Particle Therapy for Lung Cancer

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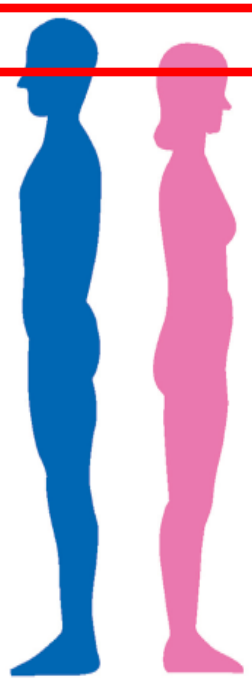
Content

- Rationale for Particle Therapy in Lung Cancer
- Proof of Principle
- Treatment Planning Challenges

Background

Estimated Deaths

Males			Females		
Lung & bronchus	87,750	29%	Lung & bronchus	72,590	26%
Prostate	28,170	9%	Breast	39,510	14%
Colon & rectum	26,470	9%	Colon & rectum	25,220	9%
Pancreas	18,850	6%	Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%	Ovary	15,500	6%
Leukemia	13,500	4%	Leukemia	10,040	4%
Esophagus	12,040	4%	Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%	Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%	Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%	Brain & other nervous system	5,980	2%
All Sites	**301,820**	**100%**	**All Sites**	**275,370**	**100%**



Siegel et al. *CA: A Cancer Journal for Clinicians* 2012

5- year Overall Survival Rates

Stage	Lung Cancer
1	50%
2/3	15%
4	3%

Siegel et al. *CA: A Cancer Journal for Clinicians* 2012

5 yr- Overall Survival Rates

Stage	Lung	Prostate	Breast
1	50%	100%	98%
2/3	15%	100%	84%
4	3%	30%	24%

Siegel et al. *CA: A Cancer Journal for Clinicians* 2012

Lung Cancer

- Non-Small Cell Lung Cancer~85%
- Small Cell Lung Cancer~15%

Acta Oncologica, 2013; 52: 506–513

informa
healthcare

ORIGINAL ARTICLE

Dosimetric rationale and early experience at UFPTI of thoracic proton therapy and chemotherapy in limited-stage small cell lung cancer

ROVEL J. COLACO[1], SOON HUH[1], ROMAINE C. NICHOLS[1], CHRISTOPHER G. MORRIS[1], HARRY D'AGOSTINO[2], STELLA FLAMPOURI[1], ZUOFENG LI[1], DAT C. PHAM[3], ABUBAKR A. BAJWA[4] & BRADFORD S. HOPPE[1]

[1]*University of Florida Proton Therapy Institute, Jacksonville, Florida, USA,* [2]*Department of Thoracic Surgery, University of Florida College of Medicine, Gainesville, FL, USA,* [3]*Department of Hematology and Medical Oncology, University of Florida College of Medicine, Gainesville, FL, USA and* [4]*Department of Medicine, University of Florida College of Medicine, Gainesville, FL, USA*

Lung Cancer

- Non-Small Cell Lung Cancer
- ~~Small Cell Lung Cancer~~

Stage I Non-Small Cell Lung Cancer

Stage I NSCLC

Grutters et al Radiotherapy Oncology 2010	
Treatment	5yr OS (95%CI)
Conventional RT	**20%** (15-24%)

Proton-Beam Radiotherapy for Early-Stage Lung Cancer*

David A. Bush, Jerry D. Slater, Reiner Bonnet, Gregory A. Cheek, Richard D. Dunbar, Michael Moyers and James M. Slater

Chest 1999;116;1313-1319

Table 1—*Treatment Schema*

Treatment 1: proton only
Target: gross tumor volume
Dose: 51 CGE in 10 fractions over 2 wk

Stage I NSCLC

Grutters et al Radiotherapy Oncology 2010	
Treatment	5yr OS (95%CI)
Conventional RT	**20%** (15-24%)
Proton Therapy	**40%** (25-55%)
Carbon Therapy	**42%** (32-52%)

Stage I NSCLC

Author	N=	FU	Dose	fractions	LC	OS
Bush et al 1999 & 2004	68	30	51-60 Gy	10	3yr- 74%	3yr- 44%
Shioyama et al 2003	28	30	60-93 Gy	10-30	5yr-89%/39%	5yr- 70%/16%
Nihei et al 2006	37	24	70-94 Gy	20	2yr- 80%	2yr-84%
Hata et al 2007	21	25	50-60 Gy	10	2yr- 95%	2yr- 74%
Nakayama et al 2010	55	18	66 Gy 72.6 Gy	10 22	2yr- 97%	2yr- 98%
Chang et al 2011	18	16	87.5 Gy	35	2yr- 89%	2yr- 55%
Westover et al 2012	15	24	42-50 Gy	3-5	2yr- 100%	2yr-64%
Iwata et al 2010	57 23	36	80Gy 60 Gy 52.8 Gy	20 10 4	3yr-82%	3yr-75%
Miyamoto et al 2002	47 34	53	59.4-95.4 Gy 68.4-79.2 Gy	18 9	71% 97%	5yr- 42%
Miyamoto et al 2007	50	59	72 Gy	9	5yr- 95%	5yr- 50%
Miyamoto et al 2007	79	39	53-60 Gy	4	3yr- 90%	3yr- 60%

Proton therapy Carbon therapy

Stage I NSCLC

Grutters et al Radiotherapy Oncology 2010	
Treatment	5yr OS (95%CI)
Conventional RT	**20%** (15-24%)
Proton Therapy	**40%** (25-55%)
Carbon Therapy	**42%** (32-52%)
Stereotactic Ablative Body Radiotherapy (SABR)	**42%** (34-50%)

Stage I NSCLC

Grutters et al Radiotherapy Oncology 2010- Grade 3 or higher toxicity				
Treatment	Pneumonitis	Dyspnea	Esophagitis	Death
Conventional RT	**0.2%**	**0.5%**	**0.1%**	**0.1%**
Proton Therapy	**0.8%**	**0**	**0**	**0**
Carbon Therapy	**1.4%**	**0**	**NA**	**0**
SABR	**2%**	**0.8%**	**0.2%**	**0.7%**

Dosimetry: Protons vs SABR for Stage I

Group	Reference	Stage
Vienna	Georg *Radiother Oncology* 2008	IA
Mayo	Macdonald *IJROBP* 2009	I
UF	Hoppe *Radiother Oncology* 2010	I
MDACC	Register *IJROBP* 2011	I
STPTC (Japan)	Kadoya *IJROBP* 2011	I

Dosimetry: Protons vs SABR for Stage I

		Mean lung		Lung V5		Lung V20	
	Dose	Xrays	Protons	Xrays	Protons	Xrays	Protons
University Vienna*	45 Gy	3.9 Gy	3 Gy	17%	10%	6%	8%
Mayo**	60 Gy	3.8 Gy	3.3 Gy	18%	11%	4%	6%
University of Florida+	48 Gy	5.7 Gy	3.9 Gy	22%	14%	10%	8%
MD Anderson++	50 Gy	5.4 Gy	3.5 Gy	23%	11%	9%	7%
Nagoya University+++	66 Gy	7.8 Gy	4.6 Gy	32%	13%	11%	9%

*Georg et al Radiotherapy and Oncology 2008
**MacDonald et al IJROBP 2009
+Hoppe et al Radiotherapy and Oncology 2010
++Register et al IJROBP 2011
+++Kadoya et al IJROBP 2011

SABR-PT

Average difference in: mean lung dose = 1.7 Gy

lung V5 = 10%

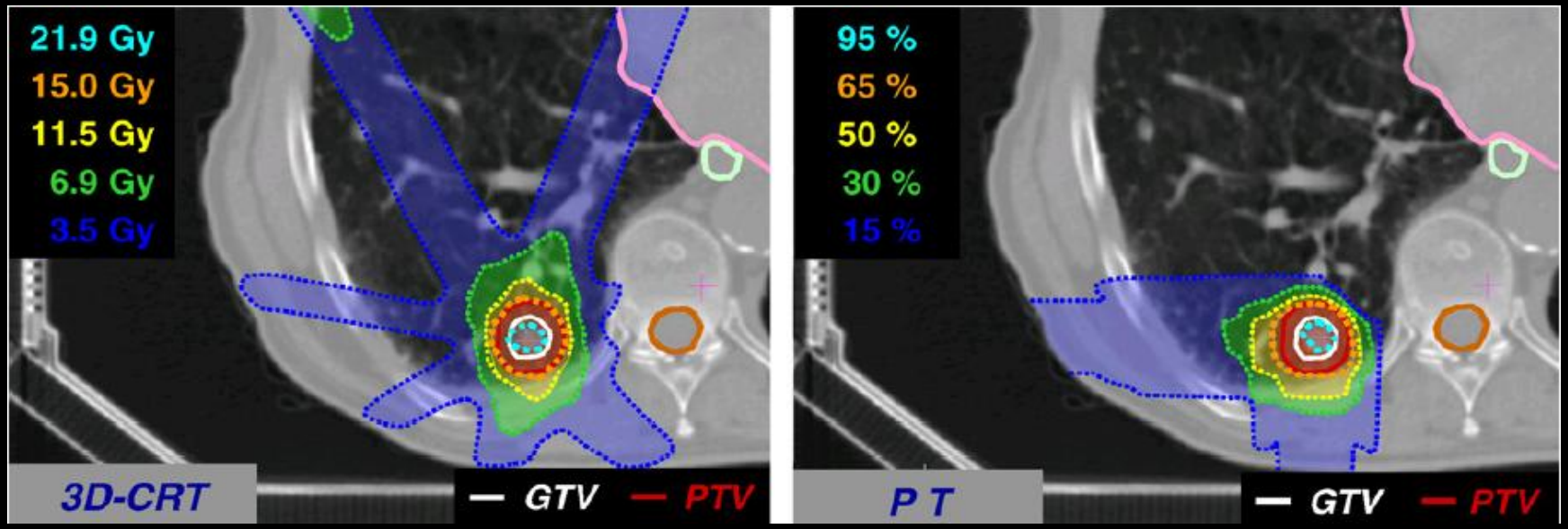
lung V20 = 1%

Dosimetry: Protons vs SABR for Stage I

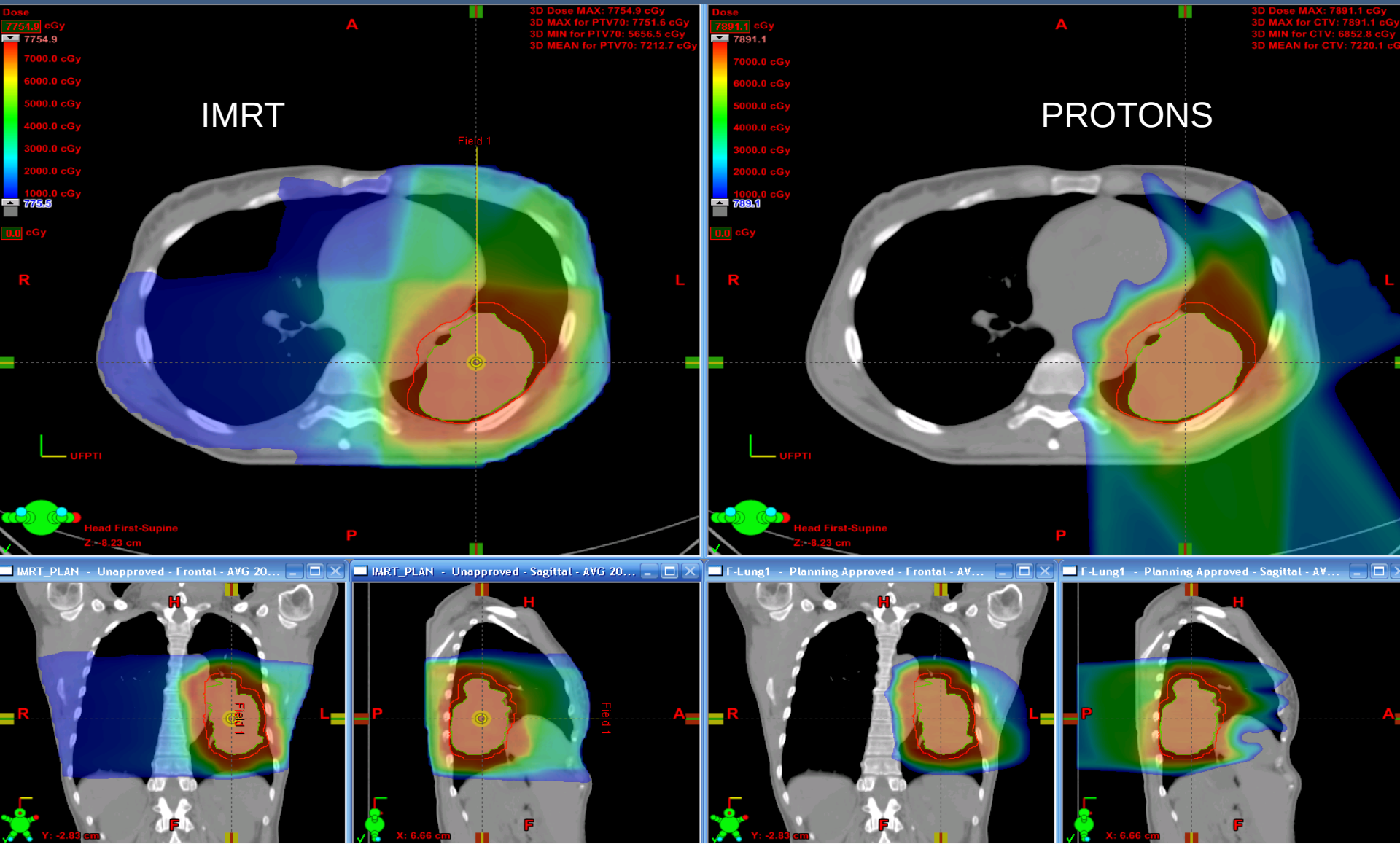
Group	Reference	Stage	Benefit
Vienna	Georg *Radiother Oncology* 2008	IA	None
Mayo	Macdonald *IJROBP* 2009	I	None
UF	Hoppe *Radiother Oncology* 2010	I	Bigger tumors ↑ benefit
MDACC	Register *IJROBP* 2011	I	Central/Superior tumors ↑ benefit
STPTC (Japan)	Kadoya *IJROBP* 2011	I	Bigger tumors & multiple tumors

Smaller tumors ↓ Benefit

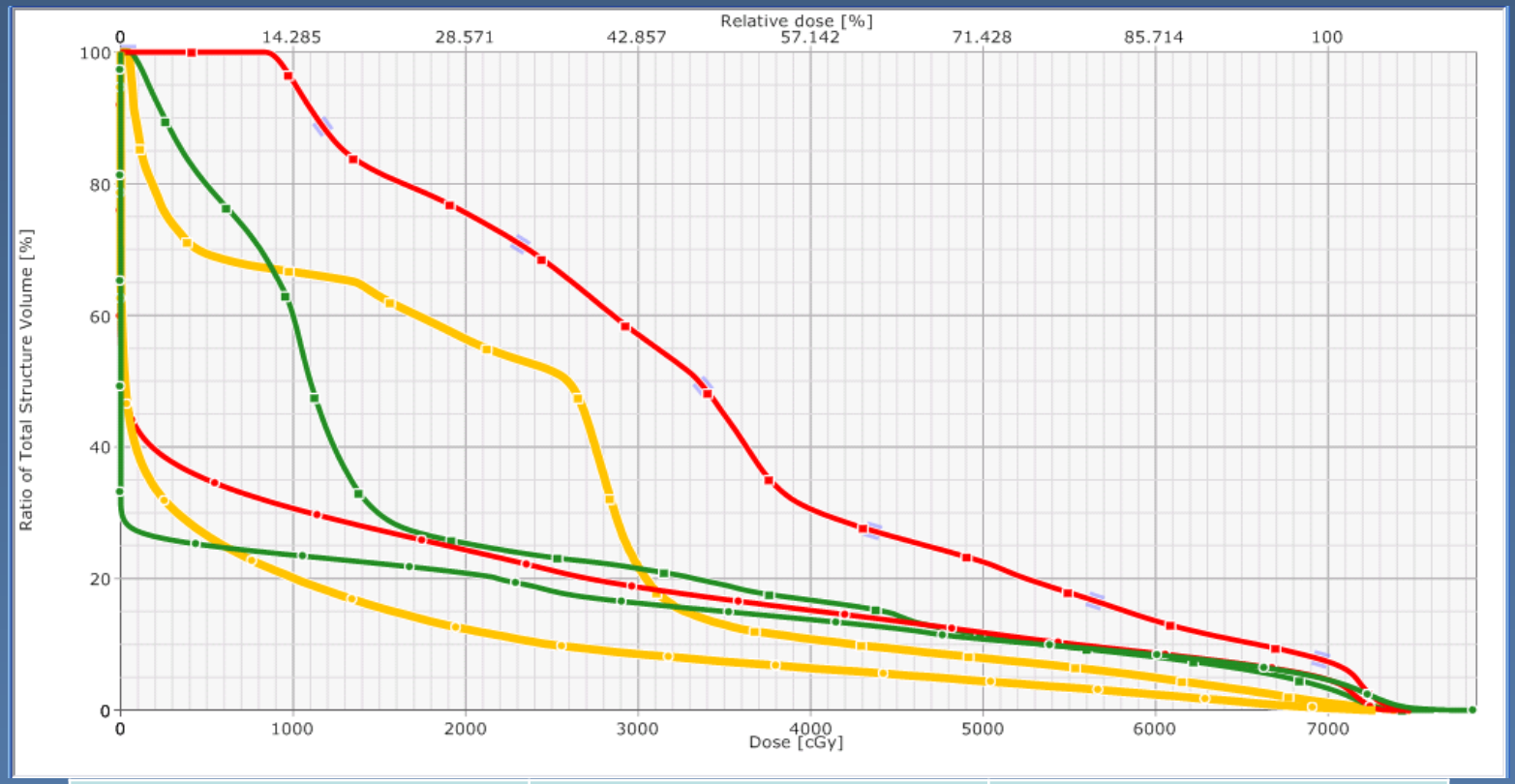
Georg Radiotherapy Oncology 2008



Bigger tumors ↑ Benefit



Bigger tumors ↑ Benefit



	IMRT	Protons
Mean lung	19 Gy	11 Gy
Mean esophagus	22 Gy	7 Gy
Mean heart	35 Gy	13 Gy

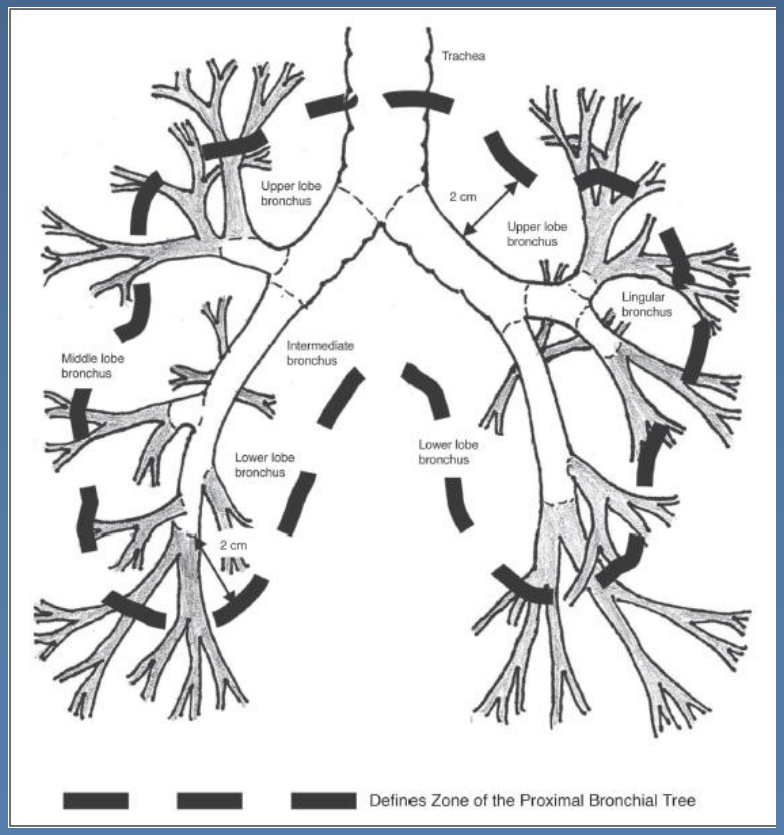
VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

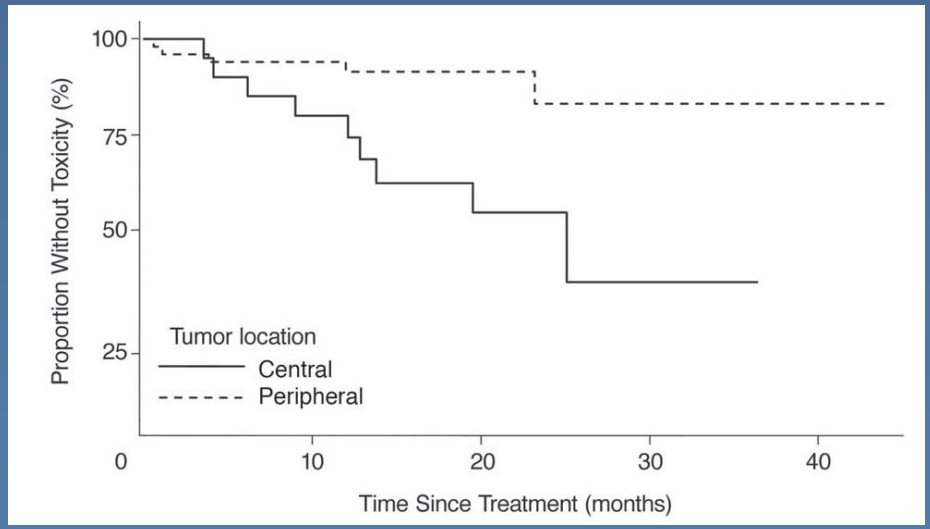
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

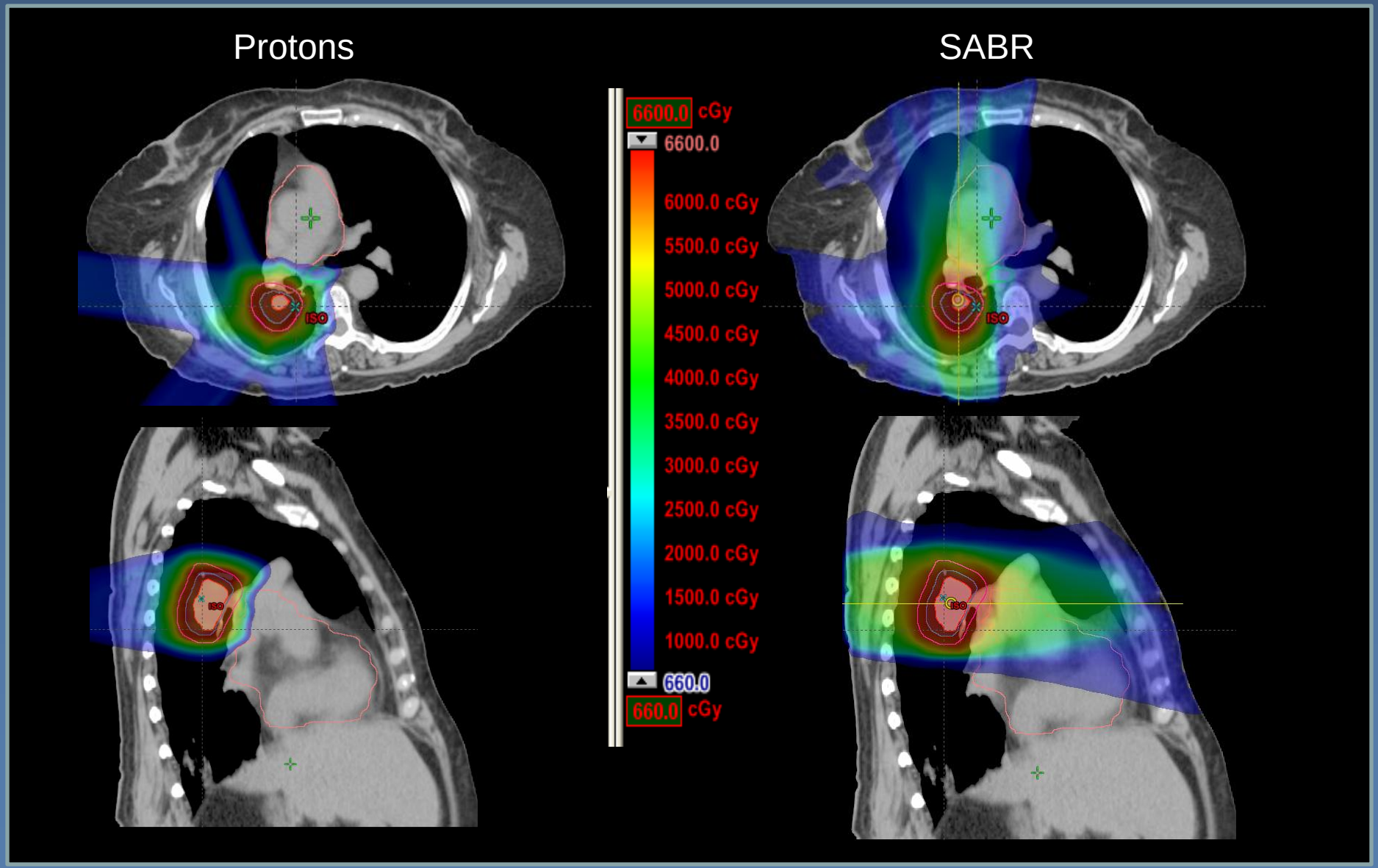
Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

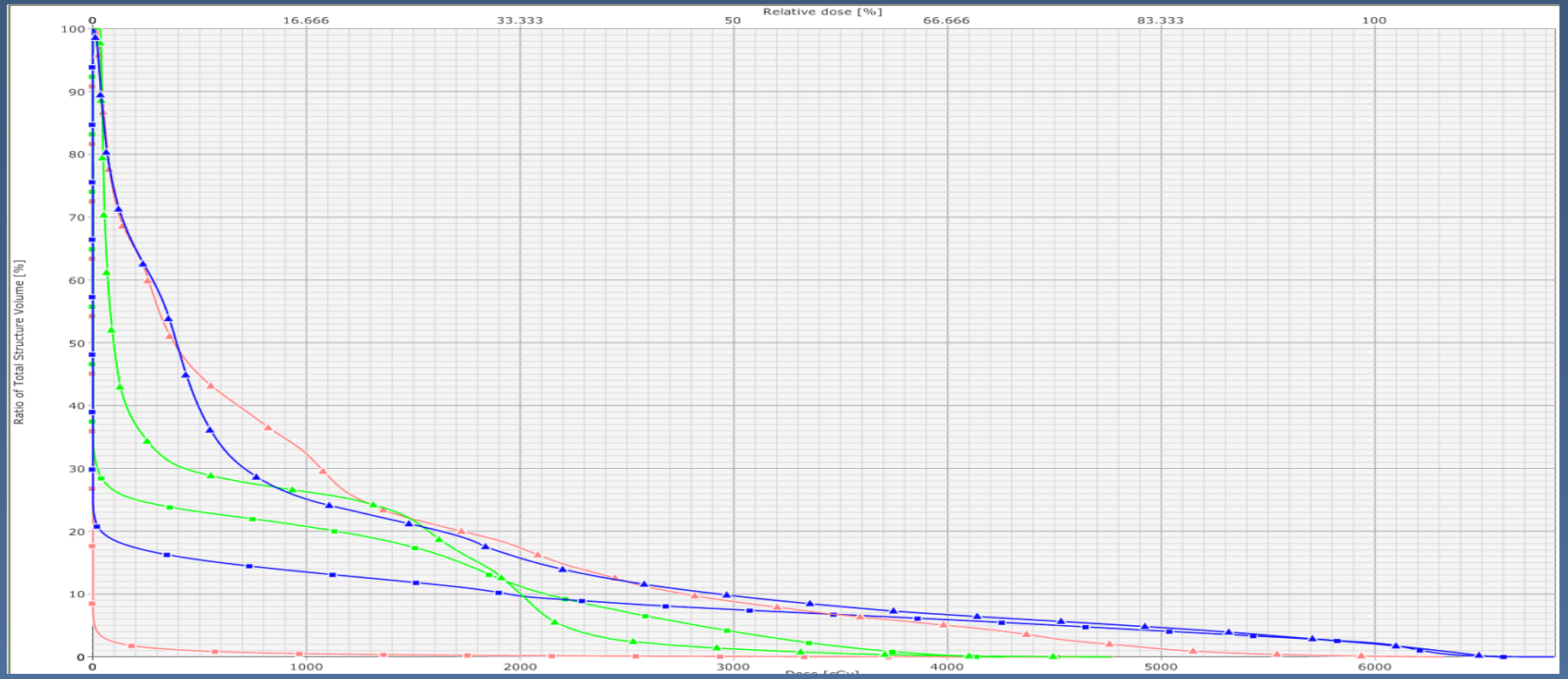
Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher





Central tumors ↑ Benefit





	SBRT	Protons
Mean lung	10 Gy	5 Gy
Lung V20	17%	10%
Mean esophagus	6 Gy	5 Gy
Mean heart	10 Gy	0.2 Gy

PT > SABR

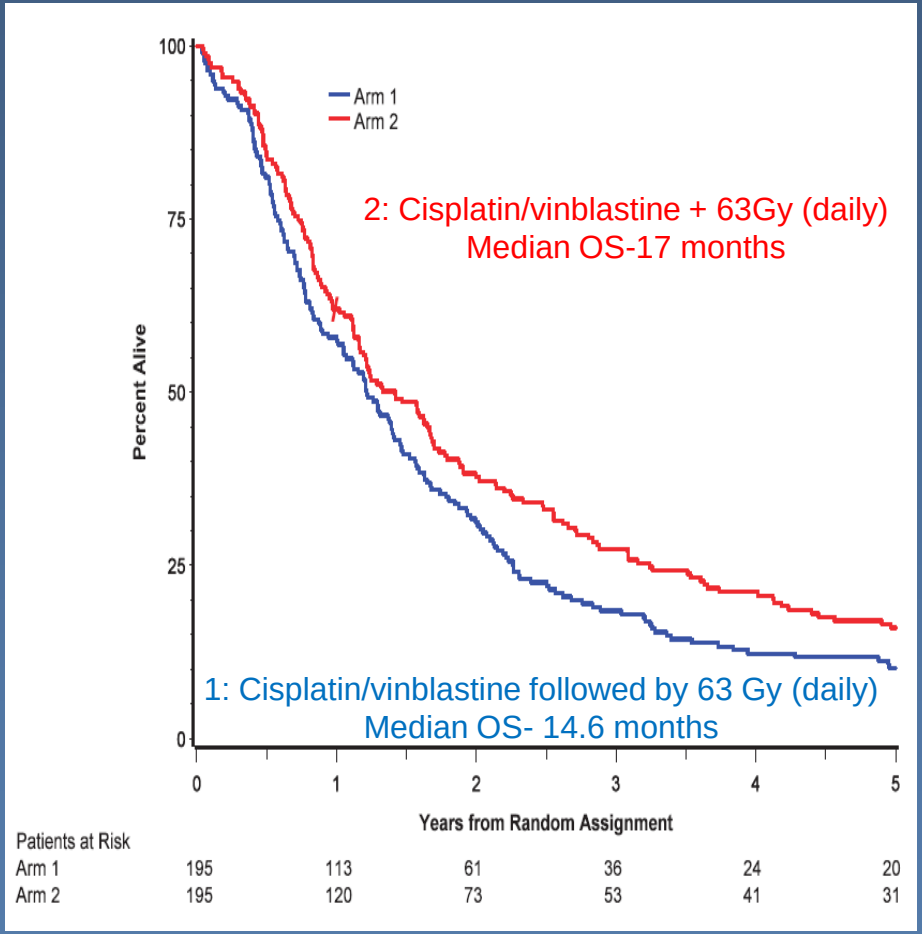
Stage I Non-Small Cell Lung Cancer
Larger tumors
Centrally located tumors
Superior located tumors (brachial plexus)
Multiple tumors (re-irradiation)

Stage II/III Non-Small Cell Lung Cancer

Sequential vs Concurrent Chemoradiation for Stage III Non–Small Cell Lung Cancer: Randomized Phase III Trial RTOG 9410

Walter J. Curran Jr, Rebecca Paulus, Corey J. Langer, Ritsuko Komaki, Jin S. Lee, Stephen Hauser, Benjamin Movsas, Todd Wasserman, Seth A. Rosenthal, Elizabeth Gore, Mitchell Machtay, William Sause, James D. Cox

Manuscript received June 14, 2010; revised July 22, 2011; accepted July 26, 2011. J Natl Cancer Inst 2011;103:1452–1460



Stage II/III NSCLC

RTOG Study	RT Dose	Med OS	Gd3+ GI	Gd3+ Lung
9410	60 Gy+ ENI	17 months	23%	15%

Local Control rates of ~40%

Stage II/III NSCLC

RTOG Study	RT Dose	Med OS	Gd3+ GI	Gd3+ Lung
9410	60 Gy+ ENI	17 months	23%	15%
0117	74Gy	26 months	24%	16%

Stage II/III NSCLC

RTOG Study	RT Dose	Med OS	Gd3+ GI	Gd3+ Lung
9410	60 Gy+ ENI	17 months	23%	15%
0117	74Gy	26 months	24%	16%
0617	60Gy	29 months	All Gd 3+ 74%	
	74Gy	20 months	All Gd 3+ 76%	

Clinical Investigation: Thoracic Cancer Int J Radiation Oncol Biol Phys, Vol. 84, No. 2, pp. 456–463, 2012

Radiation Therapy Oncology Group Protocol 02-29: A Phase II Trial of Neoadjuvant Therapy With Concurrent Chemotherapy and Full-Dose Radiation Therapy Followed by Surgical Resection and Consolidative Therapy for Locally Advanced Non-small Cell Carcinoma of the Lung

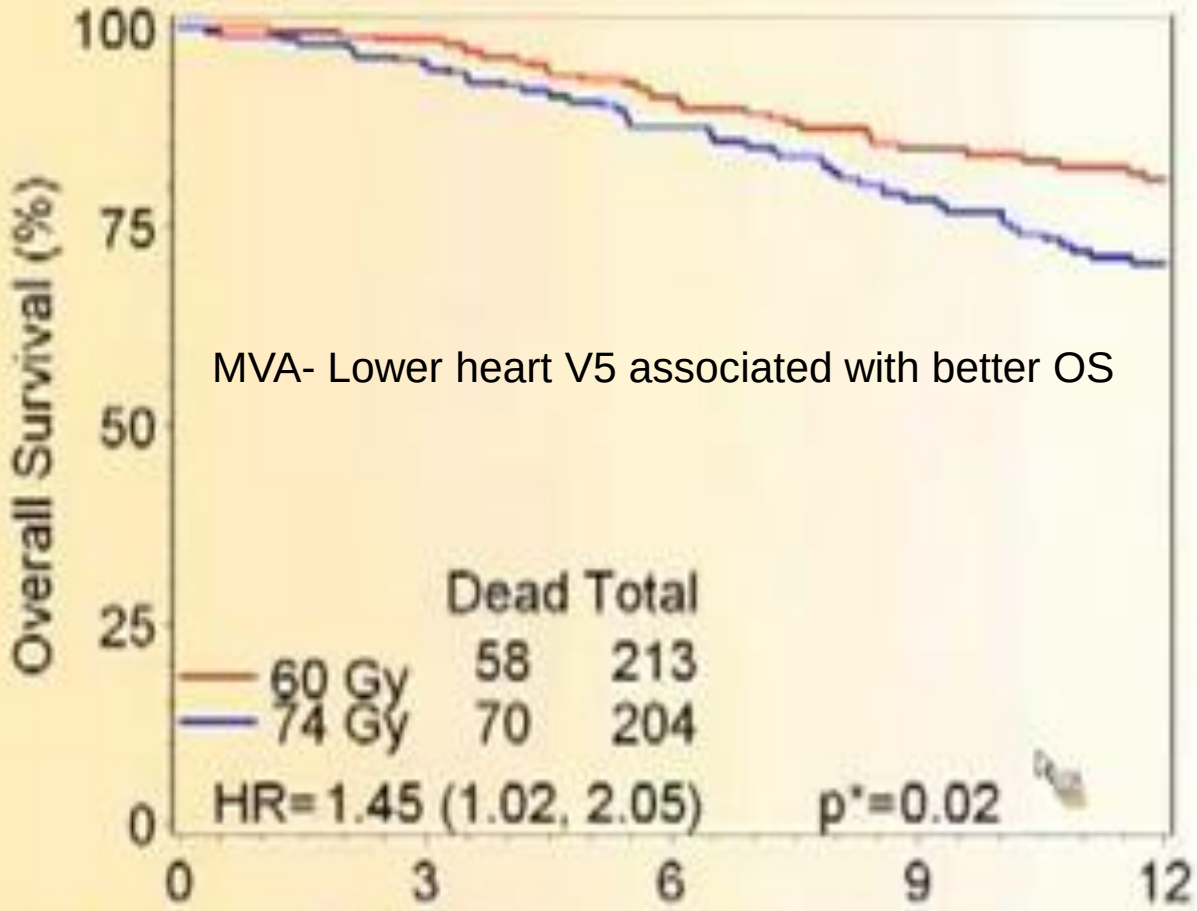
Mohan Suntharalingam, M.D.,* Rebecca Paulus,† Martin J. Edelman, M.D.,* Mark Krasna, M.D.,‡ Whitney Burrows, M.D.,* Elizabeth Gore, M.D.,§ Lynn D. Wilson, M.D.,‖ and Hak Choy, M.D.¶

Stage III NSCLC (n=57) → **Carbo/Taxol + 61.2Gy (ENI)** → **Surgery (n=37)**

- Complete Response (n=3)
- <CR (n=34)

RTOG 0617

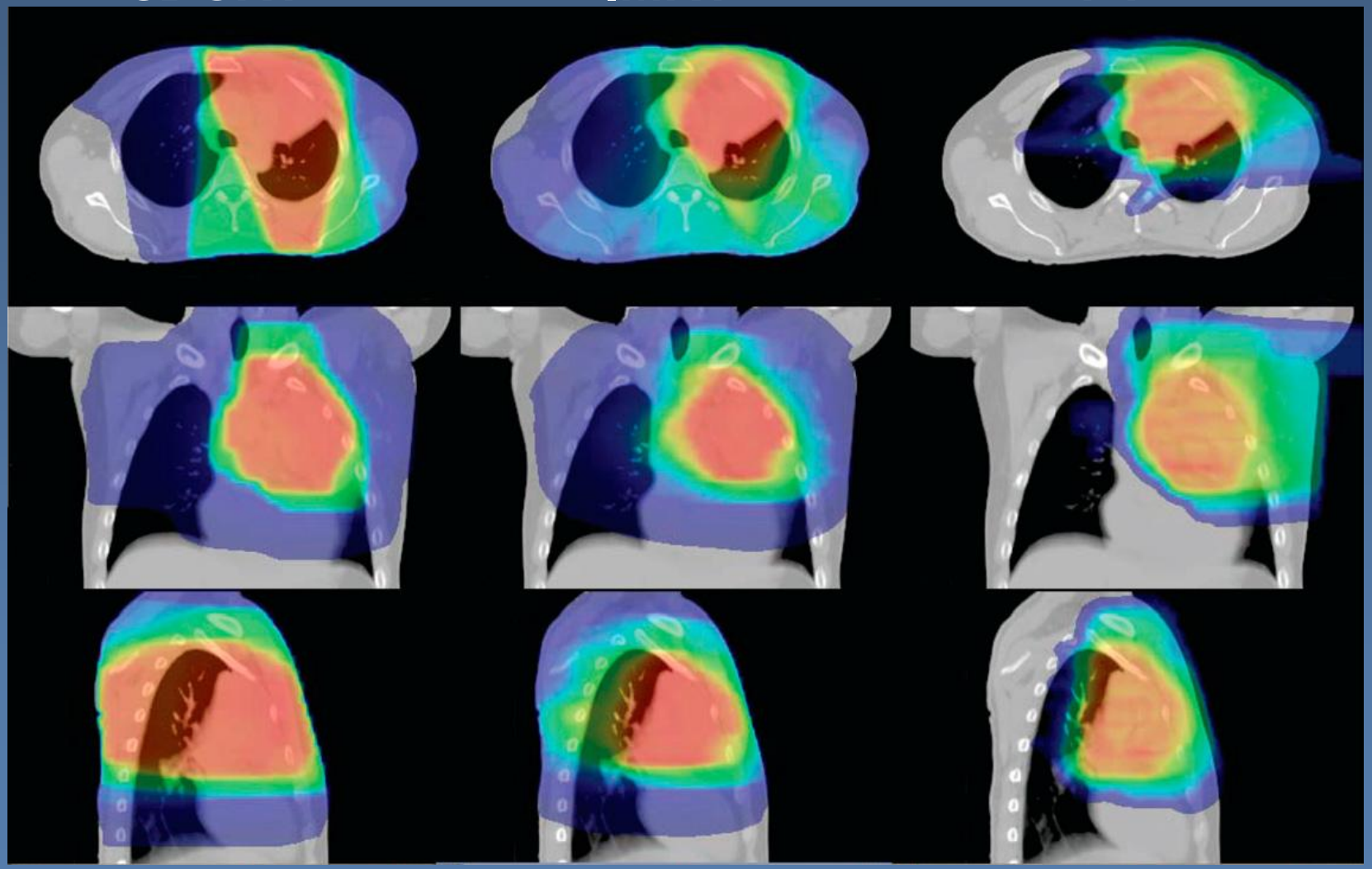
Overall Survival



Patients at Risk					
60 Gy	213	190	149	124	104
74 Gy	204	175	137	116	93

*One-sided p-value, left tail

Stage IIIA- Nichols CLC 2011



Dosimetric Advantage for Stage III Lung

		Mean lung			Lung V5			Lung V20		
	Dose	3D	IMRT	Protons	3D	IMRT	Protons	3D	IMRT	Protons
Chang	74 Gy	25 Gy	24Gy	20 Gy	58%	62%	40%	40%	37%	32%
Nichols	74 Gy	21 Gy	15Gy	11 Gy	54 %	50%	32%	27%	27%	21%
Nichols ENI	74/40	20 Gy	16Gy	13 Gy	53%	51%	31%	30%	26%	24%
Zhang	74 Gy	NA	20Gy	15 Gy	NA	59%	39%	NA	35%	28%
Vogelius	60 Gy	12Gy	10Gy	5 Gy	NA	NA	NA	22%	14%	10%

Double scatter PT IMPT

DS Protons reduced	Mean Lung	Lung V5	Lung V20
3DCRT	7 Gy	20%	7%
IMRT	4 Gy	20%	5%

Dosimetric Advantage for Stage III Heart & Esophagus

		Heart V40/mean dose			Esophagus V55/ mean dose		
	Dose	3D	IMRT	Protons	3D	IMRT	Protons
Chang	74 Gy	29%	12%	8%	41%	37%	36%
Nichols	74 Gy	11 Gy	6 Gy	4 Gy	44Gy	32Gy	29 Gy
Nichols ENI	74/40	NA	9 Gy	4 Gy	27Gy	26Gy	25 Gy
Zhang	74 Gy	NA	22%	8%	NA	32%	25%

Double scatter PT IMPT

Stage II/III NSCLC clinical studies

Author	N=	FU	Dose	DFS	OS	LC	GI tox	Lung tox
Bush 1999	10	14	28.8Gy-PT, 45Gy XRT	2yr- 19%	2yr- 13%			
Shioyama 2003	14	30	53-89 Gy/ 23-40 fx (XRT+PT)		2yr- 71%; 5yr-0%			
Nakayama 2011	35	17	67.1-91.3 Gy/ 22-38 fx	2yr-29%	2yr-59%	11%	0%	0%
Oshiro 2012	57	22	50-85 Gy	2yr- 25%	2yr- 39%	16%	0%	5%/8%
Chang 2011	44	20	74 Gy/ 37 fx + Chemo	2yr- 48%	2yr- 55%	20%	11%	5%
Hoppe 2012	19	16	60-80 Gy + chemo	Median- 14 months	Median- 18 months	5%	5%	5%/ 13%

Original Article

Early Findings on Toxicity of Proton Beam Therapy With Concurrent Chemotherapy for Nonsmall Cell Lung Cancer

Cancer
Volume 117, Issue 13, Article first published online: 24 JAN 2011

Samir Sejpal, MD[1]; Ritsuko Komaki, MD[1]; Anne Tsao, MD[2]; Joe Y. Chang, MD, PhD[1]; Zhongxing Liao, MD[1]; Xiong Wei, MD[1]; Pamela K. Allen, PhD[1]; Charles Lu, MD[2]; Michael Gillin, PhD[3]; and James D Cox, MD[1]

	3DCRT	IMRT	Protons
Years treated	2001-2003	2003-2005	2006-2008
Patients treated	N=74	N=66	N=62
RT Dose	63 Gy (60-69.9)	63 Gy (60-76)	74 Gy (63-81)
% Stage III or higher	94%	95%	89%
Median follow up	18 months	17 months	15 months
GTV size	141 cm^3	203 cm^3	68 cm^3
Grade 3+ esophagitis	18%	44%	5%
Grade 3+ pneumonitis	30%	9%	2%
Median overall survival	17.7 months	17.6 months	24.4 months

Multi-Institutional Research

- MD Anderson & MGH-- Phase II randomized study of IMRT vs Proton therapy for stage III NSCLC with concurrent chemotherapy
  - Currently enrolling patients

RTOG 1308

Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Radiochemotherapy for Inoperable Stage II-IIIB NSCLC

SCHEMA

STRATIFY

Stage
1. II
2. IIIA
3. IIIB

GTV
1. ≤ 130 cc
2. > 130 cc

Histology
1. Squamous
2. Non-Squamous

Neoadjuvant Chemo
1. No
2. Yes

RANDOMIZE

Arm 1: Photon dose—Higher achievable dose between 60-70 Gy, once daily plus platinum-based doublet chemotherapy*

Arm 2: Proton dose—Higher achievable dose between 60-70 Gy (RBE), once daily plus platinum-based doublet chemotherapy*

Both Arms: Consolidation chemotherapy x 2 is allowed*

Proton Collaborative Group (PCG)-Phase I/II Hypofractionation with concurrent chemotherapy

	Dose	Dose/fx	Fxs	Weeks	BED	tBED
1	60 CGE	2.5	24	5	75	67
2						
3						
4						

BED- biologic effective dose
tBED-time dependent BED

Proton Collaborative Group (PCG)-Phase I/II Hypofractionation with concurrent chemotherapy

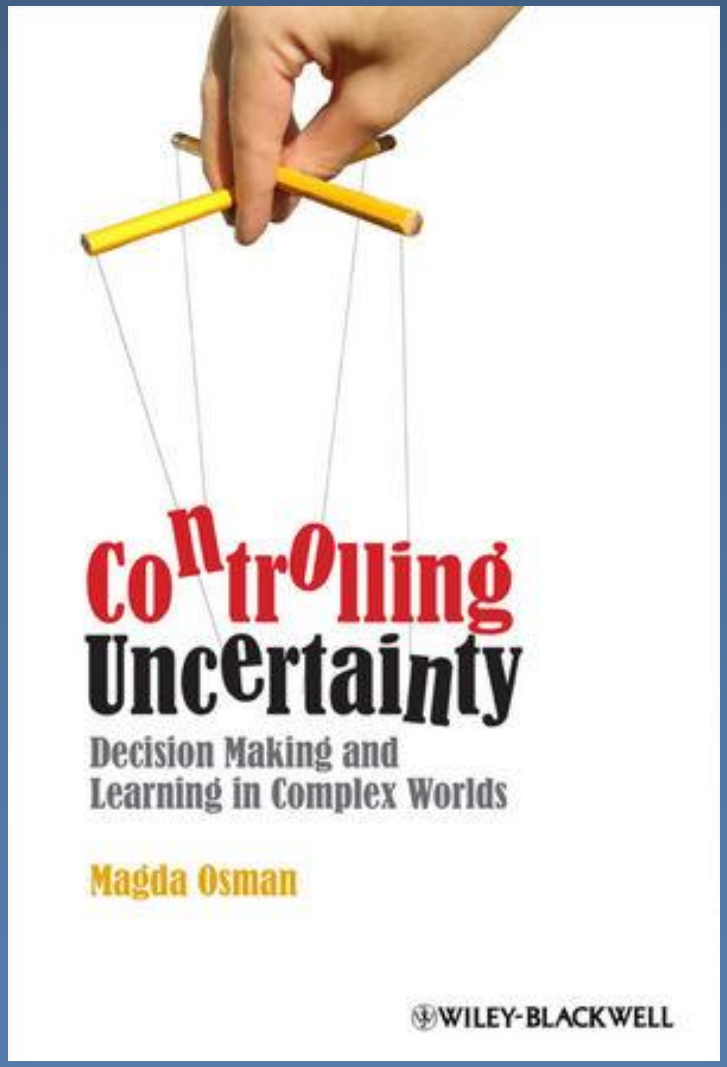
Dose	Dose/fx	Fxs	Weeks	BED	tBED
60 CGE	2.5	24	5	75	67
60 CGE	3	20	4	78	72.5
60 CGE	3.53	17	3.5	81	77.4
60 CGE	4	15	3	84	81.2
RTOG 0617 Dose Arms					
60 Gy	2	30	6	72	61
74 Gy	2	37	7.5	89	74

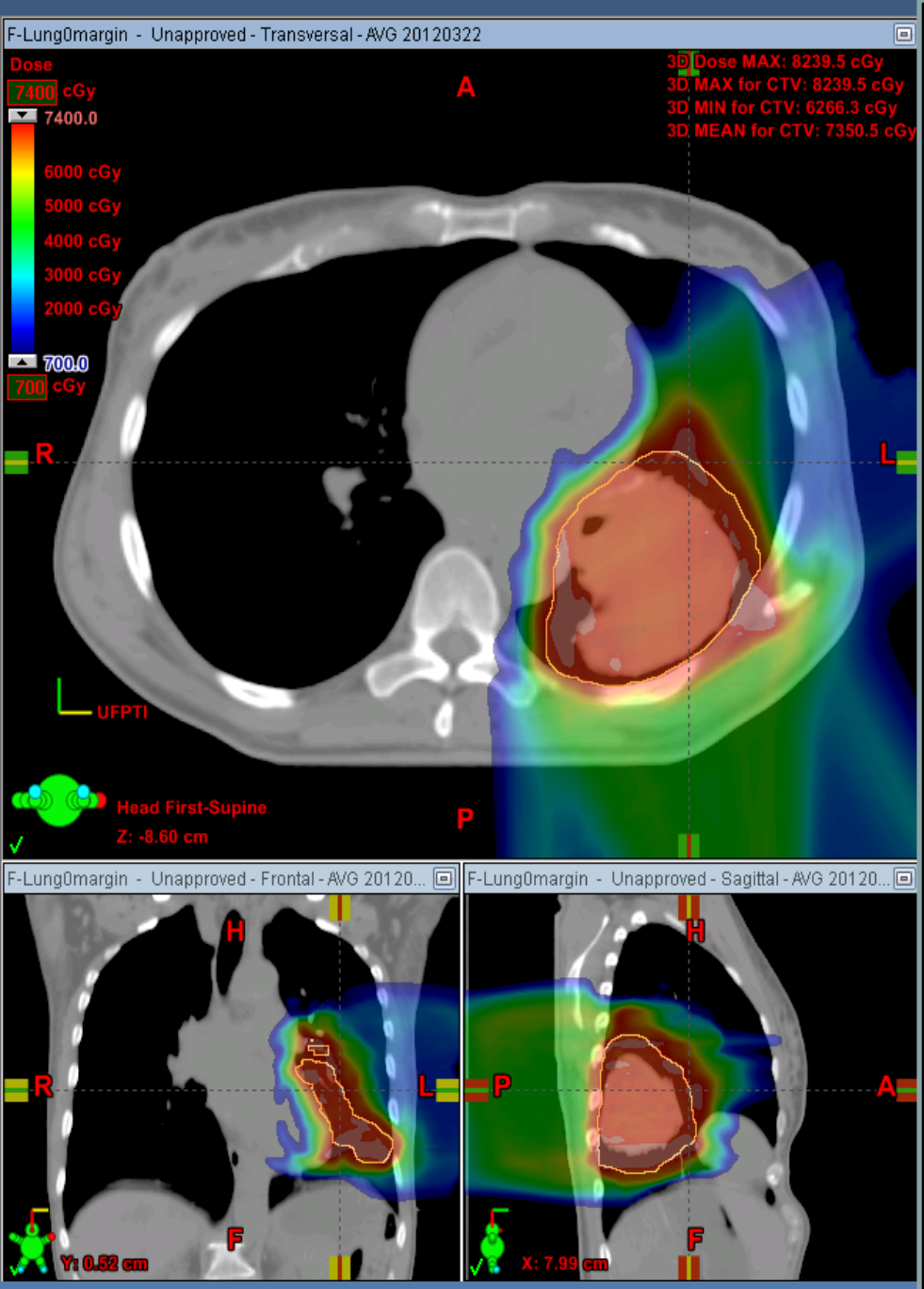
BED- biologic effective dose
tBED-time dependent BED

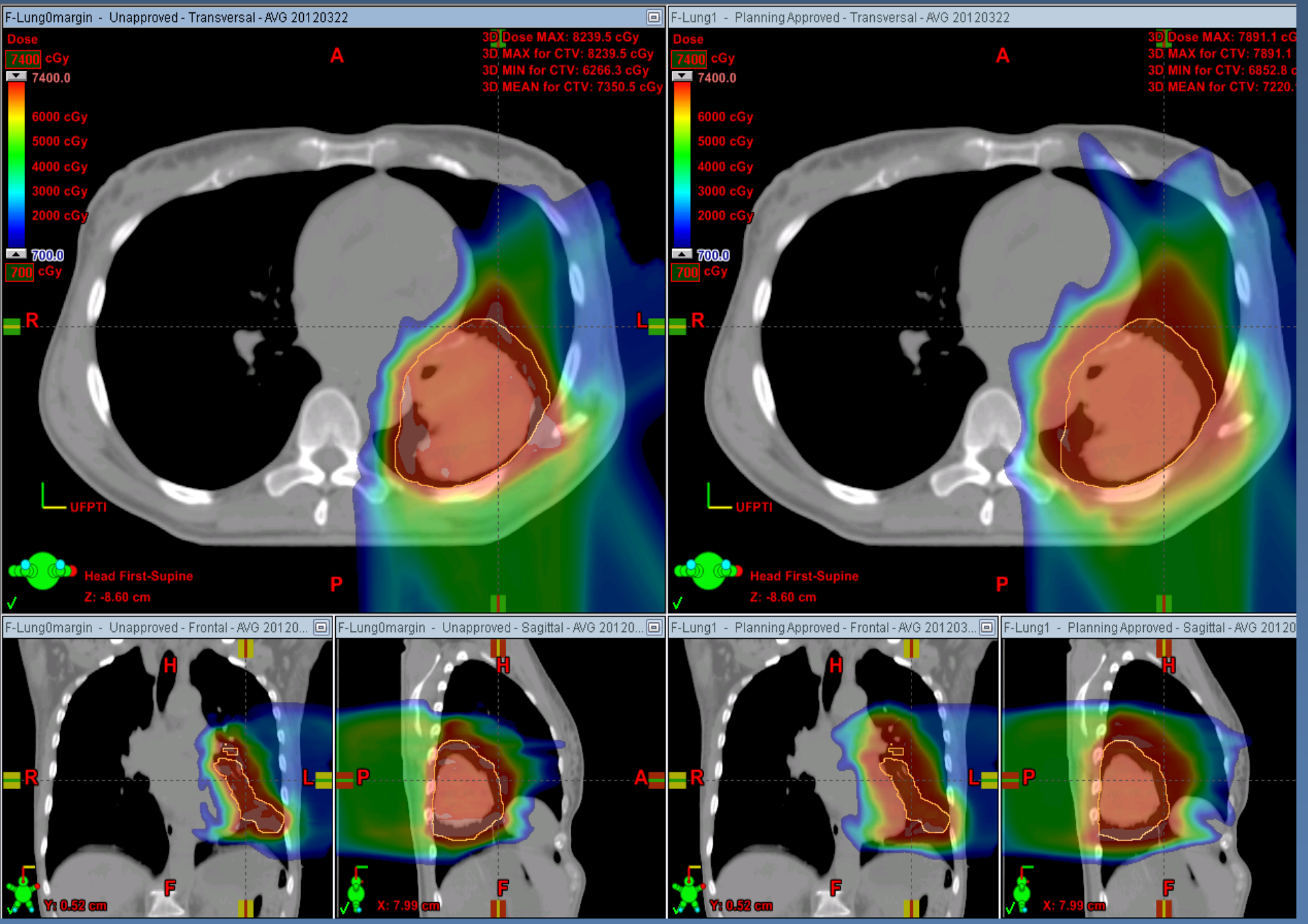
Treatment Planning

Uncertainties

Uncertainties with Protons




F-LungOmargin - Unapproved - Transversal - AVG 20120322
Dose
7400 cGy
7400.0
6000 cGy
5000 cGy
4000 cGy
3000 cGy
2000 cGy
700.0
700 cGy
3D Dose MAX: 8239.5 cGy
3D MAX for CTV: 8239.5 cGy
3D MIN for CTV: 6266.3 cGy
3D MEAN for CTV: 7350.5 cGy
A
R
L
P
UFPTI
Head First-Supine
Z: -8.60 cm
F-LungOmargin - Unapproved - Frontal - AVG 20120...
H
R
L
F
Y: 0.52 cm
F-LungOmargin - Unapproved - Sagittal - AVG 20120...
H
P
A
F
X: 7.99 cm


F-Lung0margin - Unapproved - Transversal - AVG 20120322
Dose
7400 cGy
7400.0
6000 cGy
5000 cGy
4000 cGy
3000 cGy
2000 cGy
700.0
700 cGy
3D Dose MAX: 8239.5 cGy
3D MAX for CTV: 8239.5 cGy
3D MIN for CTV: 6266.3 cGy
3D MEAN for CTV: 7350.5 cGy
A
R
L
P
UFPTI
Head First-Supine
Z: -8.60 cm
F-Lung1 - Planning Approved - Transversal - AVG 20120322
3D Dose MAX: 7891.1 cG
3D MAX for CTV: 7891.1
3D MIN for CTV: 6852.8 c
3D MEAN for CTV: 7220.
F-Lung0margin - Unapproved - Frontal - AVG 20120...
H
F
Y: 0.52 cm
F-Lung0margin - Unapproved - Sagittal - AVG 20120...
X: 7.99 cm
F-Lung1 - Planning Approved - Frontal - AVG 201203...
F-Lung1 - Planning Approved - Sagittal - AVG 20120

Uncertainties with Protons

- Do not treat with the most conformal plan
- Treat with the most conformal ROBUST plan that takes into consideration the uncertainties

A few of the uncertainties with Protons

- Range
- RBE
- Secondary neutron
- Distal fall off in low density lung

IOP Publishing Physics in Medicine and Biology
Phys. Med. Biol. 57 (2012) R99–R117 doi:10.1088/0031-9155/57/11/R99

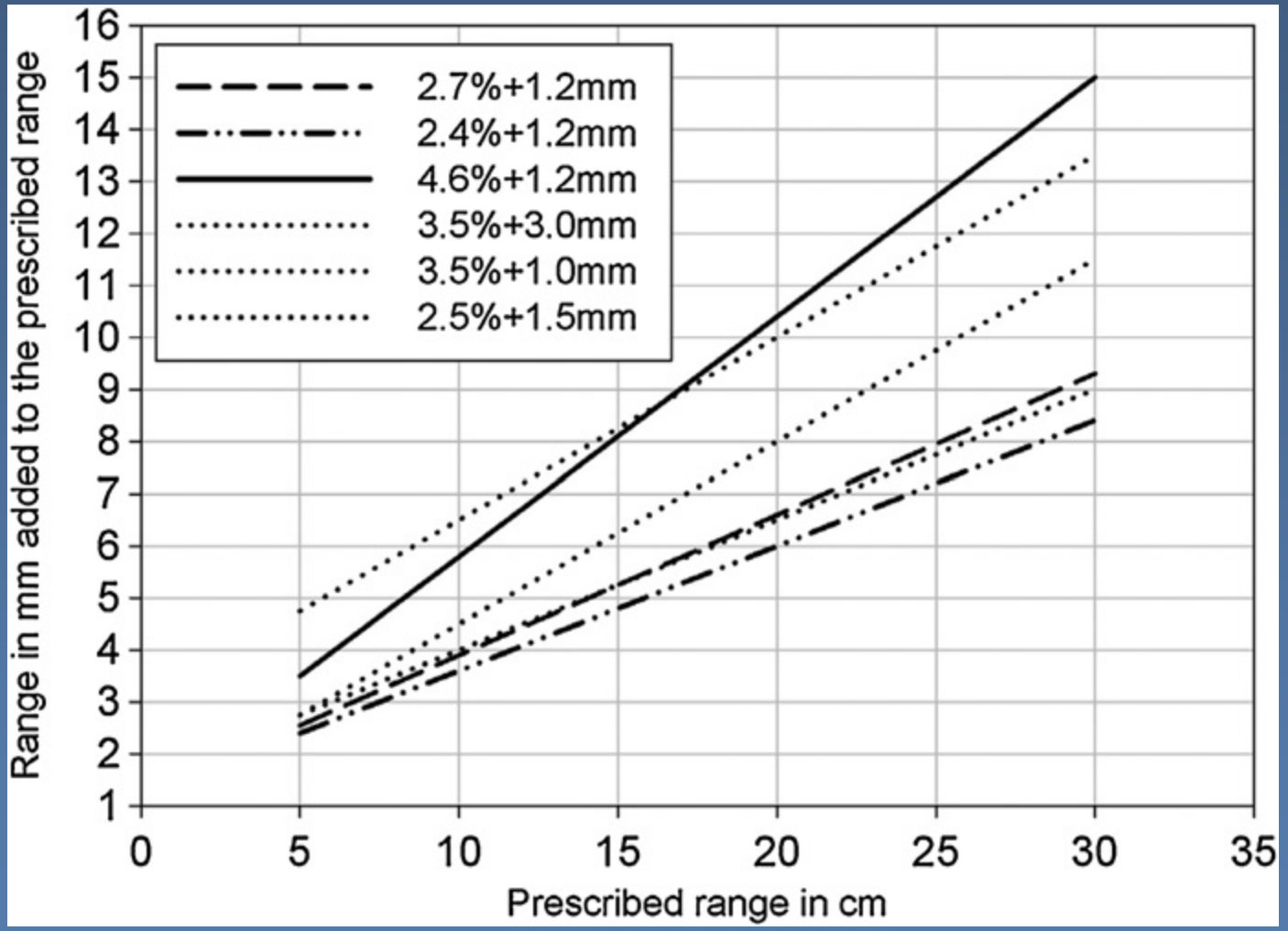
TOPICAL REVIEW

Range uncertainties in proton therapy and the role of Monte Carlo simulations

Harald Paganetti

Source of range uncertainty in the patient	Range uncertainty without Monte Carlo
Independent of dose calculation	
Measurement uncertainty in water for commissioning	±0.3 mm
Compensator design	±0.2 mm
Beam reproducibility	±0.2 mm
Patient setup	±0.7 mm
Dose calculation	
Biology (always positive) ^	+~0.8%
CT imaging and calibration	±0.5%[a]
CT conversion to tissue (excluding I-values)	±0.5%[b]
CT grid size	±0.3%[c]
Mean excitation energy (I-values) in tissues	±1.5%[d]
Range degradation; complex inhomogeneities	−0.7%[e]
Range degradation; local lateral inhomogeneities *	±2.5%[f]
Total (excluding *, ^)	2.7% + 1.2 mm
Total (excluding ^)	4.6% + 1.2 mm

Protons: Range Uncertainty



Protons: Range Uncertainty

- Add range uncertainty to the ITV target
- Avoid stopping a beam just proximal to the cord

RBE Uncertainties

- We use an RBE of 1.1 (understanding that it might be a bit higher at the distal end of the SOBP)
- Avoid stopping beams inside a major OAR
- Use multiple fields

Neutron dose Uncertainty

- Out of field neutron dose in double scatter proton therapy is similar to that of IMRT.
- Risk of 2nd cancers from neutrons
- Patients with expected 10 year survival rates of <10%.

Distal Fall-off uncertainty

- Uncertain of the ability of protons to stop in low density lung
- Try to choose beam angles that stop in the mediastinum or chest wall rather than lung
- Use multiple fields

How to make a Robust Plan

- 4D CT simulation and draw iGTV
- Treatment planning done on average scan with an over ride of the iGTV with HU=50*
- Add 8-10 mm smearing
- Add range equation to the ITV
- Add block margin to PTV
- 3-4 beams
- Avoid beams that stop just proximal to an OAR
- Check target coverage on 0 and 50 phase of 4D
- Assess OAR dose without over rides

Daily Image Guidance

- Proton therapy requires accurate alignment
- Currently, using daily orthogonal kv imaging
- Stage I- fiducial markers (and bone)
- Stage II/III- bone alignment

Weekly Verification Scans

- Tumor changes
  - Shrinking
  - Growing

- Thoracic density changes or tumor displacement
  - Pleural effusions
  - Atelectasis

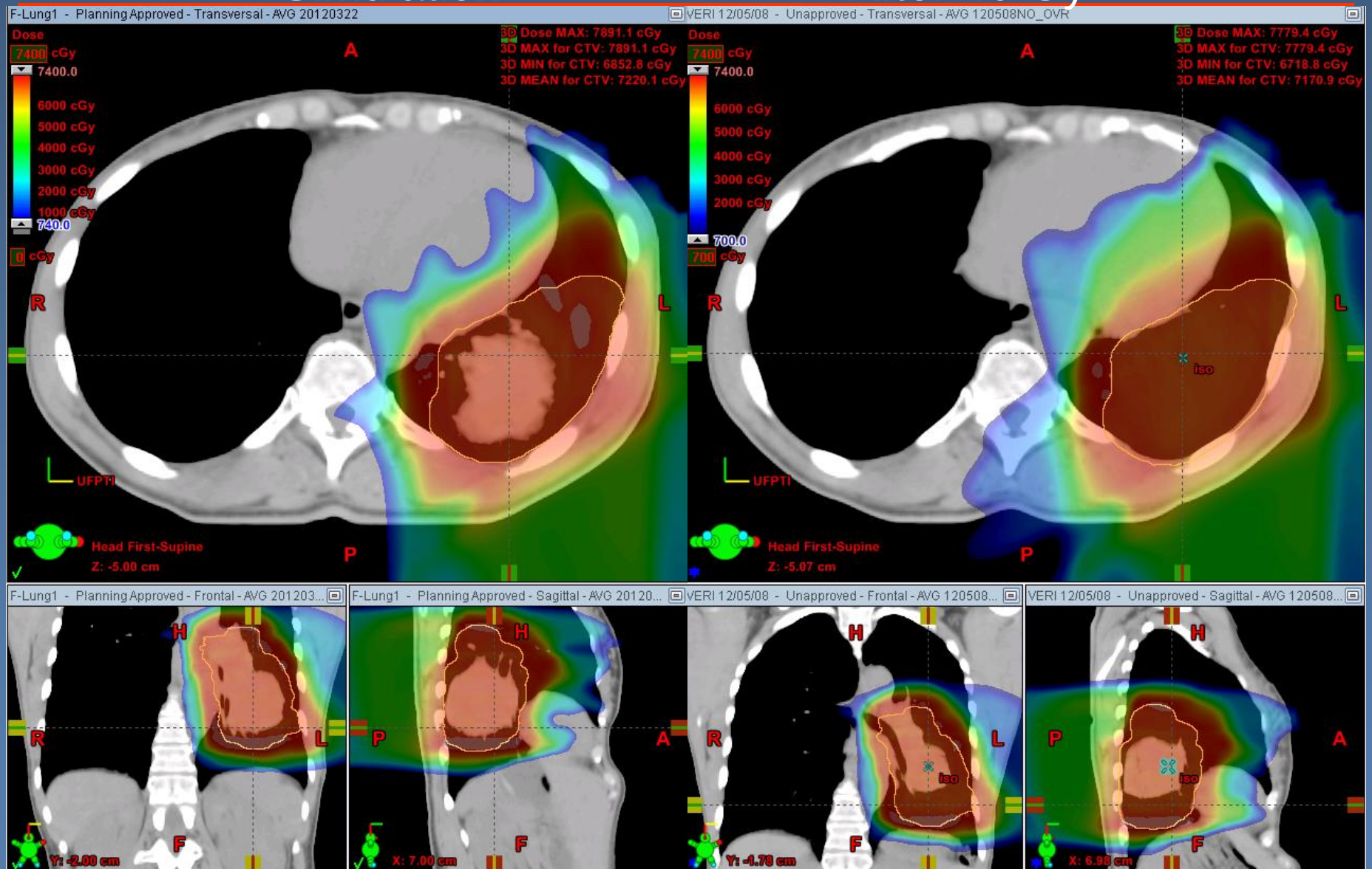
Verification Scans

- Evaluate coverage of the CTV and PTV
- Evaluate dose to critical structures (cord D0.1cc)
- Majority of the time don't replan
  - Pull back the range due to tumor regression
  - Completely replan for tumor displacement
    - Problem for any type of RT

Re-evaluations (tumor regression)

Simulation

After 40 Gy



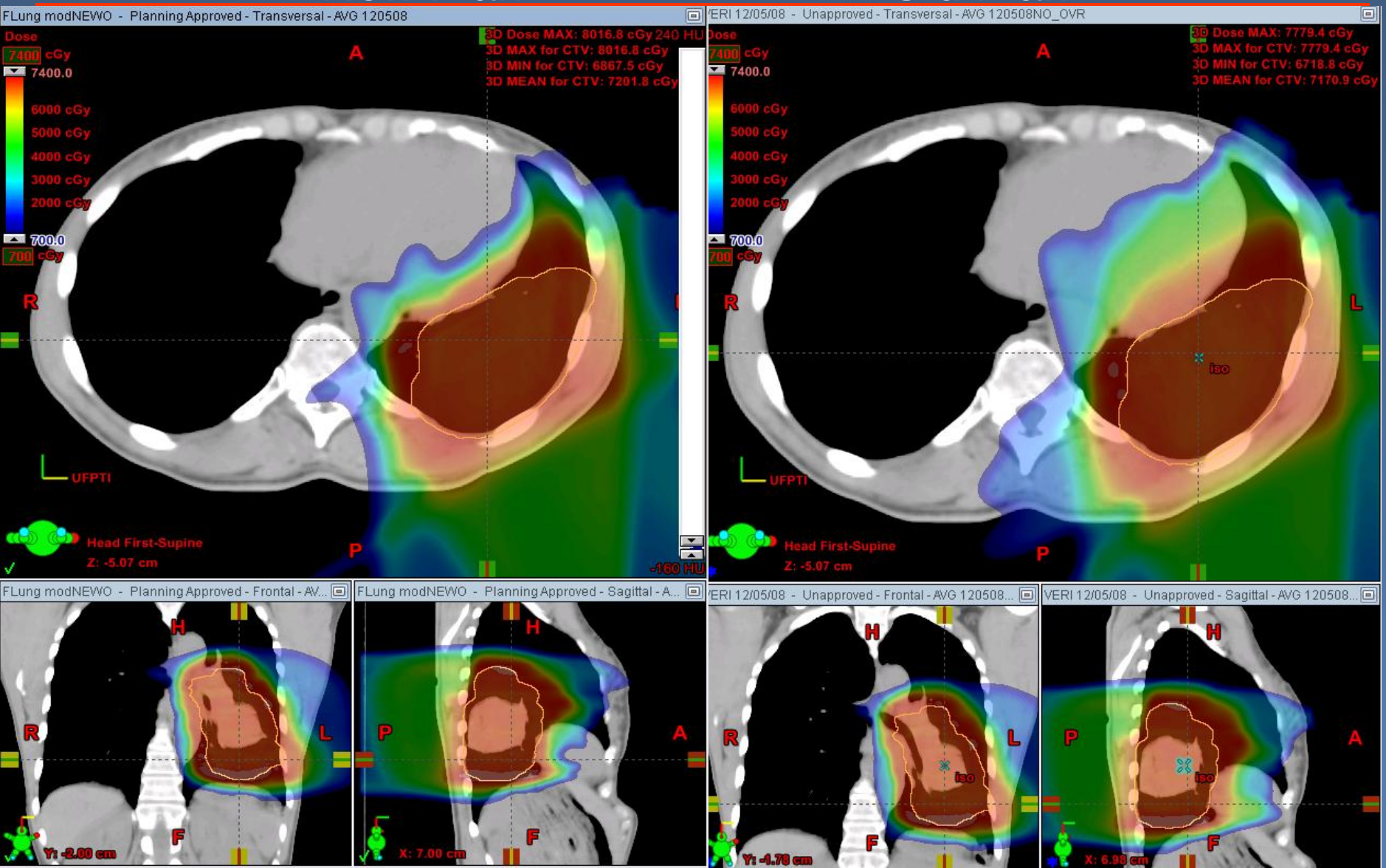
Re-evaluations (tumor regression)

Old Plan

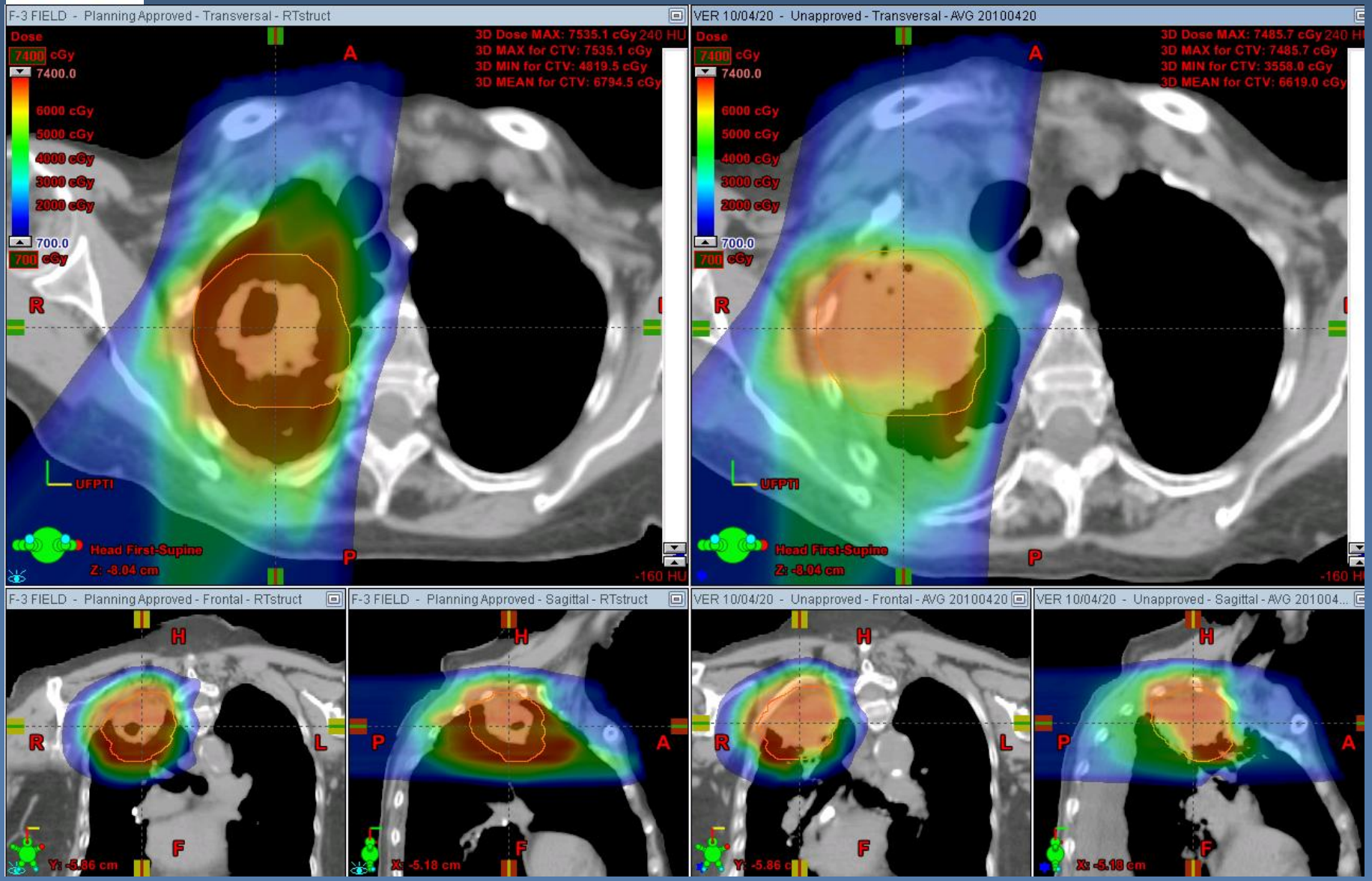
Re-evaluations (tumor regression)

New Plan

Old Plan

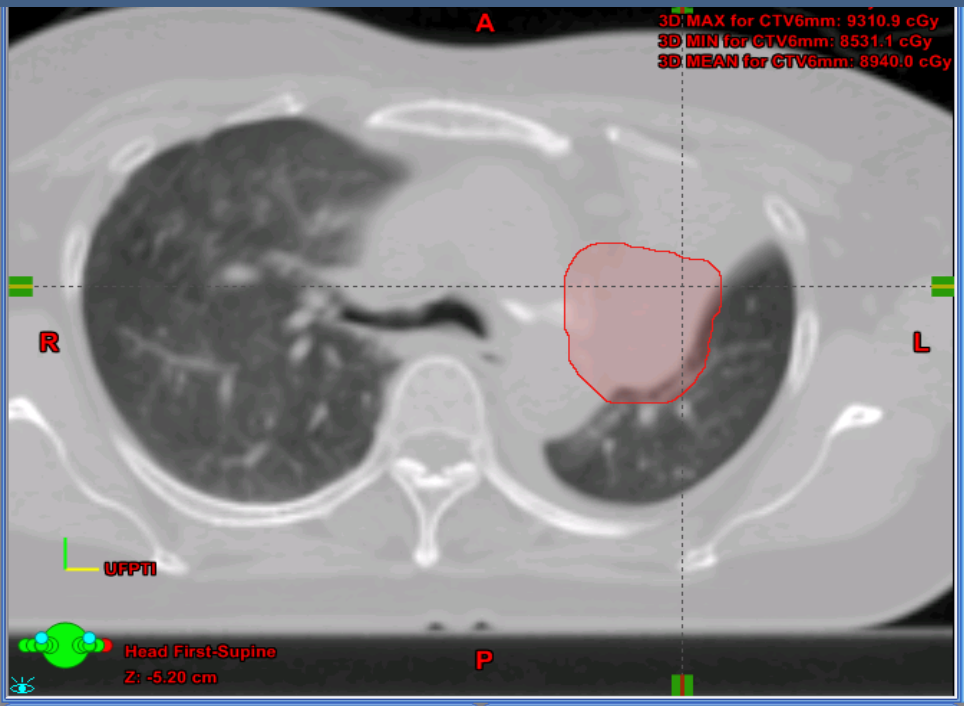


Re-evaluations- pleural effusion

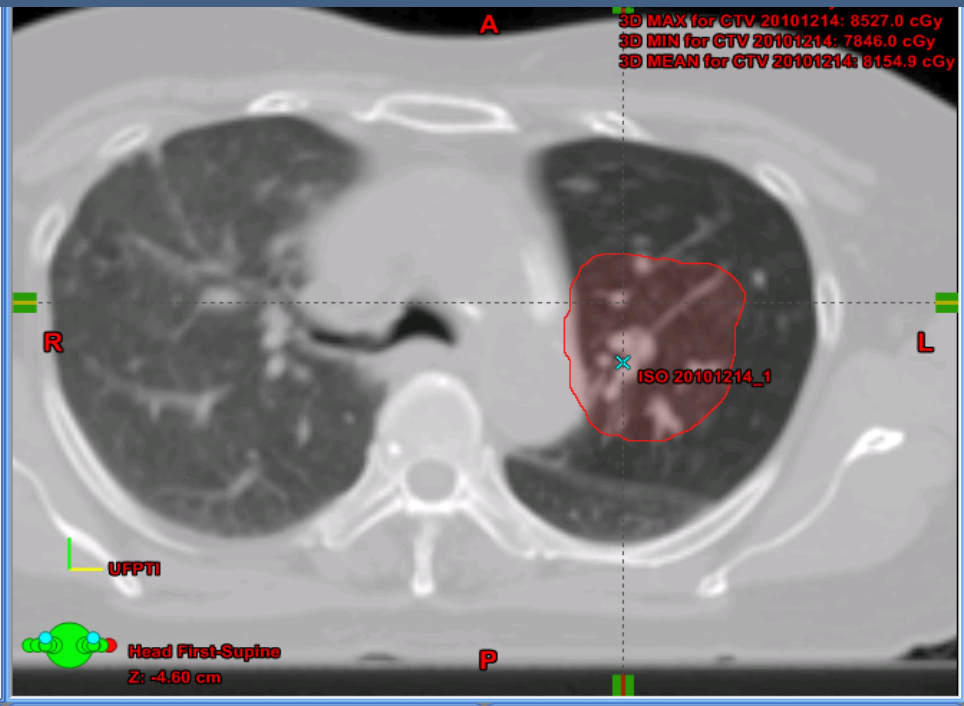


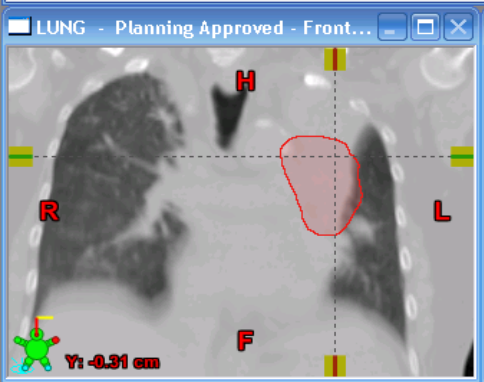
Tumor displacement

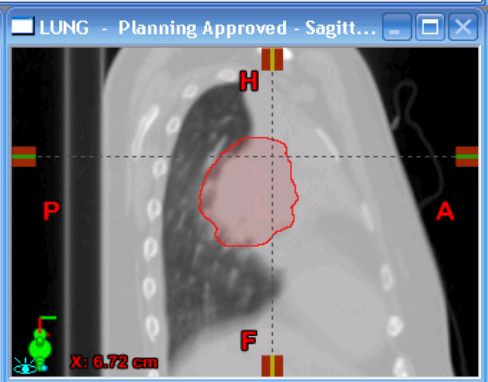
Simulation Scan

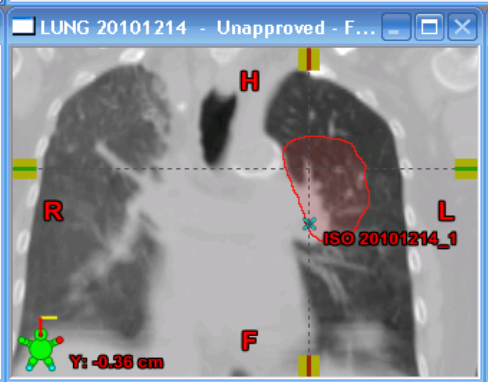


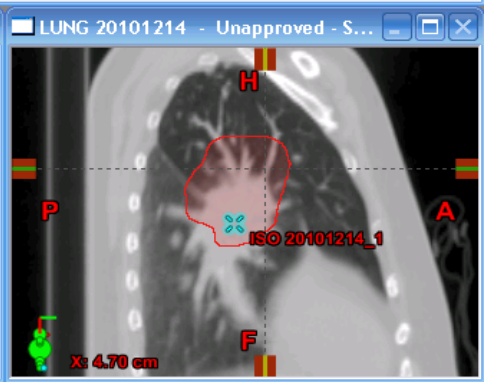
After 1 week of treatment











Conclusions

- Particle therapy reduces the dose to OARs compared with IMRT, 3DCRT, SABR.

- Many patients this is clinically meaningful and allows for improvement in therapeutic ratio.
  - Safer dose intensification
  - Hypofractionation

Conclusions

- Treatment planning is challenging!
- But, several centers have successfully established lung cancer treatment with proton therapy and the clinical results have not demonstrated any unforeseen toxicities or problems with local control.

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