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Bradford Hoppe MD, MPH
Associate Professor
bhoppe@floridaproton.org

Particle Therapy for Thoracic Malignancies: Lymphoma and Lung Cancer

Disclosures

- Travel reimbursement for talks from Procure, IBA, Texas Oncology

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Content

- Rationale
- Dosimetric comparison
- Clinical Results
- Multicenter Clinical Trials
- Treatment Planning

Improving Therapeutic Ratio

- Lymphoma
  - Improve survival by decreasing late effects

- Non-Small Cell Lung Cancer
  - Improve local control by delivering higher doses translating into improved survival
  - Reducing side effects by decreasing dose to OARs

Lymphoma?

Hodgkin Lymphoma

8,500 cases/year
Younger patients (~23 yrs)
High cure (~85%)
>20 yr life expectancy

50-60% will get RT
~5,000 patients

Non-Hodgkin Lymphoma

66,000 cases/year
Older patients (~55 yrs)
Moderate cure (~50%)
>10 yr life expectancy

10-15% will get RT
~8,000 patients

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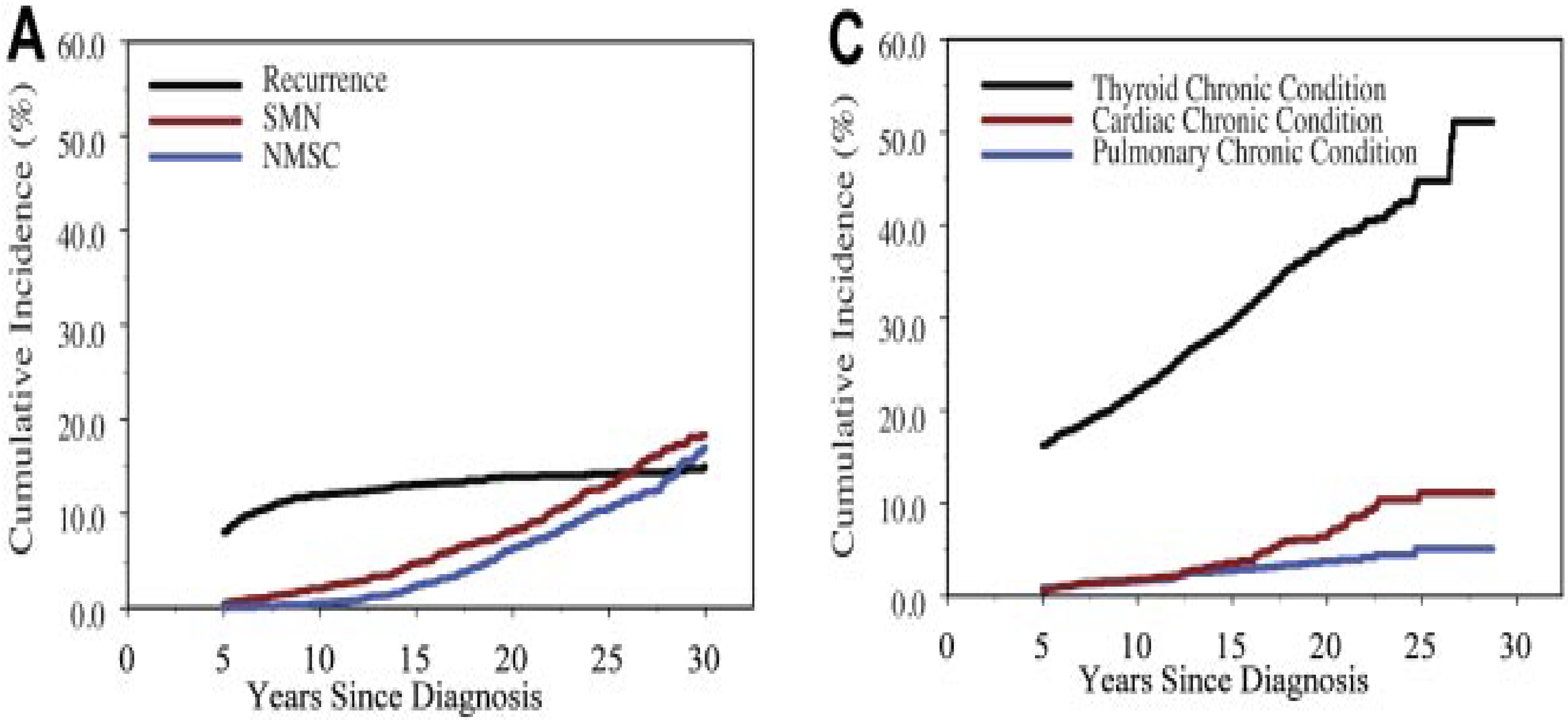
Late effects in HL

- Childhood Cancer Survivor Study- Castellino et al Blood 2011



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Late effects and OAR Dose

Author	Disease	Dose	RR
Travis et al JAMA 2002	Breast Cancer	≥ 4 Gy	3.2
Travis et al JNCI 2003	Lung Cancer	≥ 5 Gy	5.9
Bhatti et al Rad Research 2010	Thyroid Cancer	≥ 5 Gy	8.5
Neglia et al JNCI 2006	Brain tumors	>10 Gy	9.7
Belt-Dusebout et al IJROBP 2000	Gastric Cancer	>20 Gy	9.9
Tukenova et al IJROBP 2011	Sarcoma	>150 J	5.0
	Carcinoma	>150 J	5.2
Tukenova et al JCO 2012	Cardiac death	≥ 5 Gy	12.5
Mulrooney et al BJH 2009	CHF	≥ 15 Gy	2.2
	MI	≥ 15 Gy	2.4
	Pericardial	≥ 15 Gy	2.2
	Valvular	≥ 15 Gy	3.3

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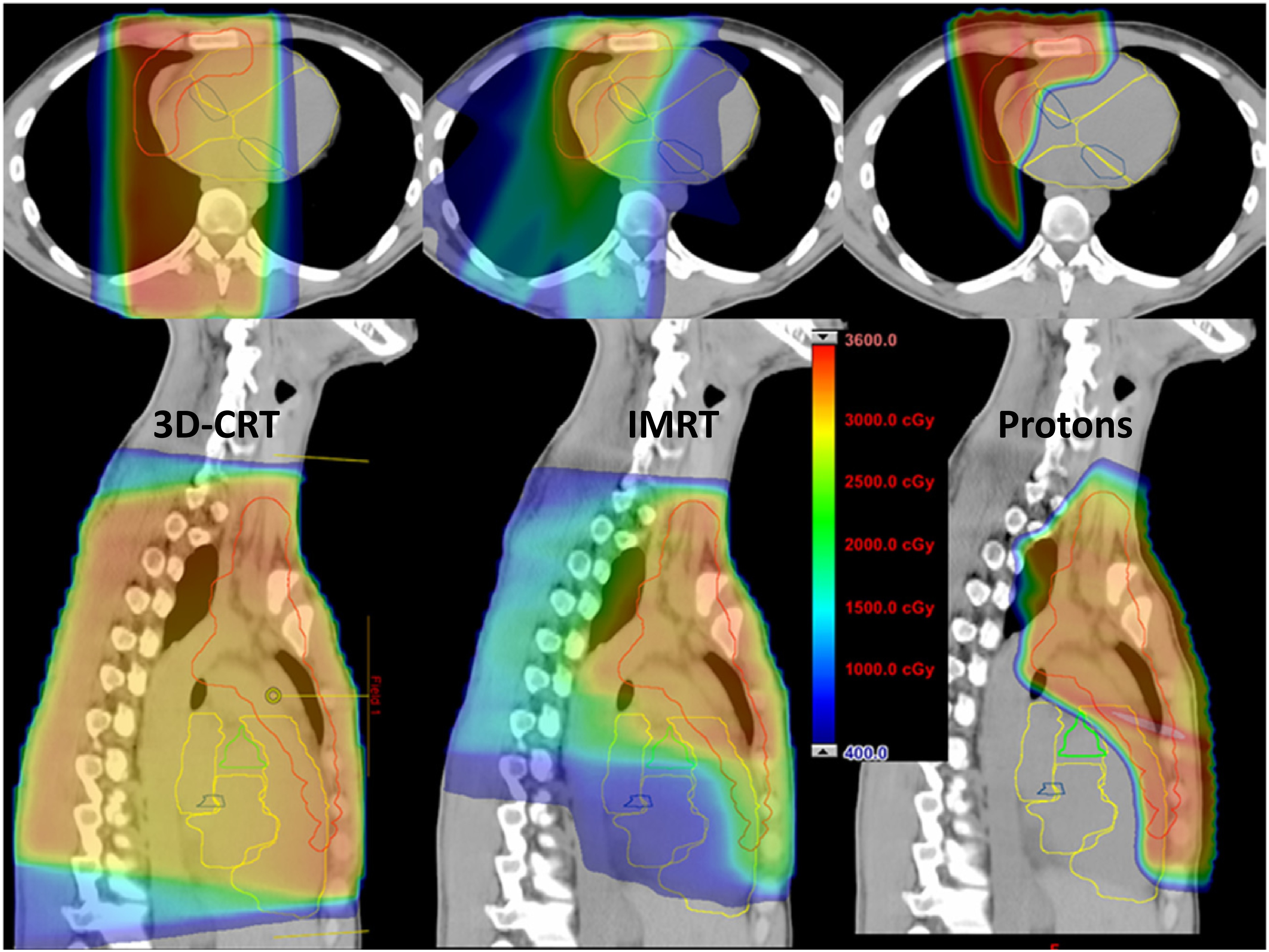
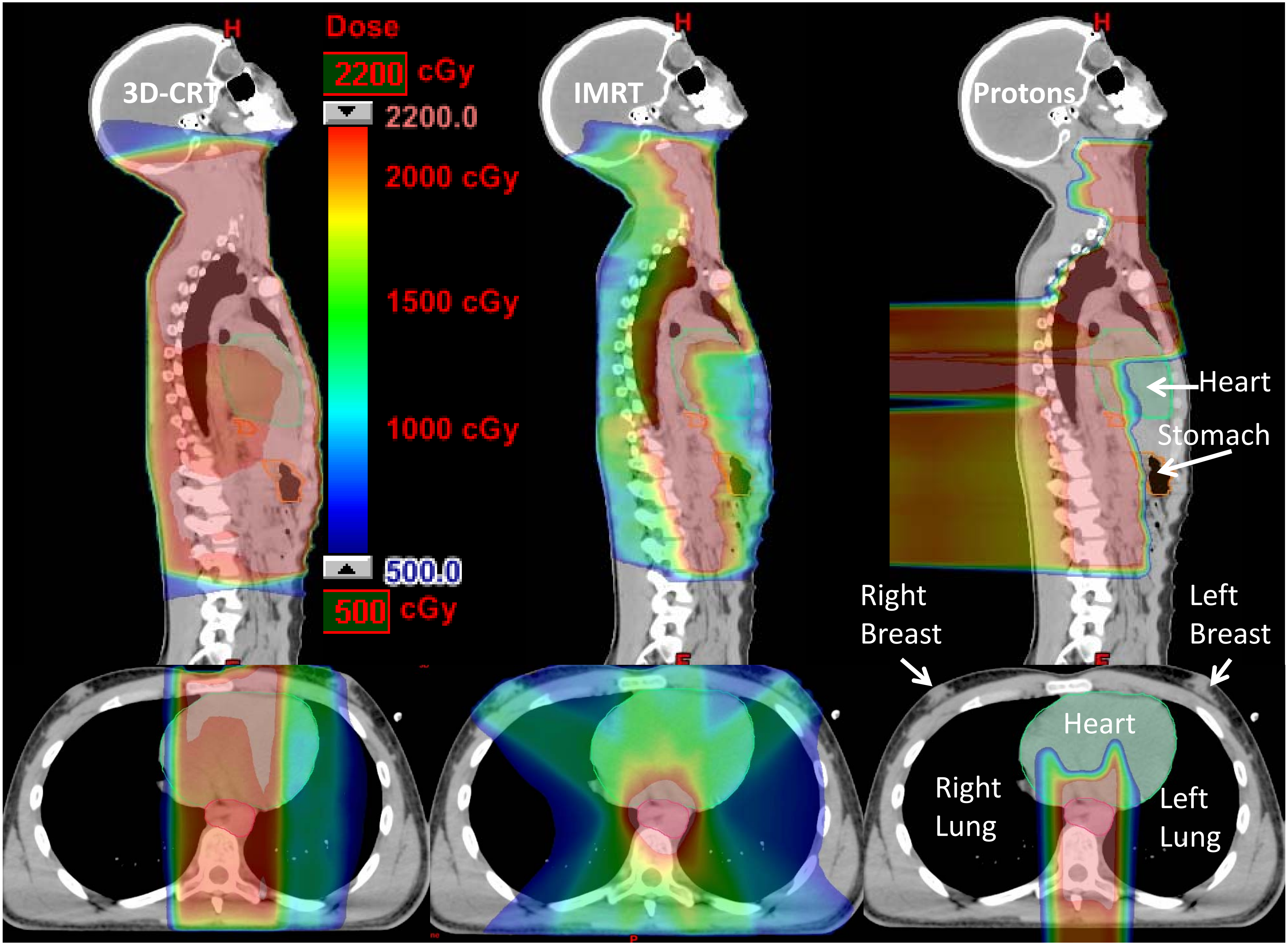

3D-CRT
IMRT
Protons
3600.0
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
400.0
Field 1



H
Dose
2200 cGy
2200.0
2000 cGy
1500 cGy
1000 cGy
500.0
500 cGy
3D-CRT
IMRT
Protons
Heart
Stomach
Right Breast
Left Breast
Heart
Right Lung
Left Lung

Dosimetric studies and who benefits?

- 13 dosimetric studies and 5 case studies have concluded that proton therapy spares the OARs better than XRT (even VMAT)
  - Heart/Lungs/Breast sparing
    - Chera et al IJROBP 2009
    - Li, Dabaja et al IJROBP 2011
    - Andolino et al IJROBP 2011
    - Maraldo et al Ann Oncology 2013
    - Hoppe et al IJROBP 2012
    - Cella et al Radiat Oncol
    - Knausl et al Strahlenther Onkol 2013
  - Stomach/Bowel/Pancreas/Kidneys
    - Sachsman et al Leuk Lymphoma 2015
    - Holtzman et al IJPT 2014
  - Thyroid/Neck muscles/Larynx/Pharyx/Parotid/Carotids
    - Maraldo et al Radiother Oncol 2014
    - Maraldo et al IJROBP 2013

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Clinical Evidence- Disease Control

Author	Disease	Patients	Local Relapse	Toxicities
Hoppe et al IJROBP 2014	Hodgkin	15	7%	No G3+
Sachsman et al Leuk &Lymph 2015	NHL	11	9%	No G3+

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Clinical Investigation: Late Effect

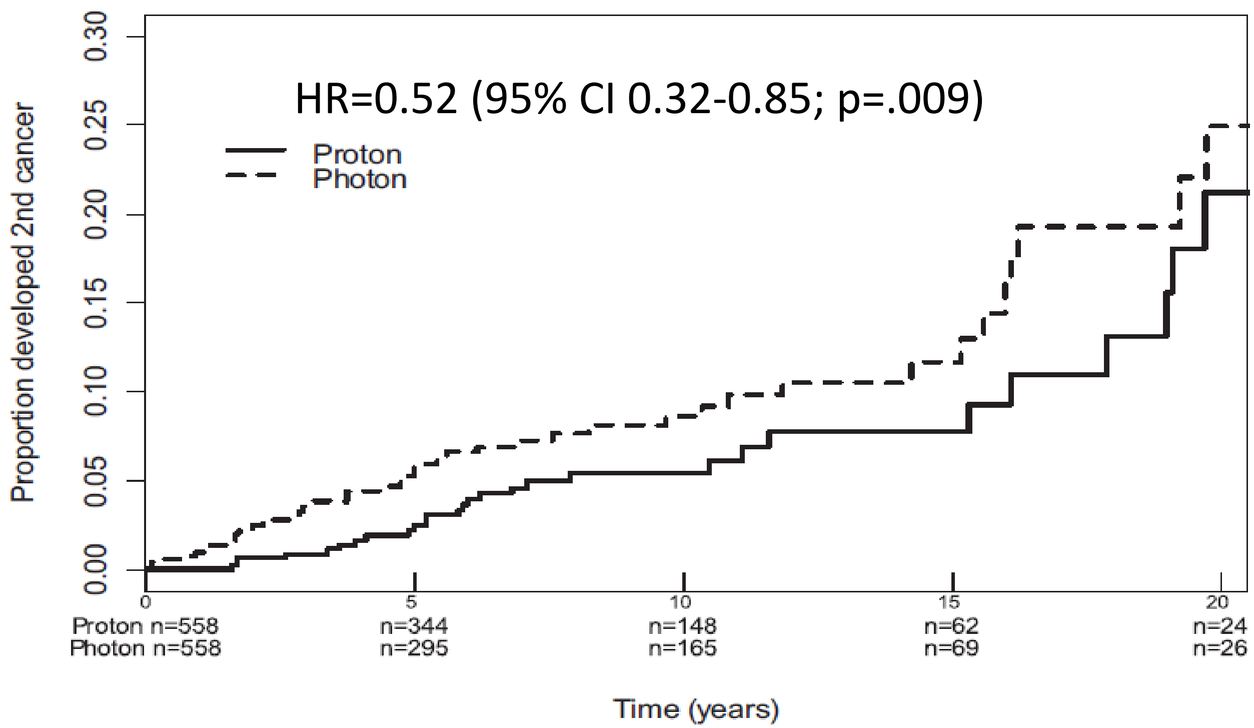
Int J Radiation Oncol Biol Phys, Vol. 87, No. 1, pp. 46–52, 2013

Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

Christine S. Chung, MD, MPH,* Torunn I. Yock, MD, MCh,† Kerrie Nelson, PhD,‡ Yang Xu, MS,§ Nancy L. Keating, MD, MPH,§,¶ and Nancy J. Tarbell, MD†,||

**Department of Radiation Oncology, Alta Bates Summit Medical Center, Berkeley, California; †Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; ‡Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; §Department of Health Care Policy and ||Office of the Executive Dean, Harvard Medical School, Boston, Massachusetts; and ¶Department of General Internal Medicine, Brigham and Women's Hospital, Boston, Massachusetts*

MGH matched to SEER patients by age, sex, treatment year, cancer histology, and site



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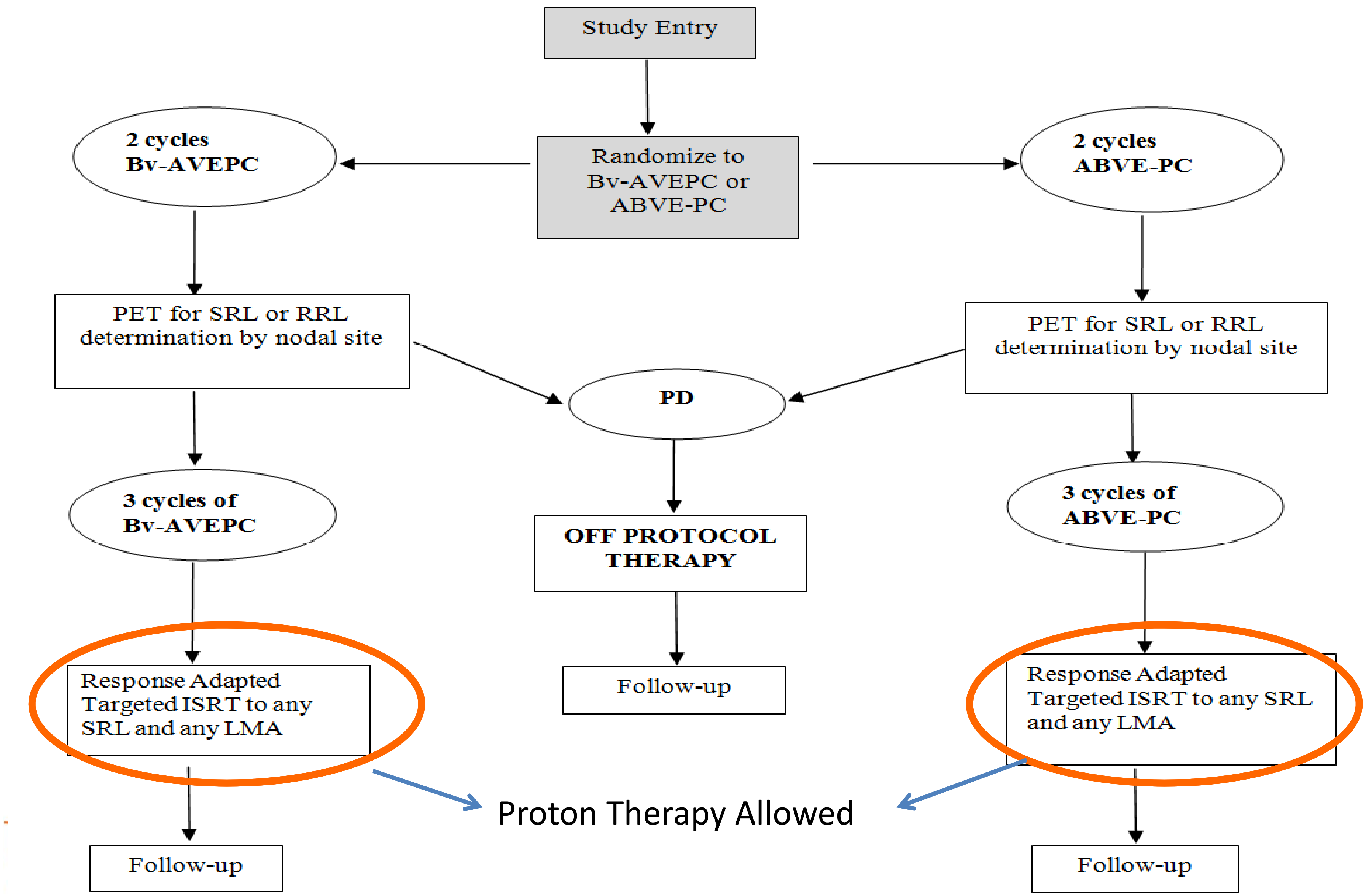
COG- AHOD 1331

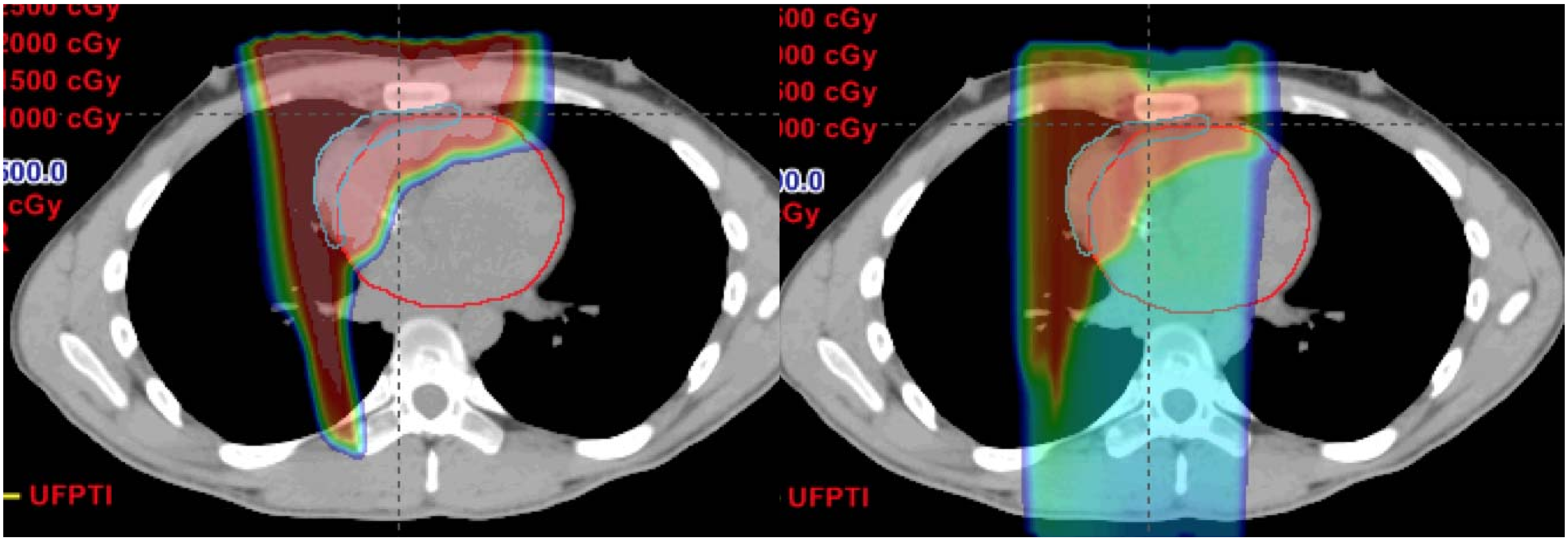


Proton Planning

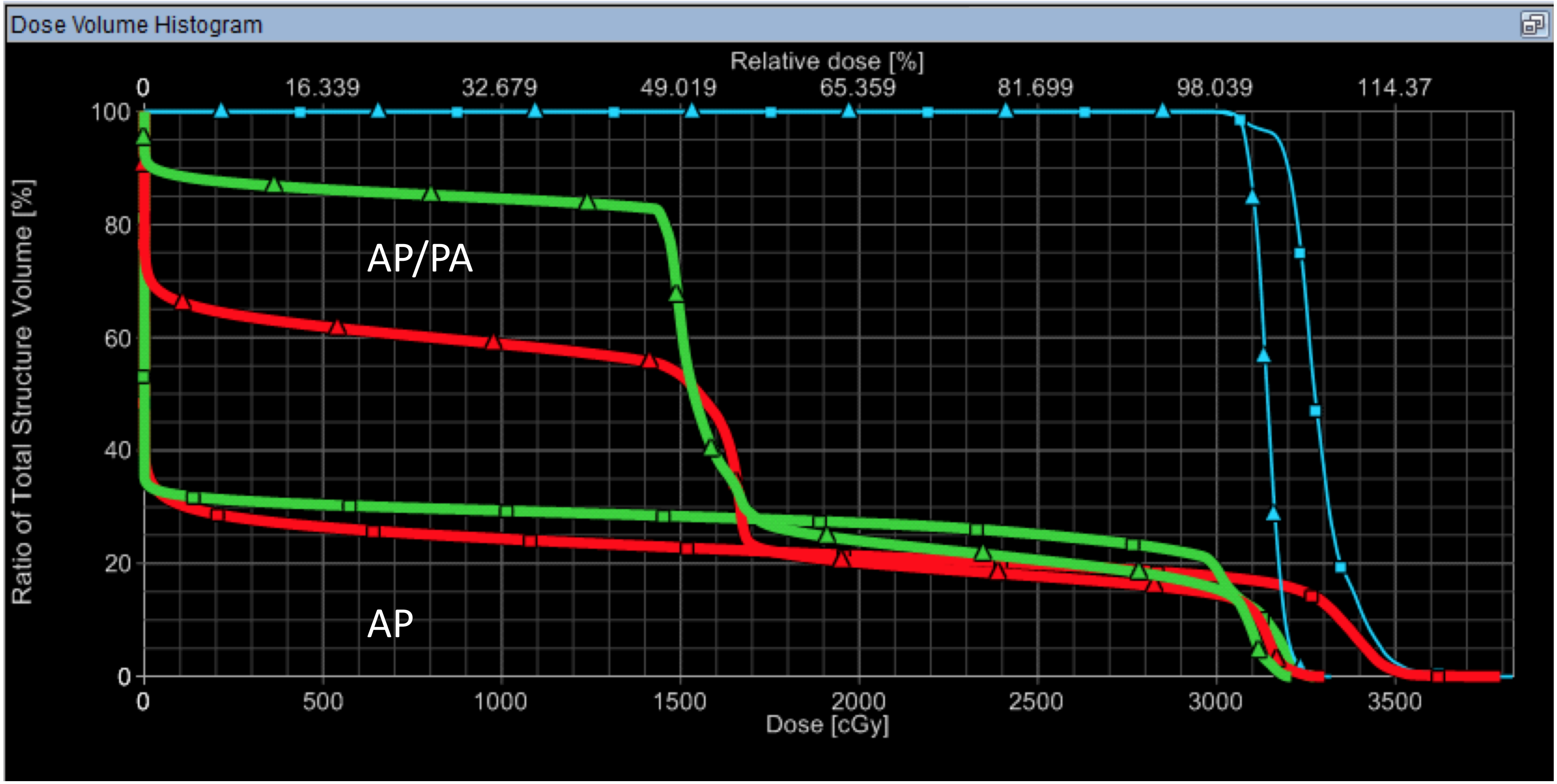
- Passive scatter proton planning
  - Use multiple fields to reduce the overall uncertainty
  - Do not stop a beam in an OAR
- Lymphoma proton planning is different, lower doses of RT used (ie 21-30 Gy)
  - Will allow single field treatment if robust
    - Generally use 2 slightly oblique fields
  - Will stop beam in heart
    - Non-static (moves with beating and breathing)
    - Dose is relative low.

Beam arrangement is critical

AP | AP/PA

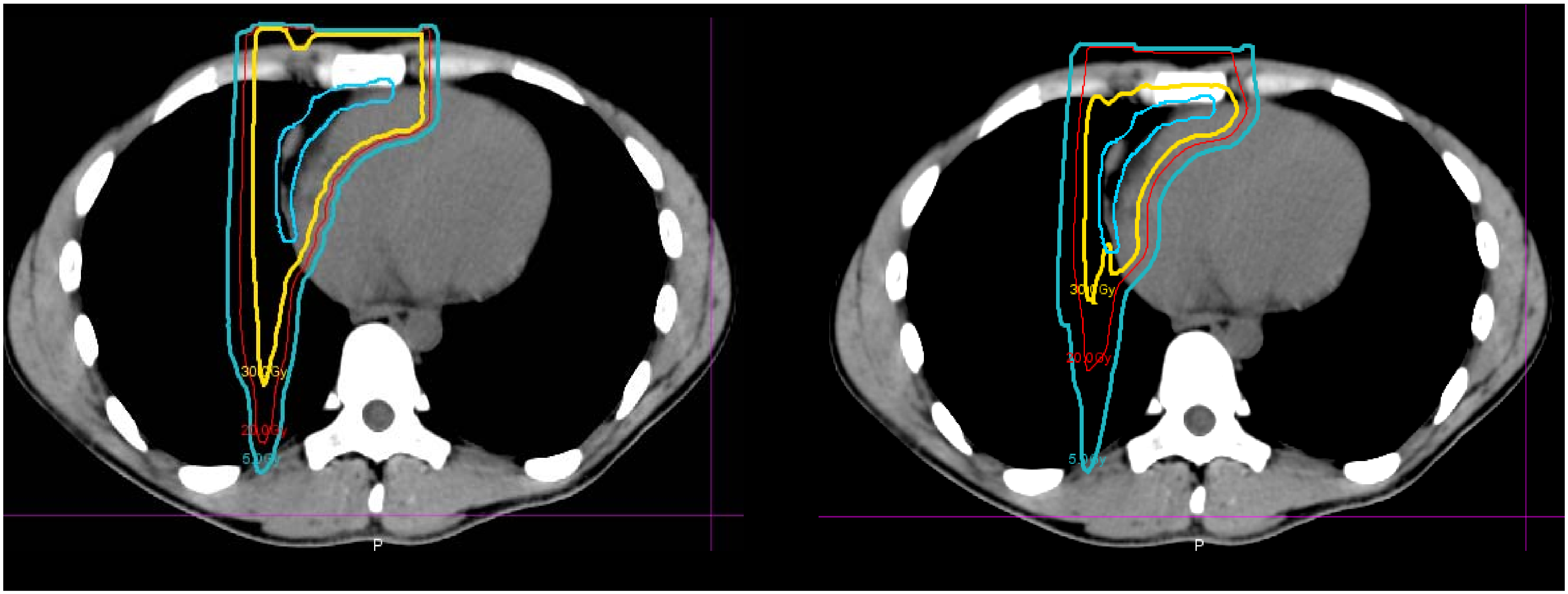


AP vs AP/PA


Dose Volume Histogram
Relative dose [%]
0
16.339
32.679
49.019
65.359
81.699
98.039
114.37
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
AP/PA
AP
0
500
1000
1500
2000
2500
3000
3500
Dose [cGy]

Passive scatter vs PBS

Passive Scatter Proton | Pencil Beam Scanning Proton



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Pencil Beam Scanning

Proton pencil beam scanning for mediastinal lymphoma: the impact of interplay between target motion and beam scanning

Physics in Medicine and Biology (In Press)

C Zeng, J P Plastaras, Z A Tochner, B M White, C E Hill-Kayser, S M Hahn and S Both

Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA 19104, USA

E-mail: Chuan.Zeng@uphs.upenn.edu

- 7 patients using PBS anterior field
  - 6 patients no problem
  - 1 patient with >5mm motion had degradation of plan
    - Replanning with larger spot size
    - Repainting
- Conclusion: Impact of interplay effect on PBS plan robustness was minimal with volumetric repainting and large spot size.

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Lung Cancer

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Epidemiology

- Lung Cancer accounts for > 25% of all cancer deaths in the US. ~90,000/year

5 year Cancer Specific Survival			
Stage	Lung	Prostate	Breast
1	50%	100%	98%
2/3	15%	100%	84%
4	3%	30%	24%

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

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Stage I Non-Small Cell Lung Cancer

Stage I NSCLC

Grutters et al Radiotherapy Oncology 95 (2010) 32-40		
Treatment	N=	5yr OS (95%CI)
Conventional RT	1326	**20%** (15-24%)

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Stage I NSCLC

Grutters et al Radiotherapy Oncology 95 (2010) 32-40		
Treatment	N=	5yr OS (95%CI)
Conventional RT	1326	**20%** (15-24%)
Proton Therapy	180	**40%** (25-55%)
Carbon Therapy	210	**42%** (32-52%)

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Stage I NSCLC

Author	N=	FU	Dose	fractions	LC	OS
Bush et al IJROBP2013	111	48	51-70 Gy	10	4yr- 74%	4yr- 54%
Shioyama et al IJROBP 2003	28	30	60-93 Gy	10-30	5yr-89%/39%	5yr- 70%/16%
Nihei et al IJROBP 2006	37	24	70-94 Gy	20	2yr- 80%	2yr-84%
Hata et al IJROBP 2007	21	25	50-60 Gy	10	2yr- 95%	2yr- 74%
Nakayama et al IJROBP 2010	55	18	66 Gy 72.6 Gy	10 22	2yr- 97%	2yr- 98%
Chang et al IJROBP 2011	18	16	87.5 Gy	35	2yr- 89%	2yr- 55%
Westover et al IJROBP 2012	15	24	42-50 Gy	3-5	2yr- 100%	2yr-64%
Kanemoto et al Clin Lung Ca 2014	74	31	66-72.6 Gy	10-22	3yr-86%	3yr-77%
Iwata et al Cancer 2010	57	36	80Gy 60 Gy	20 10	3yr-82%	3yr-75%
Miyamoto et al Radio Onco 2003	47 34	53	59.4-95.4 Gy 68.4-79.2 Gy	18 9	71% 97%	5yr- 42%
Miyamoto et al IJROBP 2007	50	59	72 Gy	9	5yr- 95%	5yr- 50%
Miyamoto et al JTO 2007	79	39	53-60 Gy	4	3yr- 90%	3yr- 60%

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Stage I NSCLC

Grutters et al Radiotherapy Oncology 95 (2010) 32-40		
Treatment	N=	5yr OS (95%CI)
Conventional RT	1326	**20%** (15-24%)
Proton Therapy	180	**40%** (25-55%)
Carbon Therapy	210	**42%** (32-52%)
Stereotactic Body Radiotherapy (SBRT)	895	**42%** (34-50%)

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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**
SBRT	**2%**	**0.8%**	**0.2%**	**0.7%**

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Dosimetry: Protons vs SBRT 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

SBRT-PT

Average difference in: mean lung dose = 1.7 Gy
lung V5 = 10%
lung V20 = 1%

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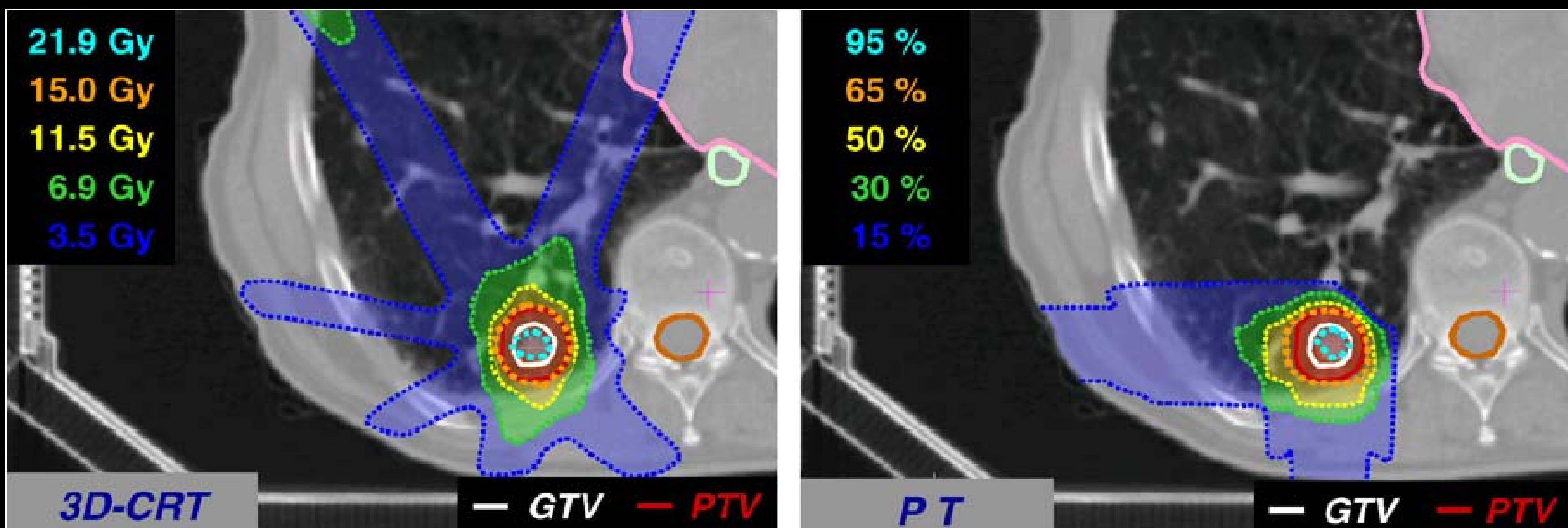
PT > SBRT

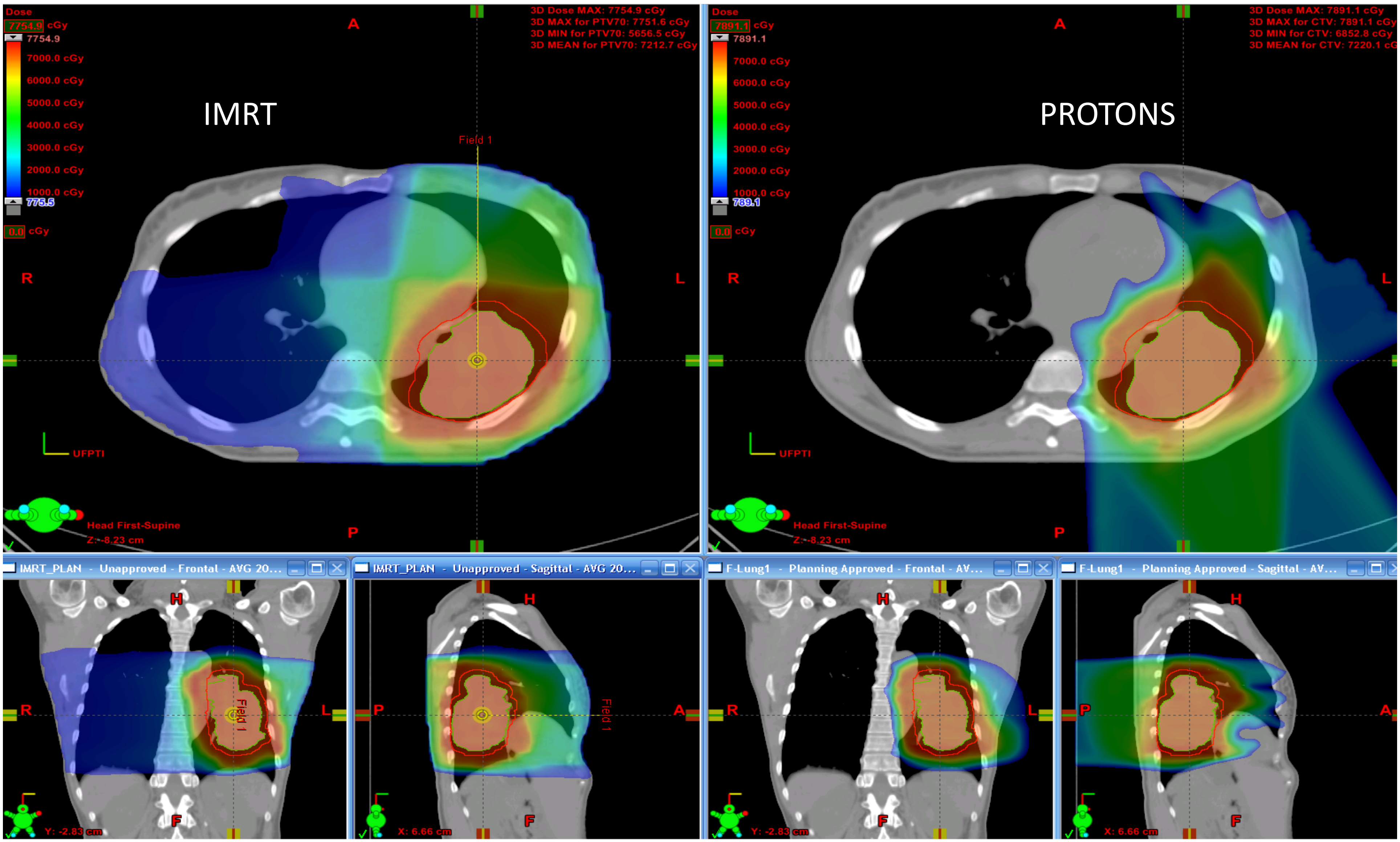
Stage I Non-Small Cell Lung Cancer
Larger tumors
Centrally located tumors
Superior located tumors (brachial plexus)
Multiple tumors (re-irradiation)

Smaller tumors ↓ Benefit

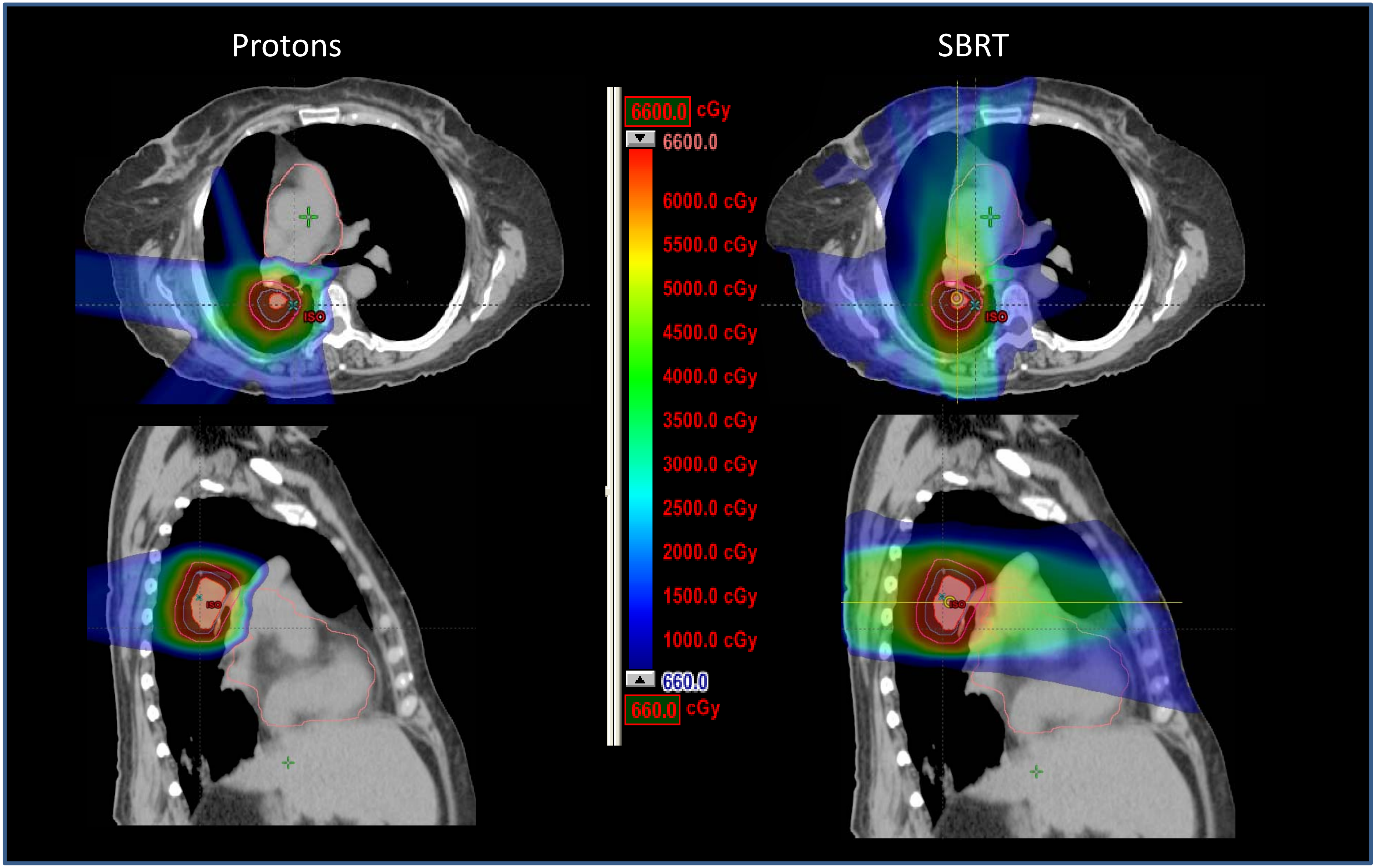
Georg Radiotherapy Oncology 2008



Bigger tumors ↑ Benefit



Central tumors ↑ Benefit



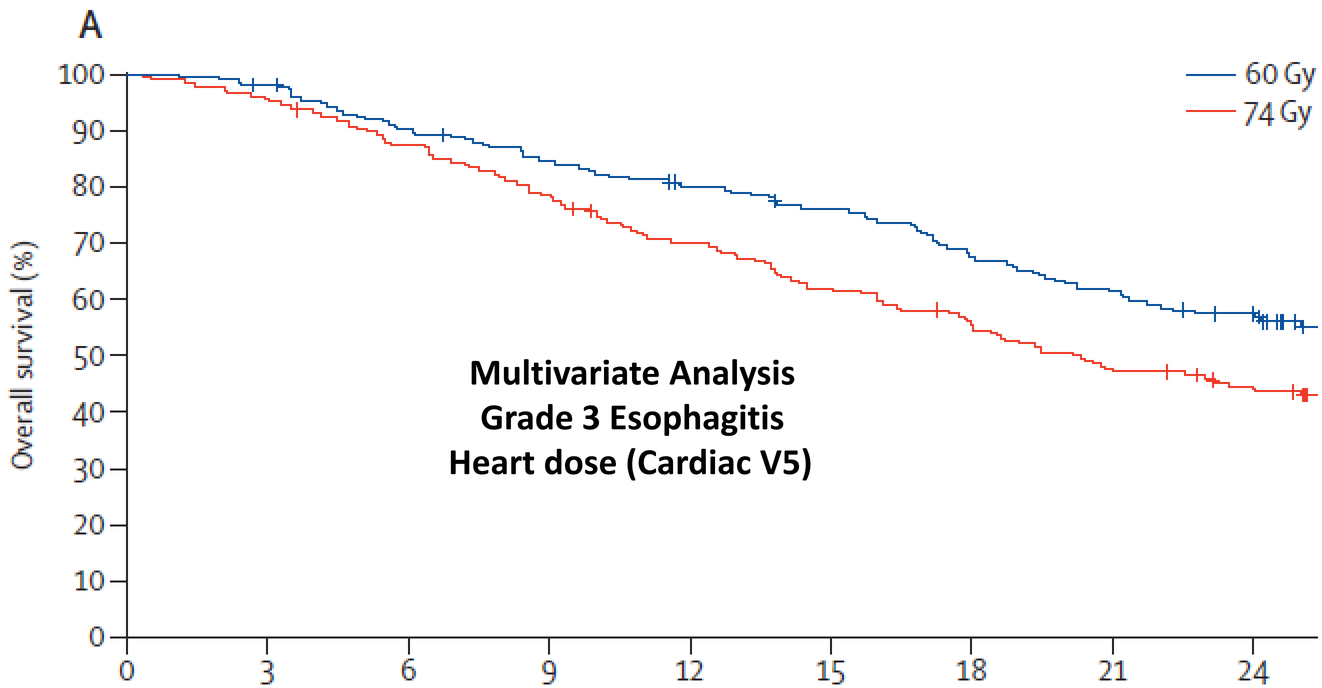
Multicenter Clinical Trials

- MD Anderson/MGH- Randomized study of SBRT (xrays) versus SBPT (protons) for centralized NSCLC using 50Gy in 4 fractions
  – Will be better once conebeam CT is more available

Stage II/III Non-Small Cell Lung Cancer

RTOG 0617

Concurrent chemotherapy and 60Gy vs 74 Gy RT in Stage 3 NSCLC



Median OS
29 months
20 months

Number at risk

60 Gy	217	212	194	181	169	160	142	129	116
74 Gy	207	198	180	162	142	126	112	95	87

Bradley et al Lancet Oncology 2015 Feb;16(2):187-99

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RTOG 0617

- Lessons learned
  - Dose to OAR impacts overall survival
    - Higher prescription dose lead to higher OAR dose
  - Dose intensification using conventional dose/fraction (2 Gy) doesn't improve survival.
    - Accelerated repopulation among NSCLC

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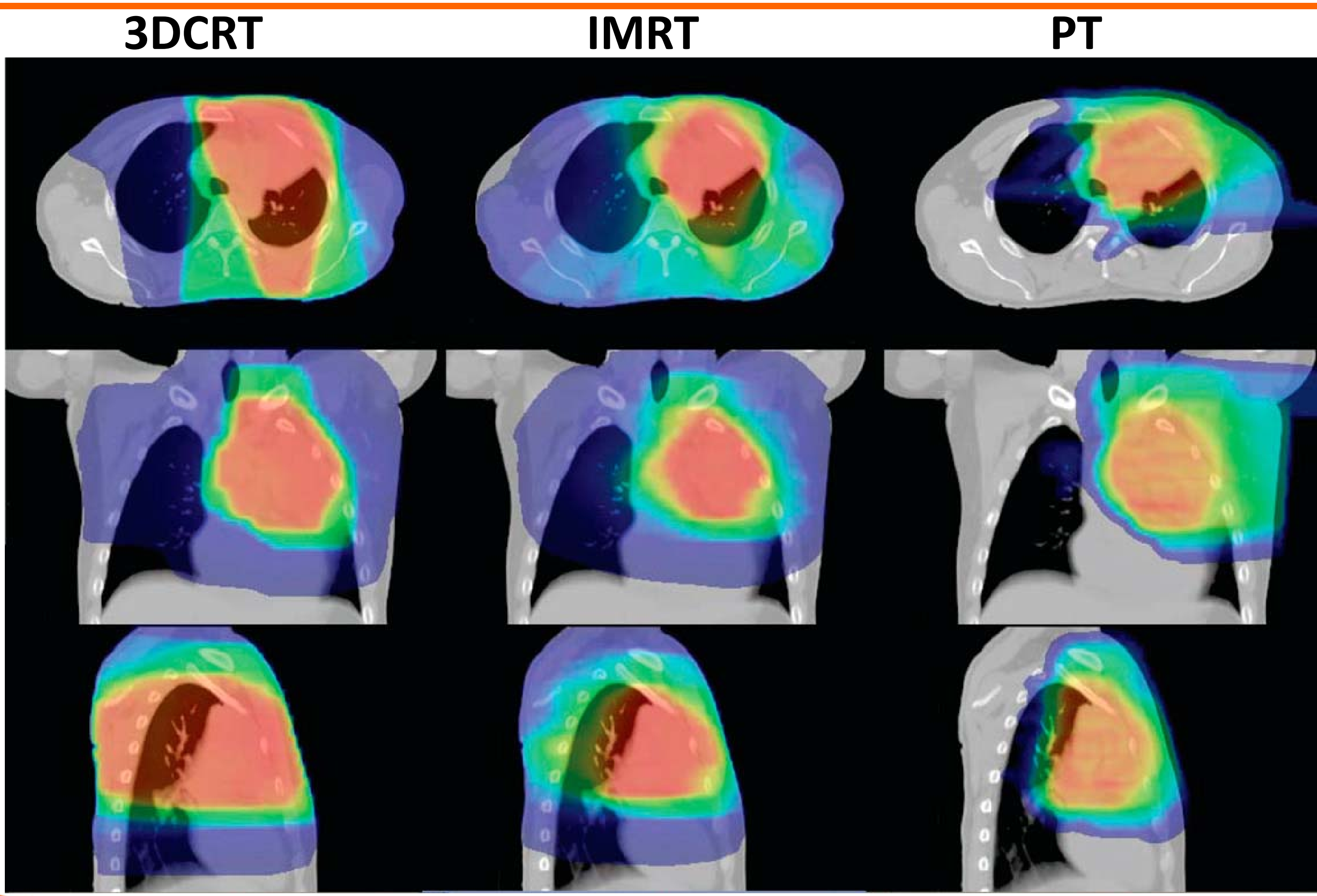
Stage IIIA- Nichols CLC 2011



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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%

Passive scatter PT IMPT

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

Chang et al IJROBP 2006
Nichols et al Clinical Lung Cancer 2011
Nichols et al Tech Cancer Research 2011
Zhang et al IJROBP 2010
Vogelius et al Acta Oncologica 2011

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Heart V5

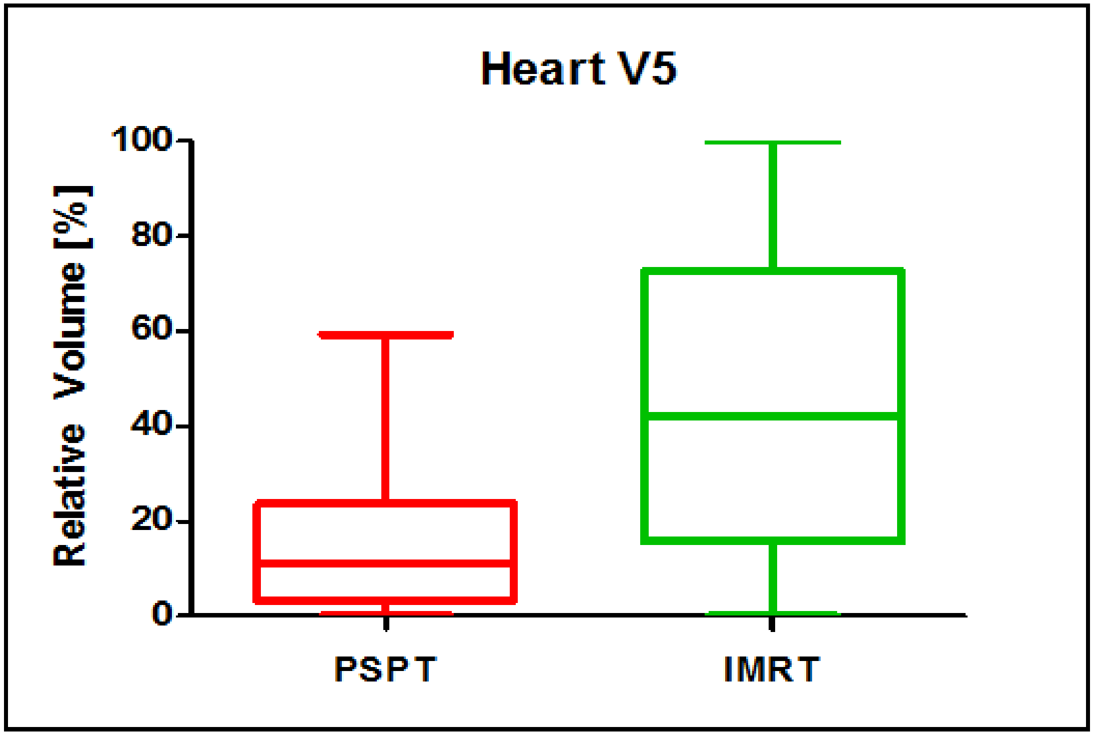

Figure 1: Box-plot shows the maximum and minimum values (whisker) and 75th and 25th percentile (box) and mean (center line) for 103 lung patients that were randomized between passive scattering proton therapy (PSPT) or IMRT

Liao et al MD Anderson

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Stage II/III NSCLC clinical studies

Author	N=	FU	Dose	DFS	OS	LF 1st site	Gd 3+ GI tox	Gd 3+ Lung tox
Bush AJR 1999	10	14	28.8Gy-PT, 45Gy XRT	2yr- 19%	2yr- 13%			
Shioyama IJROBP 2003	14	30	53-89 Gy (XRT+PT)		2yr- 71%; 5yr-0%			
Nakayama IJROBP 2011	35	17	67.1-91.3 Gy/ 22-38 fx	2yr-29%	2yr-59%	11%	0%	0%
Oshiro JTO 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%	10%	11%	5%
McGee 2012	32	21	70-80 Gy + chemo	2yr- 40%	2 yr–49%	5%	5%	5%
Oshiro 2014	15	22	74 Gy + Chemo	2yr- 16%	2yr- 50%	50%	7%	8%

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Chang et al Cancer 2011
McGee et al ASTRO 2013
Oshiro et al J Rad Res 2014

Multi-Institutional Research

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

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RTOG 1308

Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC

SCHEMA

STRATIFY

Stage
1. II
2. IIIA
3. IIIB

Histology
1. Squamous
2. Non-Squamous

Concurrent Chemotherapy Doublet Type
1. Carboplatin/paclitaxel
2. Cisplatin/etoposide

RANDOMIZE

Arm 1: Photon dose—70 Gy*(RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**

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

Both Arms: Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***

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Proton Collaborative Group (PCG)-LUN-005

Phase I/II Concurrent chemotherapy and hypofractionated proton therapy

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

tBED-time dependent BED

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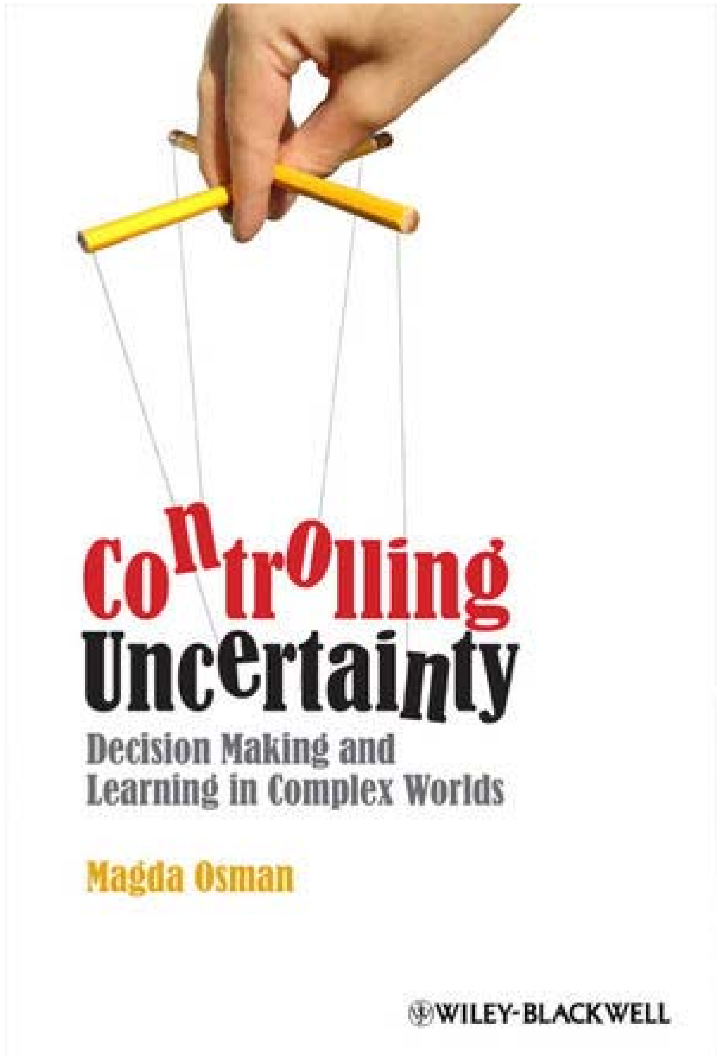
Treatment Planning and Uncertainties



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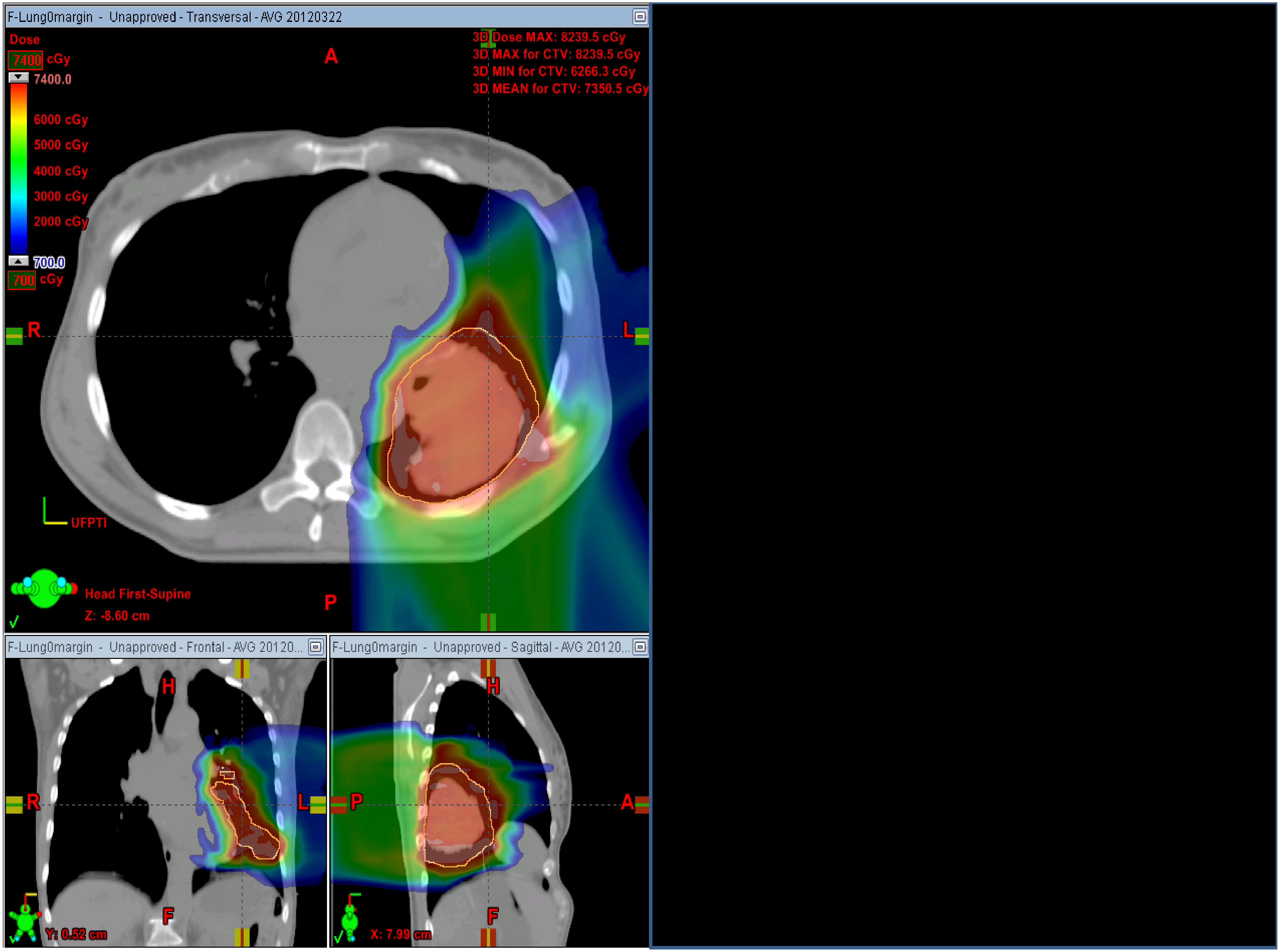
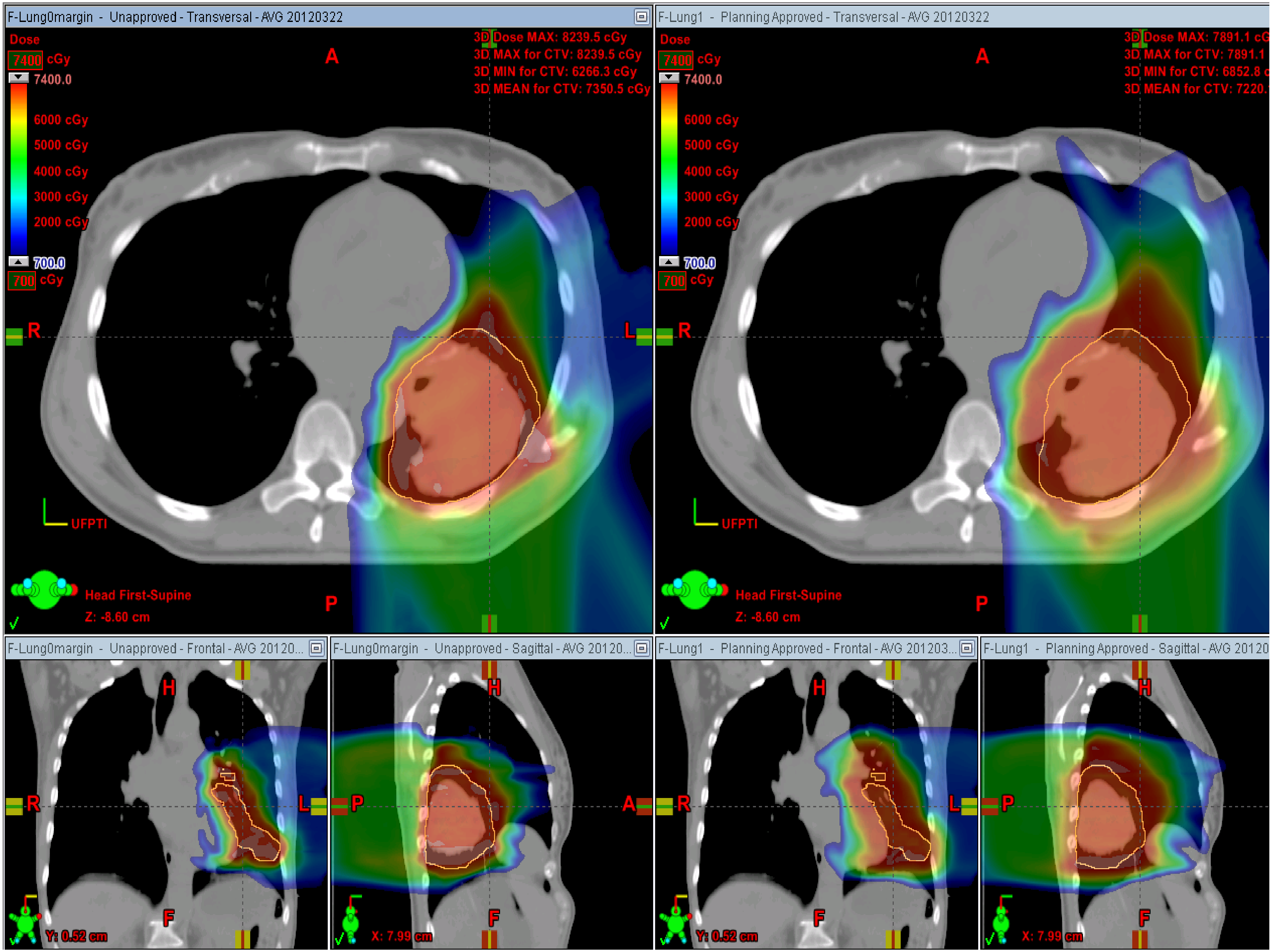

F-Lung0margin - Unapproved - Transversal - AVG 20120322
Dose
7400 cGy
7400.0
6000 cGy
5000 cGy
4000 cGy
3000 cGy
2000 cGy
700.0
700 cGy
3D Dose MAX: 8239.5 cGy
3D MAX for CTV: 8239.5 cGy
3D MIN for CTV: 6266.3 cGy
3D MEAN for CTV: 7350.5 cGy
A
R
L
P
UFPTI
Head First-Supine
Z: -8.60 cm
F-Lung0margin -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

Uncertainties with Protons

- Do not treat with the most conformal plan

- Treat with the most conformal ROBUST plan that takes into consideration the uncertainties

Protons: Range Uncertainty

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) ˆ	+∼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 *, ˆ)	2.7% + 1.2 mm
Total (excluding ˆ)	4.6% + 1.2 mm

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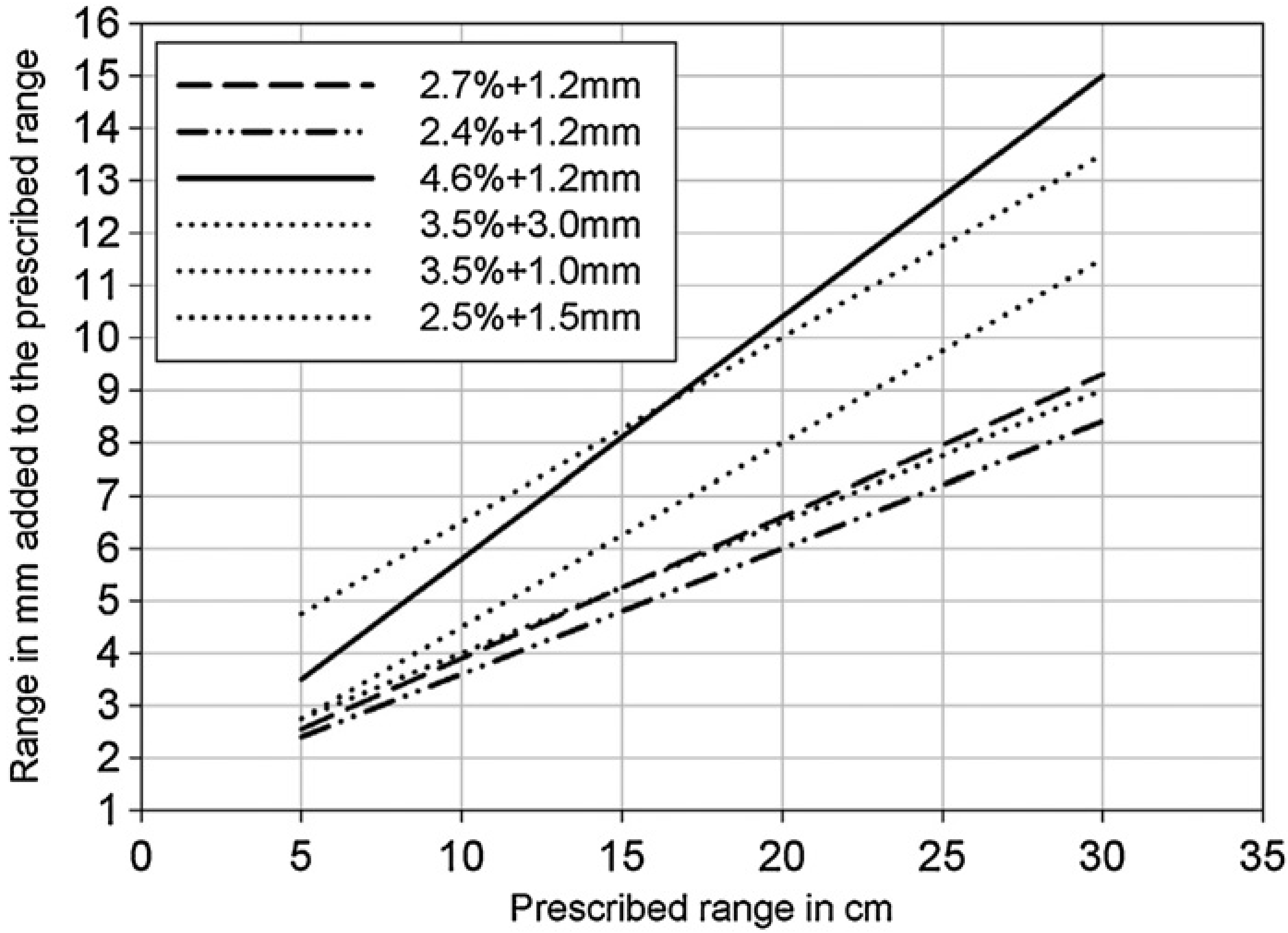
Protons: Range Uncertainty



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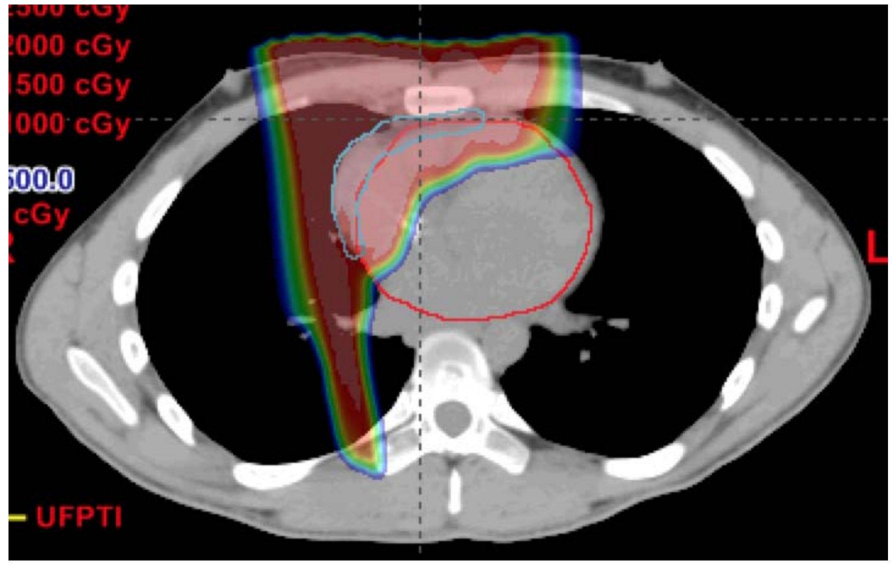
Distal Fall-off uncertainty in lung

- 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

Making a Robust Passive Scatter Plan

- 4D CT simulation and draw iGTV
- Treatment planning done on average scan with an over ride of the iGTV with HU=50* (target coverage only)
- Add 8-10 mm smearing
- Add range equation to the distal and proximal edge of ITV
- Add block margin to PTV (8-10mm)
- 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

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Passive Scatter vs IMPT

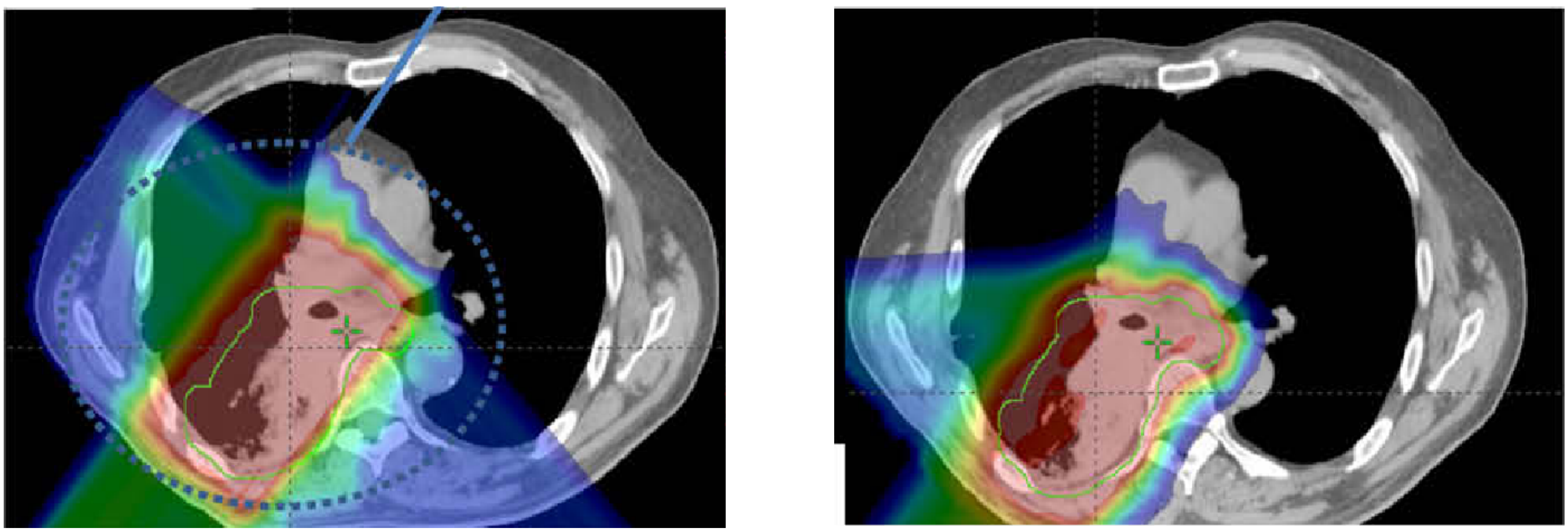
CLINICAL INVESTIGATION

INTENSITY-MODULATED PROTON THERAPY REDUCES THE DOSE TO NORMAL TISSUE COMPARED WITH INTENSITY-MODULATED RADIATION THERAPY OR PASSIVE SCATTERING PROTON THERAPY AND ENABLES INDIVIDUALIZED RADICAL RADIOTHERAPY FOR EXTENSIVE STAGE IIIB NON-SMALL-CELL LUNG CANCER: A VIRTUAL CLINICAL STUDY

IJROBP 2010

XIAODONG ZHANG, PH.D., YUPENG LI, M.S., XIAONING PAN, PH.D., LI XIAOQIANG, M.S., RADHE MOHAN, PH.D., RITSUKO KOMAKI, M.D., JAMES D. COX, M.D., AND JOE Y. CHANG, M.D., PH.D.

Division of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas



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Passive Scatter vs IMPT

Mean Dose	PS	IMPT
Lung	15.8 Gy	13.1 Gy
Contra lung	2.2 Gy	1.2 Gy
Ipsi lung	29 Gy	24.7 Gy
Cord Dmax	34 Gy	36 Gy
Heart V40	10%	9%
Esophagus V55	18%	16%

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MD Anderson IMPT flow chart

Clinical Implementation of Intensity Modulated Proton Therapy for Thoracic Malignancies

Joe Y. Chang, MD, PhD,* Heng Li, PhD,[†] X. Ronald Zhu, PhD,[†] Zhongxing Liao, MD,* Lina Zhao, MD,* Amy Liu, MS,[†] Yupeng Li, PhD,[†,‡] Narayan Sahoo, PhD,[†] Falk Poenisch, PhD,[†] Daniel R. Gomez, MD,* Richard Wu, MS,[†] Michael Gillin, PhD,[†] and Xiaodong Zhang, PhD[†]

Int J Radiation Oncol Biol Phys, Vol. 90, No. 4, pp. 809–818, 2014

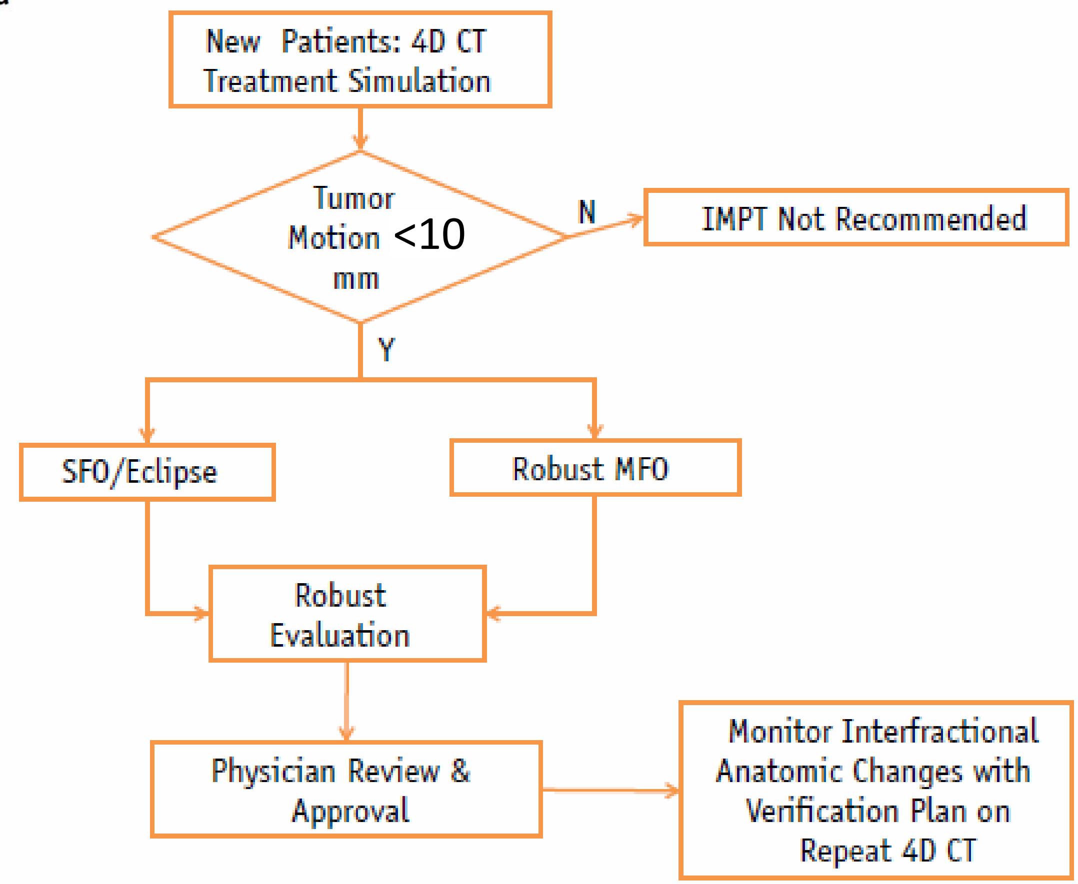

Fig. 1. Procedural flow chart for intensity modulated proton therapy (IMPT) quality assurance. 4D CT = 4-dimensional computed tomography; MFO = multifield optimization; SFO = single-field optimization.

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IMPT Planning in Lung

- Treatment planning for IMPT in lung cancer is in its infancy.

- Robust plans can be developed using:
  - Repainting
  - Larger spot size
  - Robust optimization programs
  - Fractionated treatments

- Integrated boosts are possible (dose painting)

- Clinical results needed (see scientific session PTCOG)

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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
- Conebeam CT coming (you may have it)

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Weekly Verification Scans

- Tumor changes
  - Shrinking
  - Growing
- Thoracic density changes or tumor displacement
  - Pleural effusions
  - Atelectasis
  - Lung volume changes

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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

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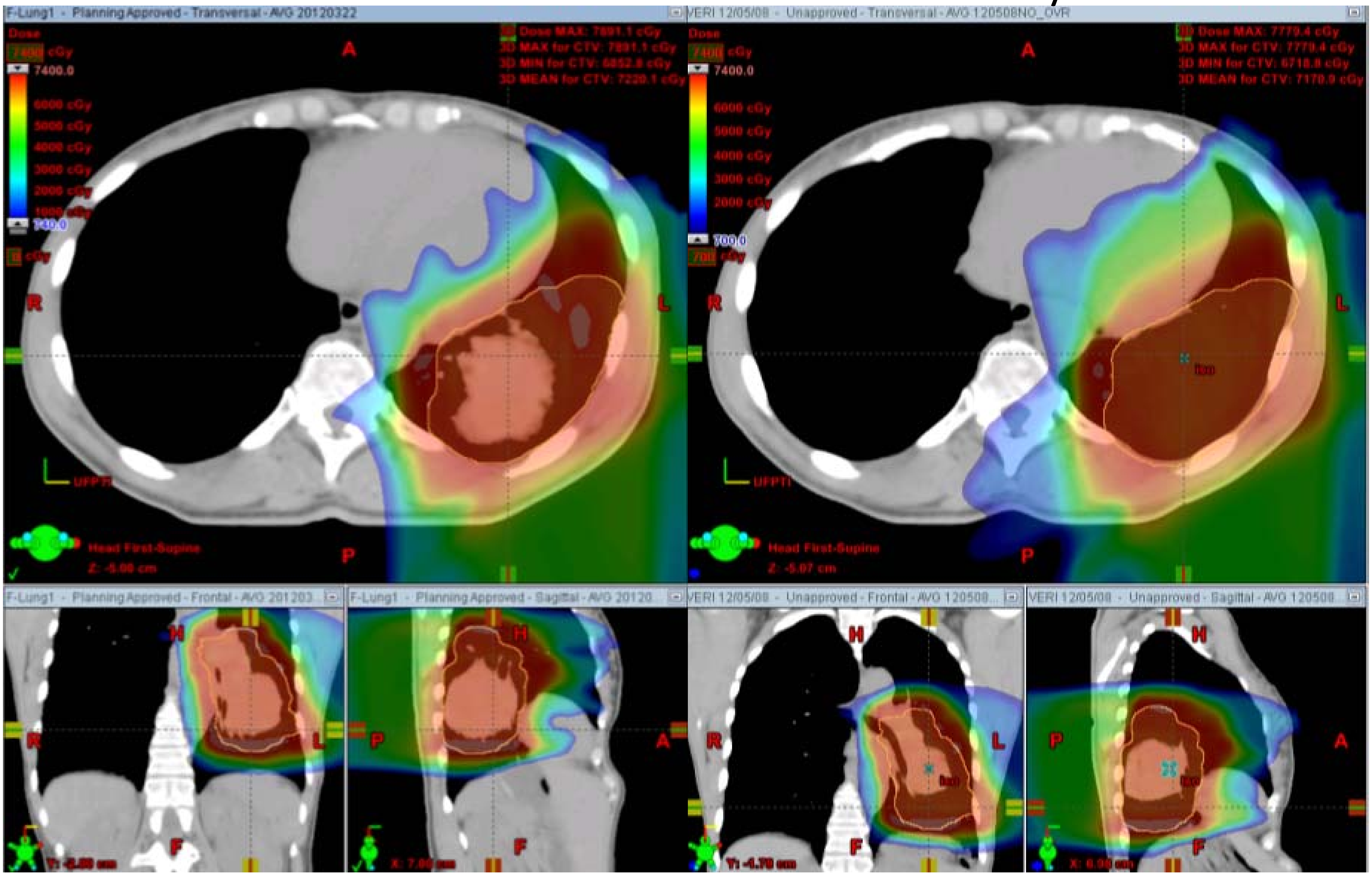
Re-Evaluation (tumor regression)

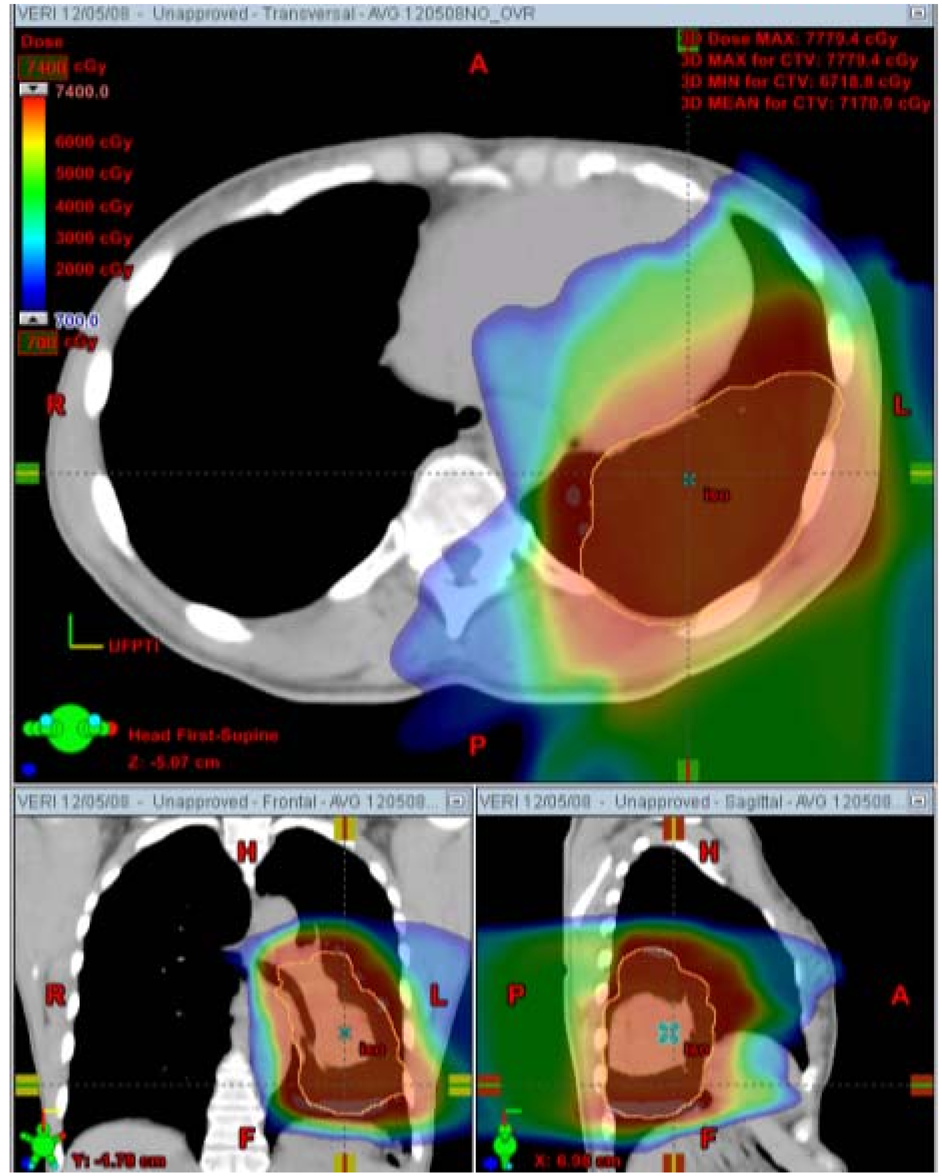
Simulation

After 40 Gy



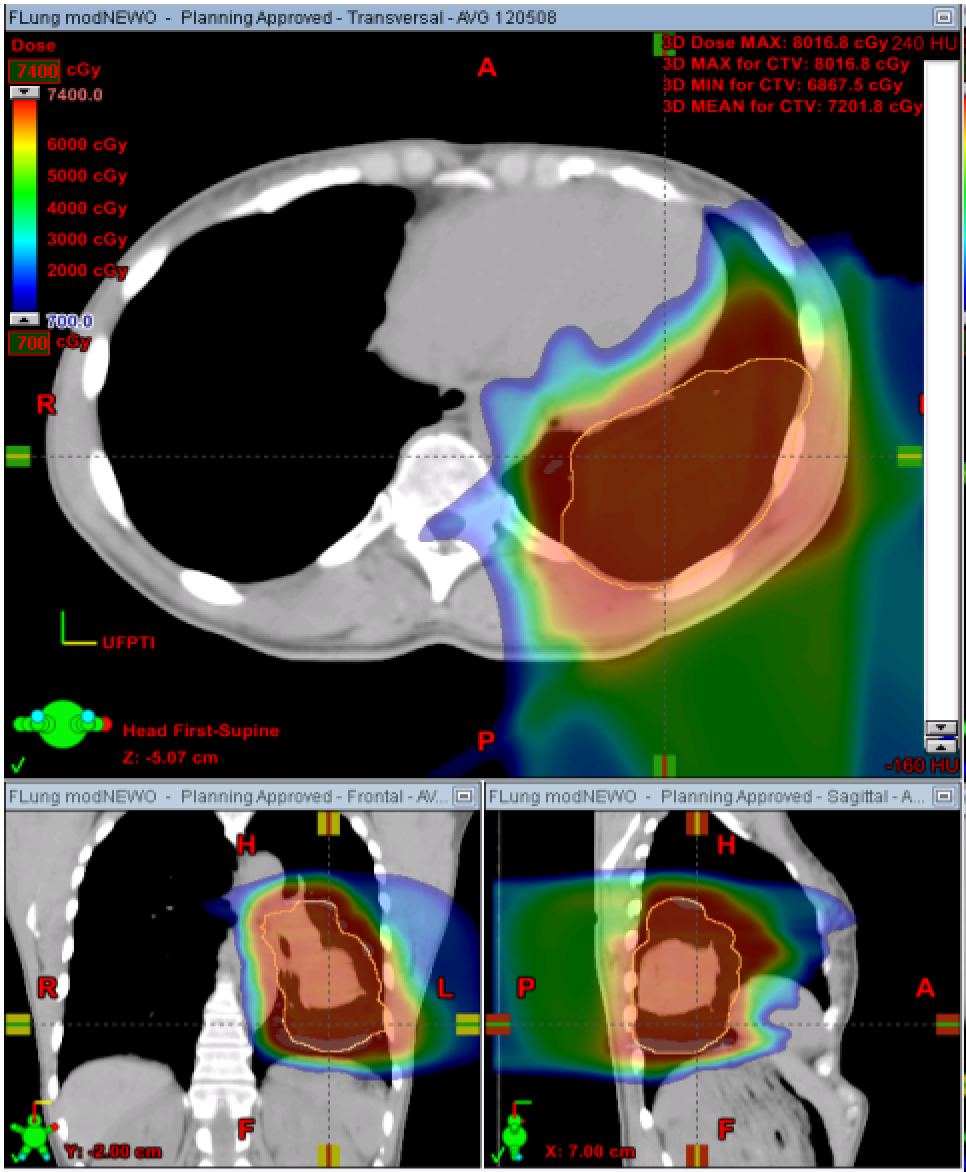
Re-Evaluation (tumor regression)

Old Plan

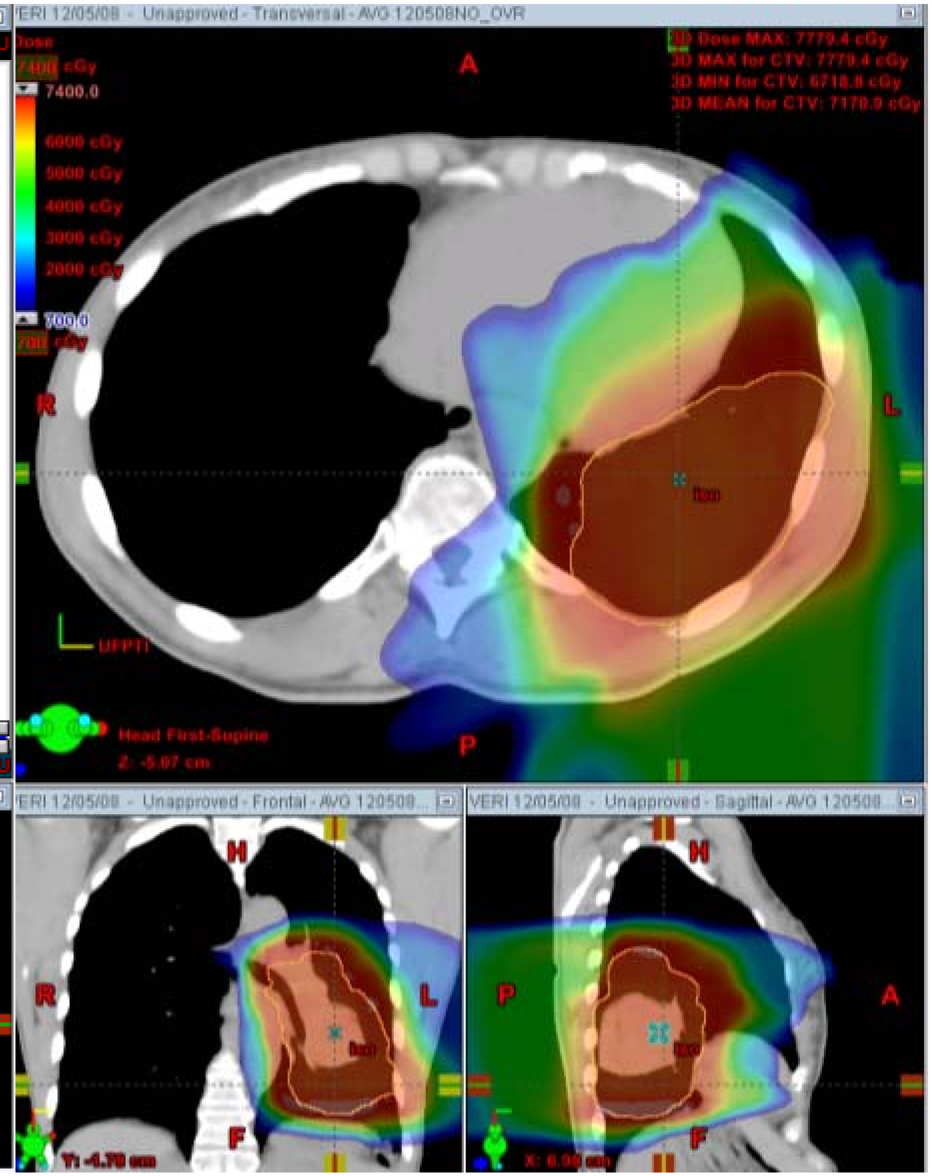


Re-Evaluation (tumor regression)

New Plan



Old Plan



Summary

- Particle therapy reduces the dose to OARs compared with IMRT, 3DCRT, SBRT.
- Many patients this is clinically meaningful and allows for improvement in therapeutic ratio.
  - Lymphoma – less late toxicities from RT
  - NSCLC
    - Less acute & subacute toxicity
    - Better local control?

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Further Lung information

- PTCOG Lung/Lymphoma Group Guidelines
    - Room Gaslamp CD, Manchester Grand Hyatt 10-11:30
  - IMPT for lung cancer
    - Lei Dong
    - Ron Zhu
    - Tony Lomax
    - Joe Chang
  - Verification CT imaging for proton therapy
    - Stella Flampouri
    - Bradford Hoppe

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Thanks!

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- Lana Cook
- Abubakr Bajwa
- Harry D'Agostino
- Dat Pham
- James Cury

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