MAYO CLINIC | Department of Radiation Oncology

Choosing Between Surgery and Stereotactic Body Radiation for Patients with Early-Stage Non-Small Cell Lung Cancer

Terence Tai-Weng Sio, MD, MS (Radiation Oncology)
Professor and Consultant, Mayo Clinic College of Medicine
Mayo Clinic Arizona

19th Annual Midwest Thoracic and GI Oncology Conference
UNO Scott Conference Center
University of Nebraska Medical Center
6450 Pine St, Omaha, Nebraska
October 31, 2024, 11:15 AM-Noon

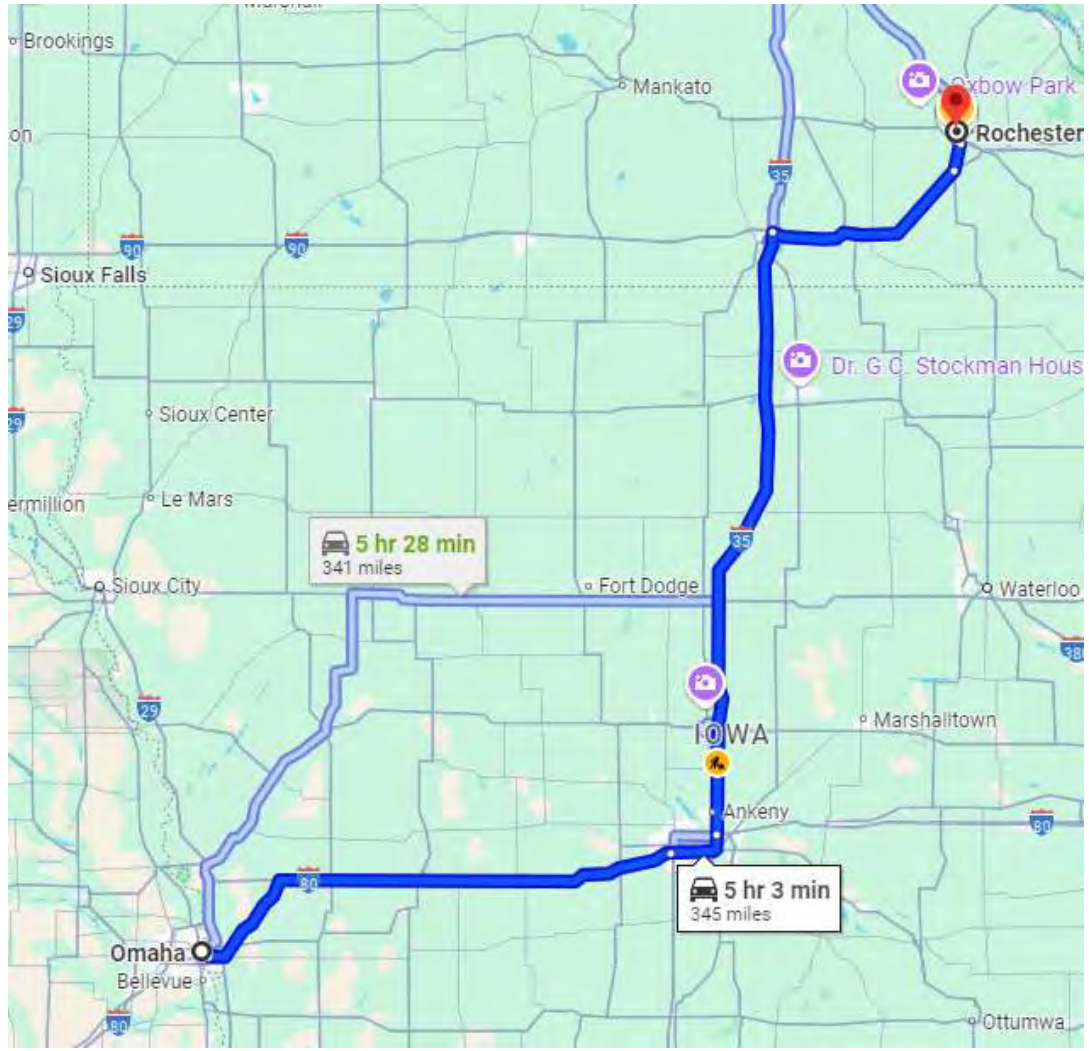
Conflicts of Interest

- **Novocure, Inc.** – Advisory Board; Speaker's Bureau
- **Galera Therapeutics, Inc.** – Advisory Board
- **Catalyst Pharmaceuticals, Inc.** – Advisory Board
- **American Board of Radiology** – Examiner
- **American College of Radiology** – Education Chair, Councilor (CARROS)
- **American Society of Radiation Oncology** – Vice Chair, Payer Relations Committee
- Senior Associate Editor, Education Editor, **Advances in Radiation Oncology** *Journal* (ASTRO)
- None above related to any of the topics today
- No off-label use will be discussed today

LEARNING OBJECTIVES

- Roles of Surgery and Radiation Therapy in Early-stage NSCLC and metastases
- Rationale and Clinical Applications for SBRT
- Technical and Dosimetric Considerations
- Future Directions
- Open Discussion; Questions and Answers

Mayo Clinic Rochester (Minnesota) – 2011-2015


Brookings
Mankato
Oxbow Park
Rochester
Sioux Falls
Dr. G C. Stockman Hous
Sioux Center
Le Mars
5 hr 28 min
341 miles
Sioux City
Fort Dodge
Waterloo
IOWA
Marshalltown
Ankeny
5 hr 3 min
345 miles
Omaha
Bellevue
Ottumwa

Mayo Clinic Cancer Center (Arizona) – Since 2016

Estimated New Cases

Males			Females		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All Sites	**983,160**	**100%**	**All Sites**	**934,870**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**	**All Sites**	**287,270**	**100%**

Cancer Statistics, 2023

Growing Population of Survivors

Figure 1. Estimated Number of US Cancer Survivors by Site as of January 1, 2022

Male		Female	
Prostate	3,523,230	Breast	4,055,770
Melanoma of the skin	760,640	Uterine corpus	891,560
Colon & rectum	726,450	Thyroid	823,800
Urinary bladder	597,880	Melanoma of the skin	713,790
Non-Hodgkin lymphoma	451,370	Colon & rectum	710,670
Kidney & renal pelvis	376,280	Non-Hodgkin lymphoma	394,180
Oral cavity & pharynx	311,200	Lung & bronchus	367,570
Testis	303,040	Uterine cervix	300,240
Leukemia	300,250	Ovary	246,940
Lung & bronchus	287,050	Kidney & renal pelvis	230,960
All sites	**8,321,200**	**All sites**	**9,738,900**

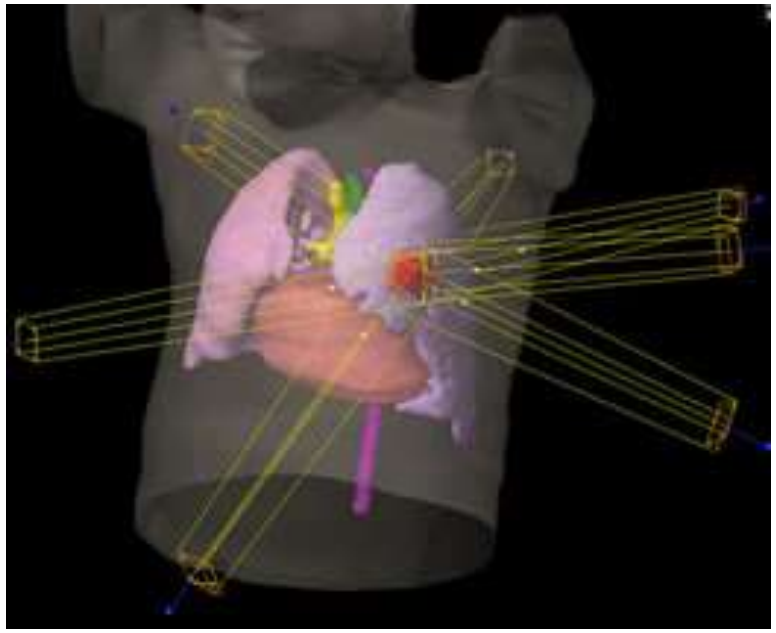
Estimates do not include in situ carcinoma of any site except urinary bladder and do not include basal cell or squamous cell skin cancers. Estimates should not be compared to previous years because they are model-based projections. (See Sources of Statistics, page 36).

Source: Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

Cancer Treatment & Survivorship Facts & Figures 2022-2024

Stereotactic Body Radiotherapy (SBRT) for Lung Tumors

- 20-year history in development
- SBRT offers durable local control and prevent morbidities
- Steep dose gradient; multi-beam angles
- The technical requirements are high
- Highly rewarding for the modern RT center
- Treatment course is shorter



SBRT vs. SABR?

- **Stereotactic Ablative Radiotherapy (SABR)**

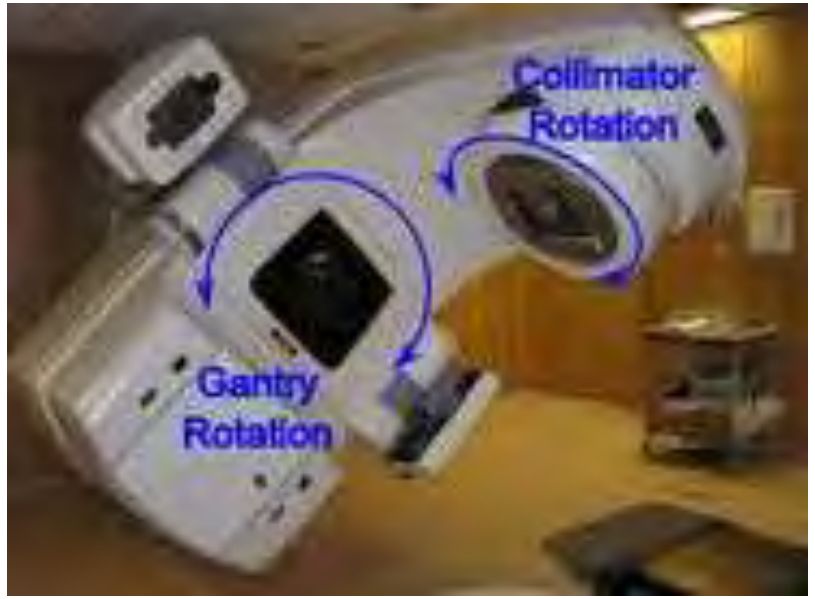
Roger Federer Hit 3 New Shot "SABR"

"Sudden/Sneaky" Attack by Roger

Traditional External Beam RT (X-ray)

Linear Accelerator (Linac)

- Delivers high energy X-rays (photons) or electrons
- Non-invasive
- Rapid treatment delivery, in minutes



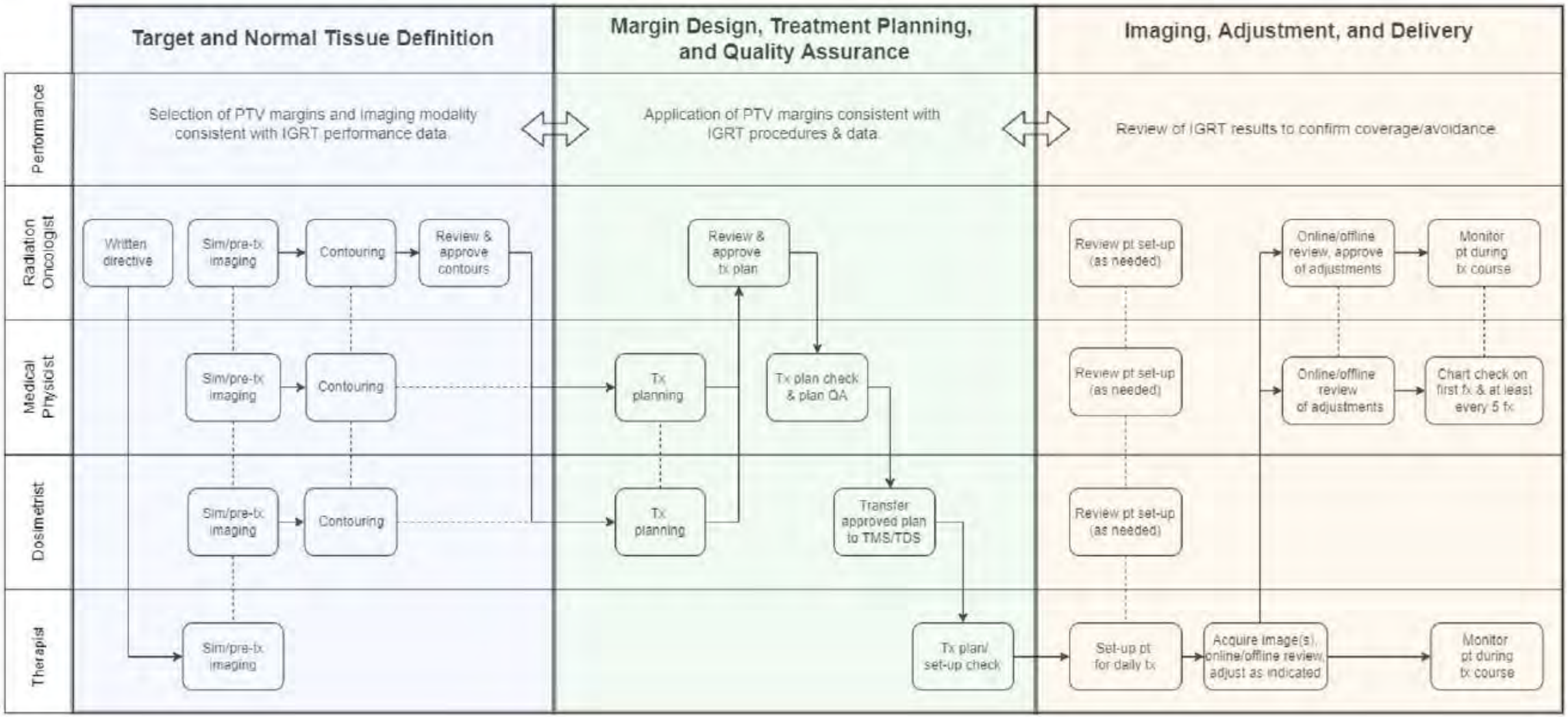


Figure 1 Sample IGRT process pathway. *Abbreviations:* fx = fraction; IGRT = image guided radiation therapy; pt = patient; PTV = planning target volume; QA = quality assurance; sim = simulation; TDS = treatment delivery system; TMS = treatment management system; tx = treatment.

Qi X, Sio TT et al. ASTRO IGRT Safety White Paper. PRO Sep 2022

Thoracic SBRT - Workup

- Is considered for early-stage lung cancer and pulmonary metastases
- Work-up
  - CT chest with IV contrast
  - PET/CT scan
  - Brain MRI (symptoms/stage II NSCLC)
- Tissue biopsy (usually)
- Pulmonary function testing
- Mediastinal sampling? Institution dependent

Operability influences SBRT decision

- ACOSOG Criteria
  - ≥ 1 Major
  - ≥ 2 Minors
- By FEV1
  - ≥ 2L: Pneumonectomy
  - ≥ 1.2L: Lobectomy
  - ≥ 0.7L: Wedge
- Discuss with surgeon

Major criteria
- $FEV_1 \leq 50\%$ predicted
- $DL_{CO} \leq 50\%$ predicted

Minor criteria
- Age ≥ 75 years
- FEV_1 51% to 60% predicted
- DL_{CO} 51% to 60% predicted
- Pulmonary hypertension (defined as a pulmonary artery systolic pressure > 40 mmHg) as estimated by echocardiography or right heart catheterization
- Poor left ventricular function (defined as an ejection fraction of ≤ 40%)
- Resting or exercise arterial $Po_2 \leq 55$ mmHg or $Spo_2 \leq 88\%$
- $Pco_2 > 45$ mmHg
- Modified Medical Research Council Dyspnea Scale ≥ 3

Fernando HC et al. J Clin Oncol. 2014 Aug 10;32(23):2456-62

High-risk COPD patients: outcome limited regardless of modality

First author	Age (Med or Mean)	30-day mortality	Complications	Follow-up (y) (med)	Median OS (y)	1-yr OS	3-yr OS	5-yr OS
Surgery								
Magdeleinat	62	8%*	>90% ICU stay	3.4†	4.2	84%*	63%*	44%
			>45% with complications	4.7†				
Lau	69	25% (open lobectomy)*, 7% (segmentectomy or VATS)*	Median hospital stay: 8–12 days; <10% admitted to ICU	Segmentectomy or VATS:	5.5*	86%*	66%*	50%*
				Open lobectomy:	0.8*	45%*	31%*	8%*
SBRT								
Henderson	70.5	0%*	~8% Grade 3	2.2†	1.6	91%*	43%*	
Stephans	74	0%*	0 Grade 3+ pneumonitis	1.5†	Not reached*	95%*	70%*	
Palma	70	0%	3% Grade 3	1.7	2.7	79%	47%	28%

Adapted from Palma D et al. Int J Radiat Oncol Biol Phys. 2012 Mar 1;82(3):1149-56 and 2017 ASTRO Refresher Course

SBRT vs. Surgery

SBRT vs. Surgery – Retrospective Data

- More than 20 studies reported
  - 12 found no difference; 8 favored surgery
- Usually stacked against radiotherapy
  - NCDB analysis (Median age: surgery 67.9; SBRT 74.7) - Puri V et al. J Thorac Oncol. 2015 Dec
- SEER Database - Shirvani et al. JAMA Surg.2014 Dec
  - No difference after propensity score matching
- The controversy will likely persist as patients may not be willing to get randomized

SBRT vs. Surgery – Operable Patients

- Patient outcomes are generally better due to a lesser degree of commodities
- RTOG: 2-year tumor control = 93%
- Surgery is still gold standard

Table 1 Single and multi-institutional series of operable patients treated with SBRT

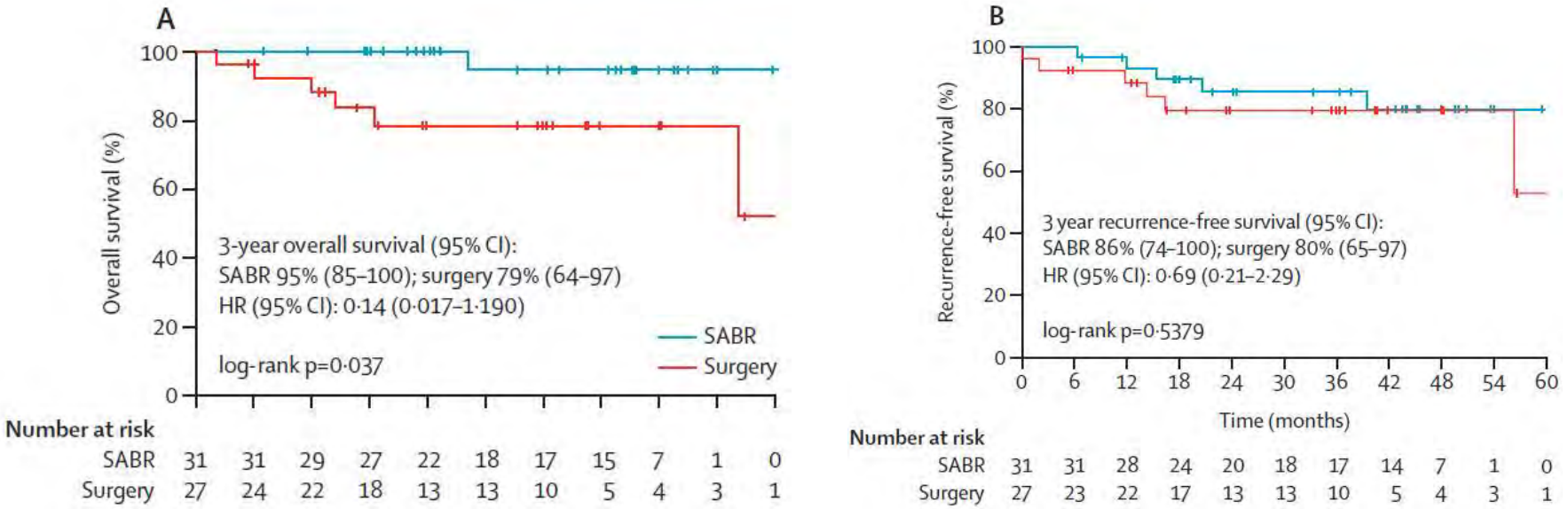
Author	Medically operable patients treated with SBRT				
	Design	Patients	2y OS (%)	3y OS (%)	5y OS (%)
STARS and ROSEL (4)	Randomized	58		95	
National Defense Medical College, Tokozawa, Japan, Single Institution [2001] (42)	Retrospective	29		86	
VU University, Single Institution [2012] (43)	Retrospective	177		85	
JCOG 0403 [2015] (44,45)	Prospective phase II	64		76	
RTOG 0618 [2013] (46)	Prospective phase II	26	84	77	
Japanese Multi-Institutional [2011] (47)	Retrospective	87		80	72
Japanese Multi-Institutional [2015] (6)	Retrospective	661		80 (IA); 77 (IB)	

SBRT, stereotactic body radiotherapy; OS, overall survival; RTOG, Radiation Therapy Oncology Group.

Moghanaki D and Chang JY. Transl Lung Cancer Res. 2016 Apr;5(2):183-9

SBRT vs. Surgery in Operable Patients

- Pooled analysis of 2 randomized trials (58 pts)
  - STARS/ROSEL
- 3-yr OS 95 vs. 79% (P=0.04); 3-yr RFS 86 vs. 80% (P=0.54)
- LC: Equally excellent (90-95%)
- QoL was better for SBRT patients (Radiotherapy oncology 2015)



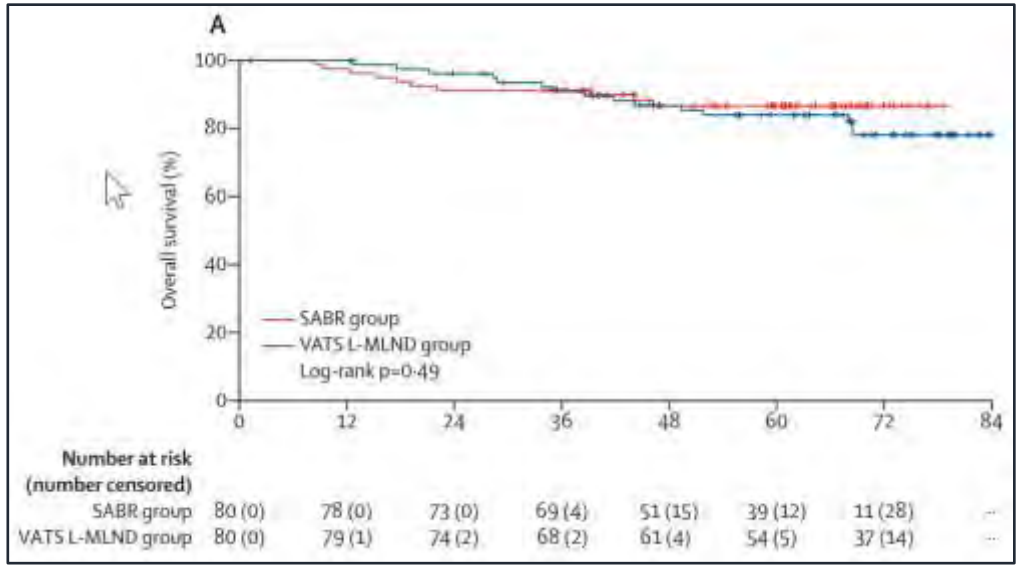
Chang JY et al. Lancet Oncol.2015 Jun;16(6):630-7.

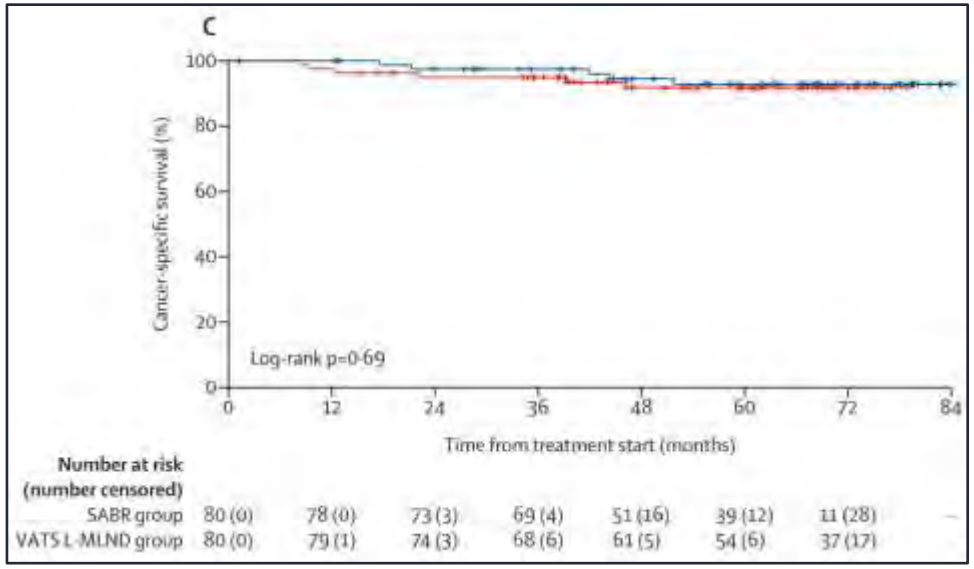
Updated Results from Revised STARS Trial

Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery

*Joe Y Chang, Reza J Mehran, Lei Feng, Vivek Verma, Zhongxing Liao, James W Welsh, Steven H Lin, Michael S O'Reilly, Melenda D Jeter, Peter A Balter, Stephen E McRae, Donald Berry, John V Heymach, Jack A Roth, on behalf of The STARS Lung Cancer Trials Group**

Lancet Oncol 2021; 22: 1448–57





Common SBRT Fractionation - Lung

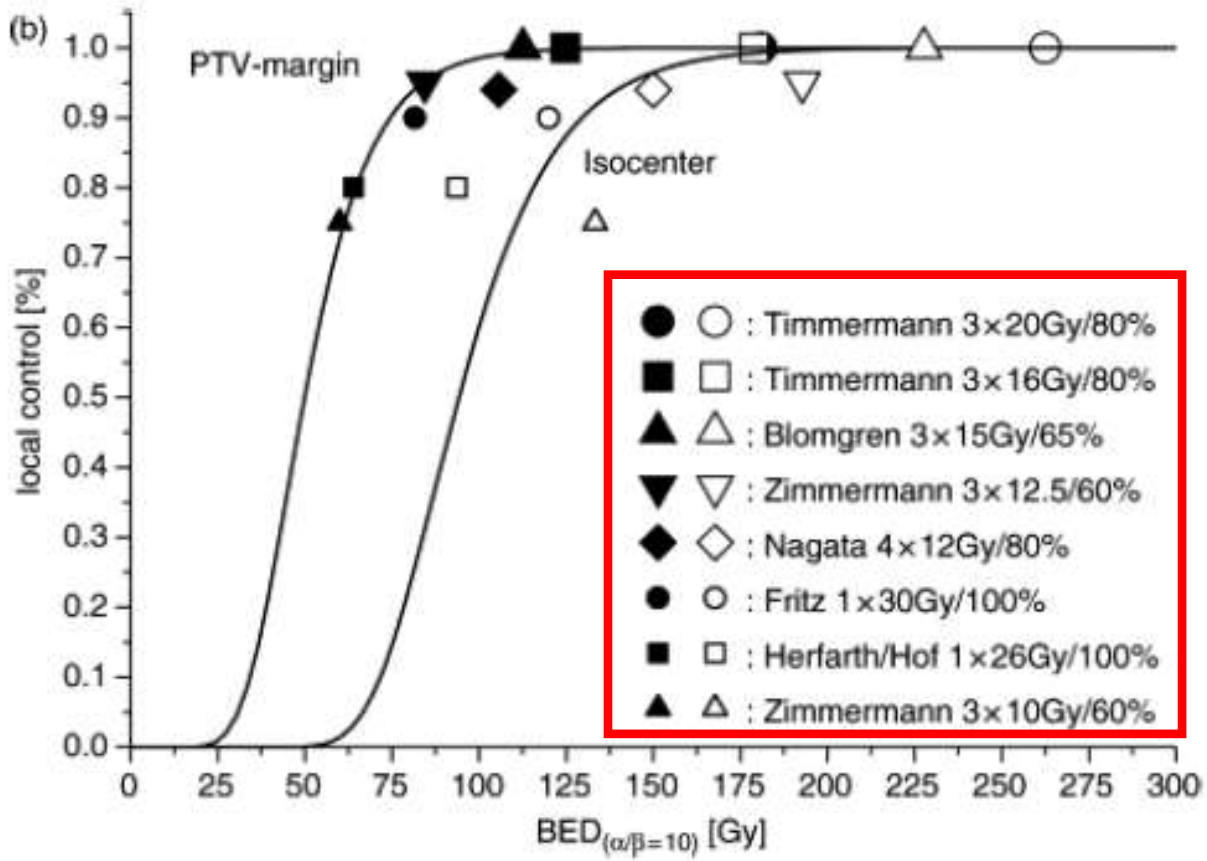
Table 1. Selected Prospective Trials Investigating the Use of Stereotactic Ablative Radiosurgery in Early-Stage Non-Small Cell Lung Cancer

Reference	Dose/Fraction #	Local Control	Overall Survival
Nagata et al, Kyoto University, Japan[50]	48 Gy/4	94% (3 year)	72-83% (3 year)
Hara et al, Tokyo, Japan[51]	30–34 Gy/1	78% (2 year)	41% (2 year)
Xia et al, Beijing, China[52]	50 Gy/10	95% (3 year)	91% (3 year)
Fakiris et al, Indiana University, USA[47]	60–66 Gy/3	88.1% (3 year)	42.7% (3 year)
Lagerwaard et al, VU University Medical Center, Netherlands[48]	60 Gy/3–8	97% (2 year)	64% (2 year)
Baumann et al, Karolinska University Hospital, Sweden[49]	45 Gy/3	92% (3 year)	60% (3 year)
RTOG 0236 Timmerman et al, Multi-Institution, USA[53]	54 Gy/3	98% (2 year)	56% (3 year)

- **My own practice (TTS) is usually 50/5 and 48/4; 34/1 (NRG), 54/3 (Indiana), 60/5 (UTSW), 70/10 (MDACC), 60/8 (Dutch), and 60/15 (NCIC) can also be considered**

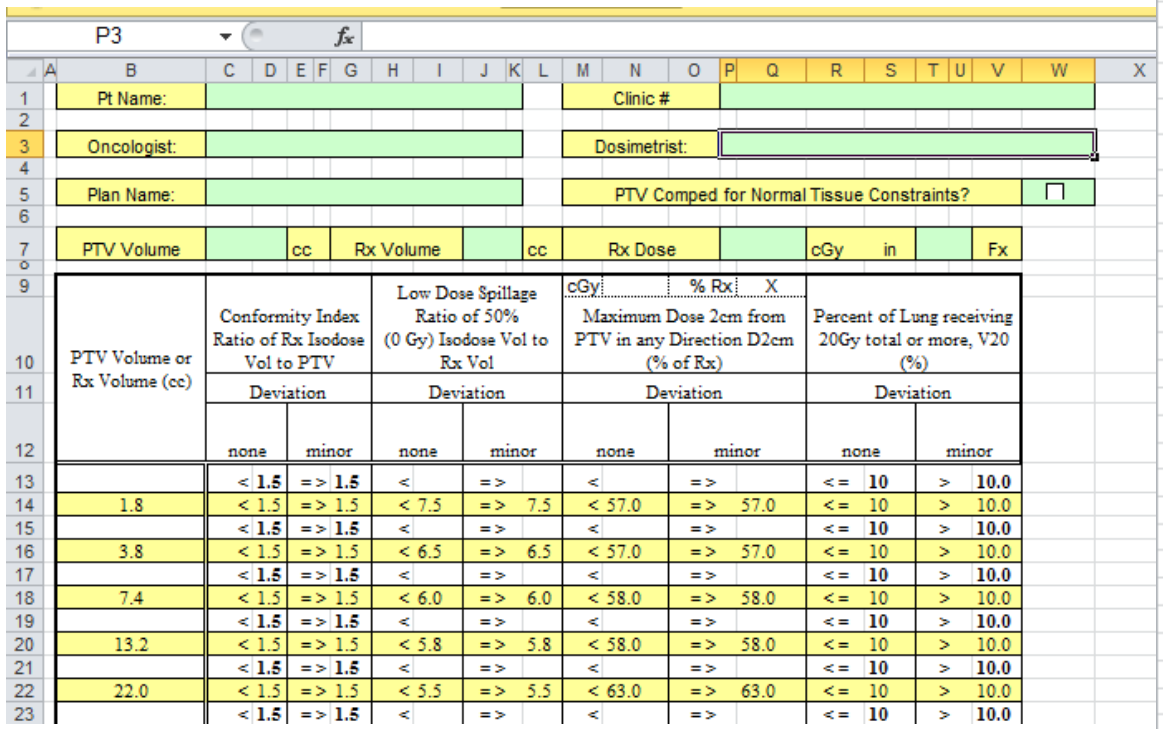
Goal of SBRT Dosing - BED > 100 Gy

- At margin of tumor/PTV- regarded as “tumoricidal”



Wulf J et al. Radiother Oncol. 2005 Oct;77(1):83-7
Onishi H et al. J ThoracOncol.2007 Jul;2(7 Suppl 3):S94-100

Dose Fall-off Calculation (Mayo)



P3

	Pt Name:											Clinic #												
	Oncologist:											Dosimetrist:												
	Plan Name:											PTV Comped for Normal Tissue Constraints?												
	PTV Volume			cc		Rx Volume			cc			Rx Dose			cGy		in			Fx			

PTV Volume or Rx Volume (cc)	Conformity Index Ratio of Rx Isodose Vol to PTV				Low Dose Spillage Ratio of 50% (0 Gy) Isodose Vol to Rx Vol				cGy	% Rx	X	Maximum Dose 2cm from PTV in any Direction D2cm (% of Rx)				Percent of Lung receiving 20Gy total or more, V20 (%)			
	Deviation				Deviation							Deviation				Deviation			
	none		minor		none		minor					none		minor		none		minor	
	<	**1.5**	=>	**1.5**	<		=>					<		=>		<=	**10**	>	**10.0**
1.8	<	1.5	=>	1.5	<	7.5	=>	7.5				<	57.0	=>	57.0	<=	10	>	10.0
	<	**1.5**	=>	**1.5**	<		=>					<		=>		<=	**10**	>	**10.0**
3.8	<	1.5	=>	1.5	<	6.5	=>	6.5				<	57.0	=>	57.0	<=	10	>	10.0
	<	**1.5**	=>	**1.5**	<		=>					<		=>		<=	**10**	>	**10.0**
7.4	<	1.5	=>	1.5	<	6.0	=>	6.0				<	58.0	=>	58.0	<=	10	>	10.0
	<	**1.5**	=>	**1.5**	<		=>					<		=>		<=	**10**	>	**10.0**
13.2	<	1.5	=>	1.5	<	5.8	=>	5.8				<	58.0	=>	58.0	<=	10	>	10.0
	<	**1.5**	=>	**1.5**	<		=>					<		=>		<=	**10**	>	**10.0**
22.0	<	1.5	=>	1.5	<	5.5	=>	5.5				<	63.0	=>	63.0	<=	10	>	10.0
	<	**1.5**	=>	**1.5**	<		=>					<		=>		<=	**10**	>	**10.0**

126.0	<	1.5	=>	1.5	<	4.0	=>	4.0	<	91.0	=>	91.0	<=	10	>	10.0
	<	**1.5**	=>	**1.5**	<		=>		<		=>		<=	**10**	>	**10.0**
163.0	<	1.5	=>	1.5	<	3.7	=>	3.7	<	94.0	=>	94.0	<=	10	>	10.0

Conformity Index

0.00 cc = Volume of Rx Dose in Body
cc = Volume of PTV (or Rx Volume)
= Ratio a/b

Low Dose Spillage

0.00 cc = Vol of tissue in Body receiving 50%of Rx at cGy
cc = Volume of PTV (or Rx Volume)
= Ratio of Volume receiving 50%Rx to PTV (or Rx Volume)

Maximum Dose 2 cm from PTV

0 cGy = Max Dose 2cm from PTV in any direction

Percent of Lung Dose

0.00 % of Total Lung = 2000 cGy (V20)

PTV Coverage

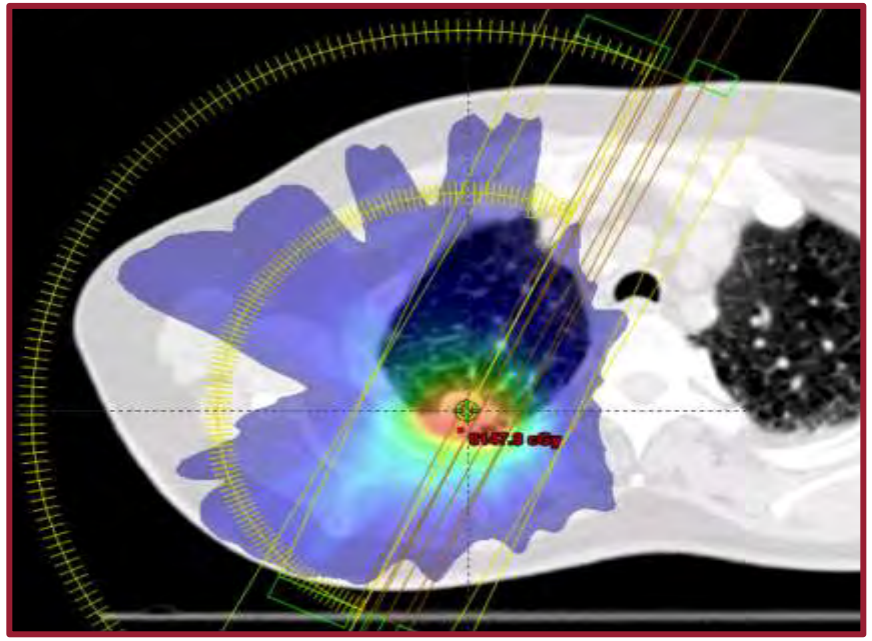
0.00 % of PTV Getting cGy (Rx Dose)
0.00 % of PTV Getting cGy (90% of Rx Dose)
0.00 % Isodose Line (when PTVcom = Rx Dose without plan normalization)

High Dose Spillage: (Body minus PTV)

0.00 cc = Vol of tissue outside Rx vol at cGy (105% of Rx Dose)
cc = Volume of PTV (or Rx Volume)
= Ratio a/b (Should be < 0.15)

Characteristics of a Good-quality SBRT Plan for Lung Tumors

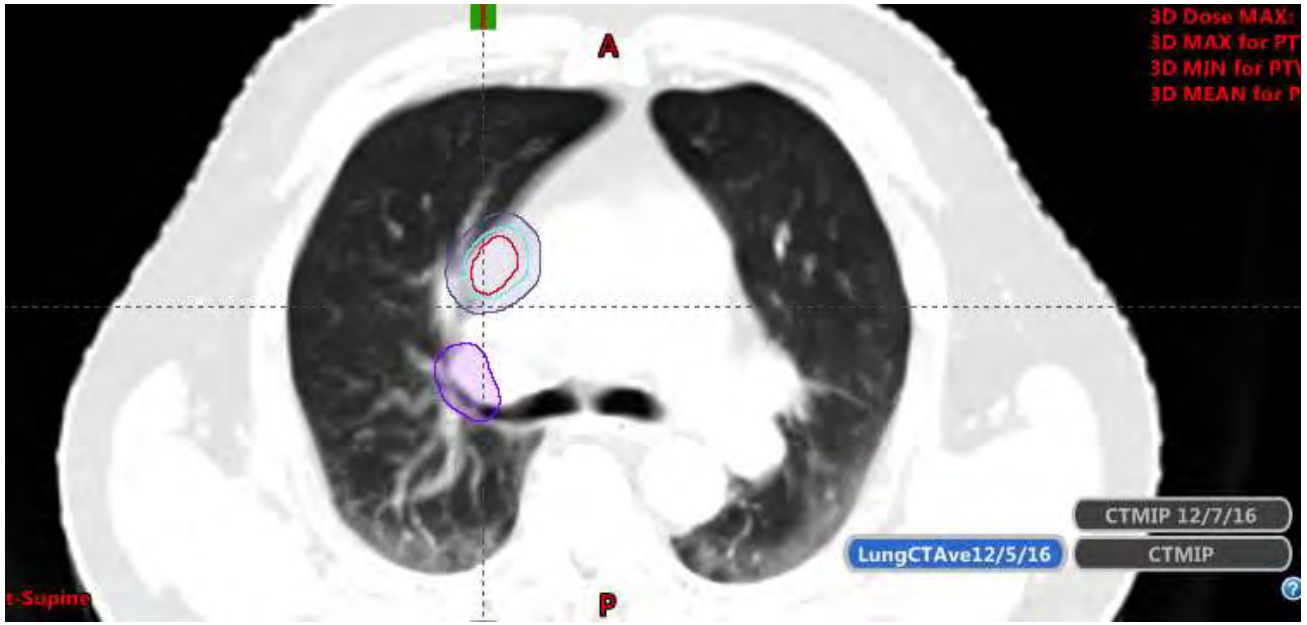
- High dose, small fraction numbers (≤5)
- Highly precise; accurate localization is paramount
- Safe toxicity profile; efficacious
- Requires sophisticated image-guided RT (IGRT)
- Our (Mayo) practice is daily for lung tumors
- Co-planar beams (Mayo)
- Evidence-based

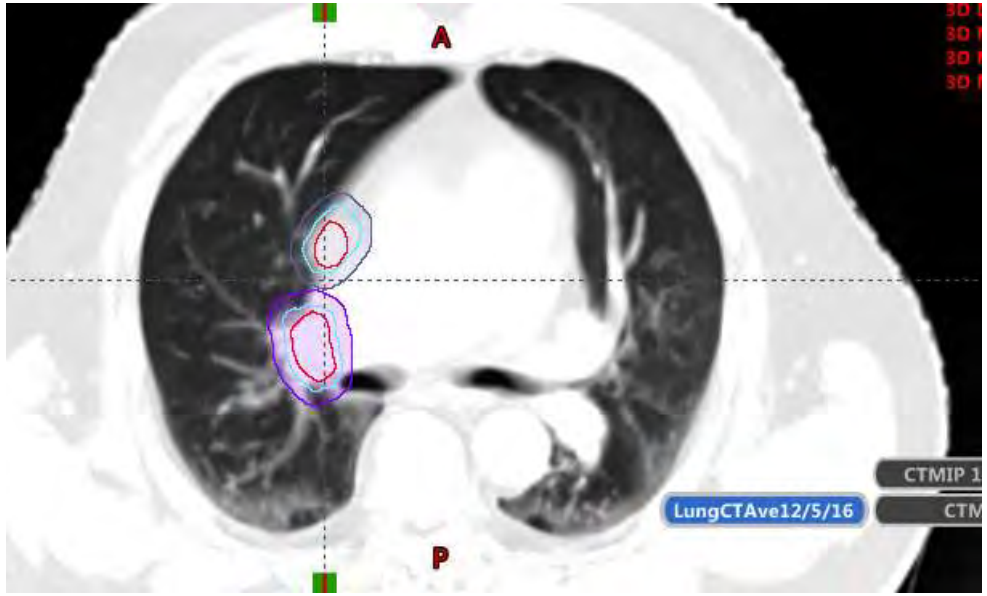


Case Presentation – SBRT for Lung Tumors

- Central lung metastases (2), with a rectal cancer primary
  - 75 years old male, little co-morbidities
  - History of APR + adjuvant chemotherapy in 2011
  - No more pelvic RT (Due to prostate RT-2005)
  - He now has isolated, pulmonary nodal recurrences, with rising CEA
  - Both small; one of them biopsy proven
  - Location: Right high mediastinal and hilar areas

Imaging – small masses, two of them, but in the “wrong” spots!





GTV
iGTV=ITV
PTV

“Ultra”-central locations

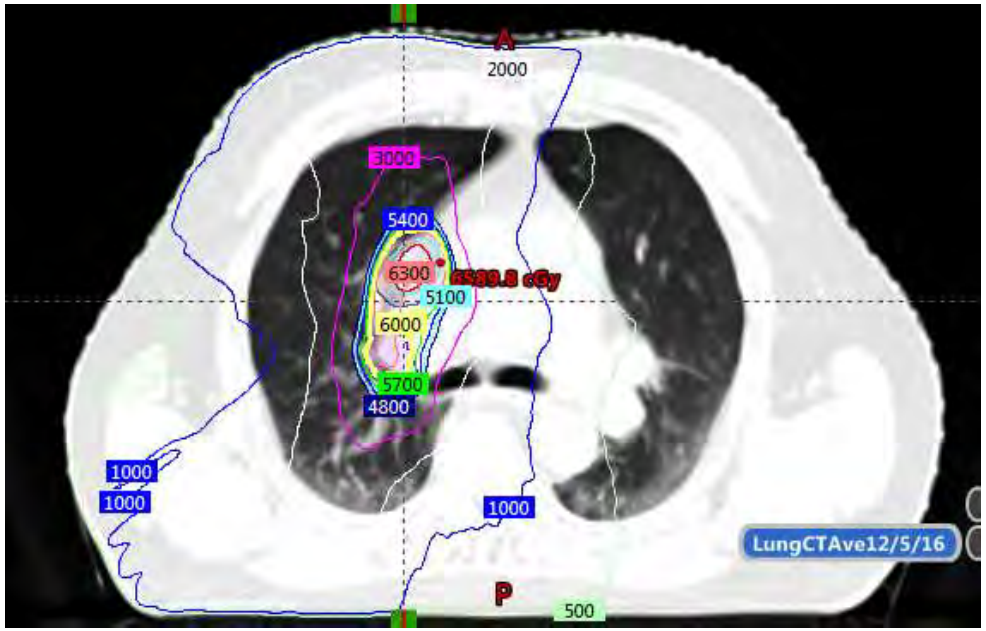
Questions/Considerations

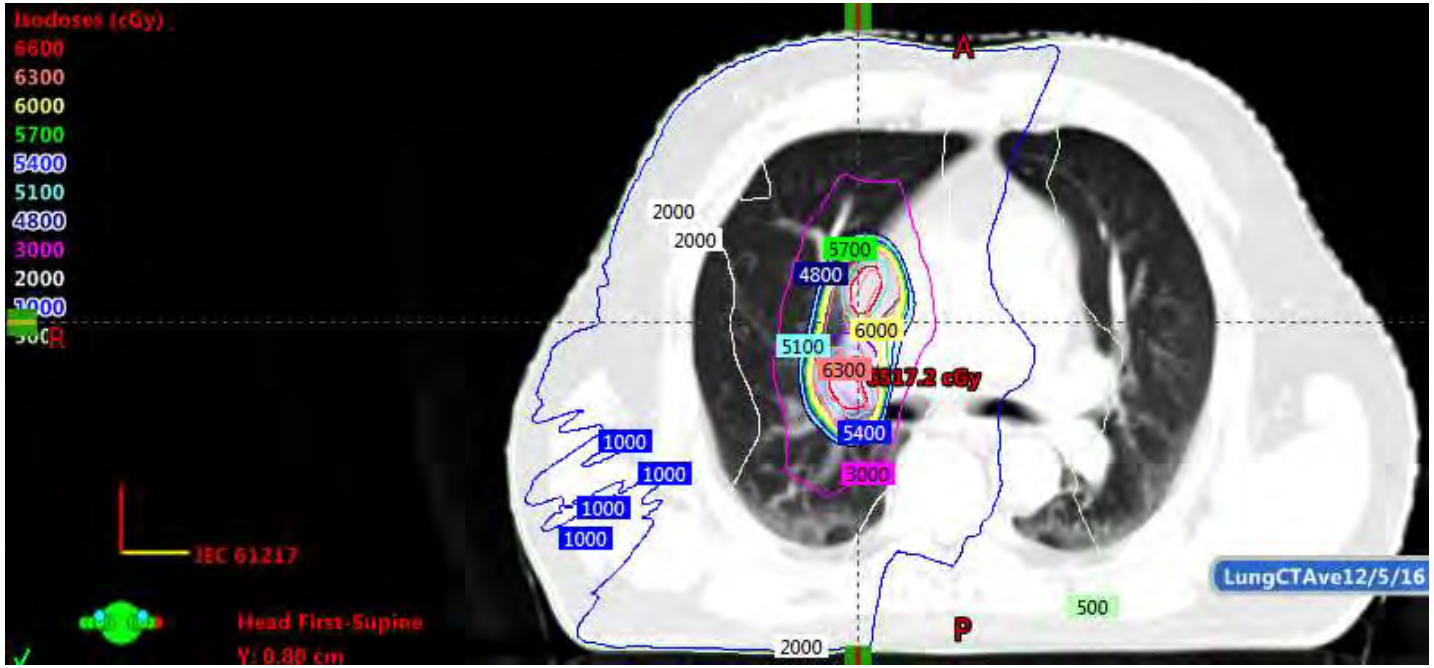
- Should we treat oligometastatic disease (if at all)?
- Systemic treatment upfront?
- Surgery?
- Dose/fractionation choices
- Multi-target SBRT?
- After multi-disciplinary discussion
  - Hold off chemo
  - Give 60 Gy in 8 fractions (avoid 50/5 to the full circumference of bronchial tree, also a significant portion of mediastinum)

Target Delineation for lung SBRT

- GTV
  - Gross tumor volume
  - On free-breathing CT; fused with diagnostic imaging
- IGTV
  - Internal gross tumor volume
  - Includes all phases of 4D data
- ITV (CTV) – microscopic disease/expansion
  - Internal tumor/target volume/clinical target volume
  - Usually zero for SBRT; in practice (esp. for liver), a small margin is typically included
- PTV
  - Planned target volume
  - Includes setup margin; with daily CBCT, 3mm suffices

RT Plan


A
2000
3000
5400
6300
5100
6000
5700
4800
1000
1000
1000
LungCTAve12/5/16
P
500


Isodoses (cGy)
6600
6300
6000
5700
5400
5100
4800
3000
2000
1000
A
2000
2000
5700
4800
6000
5100
6300
5400
3000
1000
1000
1000
1000
2000
LungCTAve12/5/16
500
P
IEC 61217
Head First-Supine

Normal Tissue DVH Objectives (Lung - SBRT 5fx)			Priority	Achieved
body-ptv	D1cc[%]	< 110 %	2	106.8 %
bronch_tree_nona	Max[Gy]	< 55 Gy	2	39.9 Gy
	Max[%]		Report	66.5 %
	D4cc[%]		Report	37.1 %
	V16.5Gy[cc]	< 6 cc	3	**7.72 cc**
	V18Gy[cc]		Report	6.33 cc
bronch_tree_prox	Max[Gy]		Report	64.86 Gy
	Max[%]	< 110 %	1	108.1 %
	D4cc[%]		Report	61.1 %
	V16.5Gy[cc]		Report	12.22 cc
	V18Gy[cc]	< 6 cc	3	**10.84 cc**
chestwall	Max[Gy]			30.36 Gy
	V30Gy[cc]			0.03 cc
cord	Max[Gy]			13.26 Gy
	D0.35cc[Gy]		Report	12.42 Gy
	V23Gy[cc]	< 0.35 cc	2	0 cc
esophagus_nonadj	Max[Gy]	< 42 Gy	2	13.92 Gy
	Max[%]		Report	23.2 %
	D5cc[Gy]		Report	9 Gy
	V19.5Gy[cc]	< 8 cc	3	0 cc
	V27.5Gy[cc]		Report	0 cc
esophagus	Max[Gy]		Report	13.92 Gy
	Max[%]	< 105 %	1	23.2 %
	D5cc[Gy]		Report	9 Gy
	V19.5Gy[cc]		Report	0 cc
	V27.5Gy[cc]	< 8 cc	3	0 cc
heart_nonadj	Max[Gy]	< 44 Gy	2	**55.86 Gy**
	Max[%]		Report	93.1 %
	D15cc[Gy]		Report	13.26 Gy
	V32Gy[cc]	< 20 cc	3	1.09 cc

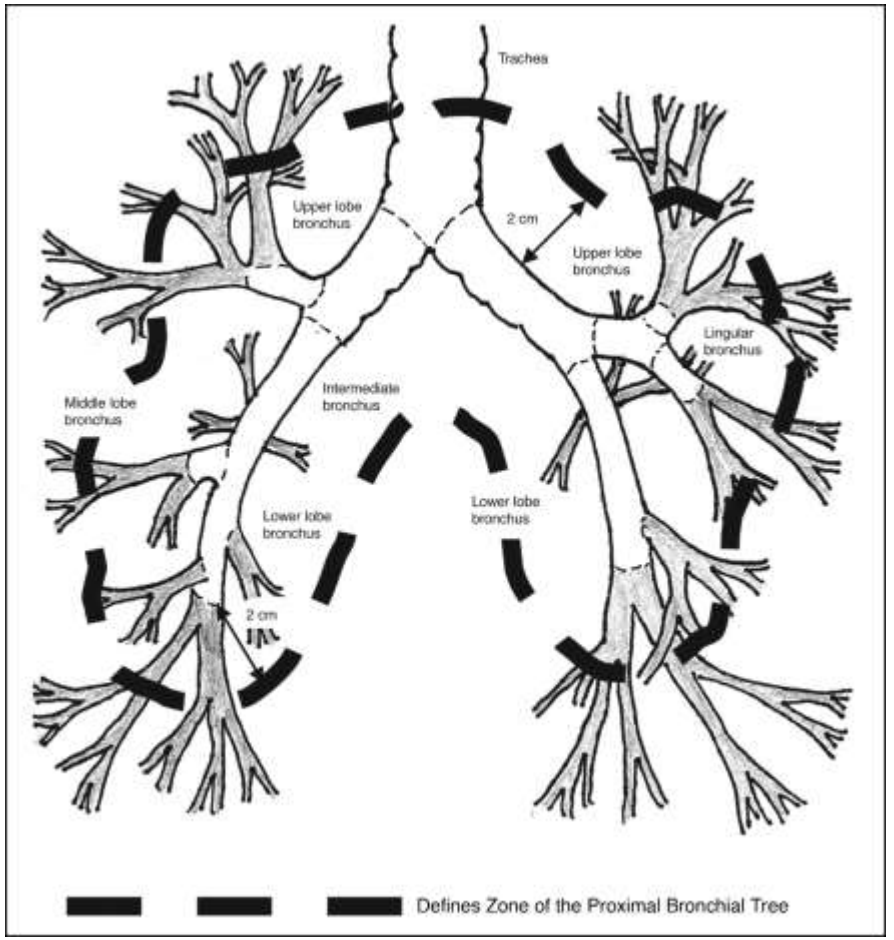
The volume receiving 30 Gy or more. Volume expressed in cc.

heart	Max[Gy]		Report	60.6 Gy
	Max[%]	< 105 %	1	101 %
	D15cc[Gy]		Report	14.16 Gy
	V32Gy[cc]	< 20 cc	2	2.35 cc
	V5Gy[%]		Report	6.3 %
great_vessels_na	Max[Gy]	< 63 Gy	2	62.22 Gy
	Max[%]		Report	103.7 %
	D10cc[Gy]		Report	42.84 Gy
	V47Gy[cc]	< 20 cc	3	6.48 cc
great_vessels	Max[Gy]		Report	66.3 Gy
	Max[%]	< 115 %	1	110.5 %
	D10cc[Gy]		Report	59.7 Gy
	V47Gy[cc]	< 30 cc	3	25.99 cc
lung_total	DC1000cc[Gy]		Report	0.78 Gy
	DC1500cc[Gy]		Report	1.38 Gy
	V20Gy[%]	< 13 %	2	12 %
	CV12.5Gy[cc]	> 1500 cc	2	2852.4 cc
	CV13.5Gy[cc]	> 1000 cc	2	2878.2 cc
lung_r	Volume[cc]		Report	2063.5 cc
lung_l	Volume[cc]		Report	1421 cc
skin	Max[Gy]	< 32 Gy	2	24.18 Gy
	D10cc[Gy]		Report	14.88 Gy
	V30Gy[cc]	< 10 cc	2	0 cc
trachea_nonadj	Max[Gy]	< 48 Gy	2	11.04 Gy
	Max[%]		Report	18.4 %
	D4cc[Gy]		Report	3.06 Gy
	V16.5Gy[cc]	< 6 cc	3	0 cc
	V18Gy[cc]		Report	0 cc
trachea	Max[Gy]		Report	11.04 Gy
	Max[%]	< 105 %	1	18.4 %
	D4cc[Gy]		Report	3.06 Gy
	V16.5Gy[cc]		Report	0 cc
	V18Gy[cc]	< 6 cc	3	0 cc

Central vs. Peripheral Lesion

- Also lesion touching mediastinum

“PBT should include the distal 2 cm of the trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi”



Timmerman et al, *JCO 2006*

Toxicities Associated with Central SBRT

Central-Airway Necrosis after Stereotactic Body-Radiation Therapy

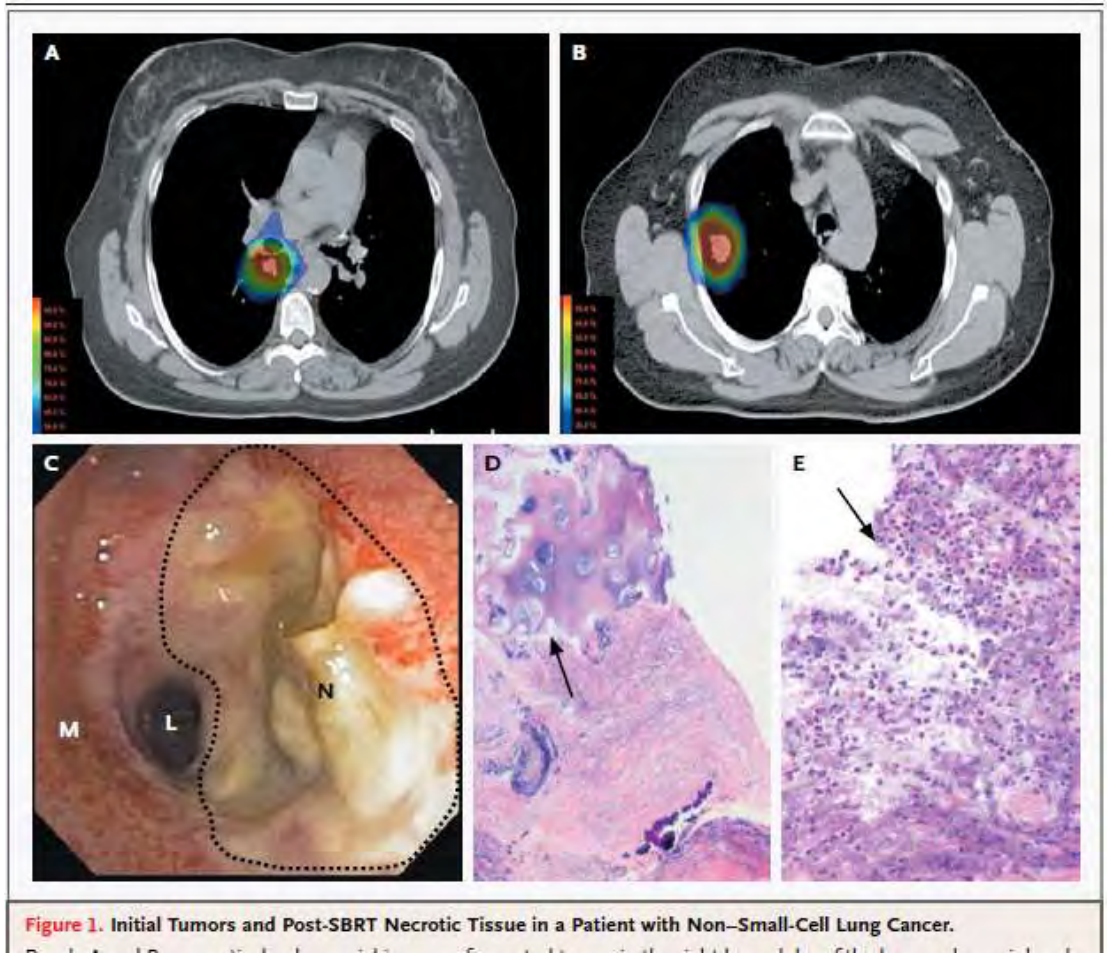


Figure 1. Initial Tumors and Post-SBRT Necrotic Tissue in a Patient with Non–Small-Cell Lung Cancer.

MN Corradetti - 2012 NEJM

60 Gy in 8 fractions is safe and efficacious

- 7.5 Gy x8; VUMC experience (2008-2013)
  - Amsterdam; Dutch data
- N=80 patients; PTV <2 cm from proximal bronchial tree
- Median f/ u47 months
  - 3-yr OS 53%, similar to peripheral tumors
  - 3-yr LC >90% on prior publications
  - 5/78 patients with grade 3 toxicity
  - No grade 4 toxicity
  - Grade 5 toxicity possible in 3 pts and likely in 3 pts

Tekatli H et al. Radiother Oncol. 2015 Oct;117(1):64-70

VUMC (Dutch) Toxicities

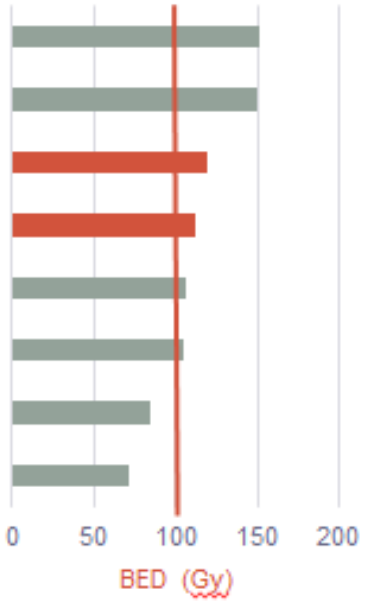
Cause of death	Pre-treatment comorbidity	Clinical details	Dosimetric details of index treatment
Likely treatment-related			
RP resulting in respiratory failure	WHO PS 1 Severe ILD	Age 72.3 years, T1bN0M0 Survival 2 months	CL V_{5Gy}: 0% TL V_{5Gy}: 16% TL V_{20Gy}: 9% PBT D0.1 cc: 13.8 Gy
Euthanasia performed due to disease progression and dyspnea	WHO PS 2 COPD GOLD IV	Age 64.8 years, T3N0M0 Patient developed RP grade 3 Survival 13 months	CL V_{5Gy}: 39% TL V_{5Gy}: 45% TL V_{20Gy}: 13% PBT D0.1 cc: 39.7 Gy
Sudden death	WHO PS 2 COPD GOLD II ILD	Age 73.1 years, T2bN0M0 Patient developed RP grade 3 Survival 5 months	Heart D0.5 cc: 56.2 Gy Heart D15 cc: 34.5 Gy CL V_{5Gy}: 51% TL V_{5Gy}: 48% TL V_{20Gy}: 9% PBT D0.1 cc: 71.2 Gy
Possible treatment-related			
Massive lung hemorrhage	WHO PS 1 COPD GOLD II	Age 48.9 years, T2aN0M0 No in-field radiological progression, but possible intrathoracic progression Survival 18 months	PBT D0.1 cc: 79.5 Gy PBT D0.5 cc: 76.1 Gy PBT D4.0 cc: 63.4 Gy
Massive lung hemorrhage	WHO PS 2 COPD GOLD IV	Age 56.9 years, T2aN0M0 Patient developed grade 1 atelectasis Survival 10 months	PBT D0.1 cc: 69.7 Gy PBT D0.5 cc: 63.6 Gy PBT D4.0 cc: 21.3 Gy
Terminal respiratory failure	WHO PS 3 COPD GOLD IV	Age 84.2 years, T2bN0M0 Patient died at a nursing home Survival 3 months	CL V_{5Gy}: 8% TL V_{5Gy}: 24% TL V_{20Gy}: 9% PBT D0.1 cc: 3.9 Gy

Tekatli H et al. Radiother Oncol. 2015 Oct;117(1):64-70

Revisiting the Fractionation Choice

Dose

Dose	Source	BED (α/β=10)
18 Gy x 3 Fx (54 Gy)	RTOG[1]	151.2 Gy
34 Gy x 1 Fx (34 Gy)	RTOG[2]	149.6 Gy
7 Gy x 10 Fx (70 Gy)	MDACC	119.0 Gy
12.5 Gy x 4 Fx (50 Gy)	MDACC	112.5 Gy
7 Gy x 9 Fx (63 Gy)	MDACC	107.1 Gy
12 Gy x 4 Fx (48 Gy)	Japanese	105.6 Gy
4 Gy x 15 Fx (60 Gy)	NCIC[3]	84.0 Gy
2 Gy x 30 Fx (60 Gy)	Conventional	72.0 Gy



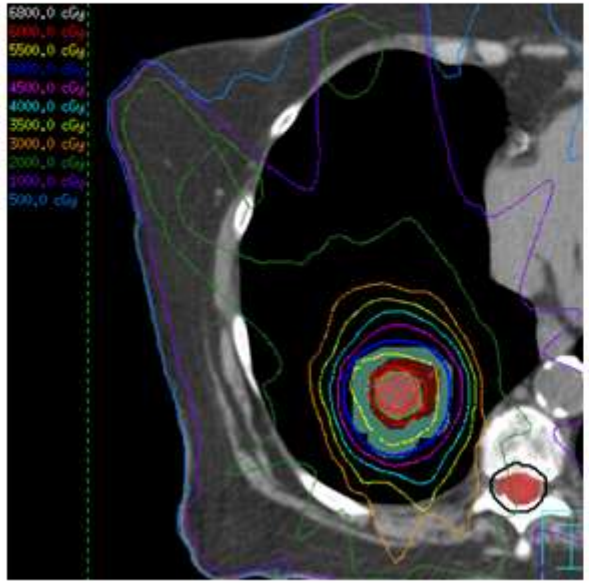
$$BED = D \cdot (1 + \frac{d}{(\alpha / \beta)})$$

Regimens with BED ≥ 100 Gy are associated with better local control and survival[4]

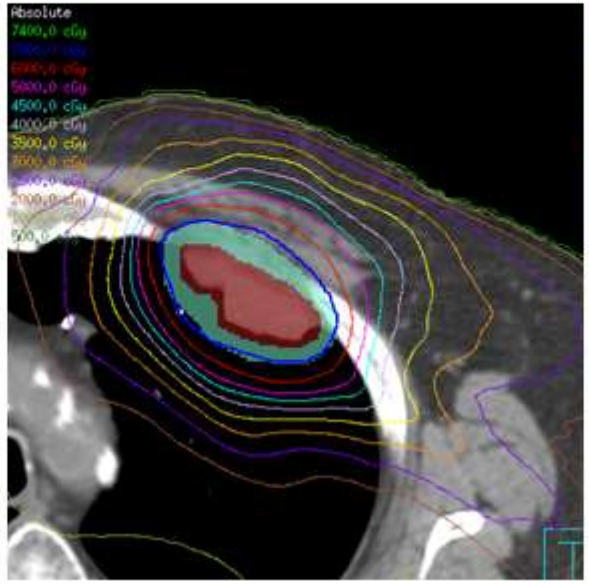
[1]Timmerman et al., JAMA. 2010 Mar 17;303(11):1070-6.
[2]Videtic et al., Int J Radiat Oncol Biol Phys. 2015 Nov 15;93(4):757-64.
[3]Cheung et al., Int J Radiat Oncol Biol Phys. 2002 Nov 15;54(4):1014-23.
[4]Onishi et al., Cancer. 2004 Oct 1;101(7):1623-31.

Examples (MDACC)

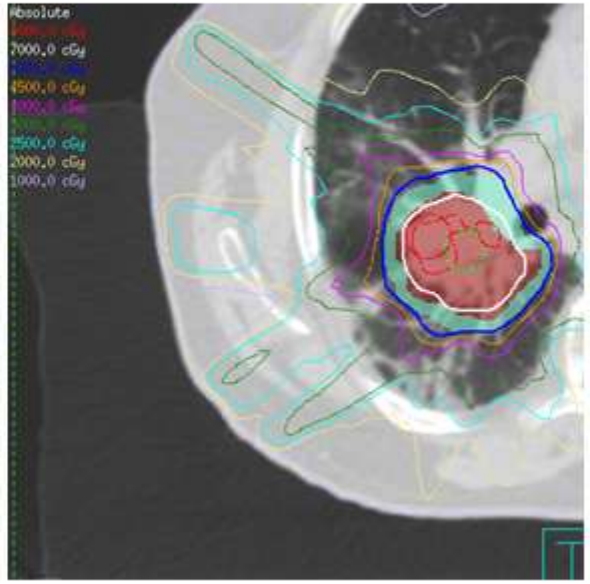
Peripheral Lesion
50 Gy in 4 Fx (to PTV)



Peripheral Lesion
Abutting Chest Wall
70 Gy in 10 Fx (to PTV)



Central Lesion
70 Gy in 10 Fx (to **GTV**)
(50 Gy in 10 Fx to PTV using SIB)



Credits: Residents' learning slides 2015

Bigger tumors with SBRT

- RTOG 0236 (Timmerman et al. 2010) included inoperable patients with biopsy-proven peripheral T1-T2N0M0 non-small cell tumors (measuring <5 cm in diameter)
- Tumors > 4 cm would benefit from adjuvant chemotherapy in the surgical literature (Strauss et al. JCO 2008), however, it's not evaluated in SBRT settings.
- The Cleveland Clinic published their report (40 patients) with tumors > 5 cm treated with SBRT with a median dose of 50 Gy in 5 fractions (Woody et al. IJROBP 2014)
  - 18-month local control of 91.2%
  - 7.5% rate of grade 3 or higher toxicity
  - Large tumors can be safely treated in 5 fractions with good local control and toxicity
- Mayo Clinic: Anecdotally, up to 7cm as well

SABR: Guidelines & evidence

SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.

[ESMO Clinical Practice Guidelines [Vansteenkiste J, Ann Oncol 2013; Guidelines of National Comprehensive Cancer Network [NCCN v3.2014]

Comparative effectiveness research suggests that survival is similar after either surgery or SABR for early-stage NSCLC

[reviewed in Louie AV, Radiotherapy Oncol 2015]

SABR versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

[Chang JY, Senan S, Lancet Oncol 2015]

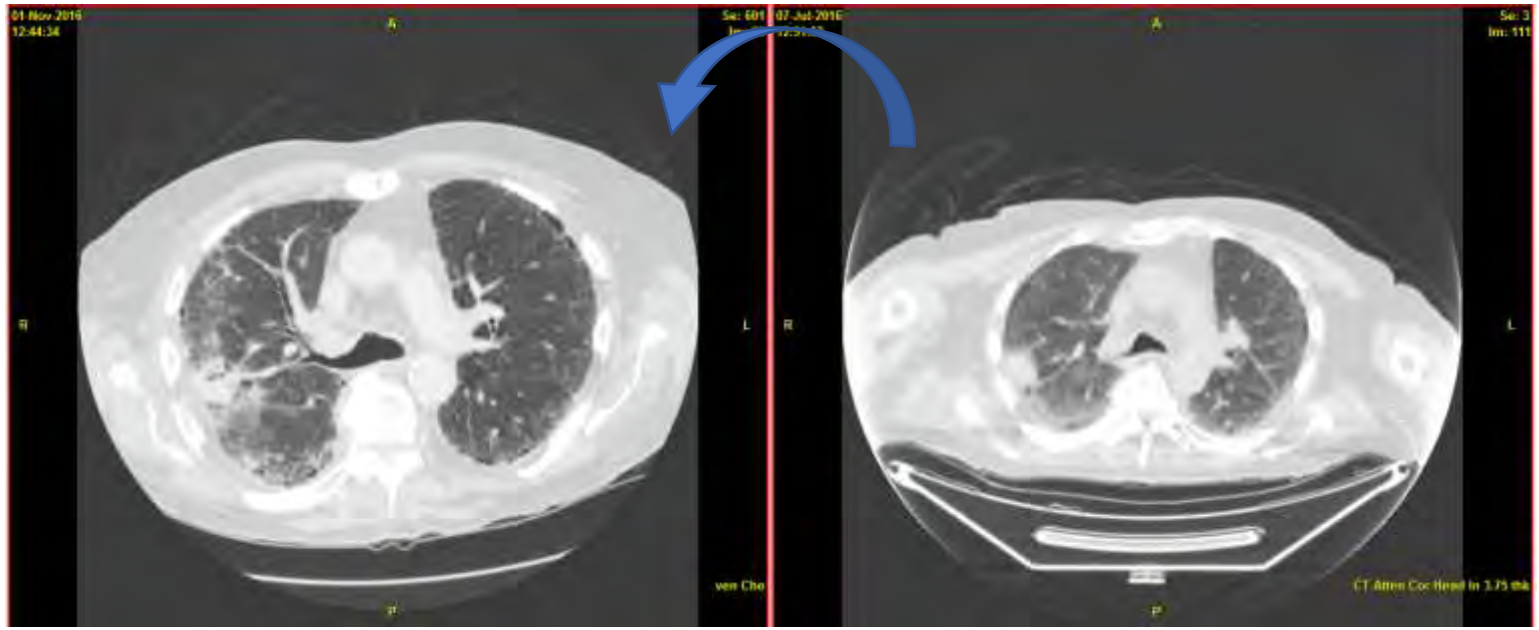
IASLC

TABLE 1. SBRT Studies for Centrally Located Lung Tumors (including non–small-cell and metastatic lesions)

First Author	Institution	Study Type	No. of Patients	Median Age (years)	Dose Per Fraction (Gy/fx)	No of Fractions	Regimen	2-Year Local Control (%)	2-Year Overall Survival (%)	Acute Grade 3+ Toxicities	Late Grade 3+ Toxicities
Bezjak[2]	NRG Oncology/ Radiation Therapy Oncology Group	Prospective, phase I/II	71	72	11.5 and 12	5	Every other weekday	88-89	68-73	6%-7% (3 patients, grade 3)	Four patients (6%) with grade 5 toxicities (3 at 11.5 Gy/fx; 1 at 12 Gy/fx)*
Chang[3]	MD Anderson Cancer Center	Retrospective	100†	73	12.5	4	Daily	90 (est.)‡	80 (est.)	3% grades 2 to 3 brachial plexopathy; 2% grade 3 radiation pneumonitis	No grade 4 or 5 toxicities
Modh[4]	Memorial Sloan Kettering	Retrospective	125	76	9§	5	Every other weekday	79	64	8%, including 2% grade 5	Two grade 5 toxicities (hemoptysis; pneumonitis)‖
Tekatli[5]	VU University Medical Center	Retrospective	80	73	7.5	8	Not mentioned	Not mentioned	62	6% (grade 3 only)	Six patients (7.5%), possible/likely grade 5¶
Arnett[6]	Mayo Clinic	Retrospective	103	74	10 (median)	5	Daily (75%)	82 (est.)‡	62 (est.)	1% (grade 3 only)	Grade 3, 8%; grade 4, 1%; grade 5, 1% (1 patient)
Roach[8]	Washington University in St Louis	Prospective, phase II	51	73	11	5	Not mentioned	85	43	6% (grades 3 to 4)	Grade 3, 27%; grade 4, 12%; grade 5, 4% (1 patient)

Sio TT et al. Journal of Clinical Oncology 2019 37:29, 2697-2699

Radiographic changes after SBRT



Usually with no or minimal decrease in lung function (by PFT's)

Summary

- Treatment of oligometastatic disease is getting more popular
  - NSCLC
  - Extensive SCLC
  - Metastatic Colorectal
  - Metastatic Breast

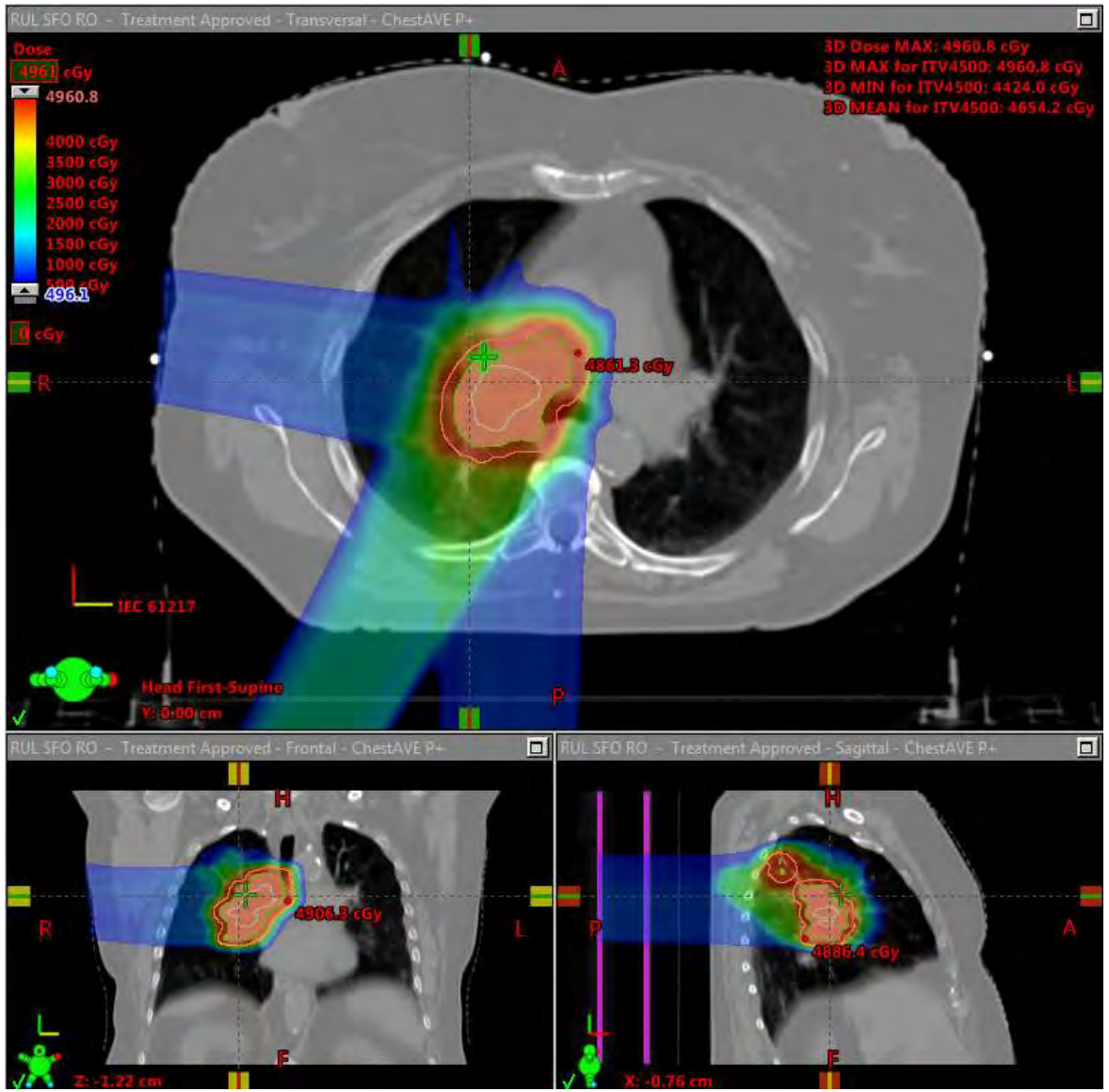
- Patient remains NED 9 months after treatment

Additional IGRT Considerations

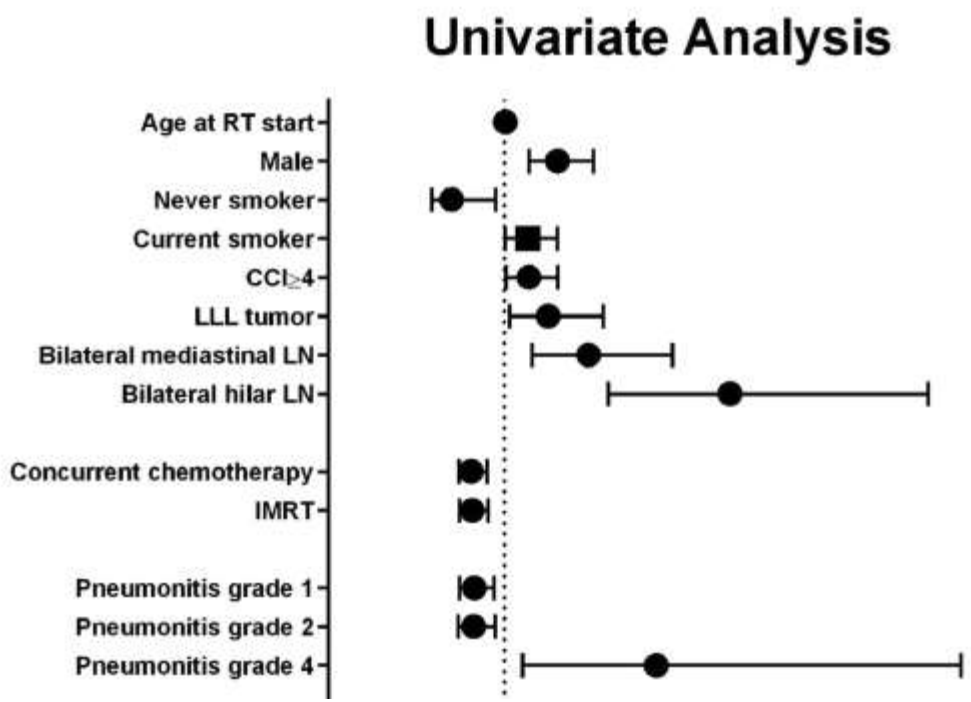
- Margin considerations vs. respiratory control
  - Respiratory coaching (audio/visual)
  - CBCT → ↓ PTV margin
  - Abdominal compression, breath-hold, gating, active breathing monitoring → ↓ ITV, ↓ motion
  - Rarely ExacTrac for lung/liver
  - Free breathing → also an excellent choice
- It is related to setup/reproducibility as well
  - E.g., S-frame better for upper lung tumors (Sio et al, JACMP, 2014)
- No “one size fits all” solution; institution dependent

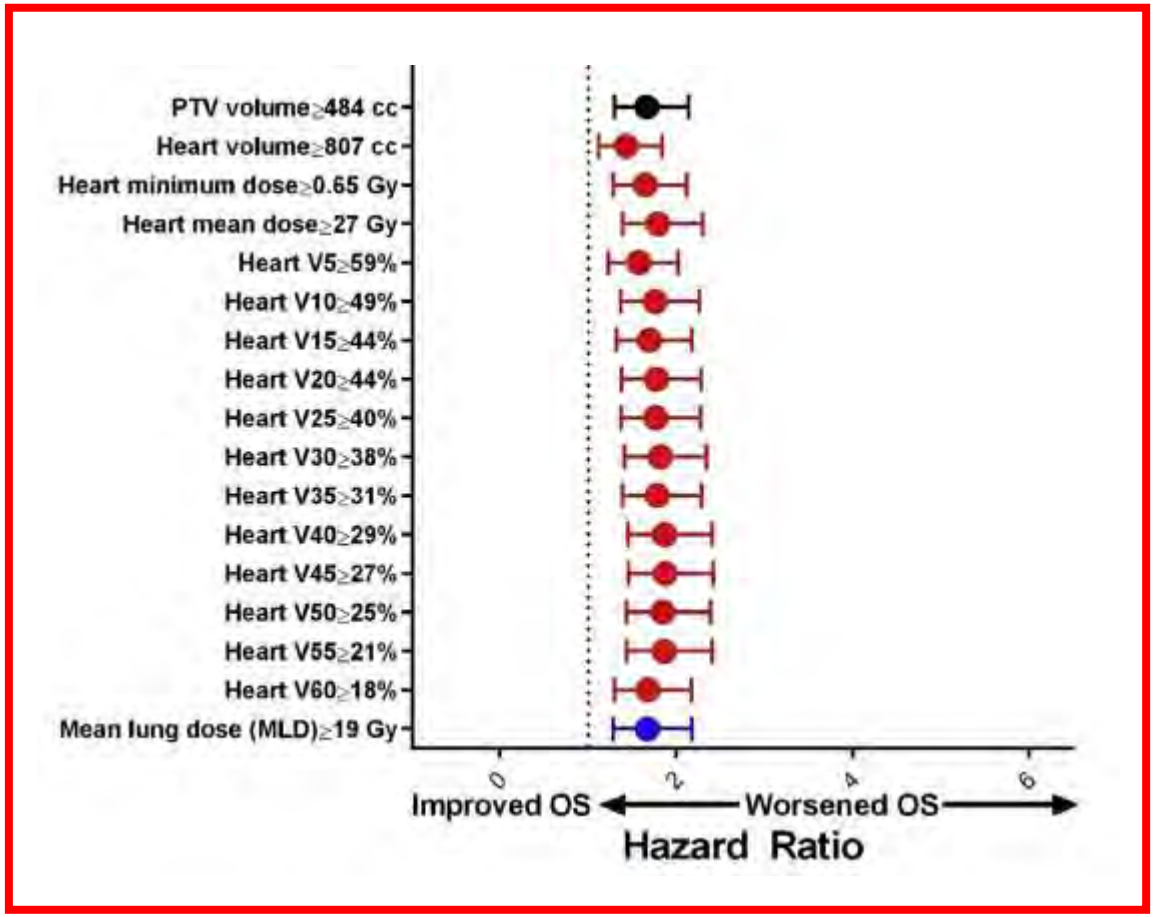
CT on-rails

Limited-stage Small Cell Lung Cancer (Protons)



Heart dose matters in lung ca. RT planning





Spiers et al, JTO Feb 2017

Thoracic IMPT (Proton Beam Radiotherapy)

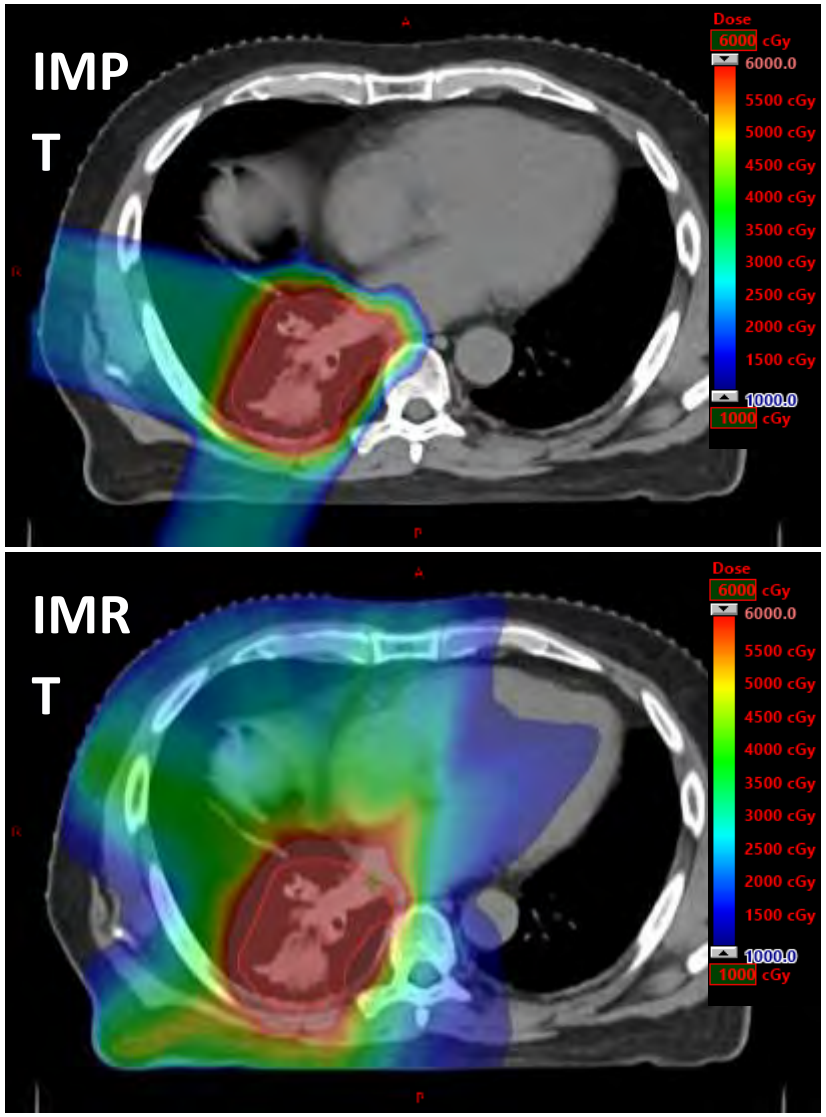


Figure 1. An axial comparison of IMPT (above) vs. IMRT (below) dose distribution. The OTV (IMPT) and PTV (IMRT) are contoured in red. This is a 74-year-old male in the present study with stage IIIB adenocarcinoma of the right lower lobe lung who received (above) 60 Gy in 30 fractions with concurrent and consolidative carboplatin and paclitaxel. At 9 months following completion of IMPT, the patient demonstrated no evidence of new or progressive disease.

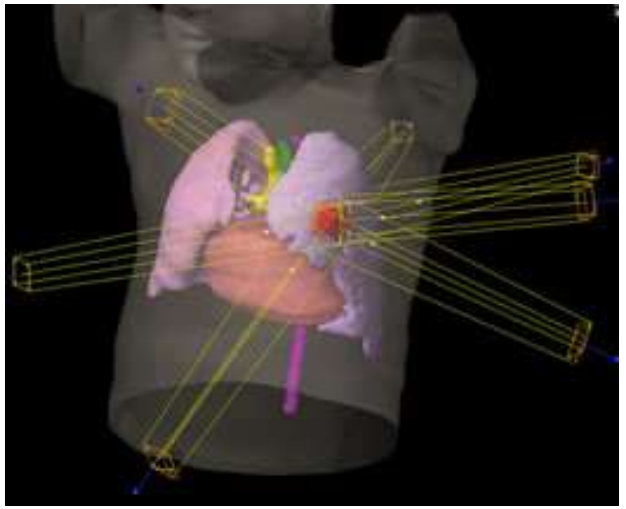
Lung Mean 9 Gy V20Gy: 19% V5Gy: 24%	Heart Mean 1.5 Gy V40Gy: 1%	**IMPT**

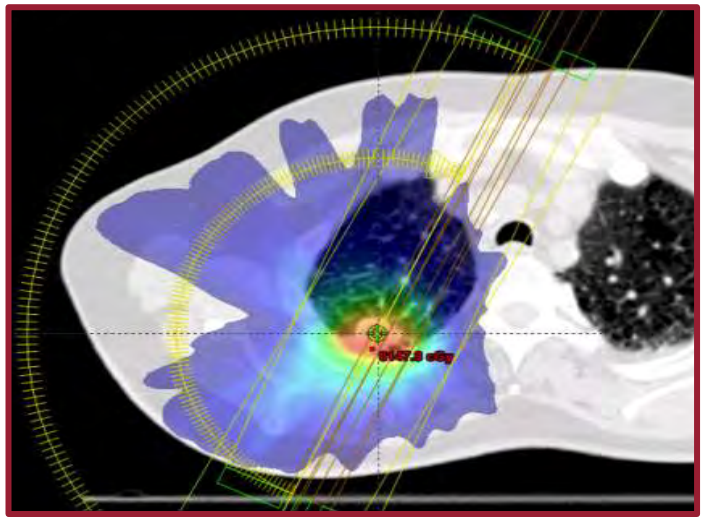
Lung Mean 15 Gy V20Gy: 34% V5Gy: 51%	Heart Mean 18 Gy V40Gy: 10%	**IMRT**

Yu NY, Sio TT et al.
Advances in Rad Onc 2019

Future Directions – Proton SBPT

- Current practice (Photon-based): High dose, small fraction numbers (≤5)
- Highly precise; accurate localization is paramount
- Safe toxicity profile; efficacious
- Requires sophisticated image-guided RT (IGRT)
- Our (Mayo) practice is daily for lung tumors
- Co-planar beams (Mayo)
- Evidence-based

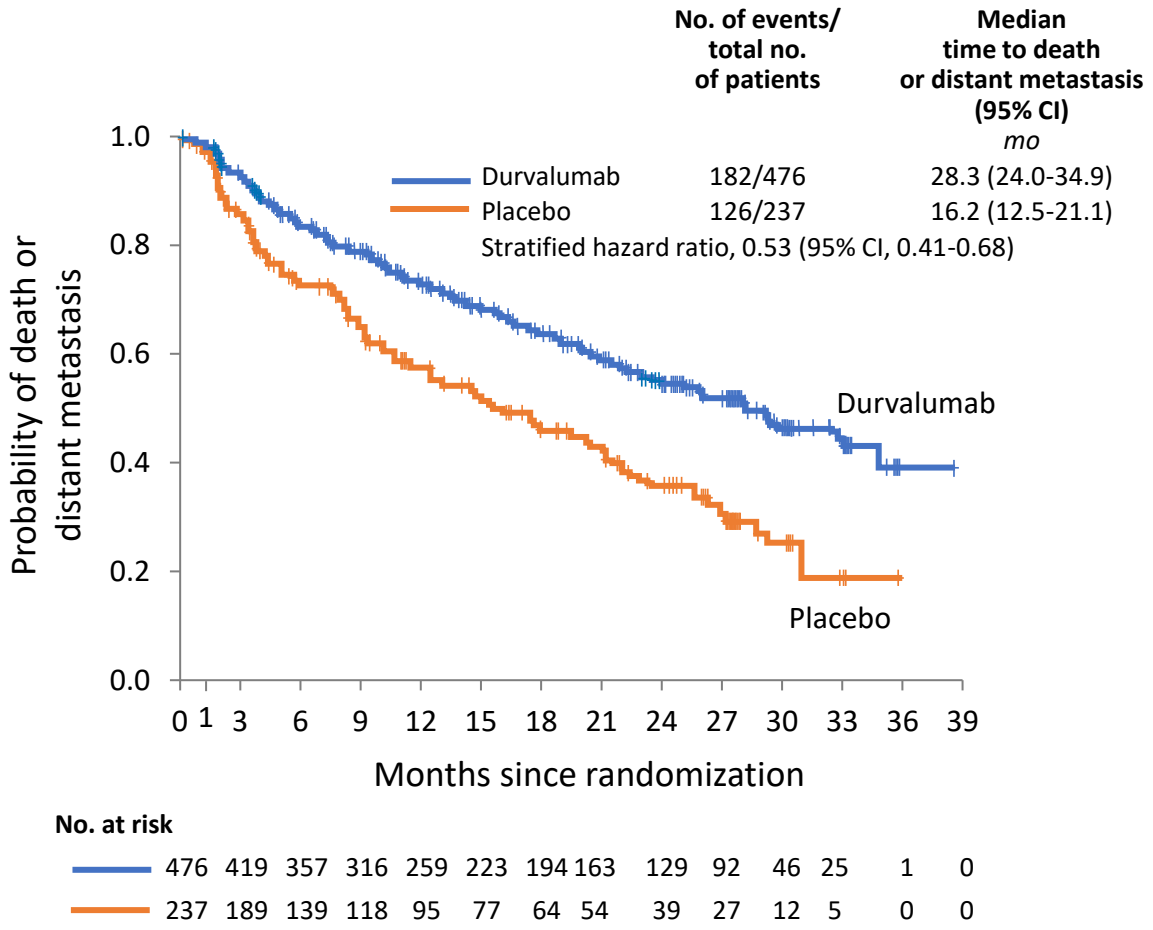




How to combine IO and RT (Protons) together?

- Next step: To explore if combining RT or proton beam therapy with immunotherapy may make the treatments safer, and potentiate the benefits of combined therapies

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer Antonia et al. New England Journal of Medicine 2017, 2018

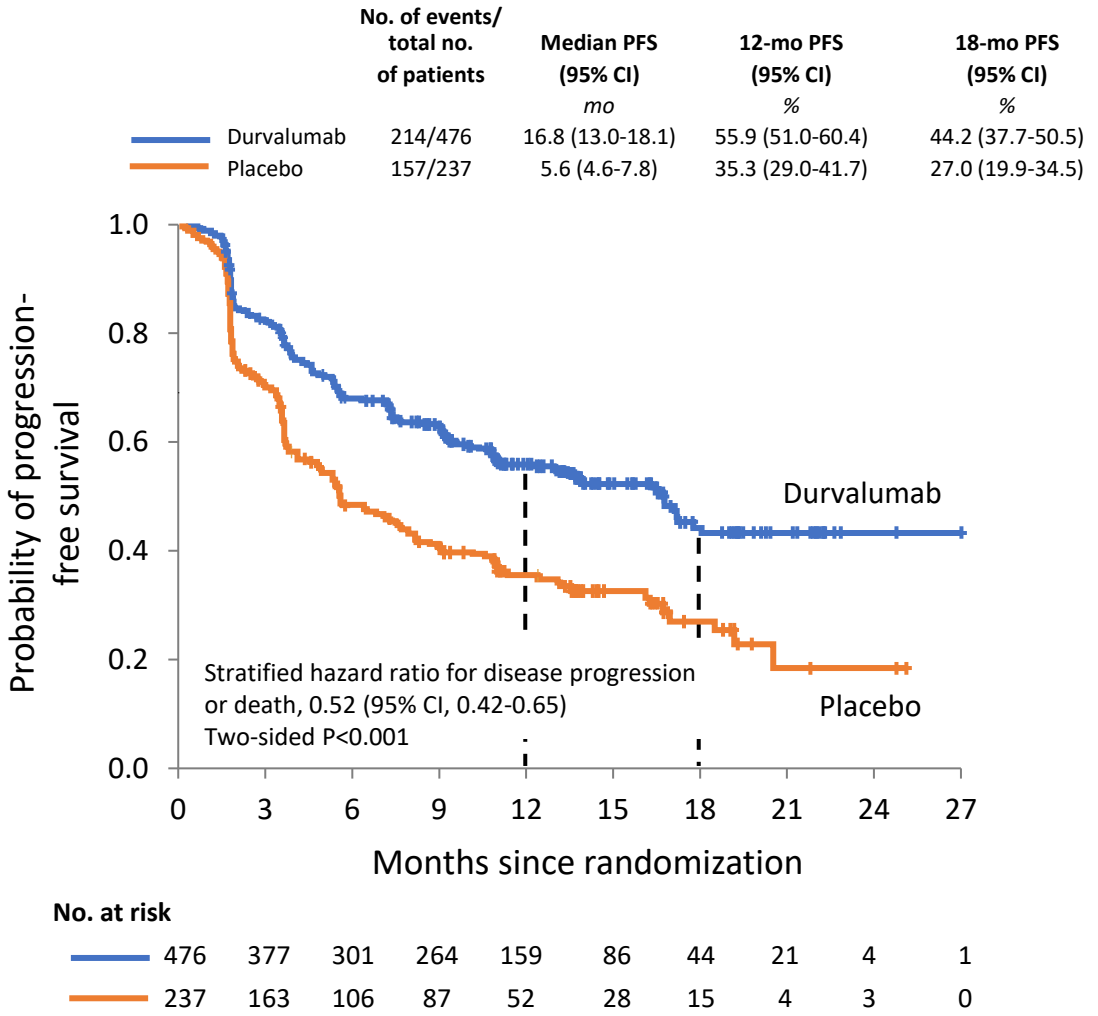


Updated Incidence of New Lesions, as Assessed by Blinded Independent Central Review, in the Intention-to-treat Population

New lesion site	Durvalumab group (N=476)	Placebo group (N=237)
	No. of patients (%)	
Any site	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal gland	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

Redrawn from: Antonia et al. New England Journal of Medicine 2017, 2018

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer Antonia et al. New England Journal of Medicine 2017, 2018



LR Control, blinded independent review

	Durvalumab (N=443)		Placebo (N=213)	
Objective response				
No. of patients	133		38	
% of patients (95% CI)	30.0 (25.79-24.53)		17.8 (12.95-23.65)	
P value	<0.001			
Best overall response – no. (%)				
Complete response	81.2%	8 (1.8)	71.9%	1 (0.5)
Partial response		125 (28.2)		37 (17.4)
Stable disease		227 (51.2)		115 (54.0)
Progressive disease		73 (16.5)		59 (27.7)
Non-evaluable		10 (2.3)		1 (0.5)
Duration of response, months				
Median (95% CI)	No reached (27.4 – not reached)		18.4 (6.7-24.5)	
Ongoing response at data cutoff, %				
At 12 months	81.3		60.2	
At 18 months	73.5		52.2	

Redrawn from: Antonia et al. New England Journal of Medicine 2017, 2018

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer Antonia et al. New England Journal of Medicine 2017, 2018

Also iSABR strategies (In Clinical Trials now)

Treatment-Related Adverse Events Reported in ≥5% of Patients

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with an event (percent)			
Any event	322 (67.8)	56 (11.8)	125 (53.4)	10 (4.3)
Fatigue	62 (13.1)	1 (0.2)	26 (11.1)	0
Hypothyroidism	50 (10.5)	1 (0.2)	1 (0.4)	0
Diarrhea	46 (9.7)	2 (0.4)	19 (8.1)	2 (0.9)
Pneumonitis	43 (9.1)	6 (1.3)	8 (3.4)	2 (0.9)
Rash	37 (7.8)	1 (0.2)	13 (5.6)	0
Pruritus	33 (6.9)	0	5 (2.1)	0
Hyperthyroidism	30 (6.3)	0	3 (1.3)	0
Asthenia	28 (5.9)	3 (0.6)	15 (6.4)	0
Dyspnea	28 (5.9)	3 (0.6)	8 (3.4)	0
Decreased appetite	27 (5.7)	0	7 (3.0)	1 (0.4)
Nausea	26 (5.5)	0	14 (6.0)	0
Cough	25 (5.3)	0	4 (1.7)	0

- **Durvalumab (n=7)**
  - Pneumonitis (n=4)
  - Cardiomyopathy (n=1)
  - Respiratory Failure (n=1)
  - Radiation Pneumonitis (n=1)
- **Placebo (n=3)**
  - Pneumonitis (n=2)
  - Unknown (n=1)

*** 2:1 randomization**

Mayo Arizona Radiation Oncology Team

Dr. Sujay Vora, M.D.
Dr. Steve Schild, M.D. (Retired)
Dr. Sameer Keole, M.D.
Dr. Michele Halyard, M.D. (Retired)
Dr. Jonathan Ashman, M.D., Ph.D.
Dr. Carlos Vargas, M.D.
Dr. Samir Patel, M.D.
Dr. Nathan Yu, M.D.
Dr. Tamara Vern-Gross, M.D.
Dr. Will Rule, M.D.
Dr. Lisa McGee, M.D.
Dr. Terence Sio, M.D., M.S.
Dr. Jean Claude (JC) M.D.
Dr. William Wong, M.D. (Retired)

Dr. Mirek Fatyga, Ph.D.
Dr. Martin Bues, Ph.D.
Dr. Rong Yi, Ph.D.
Dr. Gary Ezzell, Ph.D.
Dr. Josh Stoker, Ph.D.
Dr. Wei Liu, Ph.D.
Dr. Jason Shen , Ph.D.
Dr. Yanle Hu, Ph.D.
Dr. Yixiu Kang, Ph.D.
Dr. Xiaoning Ding, Ph.D.
Dr. Daniel Robertson, Ph.D
Entire Dosimetry
Entire Therapy
Nursing Staff

Email with any question **Sio.Terence@mayo.edu**