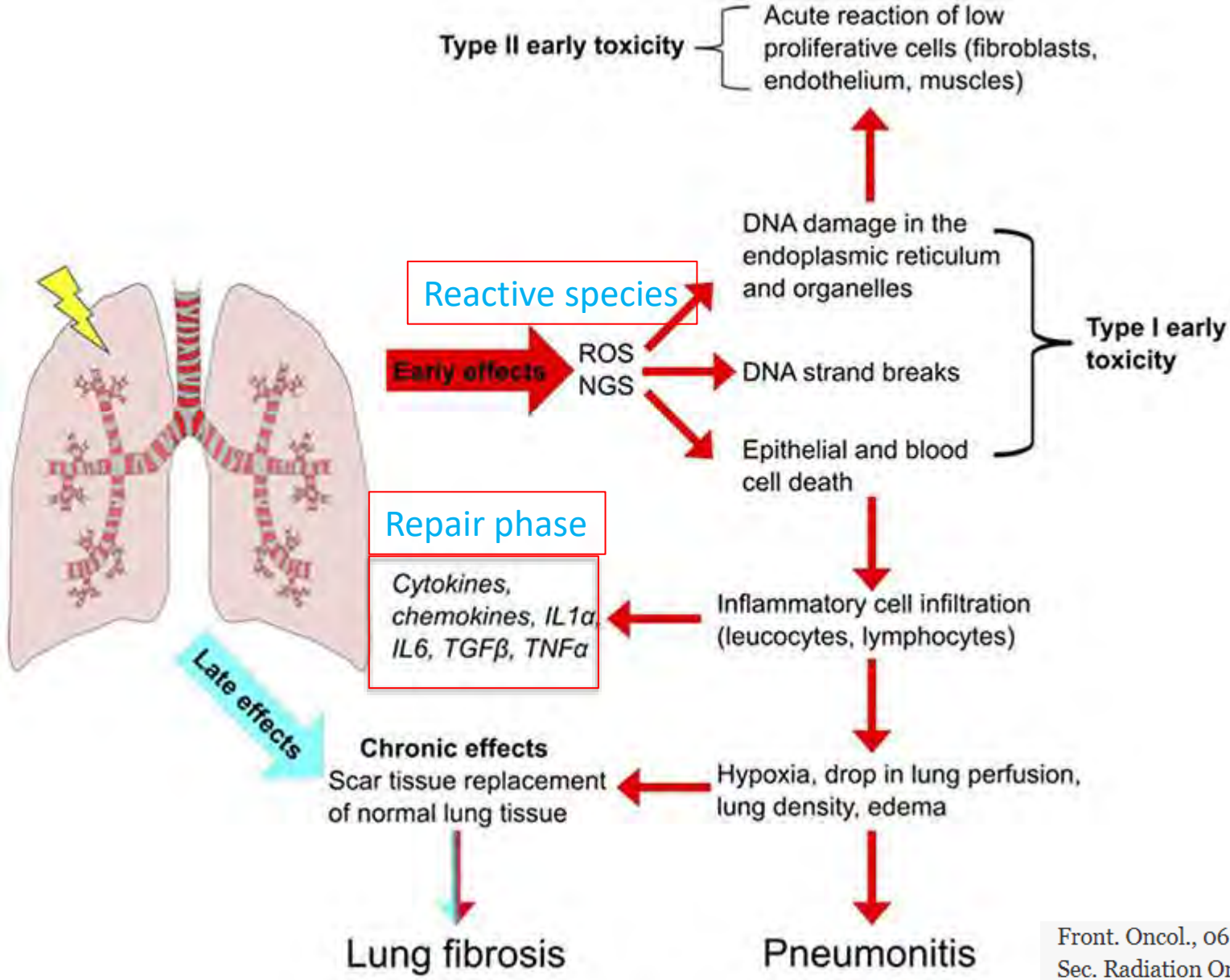


Pathophysiology of radiation-induced pneumonitis

A working hypothesis is that RILI is an abnormal healing response, which can be broken up into 3 phases;

- Injury
- Inflammation
- Repair

Semin Radiat Oncol 20:201-207 © 2010



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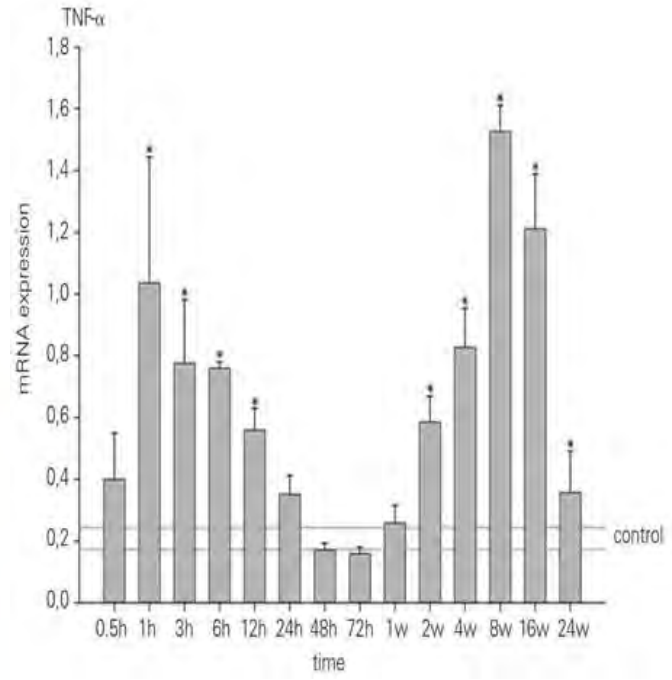
Inflammatory phase (hours to weeks)

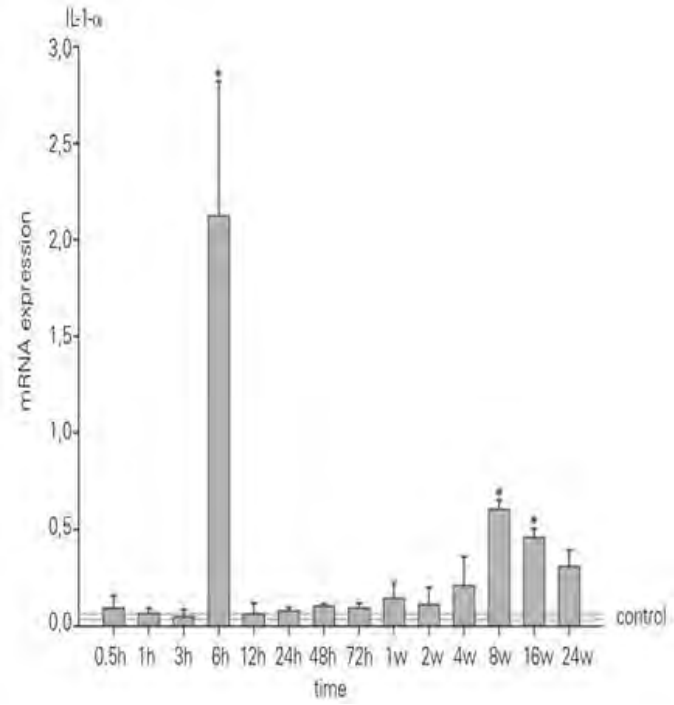
After acute injury, recruited inflammatory cells (leukocytes) secrete cytokines and growth factors to further recruit cells involved in the healing process

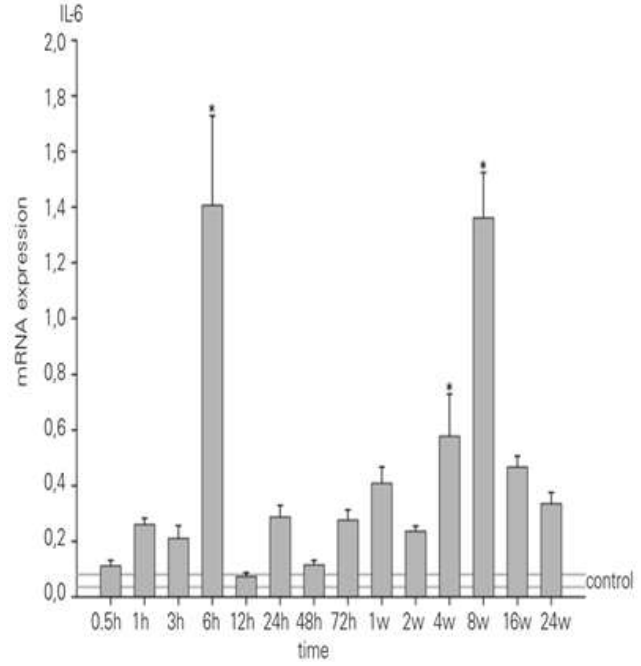
This normal inflammatory response is essential for wound healing, however in RILI, the inflammatory response is either prolonged or escalated for unclear reasons

Lung irradiation is characterized by a second wave of inflammation and cytokine release occurring at 6 – 8 weeks post exposure and associated with hypoxia, decreased perfusion and late lung injury

Irradiation Induces a Biphasic Expression of Pro-Inflammatory Cytokines in the Lung







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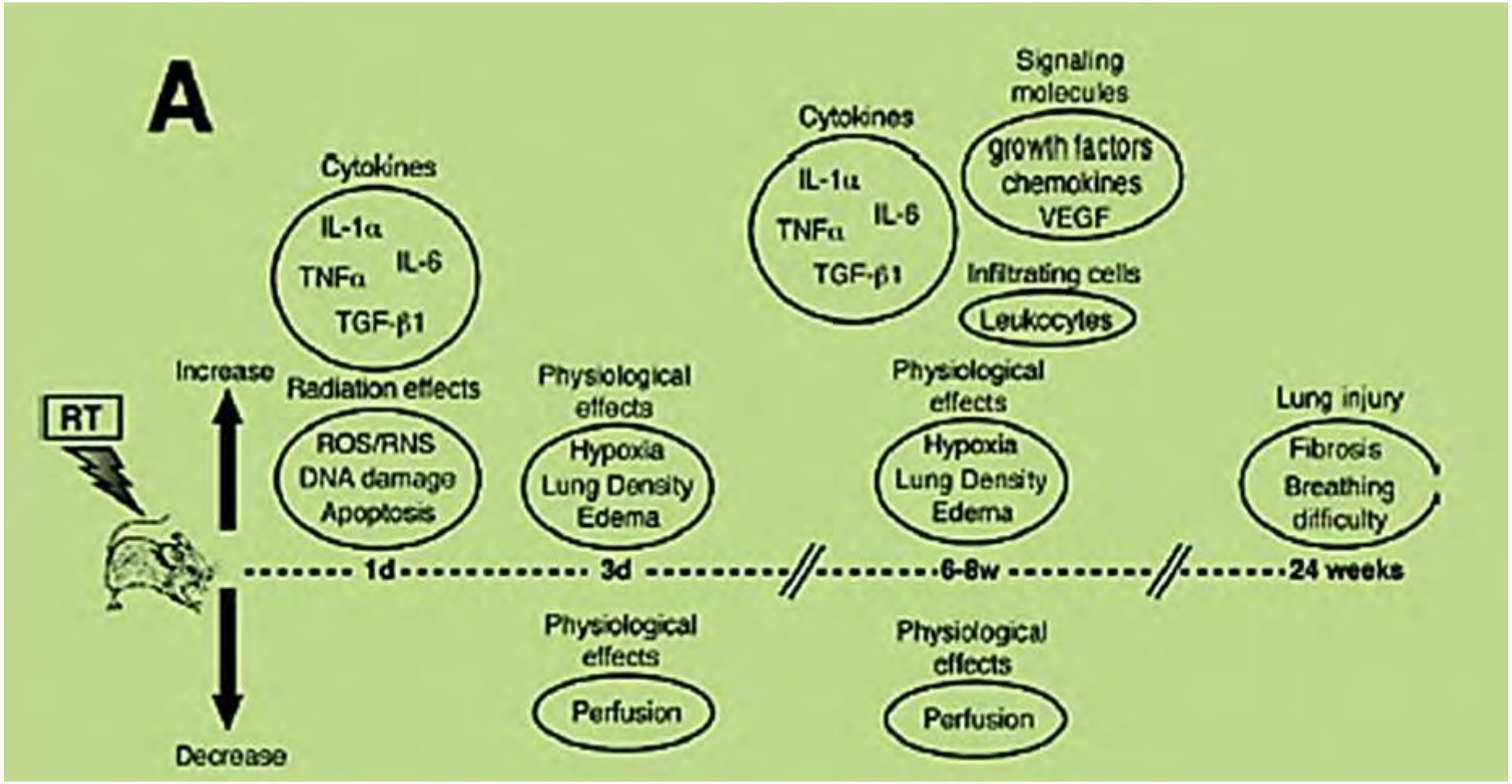
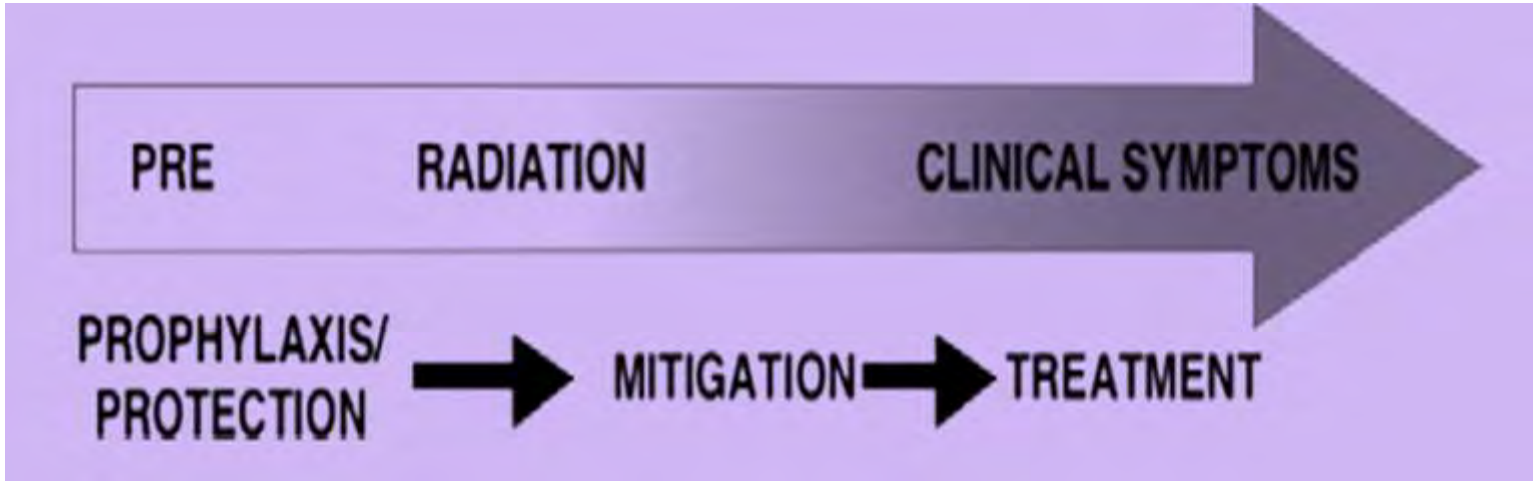

A
Cytokines
IL-1α
TNFα
IL-6
TGF-β1
Signaling molecules
growth factors
chemokines
VEGF
Infiltrating cells
Leukocytes
RT
Increase
Radiation effects
ROS/RNS
DNA damage
Apoptosis
Physiological effects
Hypoxia
Lung Density
Edema
Lung injury
Fibrosis
Breathing difficulty
1d
3d
6-8w
24 weeks
Perfusion
Decrease

RILI Prevention/Mitigation/Treatment



Amifostine

Captopril /ACE-is

Pentoxifylline

Nintedanib

Current Status of Molecular Interventions for RILF

Name	Molecular Type	Target/Action	Stage
SM16	Antibody	Anti-TGF-β type 1 receptor	Animal testing
LY2109761	Quinoline-derived compound	Dual inhibitor of TGF-β receptor types I and II	Animal testing
AKF-PD	Pyridone	Inhibitor of connective tissue growth factor expression	Animal testing
TGF-β inhibitor	Antibody	Anti-TGF-β	Animal testing
SB203580	Pyridinylimidazole compound	Inhibitor of TGF-β/Smad signal transduction	Cellular assays
WP631	Bisintercalating anthracycline antibiotic	DNA intercalator, inhibits cell proliferation	Cellular assays
MyD88	Recombinant protein	A key intracellular adaptor of TLR signaling, regulates innate immunity	Animal testing
SOD-TAT	Recombinant protein	Targets oxidative damage	Animal testing
Amifostine	Phosphate compound	Scavenges oxygen free radicals to reduce oxidative damage	In clinical use
H_2	Hydrogen molecule	Antioxidant that reduces ROS and suppresses oxidative stress-induced injury	In cell and animal testing
TNF-α receptor I expression vector	Plasmid	Inhibitor of TNF-α activity	In cell and animal testing

Curr Drug Targets. 2013 Oct; 14(11): 1347–1356.

Amifostine

An organic thiophosphate prodrug that is hydrolyzed *in vivo* by alkaline phosphatase to form active drug WR 1065, which functions as a free radical scavenger

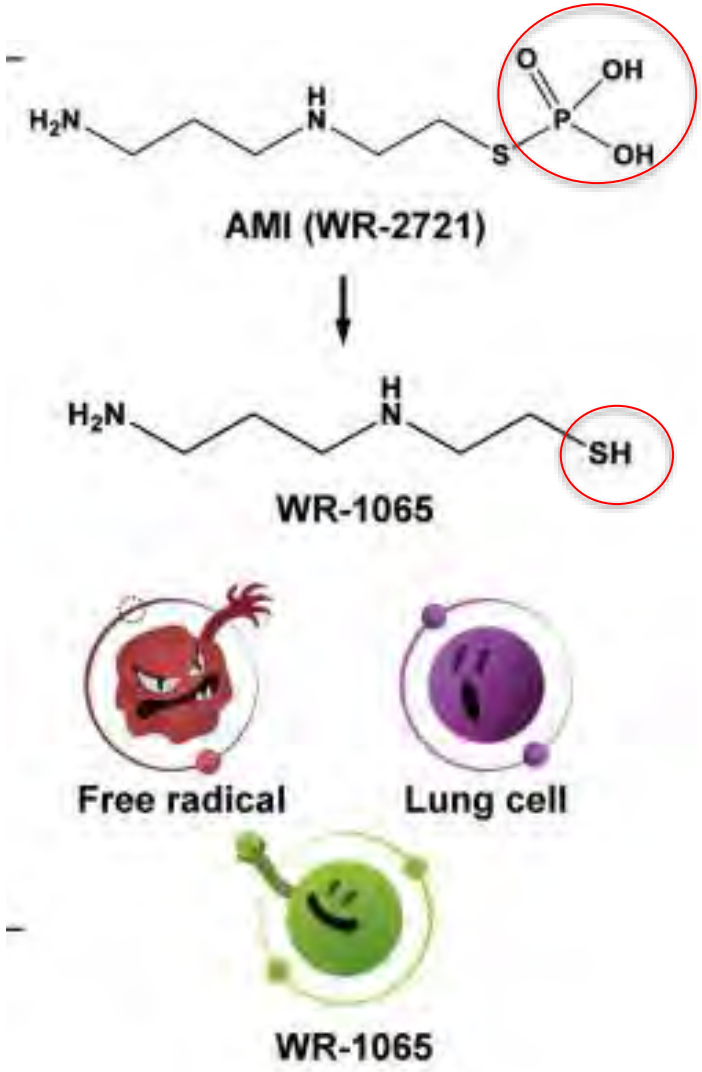


Table 6. Randomized Trials of Amifostine in Lung Cancer (mostly stage III NSCLC)

Author and Reference	No. of Patients	Phase	RT	Concurrent CT	Amifostine	% Esophagitis* (no amifostine)	% Esophagitis* (with amifostine)	% Pneumonitis* (no amifostine)	% Pneumonitis* (with amifostine)	Comments
Antonadou et al[7]	146†	III	55-60 Gy (2 Gy every day)	None	340 mg/m^2 IV 5 times per week	42‡	4‡	43§	9§	No concurrent CT
						$P < .001$		$P < .001$		
Antonadou et al[8]	73	II	55-60 Gy (2 Gy every day)	PXT 50 mg/m^2 or CARBO AUC 2 weekly	300 mg/m^2 IV 5 times per week	84	39	56	19	Higher than expected rates of esophagitis and pneumonitis
						$P < 0.001$		$P = .002$		
Komaki et al[10]	62	III	69.6 Gy (1.2 Gy bid)	Cisplatin 50 mg/m^2 days 1, 8, 29, 36 and oral etoposide 50 mg bid days 1-10, 29-39	500 mg IV 2 times per week	35	16	16	0	Also reported decrease in neutropenic fever with amifostine (16% *v* 39%; $P = .046$)
						$P = .02$		$P = .02$		
Koukourakis et al[9]	60‖	II	50-64 Gy (2 Gy every day)	None	500 mg SC 5 times per week	67	16	NR	NR	Only trial using SC amifostine
						$P = .08$¶				
Leong et al[11]	60	III	60-66 Gy (2 Gy every day)	PXT 60 mg/m^2 weekly	740 mg/m^2 IV approximately once per week	70#	43#	NR	NR	Only placebo-controlled trial
						$P =$ NS				
Senzer et al[12]	100	III	64.8 Gy (1.8 Gy every day)	PXT 50 mg/m^2 and CARBO AUC 2 (weekly)	500 mg IV every week before CT and 200 mg/m^2 IV every day before RT	21	17	NR	NR	Preliminary data (study not completed)**
						$P =$ NS				
Movsas (RTOG 98-01)	243	III	69.6 Gy (1.2 Gy bid)	PXT 50 mg/m^2 and CARBO AUC 2 (weekly)	500 mg IV 4 times per week	34	30	16.7	8	Largest trial (in cooperative group setting) and only trial with prospective QOL
						$P = .9$		$P =$ NS		

Lung Cancer. 2013 June ; 80(3): 298–305. doi:10.1016/j.lungcan.2013.02.008.

The addition of amifostine to carboplatin and paclitaxel based chemoradiation in locally advanced non-small cell lung cancer: long-term follow-up of Radiation Therapy Oncology Group (RTOG) randomized trial 9801

Lawrence Yaacov Richard, MRCP[1,4], **Paulus Rebecca, BS**[2], **Langer Corey, MD**[3], **Werner-Wasik Maria, MD**[4], **K Buyyounouski Mark, MD, MS**[5], **Komaki Ritsuko, MD**[6], **Machtay Mitchell, MD**[7], **Smith Colum, MD**[8,10], **S Axelrod Rita, MD**[4], **Wasserman Todd, MD**[9], **D Bradley Jeffrey, MD**[9], and **Movsas Benjamin, MD**[11]

Table II

Late adverse events ≥ grade 3 possibly related to radiation

These are raw patient numbers, unless otherwise indicated.

	Amifostine n=108		No Amifostine n=114	
	Grade 3,4	**Grade 5**	**Grade 3,4**	**Grade 5**
Bone	1 (1%)	0	1 (1%)	0
Esophagus	4 (4%)	0	3 (3%)	0
Heart	6 (6%)	0	4 (4%)	0
Lung	12 (11%)	2 (2%)	12(11%)	2 (2%)
Skin	0	0	0	0
Spinal cord	1 (1%)	0	0	0
Subcutaneous tissue	0	0	0	0
Other	0	0	2 (2%)	0
Worst Toxicity per Patient	15 (14%)	2 (2%)	20 (18%)	2 (2%)

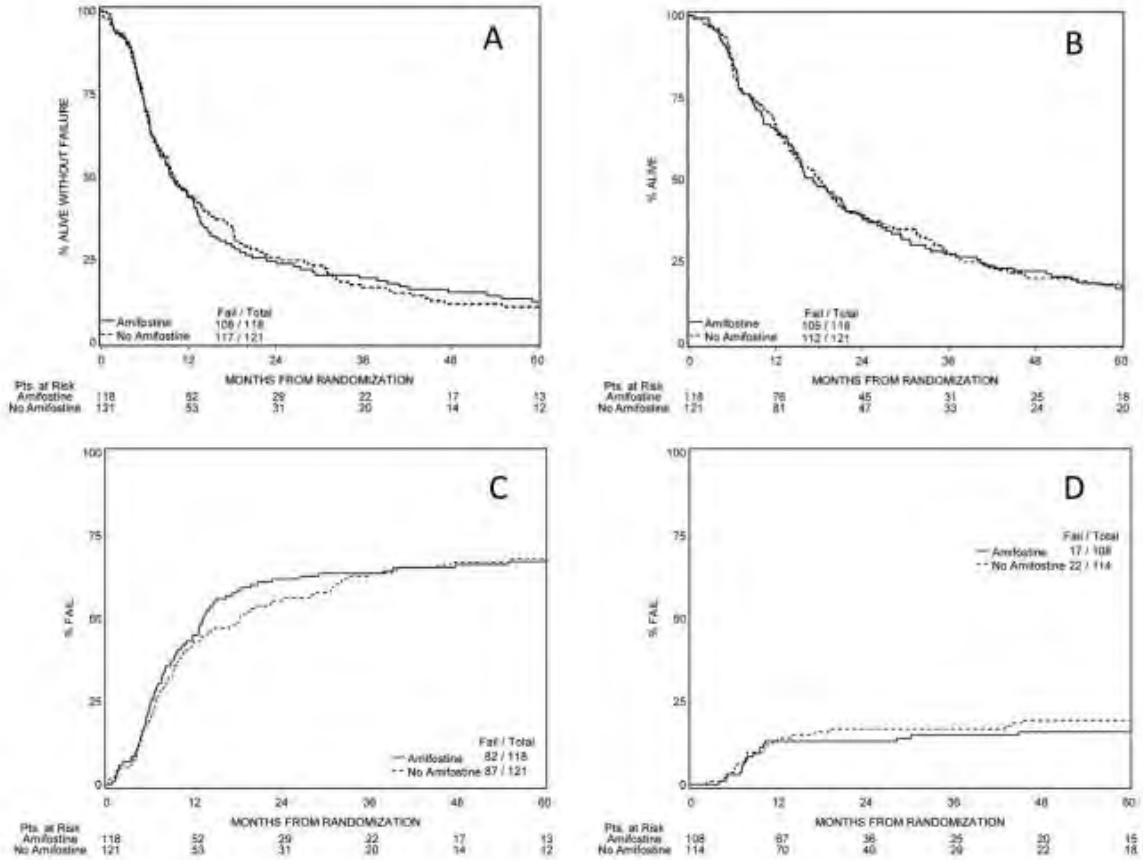


Figure 2.
(a) Disease-Free Survival, hazard ratio between the arms: 1.07, confidence interval (0.82, 1.38) p=0.64
(b) Overall Survival, hazard ratio between the arms: 1.03, confidence interval (0.79, 1.34) p=0.85
(c) Time to Progression, hazard ratio between the arms: 0.98, confidence interval (0.72, 1.32) p=0.88
(d) Cumulative Severe Toxicity (>= grade 3), hazard ratio between the arms: 1.24, confidence interval (0.66, 2.32) p=0.51.
Overall survival and disease-free survival hazard ratios from Cox proportional hazards model; hazard ratios for time to progression and toxicity from Fine-Gray proportional hazards model.

ANTICANCER RESEARCH *36*: 5-12 (2016)

Review

Potential of Amifostine for Chemoradiotherapy and Radiotherapy-associated Toxicity Reduction in Advanced NSCLC: A Meta-Analysis

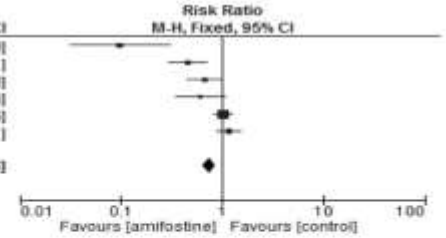
ANNEMARIE DEVINE and LAURE MARIGNOL

Applied Radiation Therapy Trinity (ARTT), Discipline of Radiation Therapy, Trinity College Dublin, Dublin, Ireland

A

Study or Subgroup	Amifostine Events	Amifostine Total	Control/placebo Events	Control/placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	3	73	31	73	15.4%	0.10 [0.03, 0.30]
Antonadou 2003	14	36	27	32	14.2%	0.46 [0.30, 0.71]
Komaki 2004	16	31	24	31	11.9%	0.67 [0.45, 0.98]
Leong S.S 2003	9	21	19	27	8.2%	0.61 [0.35, 1.06]
Movsas 2005	70	120	70	122	34.4%	1.02 [0.82, 1.26]
Senzer 2002	35	47	34	53	15.9%	1.16 [0.89, 1.51]
Total (95% CI)		**328**		**338**	**100.0%**	**0.74 [0.65, 0.86]**
Total events	147		205			

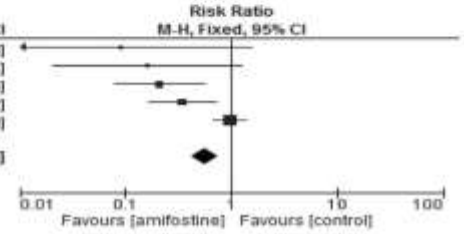
Heterogeneity: Chi² = 36.94, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.08 (P < 0.0001)



B

Study or Subgroup	Amifostine Events	Amifostine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Komaki 2004	0	31	5	31	6.0%	0.09 [0.01, 1.58]
Komaki 2002	1	27	6	26	6.7%	0.16 [0.02, 1.24]
Antonadou 2001	4	44	23	53	22.9%	0.21 [0.08, 0.56]
Antonadou 2003	7	36	18	32	20.9%	0.35 [0.17, 0.72]
Movsas 2005	38	120	40	122	43.5%	0.97 [0.67, 1.39]
Total (95% CI)		**258**		**264**	**100.0%**	**0.56 [0.41, 0.75]**
Total events	50		92			

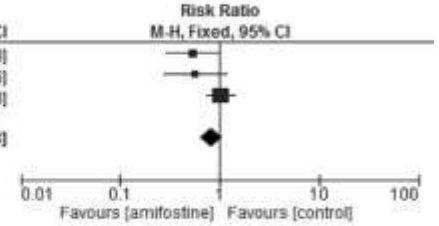
Heterogeneity: Chi² = 17.12, df = 4 (P = 0.002); I² = 77%
Test for overall effect: Z = 3.88 (P = 0.0001)



C

Study or Subgroup	Amifostine Events	Amifostine Total	No Amifostine/Placebo Events	No Amifostine/Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	9	32	19	36	23.7%	0.53 [0.28, 1.00]
Antonadou 2003	8	28	12	24	17.1%	0.57 [0.29, 1.16]
Movsas 2005	46	102	45	103	59.2%	1.03 [0.76, 1.40]
Total (95% CI)		**162**		**163**	**100.0%**	**0.84 [0.65, 1.08]**
Total events	63		76			

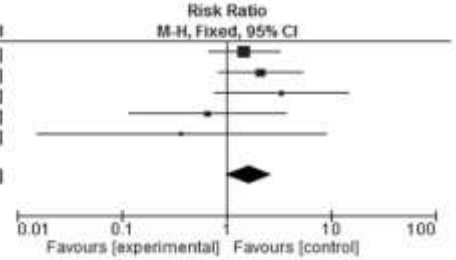
Heterogeneity: Chi² = 4.86, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 1.38 (P = 0.17)



D

Study or Subgroup	Amifostine Events	Amifostine Total	Control/Placebo Events	Control/Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	11	44	9	53	41.0%	1.47 [0.67, 3.23]
Antonadou 2003	12	36	5	32	26.6%	2.13 [0.84, 5.40]
Komaki 2002	7	27	2	26	10.2%	3.37 [0.77, 14.75]
Leong S.S 2003	2	30	3	30	15.1%	0.67 [0.12, 3.71]
Senzer 2002	0	47	1	53	7.1%	0.38 [0.02, 8.99]
Total (95% CI)		**184**		**194**	**100.0%**	**1.64 [0.99, 2.73]**
Total events	32		20			

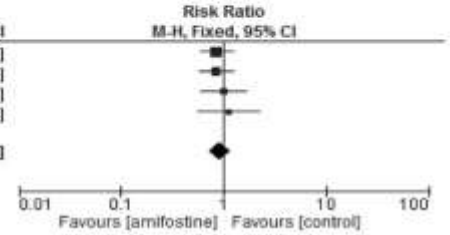
Heterogeneity: Chi² = 3.18, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.06)



E

Study or Subgroup	Amifostine Events	Amifostine Total	Control/Placebo Events	Control/Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	22	44	31	53	36.7%	0.85 [0.59, 1.24]
Antonadou 2003	20	36	21	32	29.0%	0.85 [0.58, 1.24]
Leong S.S 2003	15	30	15	30	19.6%	1.00 [0.60, 1.66]
Senzer 2002	12	47	12	53	14.7%	1.13 [0.56, 2.26]
Total (95% CI)		**157**		**168**	**100.0%**	**0.92 [0.73, 1.16]**
Total events	69		79			

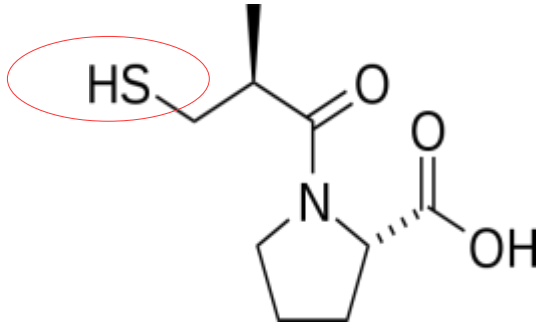
Heterogeneity: Chi² = 0.76, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)



Conclusion

- Amifostine appears efficacious for acute esophageal and pulmonary toxicity reduction when administered to patients receiving CRT or RT alone for advanced-stage, inoperable NSCLC.
- The results for both end-points are inconsistent, due to high statistical heterogeneity.
- The optimum amifostine protocol for maximal efficacy is unclear.
- Subcutaneous administration may reduce amifostine-related toxicity.
- Amifostine does not appear to alter response rates or survival after CRT or RT alone.
- Further clinical data are required to determine whether amifostine should be routinely administered in patients with advanced NSCLC treated with
- radiotherapy.

Captopril // ACE-i // ARB



ACE-inhibitor and thiol free radical scavenger

Angiotensin-converting enzyme inhibitors (ACE-inhibitors) exhibit significant antifibrotic activity against collagen accumulation in the lungs; however, its effectiveness has proved in retrospective trials.

Am J Clin Oncol. 2018 April ; 41(4): 396–401. doi:10.1097/COC.0000000000000289.

Utility of the ACE inhibitor captopril in mitigating radiation-associated pulmonary toxicity in lung cancer: Results from NRG Oncology RTOG 0123

William Small Jr., MD, FASTRO[1], **Jennifer L. James, MS**[2], **Timothy D. Moore, MD**[3], **Dan J. Fintel, MD**[4], **Stephen T. Lutz, MD**[5], **Benjamin Movsas, MD, FASTRO**[6], **Mohan Suntharalingam, MD**[7], **Yolanda I. Garces, MD**[8], **Robert Ivker, MD**[9], **John Moulder, PhD, FASTRO**[10], **Stephanie Pugh, PhD**[2], and **Lawrence B. Berk, MD**[11]

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0123

A PHASE II RANDOMIZED TRIAL WITH CAPTOPRIL IN PATIENTS WHO HAVE RECEIVED RADIATION THERAPY +/- CHEMOTHERAPY FOR STAGE II-IIIB NON-SMALL CELL LUNG CANCER, STAGE I CENTRAL NON-SMALL CELL LUNG CANCER, OR LIMITED-STAGE SMALL-CELL LUNG CANCER

R		**S**	**Amount of Lung**	**Pre-**	**R**		
E		**T**	**Irradiated**	**Randomizatio n**	**A**		**Observation**
G	Within 7 days prior	**R**	1. < 25%	**Evaluations**	**N**		
I	to the start of	**A**	2. 25-37%		**D**	Randomization	
S	radiation therapy	**T**	3. > 37%	Within 2 weeks	**O**	within 48 hours	**Versus**
T	OR	**I**		prior to	**M**	prior to start of	
E	During radiation	**F**	**Prior Lung**	randomization	**I**	observation or	
R	therapy up to	**Y**	**Surgery**		**Z**	captopril	
	48 hours prior		1. No		**E**		**Captopril**
	to observation or		2. Yes				
	captopril						
			Chemotherapy				
			1. No				
			2. Yes				

Terminated prematurely due to poor accrual

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2019 Mar 23.
Published in final edited form as:
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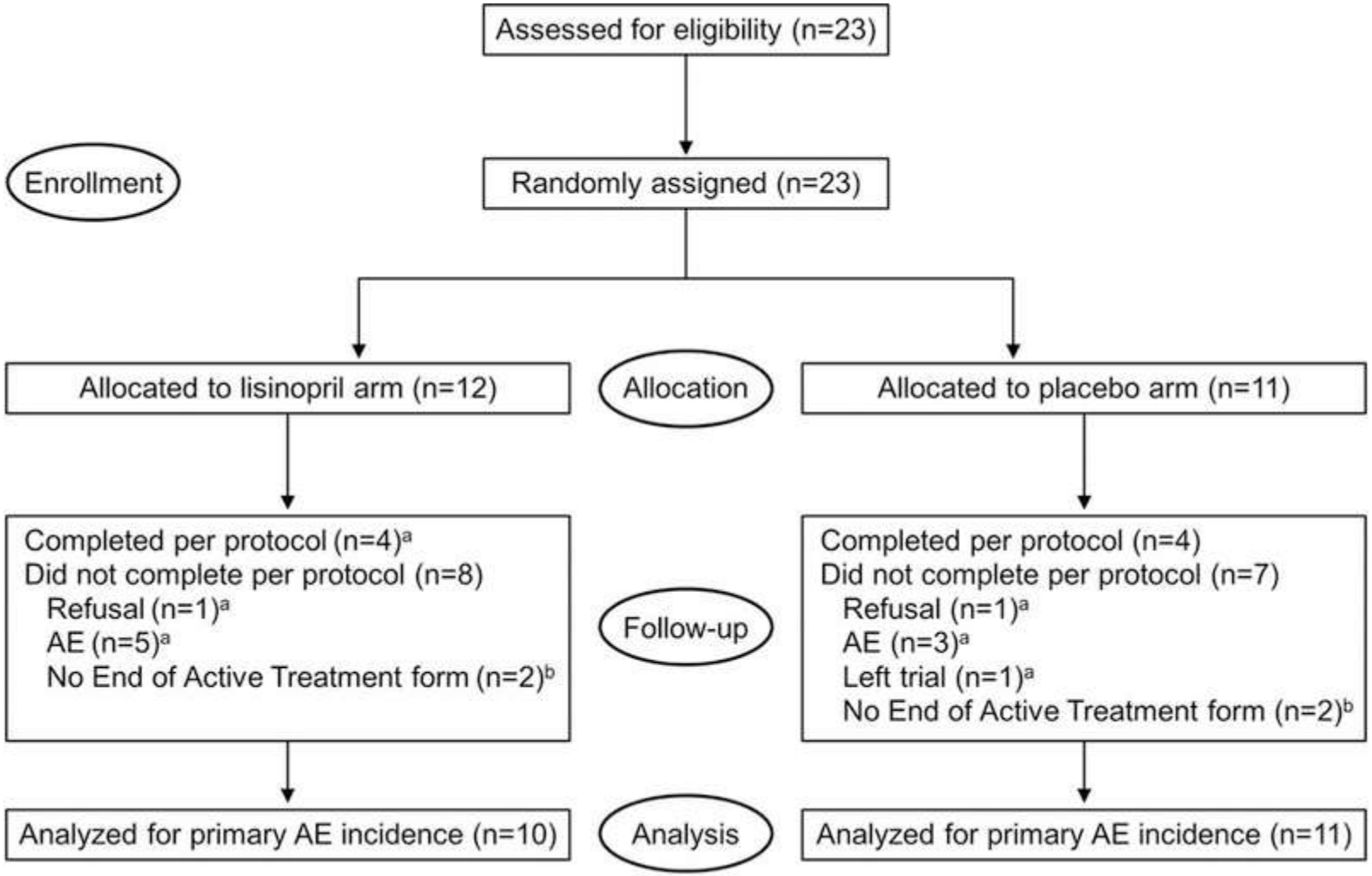
Published online 2018 Nov 2. doi: 10.1016/j.ijrobp.2018.10.035

PMCID: PMC6431240
NIHMSID: NIHMS997693
PMID: 30395904

Daily Lisinopril vs Placebo for Prevention of Chemoradiation-Induced Pulmonary Distress in Patients With Lung Cancer (Alliance MC1221): A Pilot Double-Blind Randomized Trial

Terence T. Sio, MD, MS, Pamela J. Atherton, MS, Levi D. Pederson, MS, W. Ken Zhen, MD, Robert W. Mutter, MD, Yolanda I. Garces, MD, Daniel J. Ma, MD, James L. Leenstra, MD, Jean-Claude M. Rwigema, MD, Shaker Dakhil, MD, James D. Bearden, MD, Sonja J. van der Veen, MD, PhD, Apar K. Ganti, MD, Steven E. Schild, MD, and Robert C. Miller, MD, MS, MBA

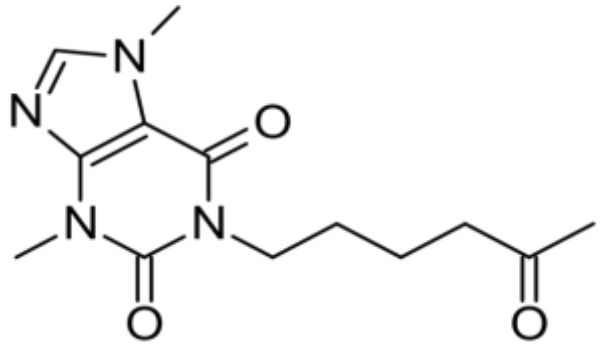
Randomization between 20 mg of lisinopril or placebo once daily


Assessed for eligibility (n=23)
Enrollment
Randomly assigned (n=23)
Allocated to lisinopril arm (n=12)
Allocation
Allocated to placebo arm (n=11)
Completed per protocol (n=4)[a]
Did not complete per protocol (n=8)
Refusal (n=1)[a]
AE (n=5)[a]
No End of Active Treatment form (n=2)[b]
Follow-up
Completed per protocol (n=4)
Did not complete per protocol (n=7)
Refusal (n=1)[a]
AE (n=3)[a]
Left trial (n=1)[a]
No End of Active Treatment form (n=2)[b]
Analyzed for primary AE incidence (n=10)
Analysis
Analyzed for primary AE incidence (n=11)

Adverse Effects Between Arms* (Primary End Point)

	Trial Arm, No. (%)		
Adverse Effect, Maximum Grade[a]	**Lisinopril (n=11)**	**Placebo (n=10)**	***P* Value[b]**
Hypotension			.26
0	7 (64)	6 (60)	
1	0 (0)	2 (20)	
2	4 (36)	2 (20)	
Acute kidney injury			.20
0	8 (73)	10 (100)	
1	2 (18)	0 (0)	
2	1 (9)	0 (0)	
Allergic reaction			
0	11 (100)	10 (100)	N/A
Anaphylaxis			
0	11 (100)	10 (100)	N/A

Pentoxifylline



Xanthine derivative and phosphodiesterase inhibitor that blocks the synthesis of TNFa

Pentoxifylline has immunomodulatory and anti-inflammatory properties mediated by the suppression of TNF-α and IL-1, which may play a role in treating of RF.

There are multiple reports of decreased cutaneous fibrosis with pentoxifylline and one small randomized trial reports efficacy in preventing lung injury

Clinical Trial > Int J Radiat Oncol Biol Phys. 2004 Jan 1;58(1):213-9.
doi: 10.1016/s0360-3016(03)01444-5.

Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial

Berrin Ozturk [1], Ibrahim Egehan, Sevil Atavci, Mehmet Kitapci

Table 6 Chest X-ray and high-resolution CT assessment of patients in Ptx and placebo groups

Grade	3 mo (*n*)				6 mo (*n*)			
	CXR*		CT†		CXR‡		CT§	
	Ptx	Placebo	Ptx	Placebo	Ptx	Placebo	Ptx	Placebo
0	14 (70)	8 (40)	11 (55)	7 (35)	11 (55)	8 (40)	11 (55)	6 (30)
1	6 (30)	5 (25)	4 (20)	6 (30)	8 (40)	5 (25)	4 (20)	3 (15)
2	0 (0)	7 (35)	4 (20)	3 (15)	1 (5)	7 (35)	3 (15)	6 (30)
3	0 (0)	0 (0)	1 (5)	4 (20)	0 (0)	0 (0)	2 (10)	5 (25)

* $\chi^2 = 8.72$; $p = 0.013$.
† $\chi^2 = 3.23$; $p = 0.36$.
‡ $\chi^2 = 5.67$; $p = 0.059$.
§ $\chi^2 = 3.9$; $p = 0.27$.

- A statistically significant difference only for the 3-month chest X-ray results. The 6-month results were borderline significant (p = 0.059)
- The Grade 3 changes observed on the 3- and 6-month CT scans were more common in patients in the placebo group (25% and 20% vs. 10% and 5%, respectively), but the difference was not statistically significant.
- The 6-month chest X-ray results were not statistically significant, but a higher grade of radiation lung damage was more pronounced in the placebo group.

Clinical Trial > Int J Radiat Oncol Biol Phys. 2023 Aug 1;116(5):1091-1099.
doi: 10.1016/j.ijrobp.2023.02.030. Epub 2023 Mar 7.

Randomized Phase 2 Placebo-Controlled Trial of Nintedanib for the Treatment of Radiation Pneumonitis

Andreas Rimner [1], Zachary R Moore [2], Stephanie Lobaugh [3], Alexander Geyer [4], Daphna Y Gelblum [2], Raja-Elie E Abdulnour [5], Annemarie F Shepherd [2], Narek Shaverdian [2], Abraham J Wu [2], John Cuaron [2], Jamie E Chaft [4], Marjorie G Zauderer [4], Juliana Eng [6], Gregory J Riely [4], Charles M Rudin [4], Nicholas Vander Els [4], Mohit Chawla [4], Megan McCune [2], Henry Li [2], David R Jones [7], Dennis M Sopka [8], Charles B Simone 2nd [2], Raymond Mak [9], Gerald L Weinhouse [5], Zhongxing Liao [10], Daniel R Gomez [2], Zhigang Zhang [3], Paul K Paik [4]

- There are no established guidelines for the management of radiation-induced lung fibrosis.

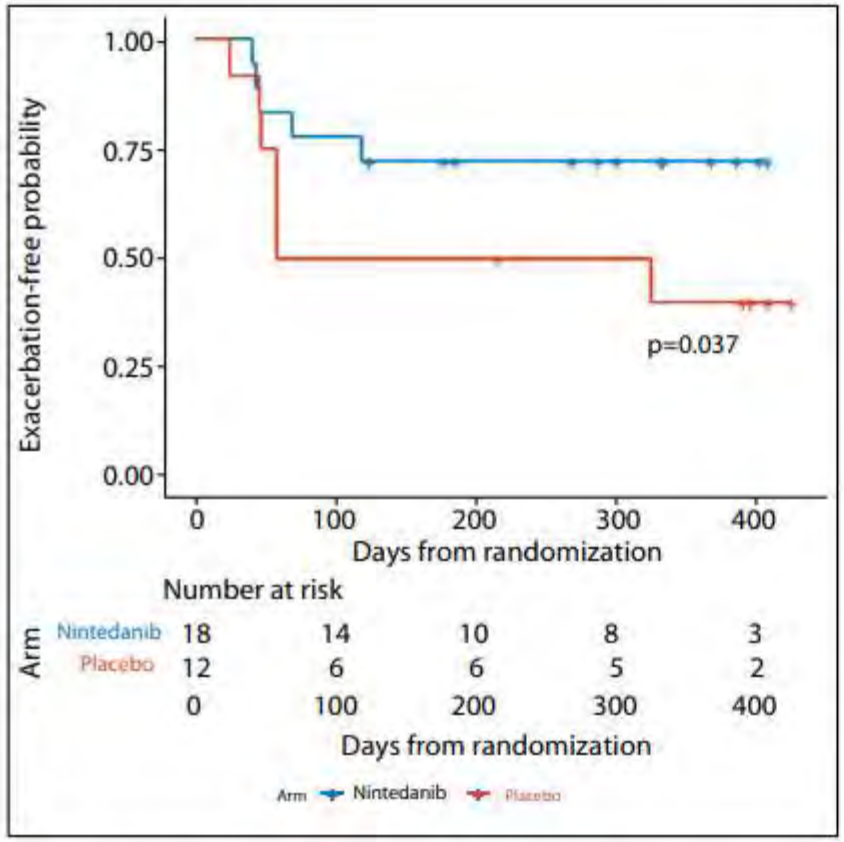
- There is interest in studying antifibrotic therapy, such as nintedanib, for progressive fibrosing disease, but there are limited data to support efficacy.

- Two small studies have suggested that the use of the TKI nintedanib may prevent radiation pneumonitis and/or decrease the risk of recurrence of radiation pneumonitis in combination with prednisone.

- Nintedanib (BIBF 1120) is an inhibitor of multiple tyrosine kinases that have been implicated in pulmonary fibrosis.
- It inhibits fibroblast growth factor receptor 1 and 3, platelet-derived growth factor receptor a and b, and vascular endothelial growth factor receptor 1, 2, and 3.
- These growth factors have been investigated as possible standalone therapeutic targets for pulmonary fibrosis

It is given orally at an initial dose of 150 mg 2 times per day for 12 weeks.

A.



B.

Arm	N	Events	Median FFE Months (95% CI)	FFE at 1 year % (95% CI)
Nintedanib	18	5	NR	72% (54%-96%)
Placebo	12	7	6.4 (2-NR)	40% (20%-82%)

Fig. 2. Freedom from pulmonary exacerbations. (A) Kaplan-Meier plot of time to first acute pulmonary exacerbation beginning 2 weeks after the start of treatment with nintedanib + prednisone or placebo + prednisone. In the prespecified, 1-sided *Z*-test for significance at 1 year, $P = .037$. (B) Kaplan-Meier estimate of median freedom from exacerbation (FFE) and estimated freedom from pulmonary exacerbation at 1 year. *Abbreviation:* NR = not reached.

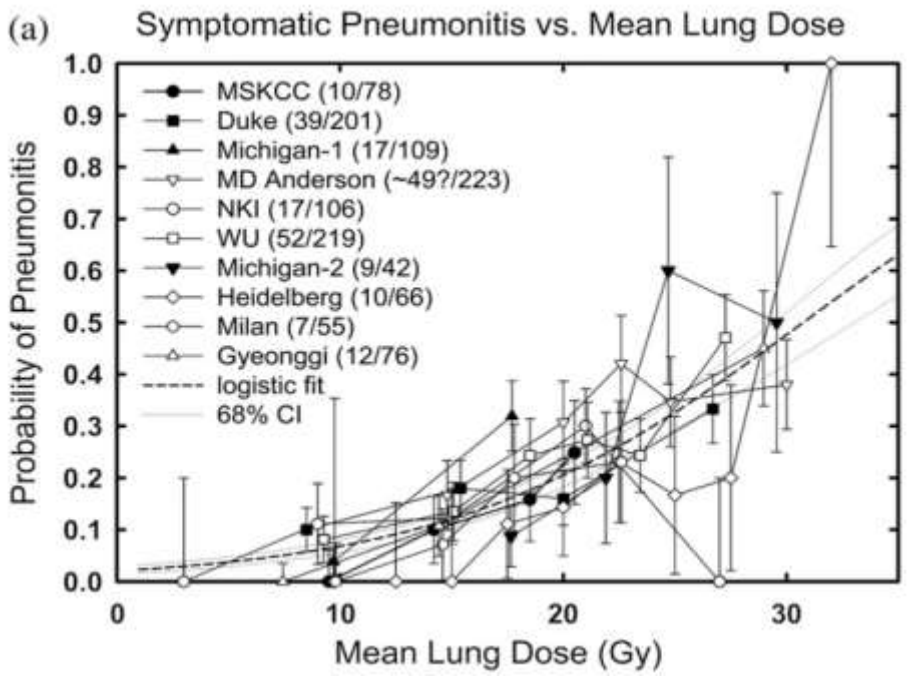
Conclusions

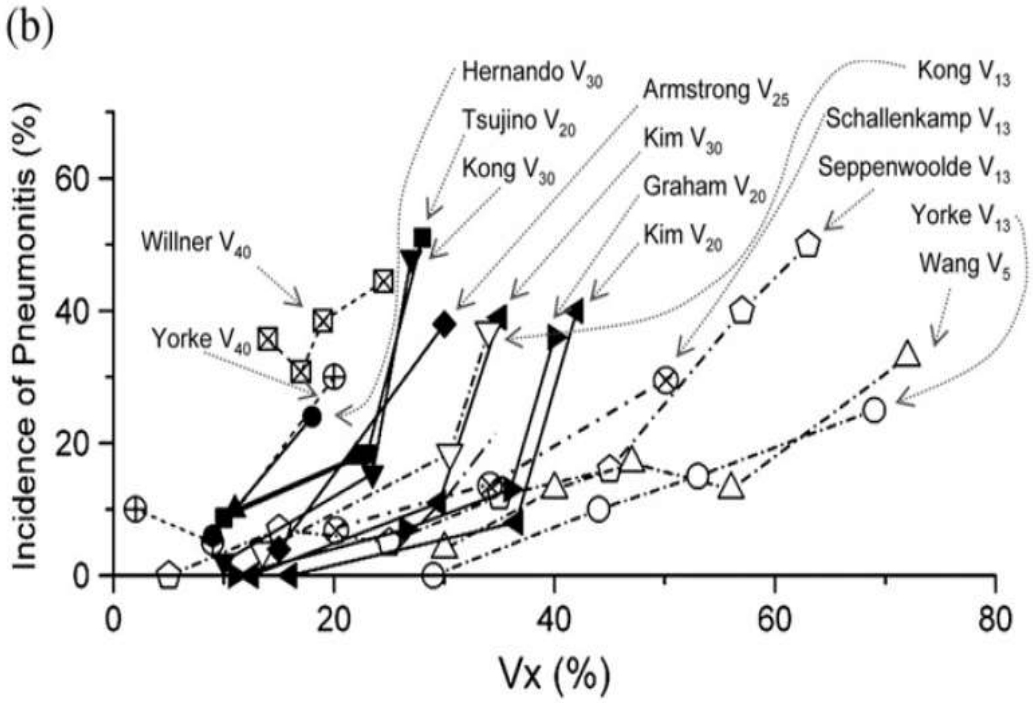
- There was an improvement in pulmonary exacerbations by the addition of nintedanib to a prednisone taper.
- Further investigation is warranted for the use of nintedanib for the treatment of RP.

The Radiation factors that influence the time to onset and the severity of radiation-associated pneumonitis

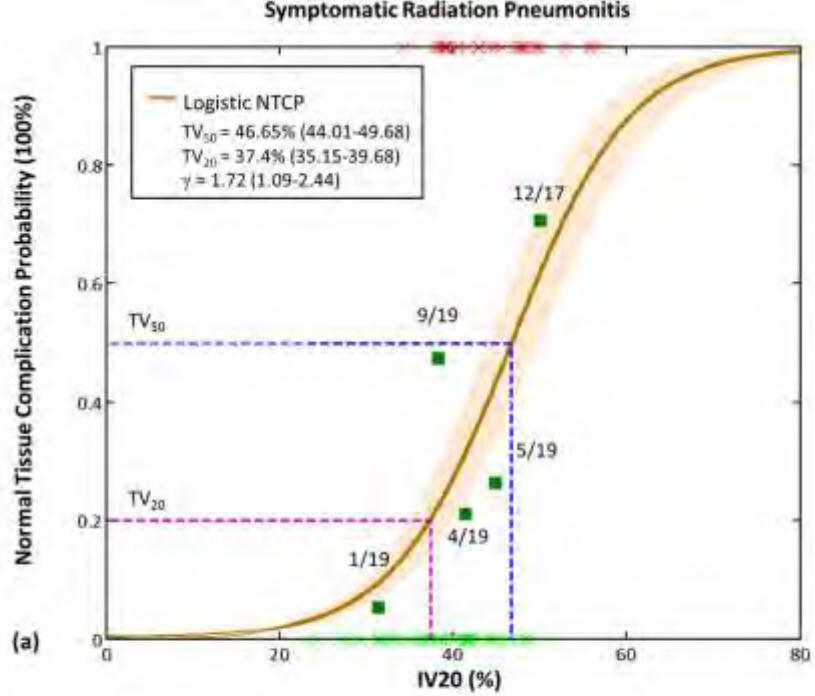
- Volume of the irradiated parenchyma
- Absorbed radiation dose
- Number of fractions
- Size of the individual dose per fraction
- Dose rate (the radiotherapy output device)

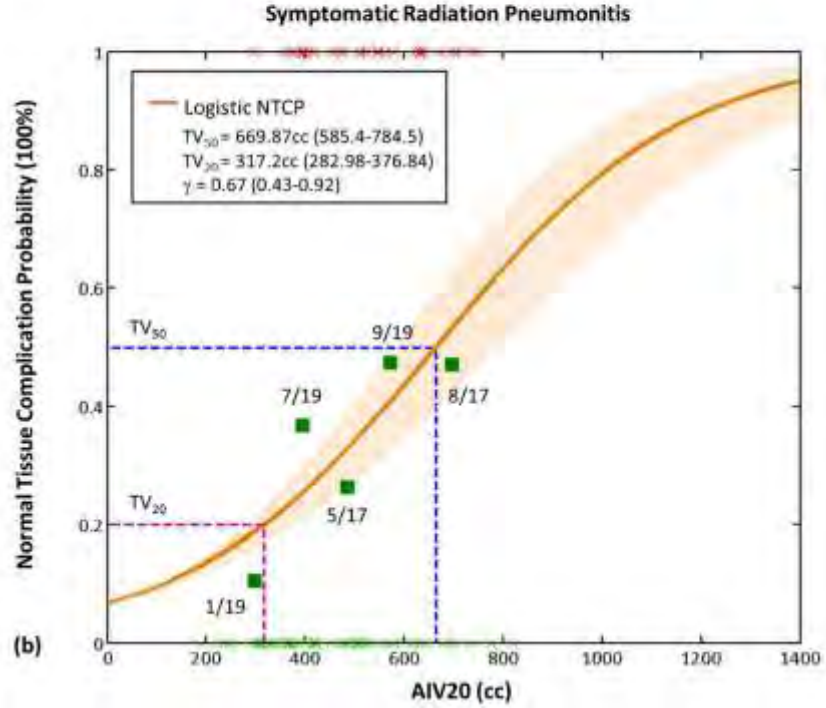
Radiation dose/volume considerations



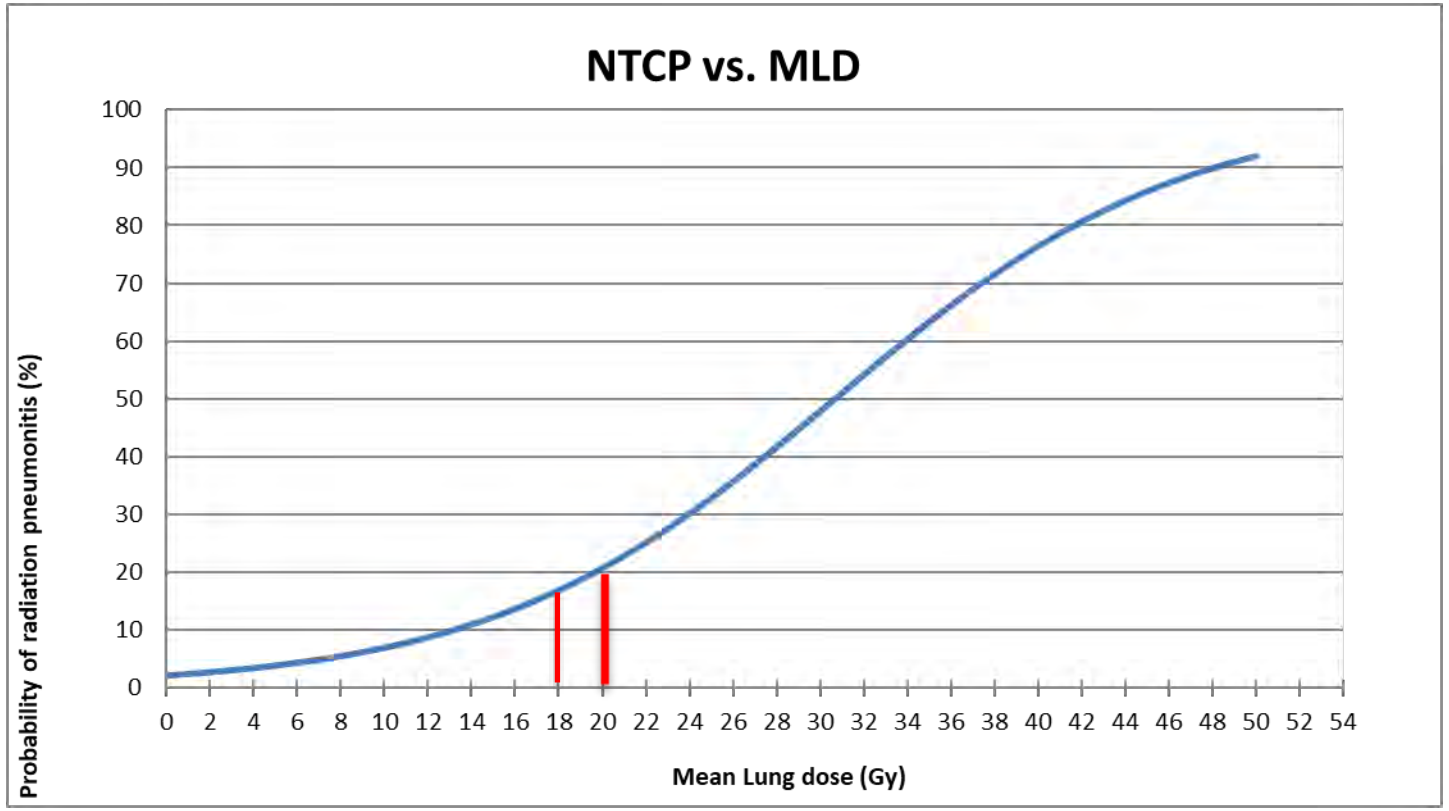


I. J. Radiation Oncology ● Biology ● Physics Volume 76, Number 3, Supplement, 2010


Symptomatic Radiation Pneumonitis
Logistic NTCP
TV50 = 46.65% (44.01-49.68)
TV20 = 37.4% (35.15-39.68)
γ = 1.72 (1.09-2.44)
12/17
9/19
5/19
4/19
1/19
TV50
TV20
Normal Tissue Complication Probability (100%)
IV20 (%)
(a)


Symptomatic Radiation Pneumonitis
Logistic NTCP
TV50 = 669.87cc (585.4-784.5)
TV20 = 317.2cc (282.98-376.84)
γ = 0.67 (0.43-0.92)
9/19
8/17
7/19
5/17
1/19
TV50
TV20
Normal Tissue Complication Probability (100%)
AIV20 (cc)
(b)

$$p = \frac{\exp(b_0 + b_1 \cdot MLD)}{1 + \exp(b_0 + b_1 \cdot MLD)}$$



The incidence of radiation pneumonitis is likely correlated with the percentage of total lung receiving greater than 20 Gy (V20)

V20 (%)	Risk of RP (%)
<25	2-4
25-37	2-12
>37	9-30

Current radiotherapy guidelines recognize mean lung dose and V20 as important dosimetric considerations and recommend a MLD < 20 Gy and V20 < 30-35% to keep risk of acute pneumonitis < 20%

Dose Constraints for Lung SBRT

Five Fraction(10Gy x 5) Based on RTOG 0813:

Heart: <15cc receives ≥32 Gy (6.4 Gy/fx); maximum point dose ≤52.5 Gy

Trachea/ipsilateral bronchus (non-adjacent wall): <4 cc receives ≥18 Gy (3.6 Gy/fx); maximum point dose ≤52.5 Gy

Great vessels (non-adjacent wall): <10 cc receives >47 Gy (9.4 Gy per fraction); maximum point dose ≤52.5 Gy

Ipsilateral brachial plexus: <3 cc receives ≥ 30 Gy (6 Gy/fx); maximum point dose ≤32 Gy (6.4 Gy per fraction)

Spinal Cord:

<0.25 cc receives≥ 22.5 Gy (4.5 Gy/fx)

<0.5 cc receives≥ 13.5 Gy (2.7 Gy/fx)]

Maximal point dose is 30 Gy (6 Gy per fraction)

Esophagus: <5 cc receives ≥27.5 Gy (5.5 Gy per fraction); maximum point dose ≤52.5 Gy

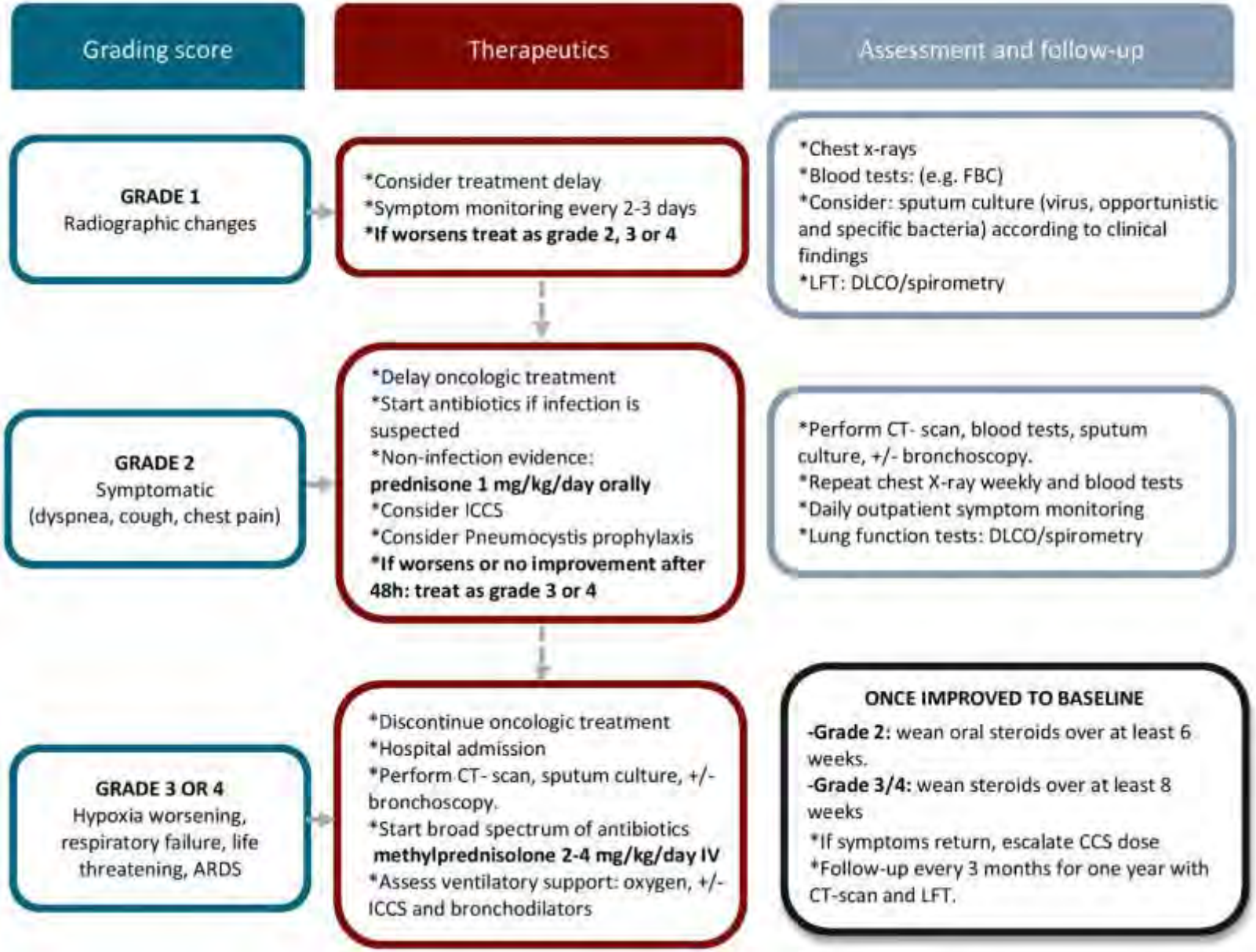
Whole lung minus GTV:

<1500 cc receives ≥12.5 Gy (2.5 Gy per fraction)

<1000 cc receives ≥13.5 Gy (2.7 Gy per fraction)

Skin: <10 cc receives ≥30 Gy (6 Gy/fx). Maximal point dose is 32 Gy (6.4Gy per fraction)

RP Management and follow-up



BMC Pulmonary Medicine volume 21, Article number: 9 (2021)

[Evidence-Based Medicine]

CHEST

Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer

CHEST Guideline and Expert Panel Report

Alex Molassiotis, RN, PhD; Jaclyn A. Smith, MBChB, PhD; Peter Mazzone, MD, MPH; Fiona Blackhall, MD, PhD; and Richard S. Irwin, MD, Master FCCP; on behalf of the CHEST Expert Cough Panel

CHEST2017;151(4):861-874

TABLE 3] Indicative Doses for Antitussives, Demulcents, and Topical Anesthetics[a]

Medication	Dosage
Simple linctus	5 mL tid or qid
Dextromethorphan	10-15 mg tid or qid (10-30 mg in some publications, maximum dose of 120 mg/d)
Codeine	30-60 mg qid
Pholcodine	10 mL qid
Morphine (Oramorph)	5 mg (single-dose trial of Oramorph; if effective 5-10 mg slow-release morphine bid)
Diamorphine	5-10 mg subcutaneously/24 hrs
Methadone linctus	Single dose 2 mg (2 mL of 1 mg/mL solution)
Dihydrocodeine[b]	10 mg tid
Hydrocodone	5 mg bid
Inhaled cromoglycate	10 mg qid
Levodropropizine[b]	75 mg tid
Moguisteine[b]	100-200 mg tid
Levocloperastine[b]	20 mg tid
Nebulized lidocaine[c]	5 mL of 0.2 tid
Nebulized bupivacaine[c]	5 mL of 0.25% tid
Benzonatate[b]	100-200 mg qid
Prednisolone	30 mg daily for 2 wk

Summary in therapy for RILI

- Without significant prospective evidence, corticosteroids are the empiric mainstay of treatment for acute pneumonitis.
- Doses typically start at 60 – 100 mg of prednisone daily and are tapered over the course of 3 – 12 weeks
- As of yet, there are no therapies found to reverse or ameliorate established radiation fibrosis

Summary in radiation lung injury

- It is a clinical syndrome that occurs on a spectrum of mild symptoms to life-threatening ARDS and can be divided into acute pneumonitis (<6 months) and chronic fibrosis (> 6 months) phases

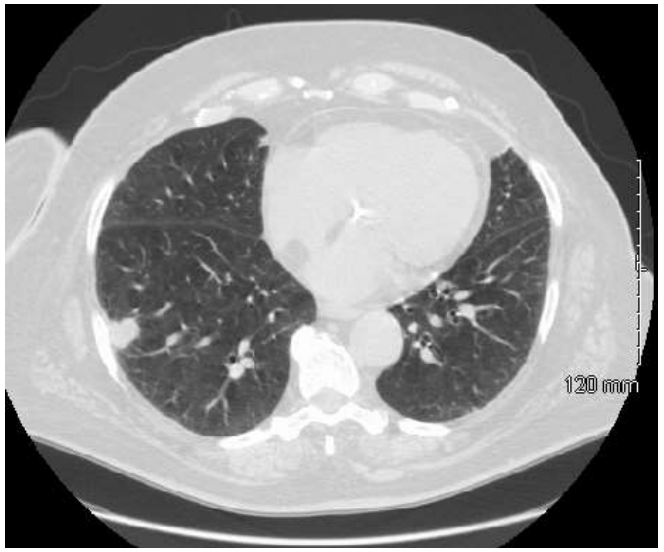
- Pneumonitis is likely the result of an abnormal healing response to ROS induced depletion of alveolar epithelium and the resultant inflammatory infiltrate. This is further exacerbated and perpetuated by chronic hypoxia.

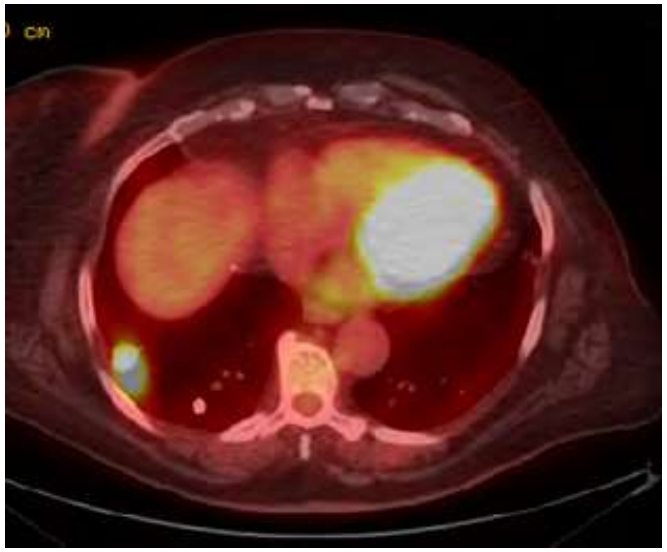
Summary in radiation lung injury

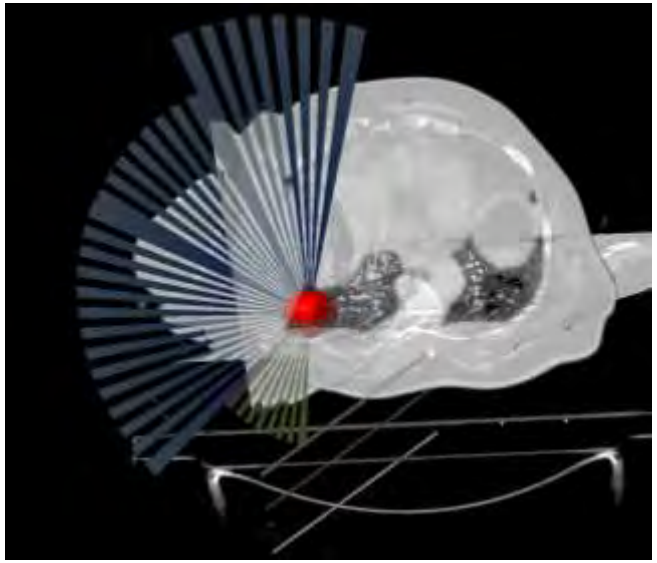
- Fibrosis results from TGFB induced fibroblast proliferation and activation incurred during the exaggerated inflammatory response.
- Agents such as amifostine, ACE inhibitors, pentoxifylline, TKI have been variably successful in preventing/mitigating radiation induced lung injury
- Corticosteroids (prednisone) are the empiric treatment of choice for pneumonitis, without significant supporting data. There are no current effective therapies for radiation fibrosis.
- Patient and treatment factors play a role in the risk of RILI
- Careful radiation planning is critical

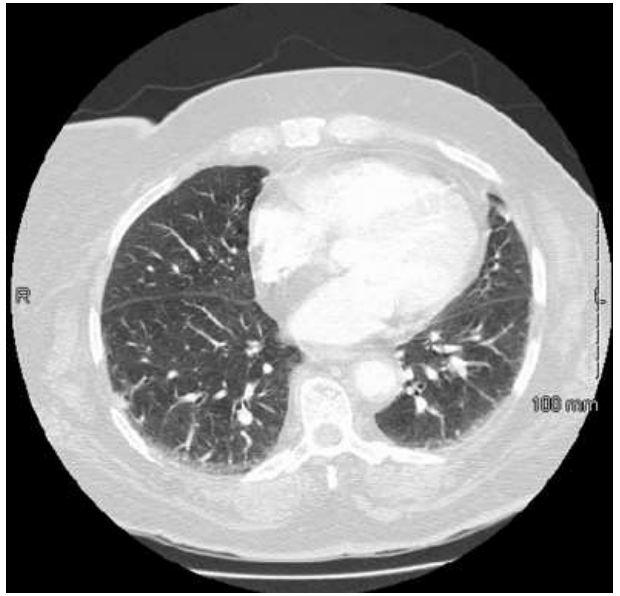
Follow up can be challenging after SBRT

- Tumor regression can take long time to occur
- Post SBRT fibrosis can complicate the interpretation of follow up imaging



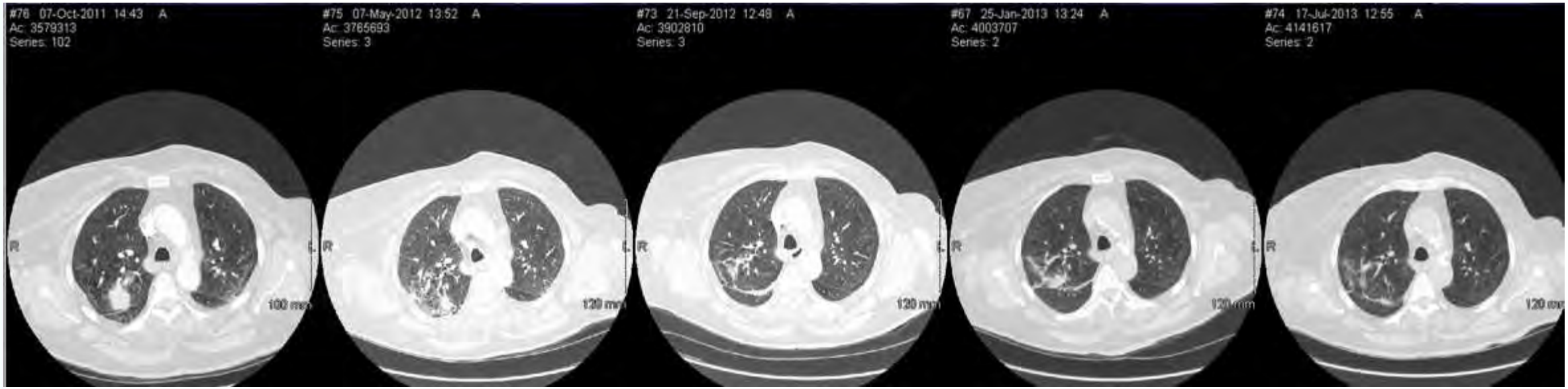


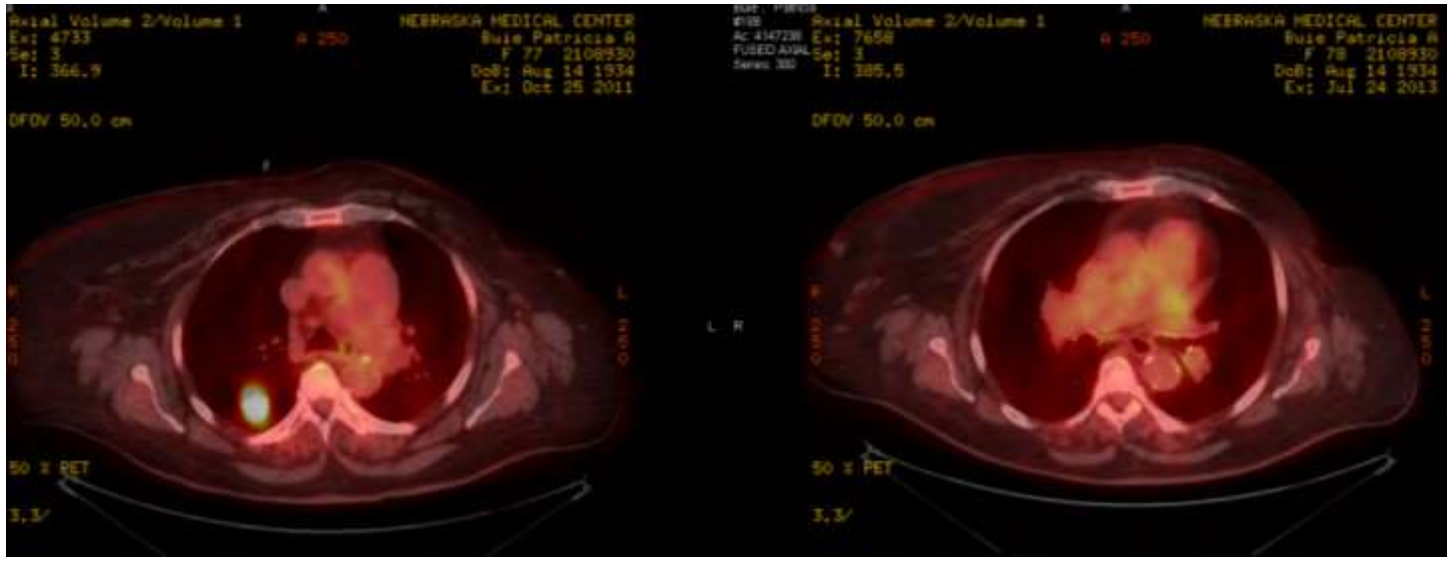




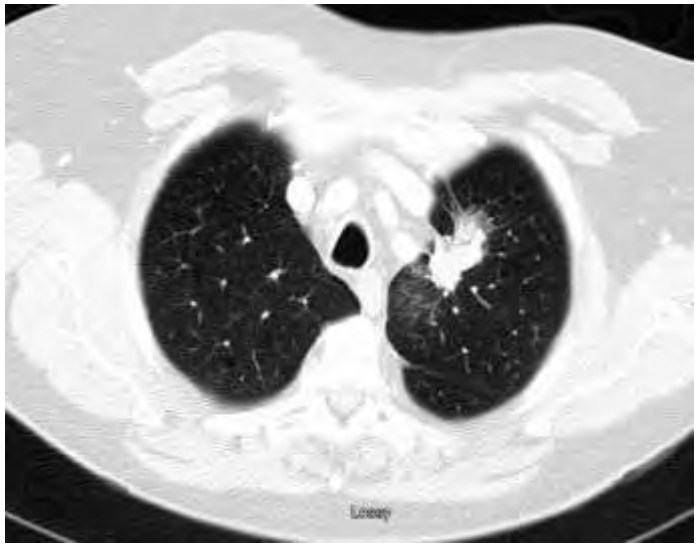
2 years post SBRT

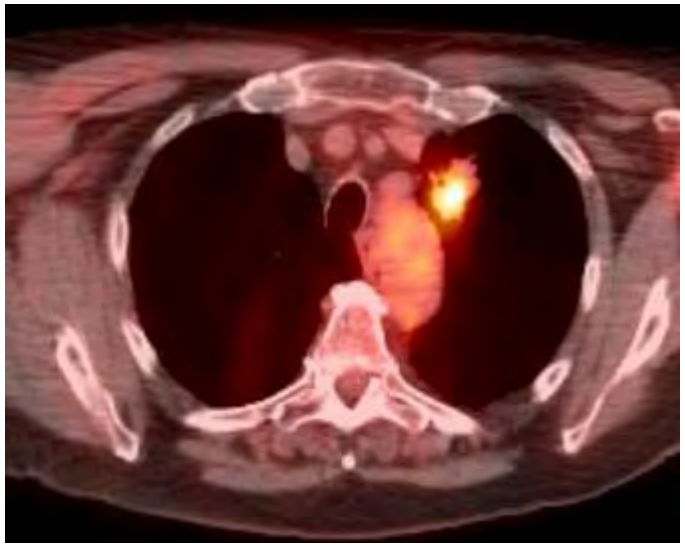
Prior to SBRT | 6 month post SBRT | 10 month post SBRT | 20 month post SBRT | 2 years post SBRT



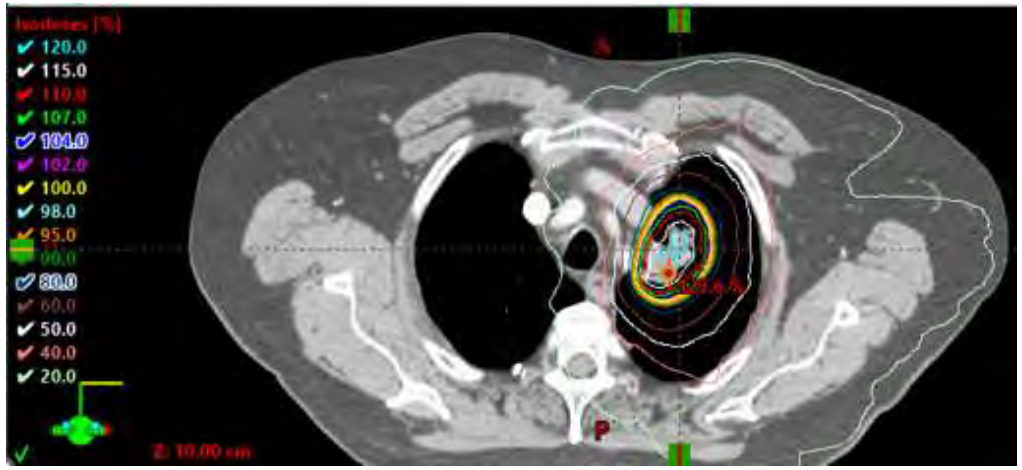


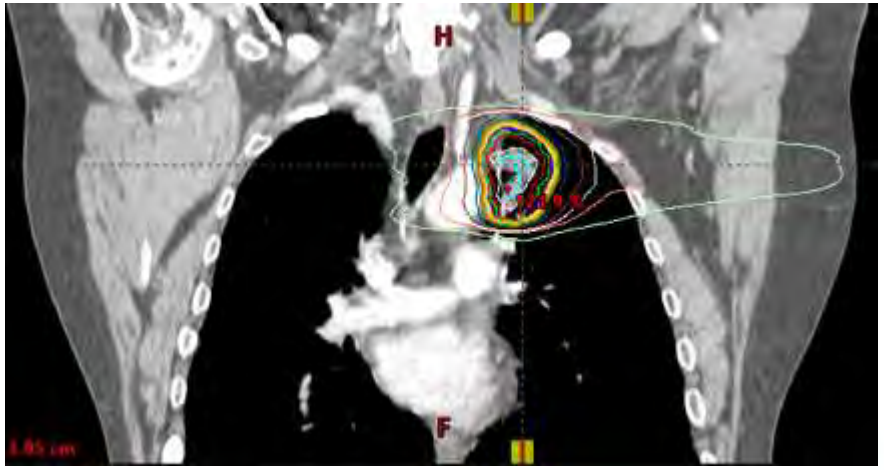
T2N0M0 Squamous cell carcinoma



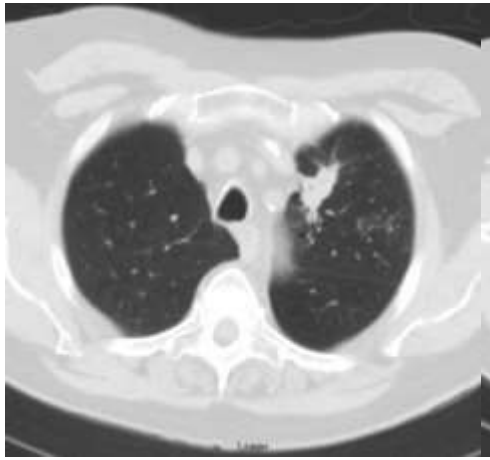


50Gy in 5 fractions SBRT

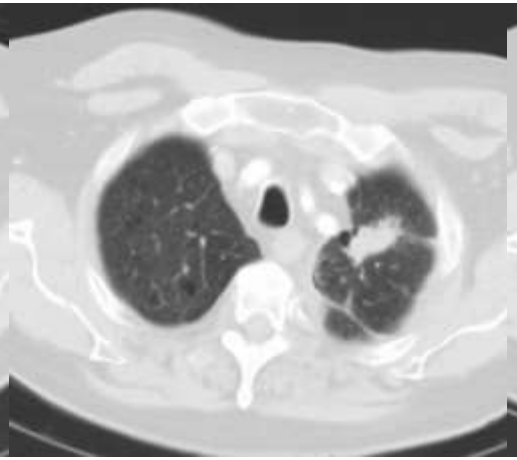




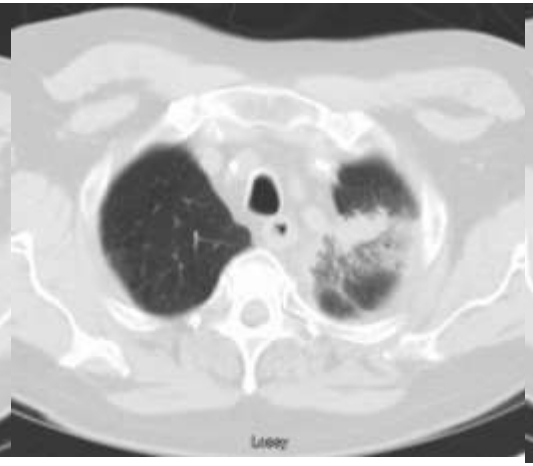
3 months



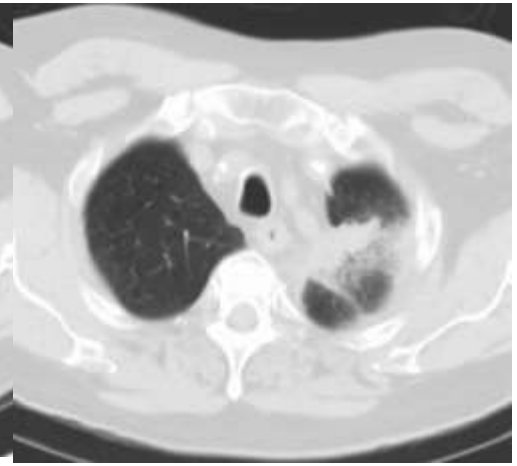
6 months



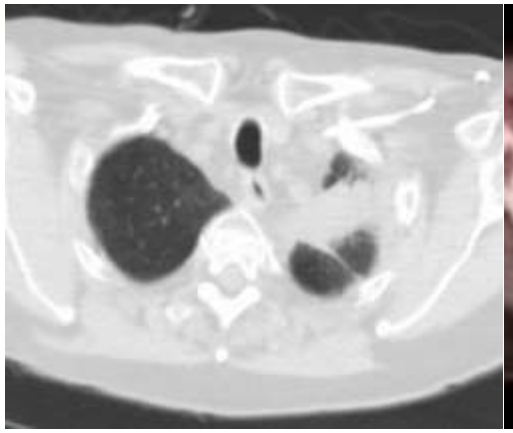
9 months

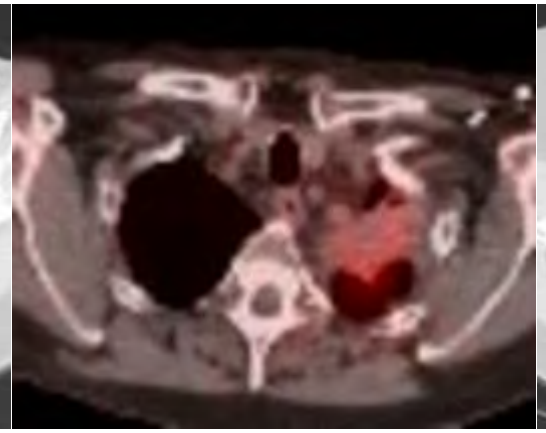


12 months



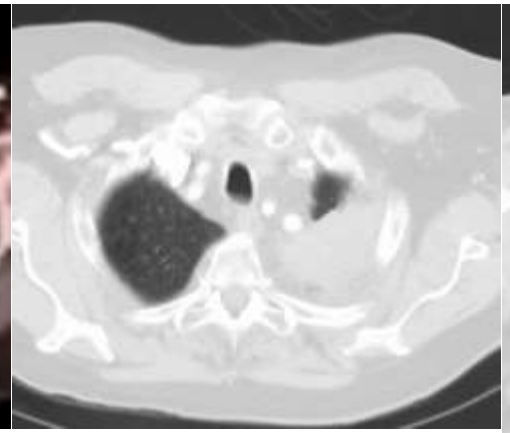
15 months

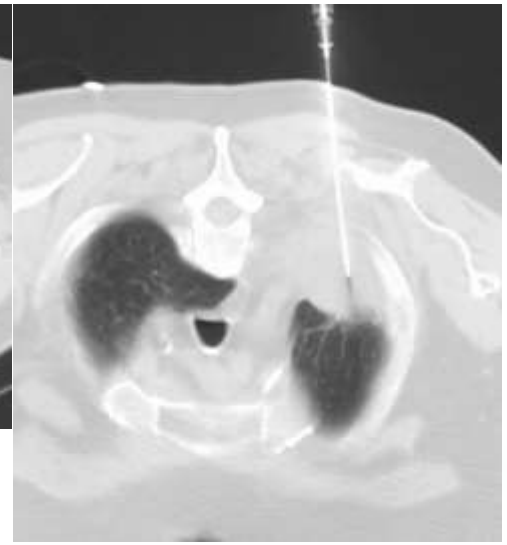




SUV 2.3, previously 4.7

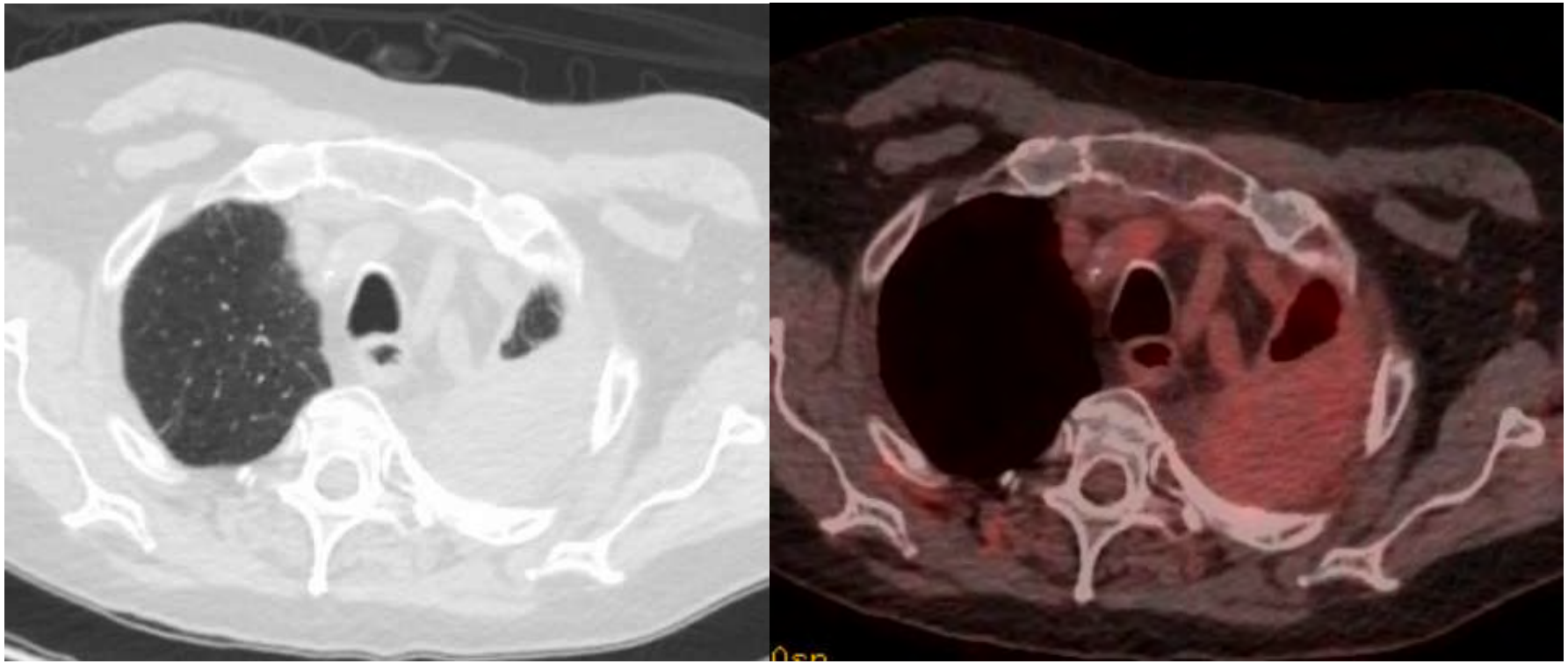
21 months





FOCI OF SCARRING AND MILD INFLAMMATION
NEGATIVE FOR MALIGNANCY

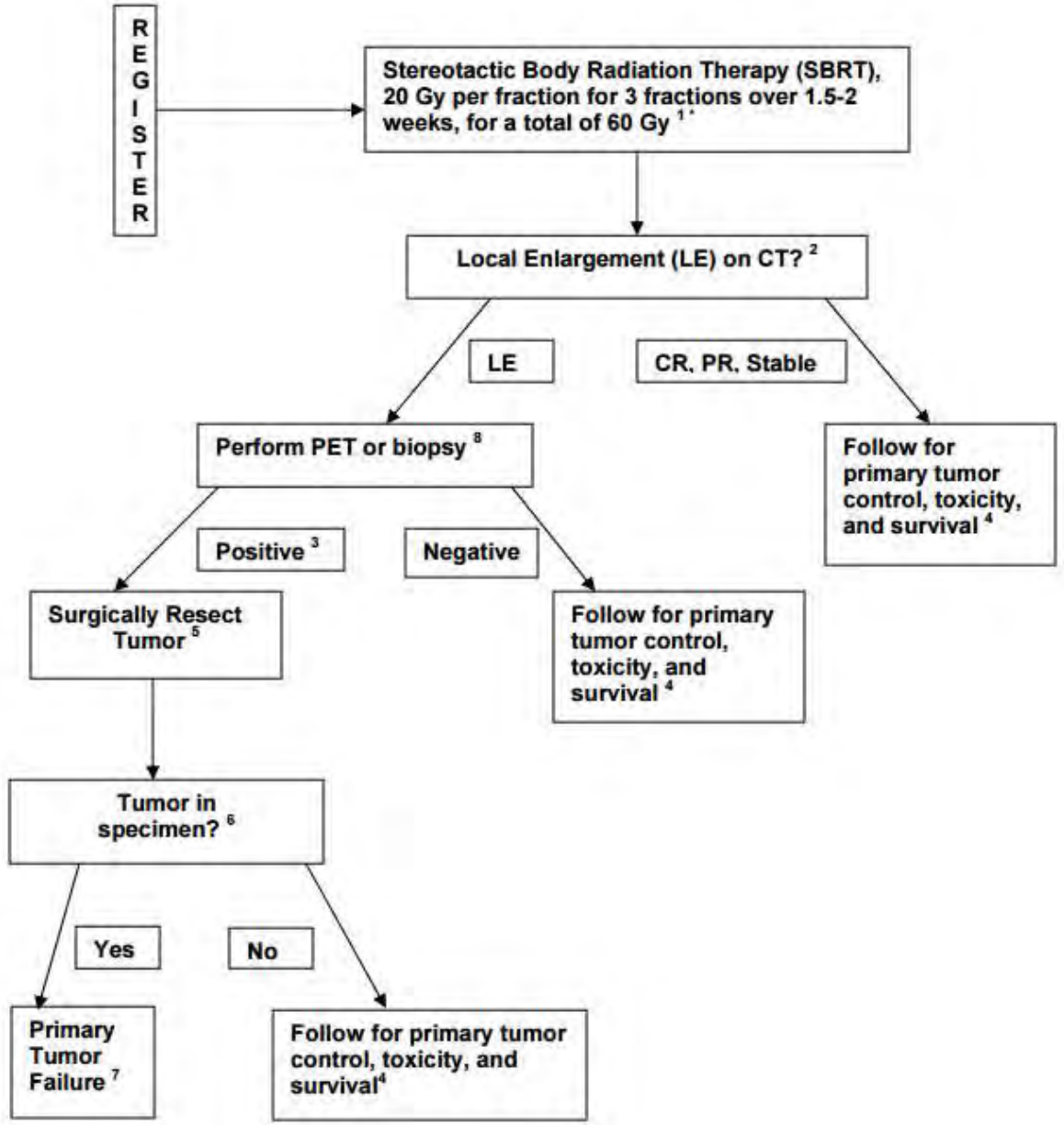
5 years post SBRT

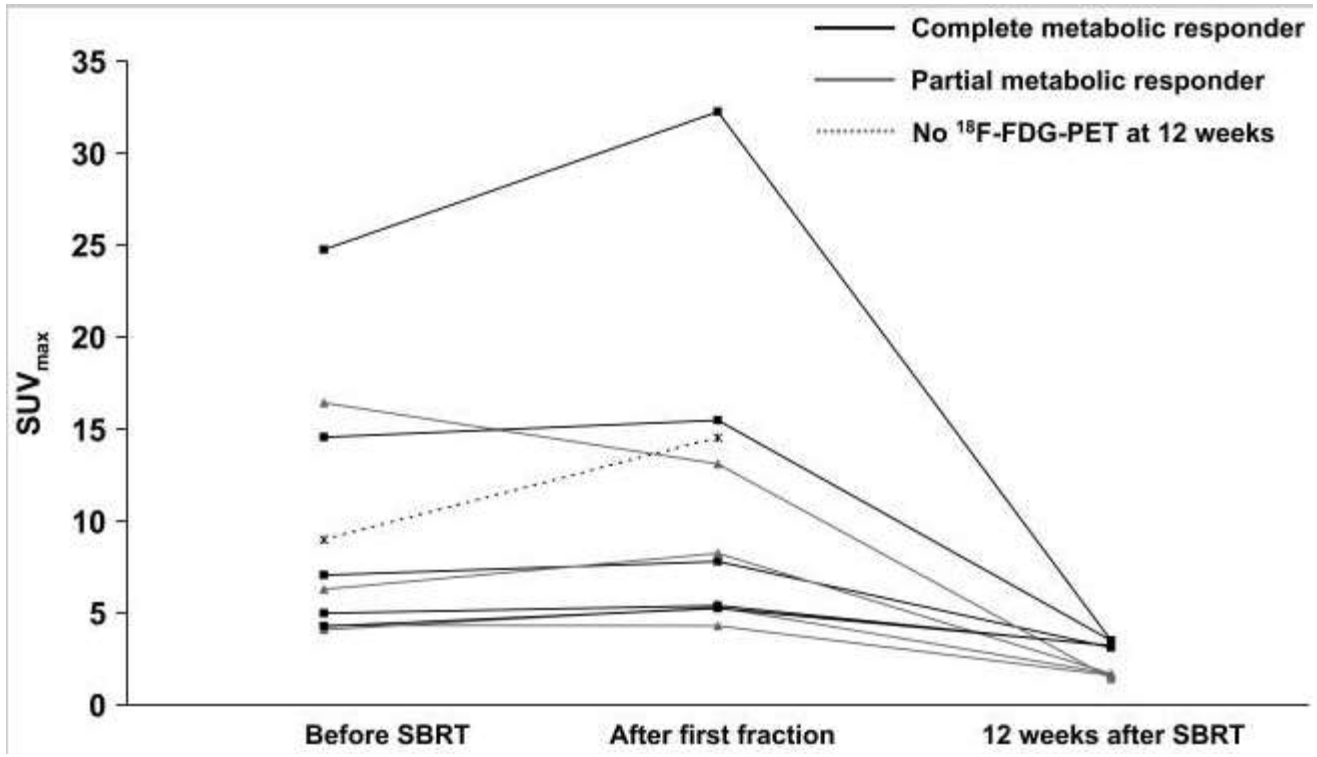


In general, pulmonary fibrosis typically develops between 6 and 24 months post-irradiation and stabilizes after 2 years

RTOG 0618

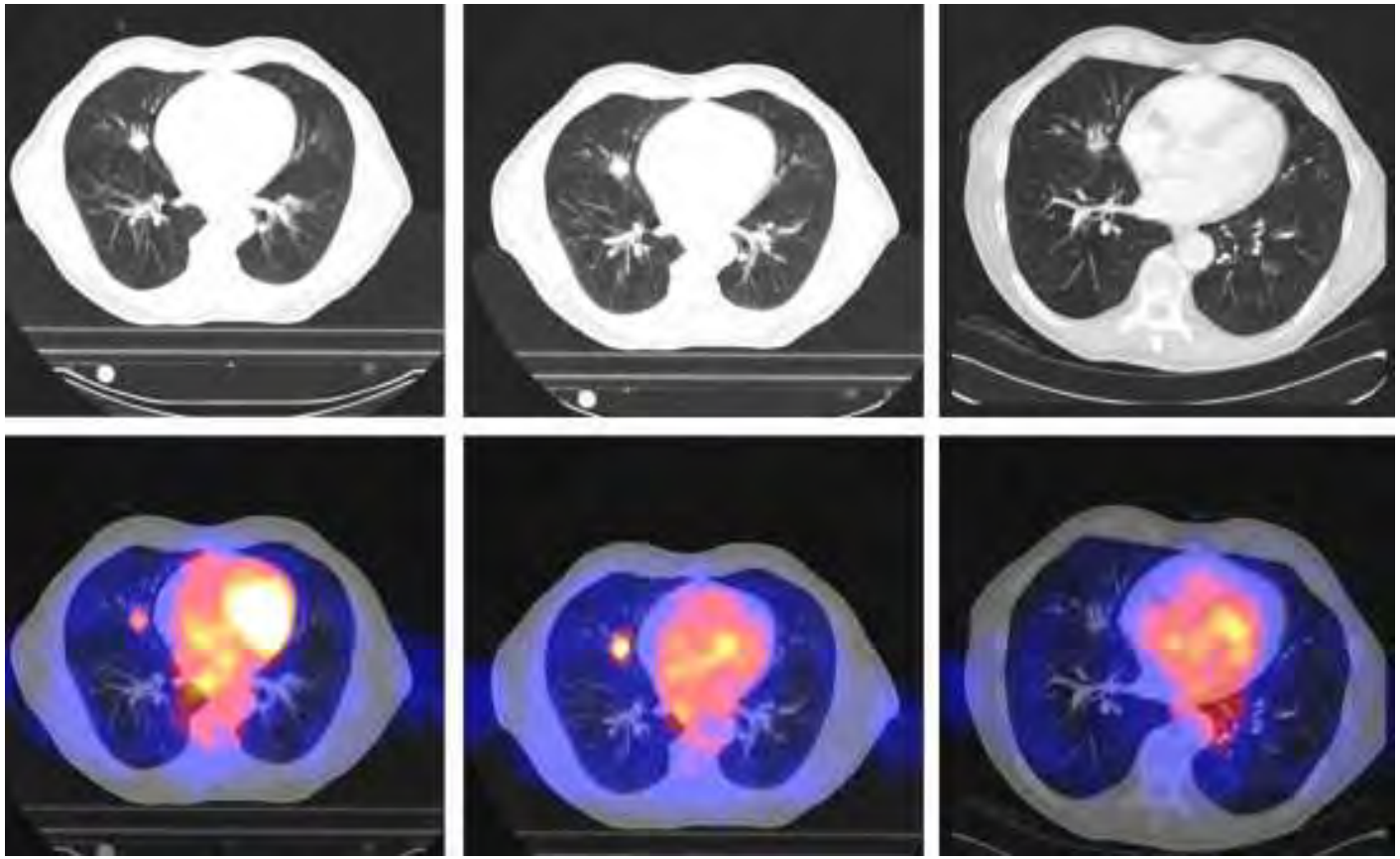
A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer





Absolute SUVmax before, after the first fraction and 12 weeks after completion of SBRT. SUVmax increased after the first fraction ($p = 0.07$) and decreased significantly 12 weeks after SBRT ($p = 0.008$)

Eur J Nucl Med Mol Imaging. 2011 38-38(6): 1059–1063.



Sequential axial PET (upper row), CT (middle row) and fused PET/CT (lower row) images of patient 3, before (a), after the first fraction (b) and 12 weeks after SBRT (c). SUVmax increased from 6.3 to 8.3 after the first fraction. At 12 weeks SUVmax decreased to 1.3 (CMR) and was considered a partial response according to RECIST criteria

Eur J Nucl Med Mol Imaging. 2011 38-38(6): 1059–1063.

Follow-up

Definition of local control?

- CT scan every 3-4 months for 1-2 year, then every 6 months
- PET scan only when progressive consolidation on CT within or adjacent to tumor
- If PET uptake similar to pre-SBRT scan is considered as recurrent disease
- Otherwise continue to follow as NED

Definition of metabolic response according to EORTC criteria

Response	Definition
CMR	Complete resolution of FDG uptake in tumour, not distinguishable from surrounding tissue
PMR	Reduction of more than 25% in SUV
SMD	Changes of less than 25% in SUV
PMD	Increase of SUV of more than 25% or new (metastatic) lesions

CMR complete metabolic response, PMR partial metabolic response, SMD stable metabolic disease, PMD progressive metabolic disease

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Thank you!