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Robust Optimization of Intensity Modulated Particle (Hadron) Therapy Dose Distributions

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Robustness of a Radiation Dose Distribution

- Resilience of a dose distribution in the face of factors that cause uncertainty
- Degree of confidence that dose distribution seen on a treatment plan is delivered

Robustness Can be Improved

- **Through reduction in uncertainties**
- **Through margin assignments – for 3DCRT with photons or particles and for IMRT**
- **Through robust optimization – for Intensity-modulated particle therapy (IMPT):**
  - **Incorporates in the optimization process of factors that cause uncertainty in dose distributions**

Robust Optimization

- A field of optimization theory evolving since the 1950's
- Applications in statistics, finance, manufacturing engineering, chemical engineering, medicine, ...
- Relatively new to radiation therapy

Sources of Uncertainty in Dose Distributions

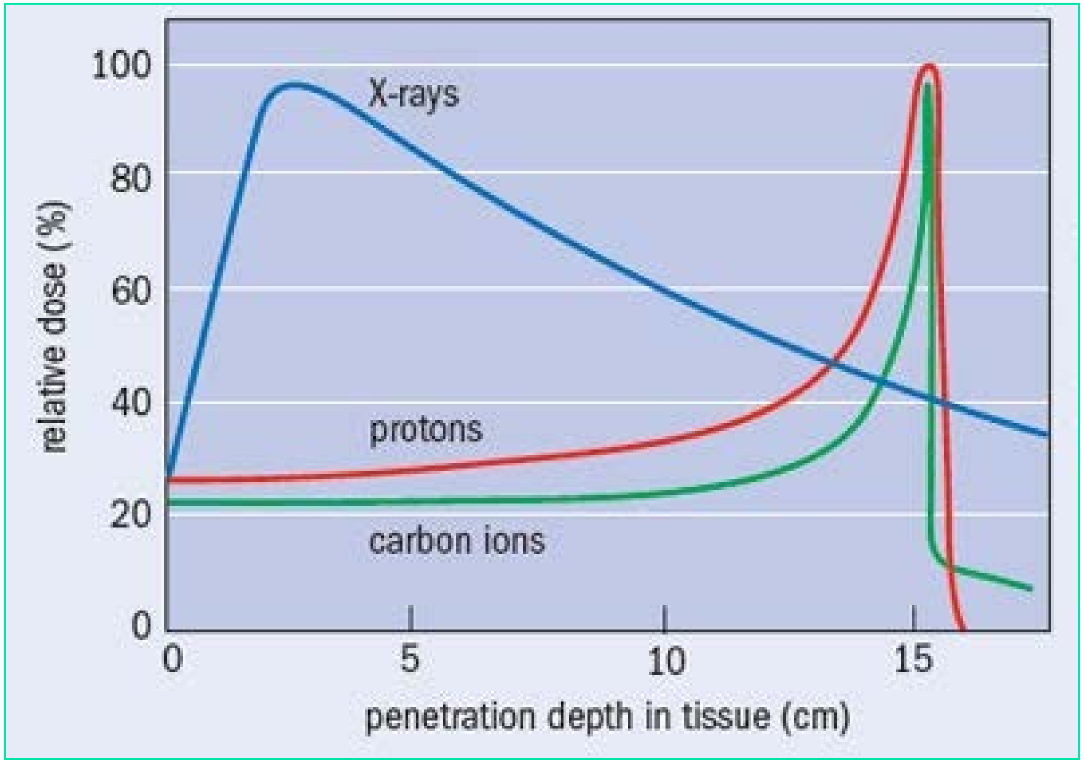
- Approximations in dose calculation algorithms
  - e.g., due to passage of beams through heterogeneities
- Uncertainties in beam characteristics
- Uncertainties in CT data and in factors to convert them to numbers for dose calculations

Sources of Uncertainty in Dose Distributions (cont'd)

- Inter-fractional variations
  - Set up variability
  - Anatomy changes (tumor shrinkage, weight gain or loss, …)
- Intra-fractional motion
- Relative biological effectiveness (RBE)
- …

Particle Therapy is More Vulnerable to Uncertainties

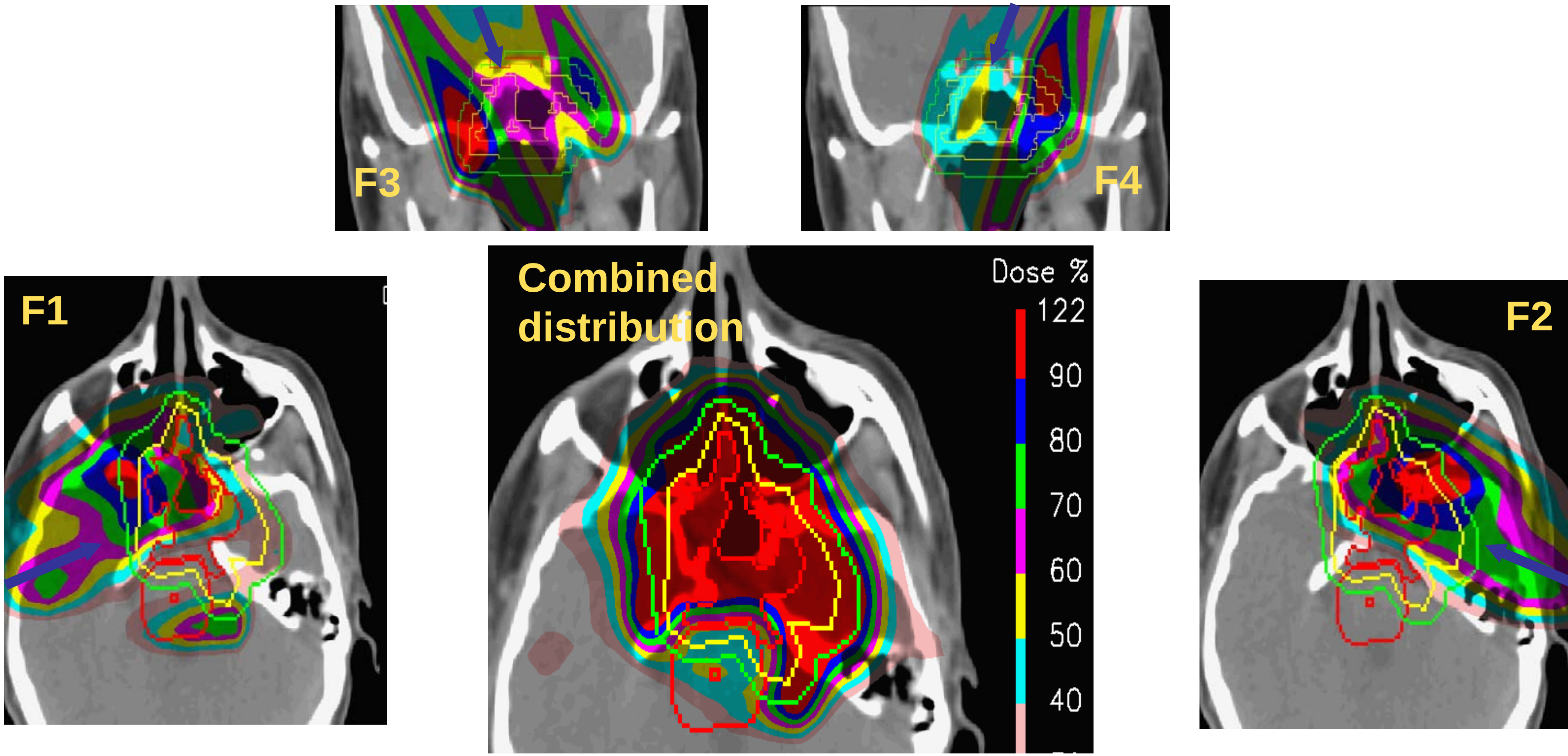
Physical characteristics that make particle therapy attractive are also its Achilles heel



Intensity-Modulated Particle Therapy is the Most Powerful Tool in Radiation Therapy

But it is also the most vulnerable to uncertainties (> PSPT, >> IMRT)

Multi-Field Optimized IMPT



Lomax

Strategies for Robust Optimization are Required

- Probabilistic
- Worst case analysis

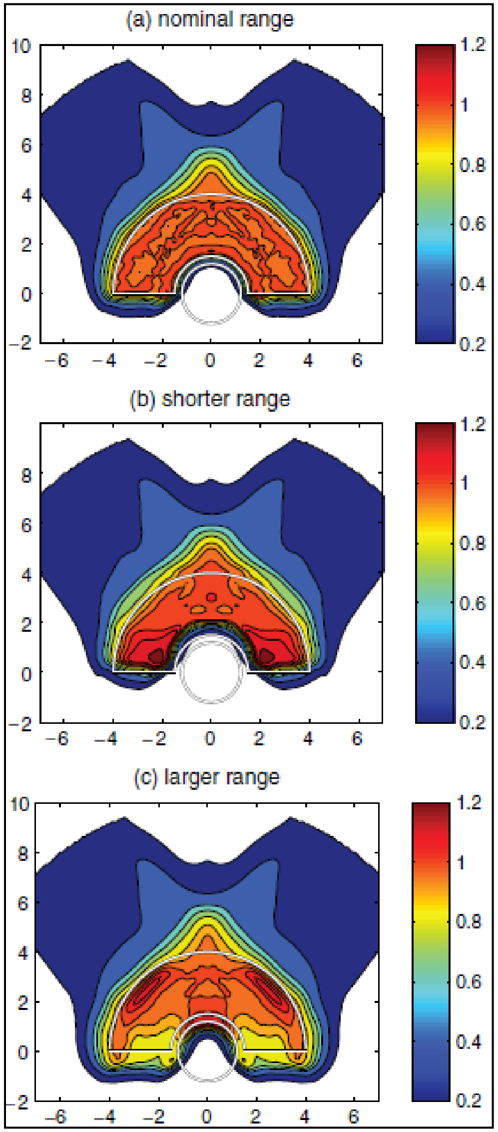
Probabilistic Approaches

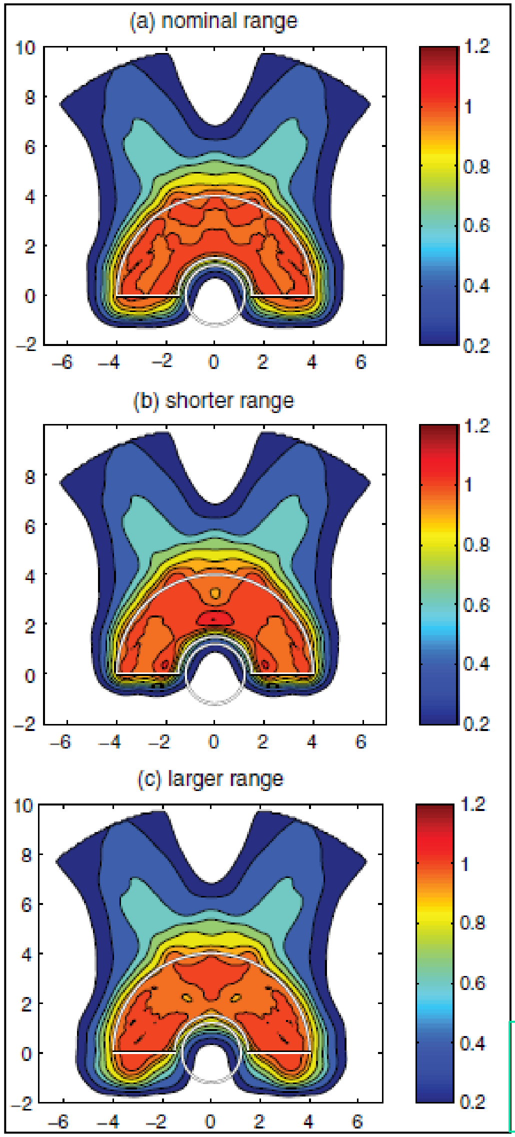
- Probability distribution for each uncertainty is assumed to be known
- A sufficiently large set of uncertainty scenarios are sampled randomly
- IMPT optimization process minimizes the expectation value of the objective function
  - Finds the dose distribution that aims to satisfy the criteria for every uncertainty scenarios

Unkelbach, PMB 2007, Med Phys 2009

Probabilistic Robust Optimization – Illustrative Example

Conventionally Optimized





Robustly Optimized

To make the problem tractable, only a subset of scenarios are considered

Unkelbach, PMB 2007, Med Phys 2009

“Worst Case” Approaches

- Analogous to PTV and PRV margins-based approach in IMRT
- Two strategies
  - minimax
  - Voxel-by-voxel

Worst Case Analysis – minimax

- Multiple scenarios of maximum range and set up uncertainties considered
- Example:
  - $\pm\delta x$, $\pm\delta y$, $\pm\delta z$ shifts (= PTV margins)
  - $\pm\delta r$ for range uncertainty
  - Nominal
- One dose distribution computed for each uncertainty scenario in each optimization iteration
- The scenario with the worst (maximum) score selected in objective function minimization process
- Criteria are intended to be met under the worst case

Fredrikson (2011) and Chen (2012)

Worst Case Analysis – Voxel-by-Voxel

- **Multiple scenarios of maximum range and uncertainty considered (same as for minimax)**
- **One dose distribution computed for each uncertainty scenario in each optimization iteration**
- **Worst case dose in <u>each voxel (minimum in target voxel and maximum in normal tissue voxel)</u> selected to compute objective function and minimize the objective function**
- **More conservative than minimax (uncertainty combination unrealistic), but ...**

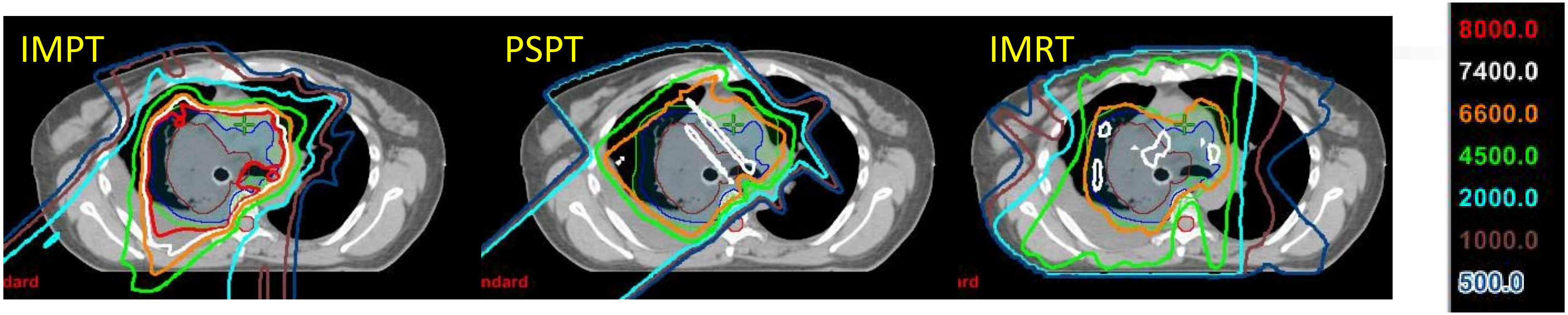
Pflugfelder (2008) and Liu (2012)

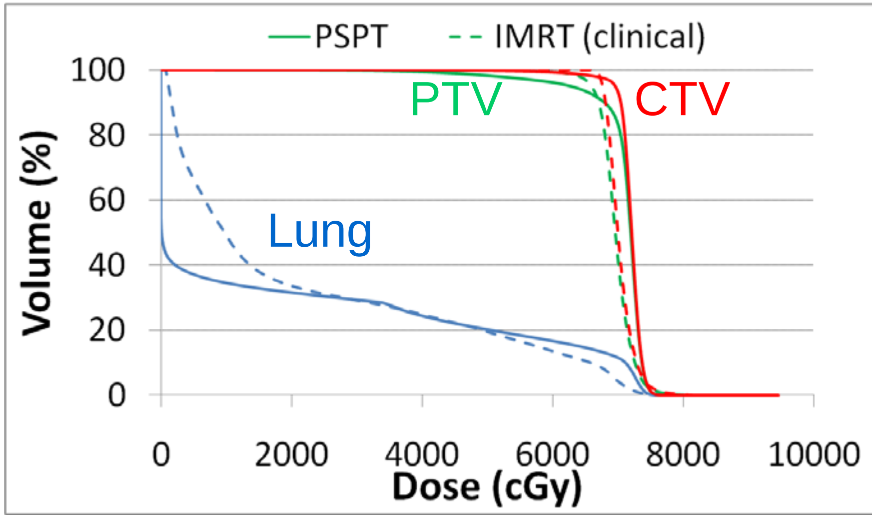
Voxel-by-Voxel
Worst Case Robust Optimization

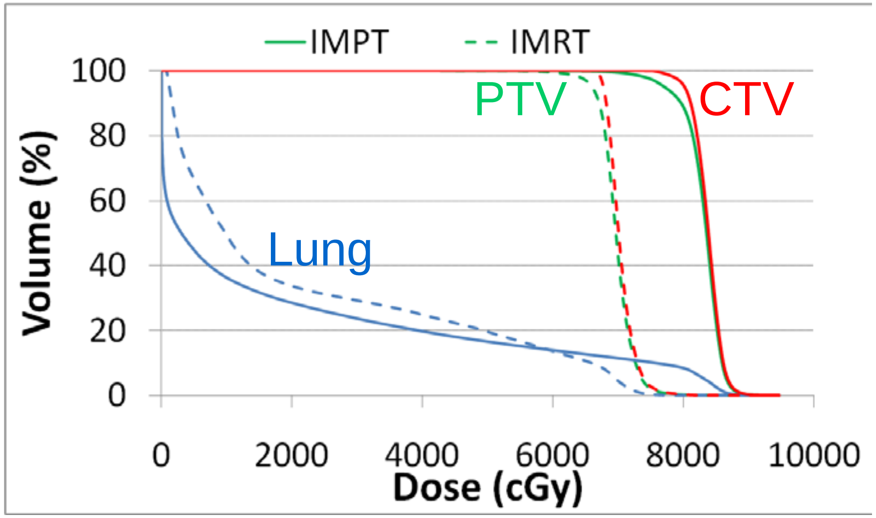
A Lung Example

Robustness Quantification and Robust Optimization Example

A recent lung case from P01 2008-0133 protocol



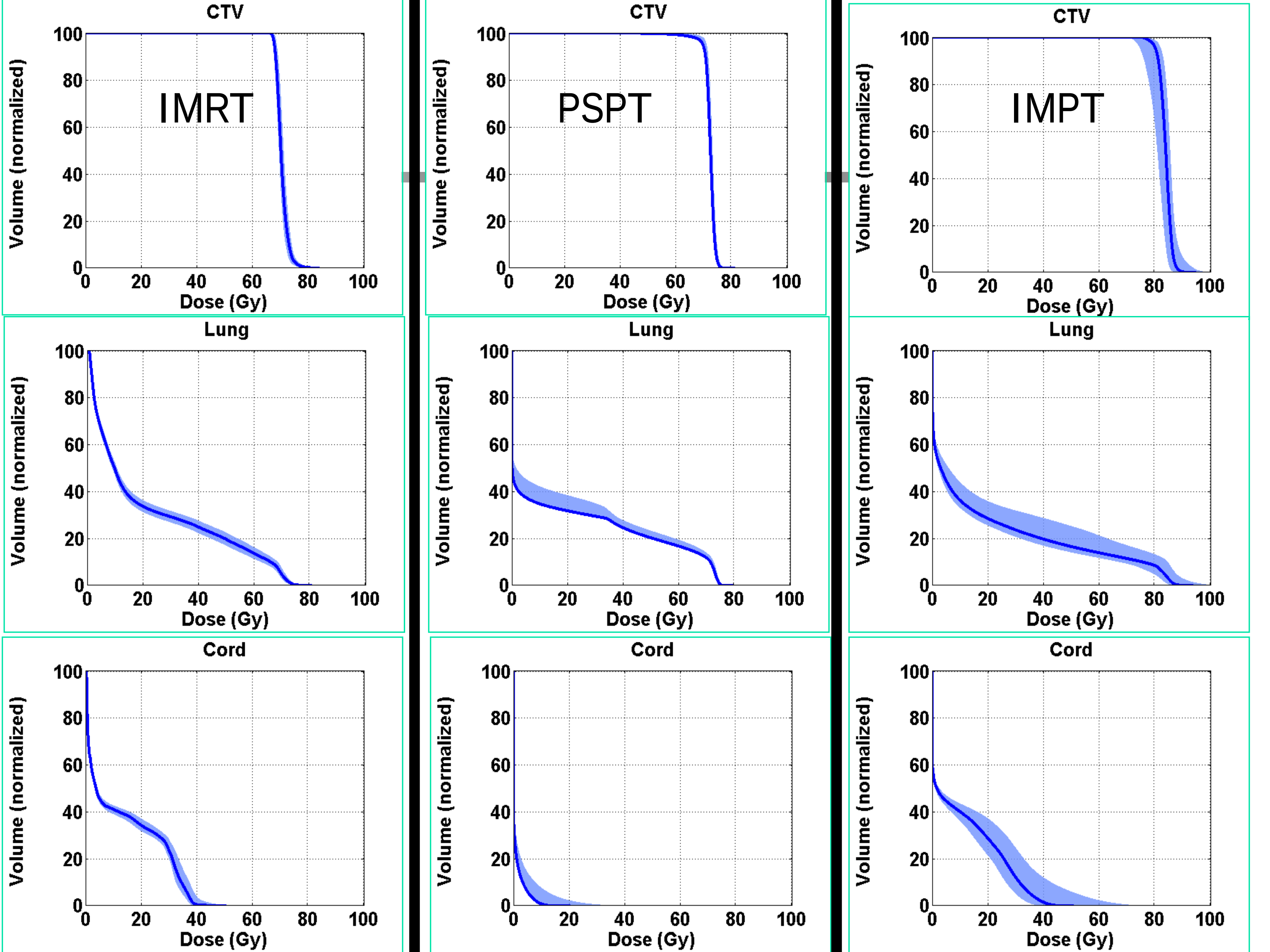


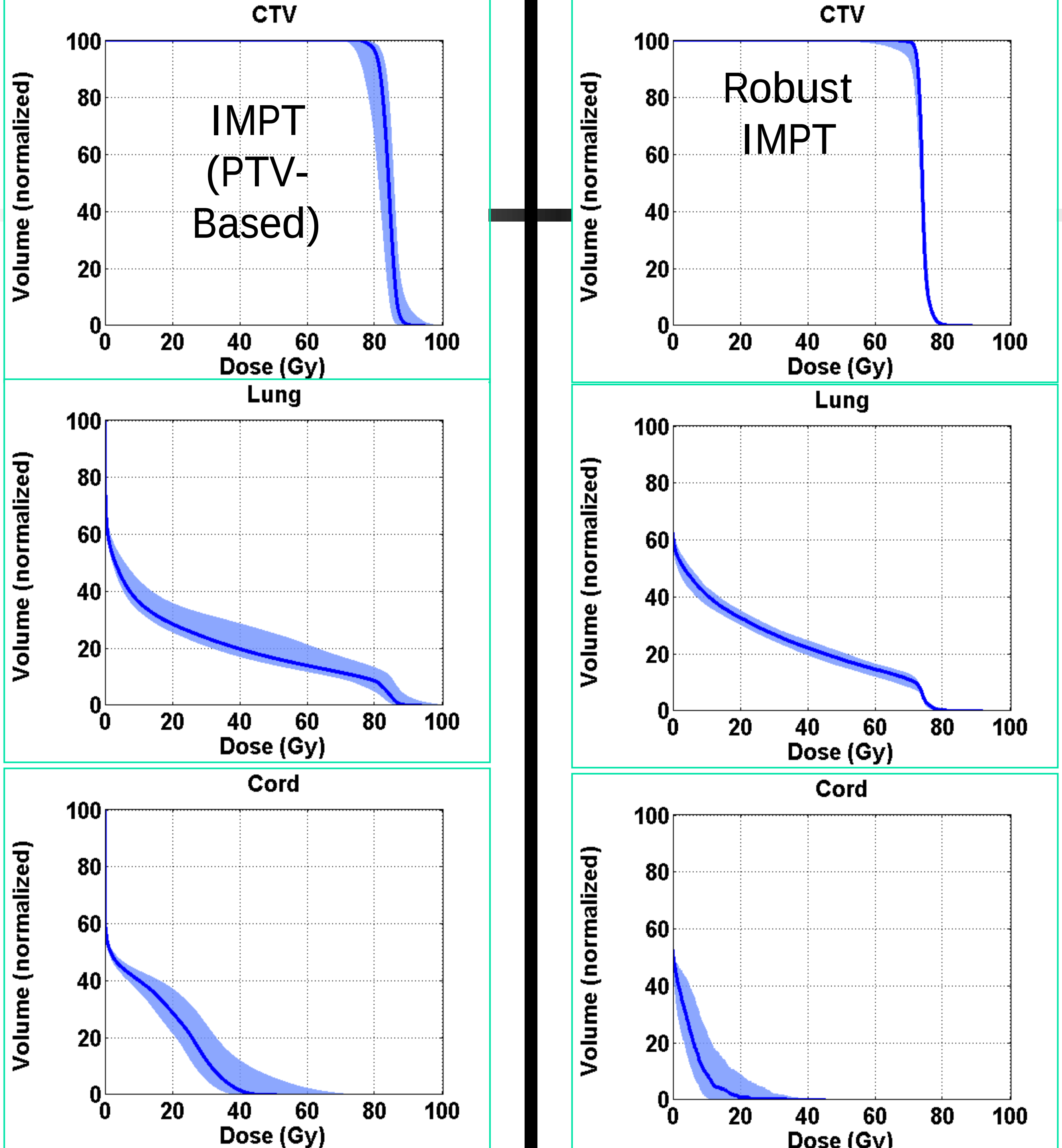


The patient was randomized to IMRT. Both PSPT and IMRT plans could deliver only 66 GyR limited by MLD constraint (22 GyR).

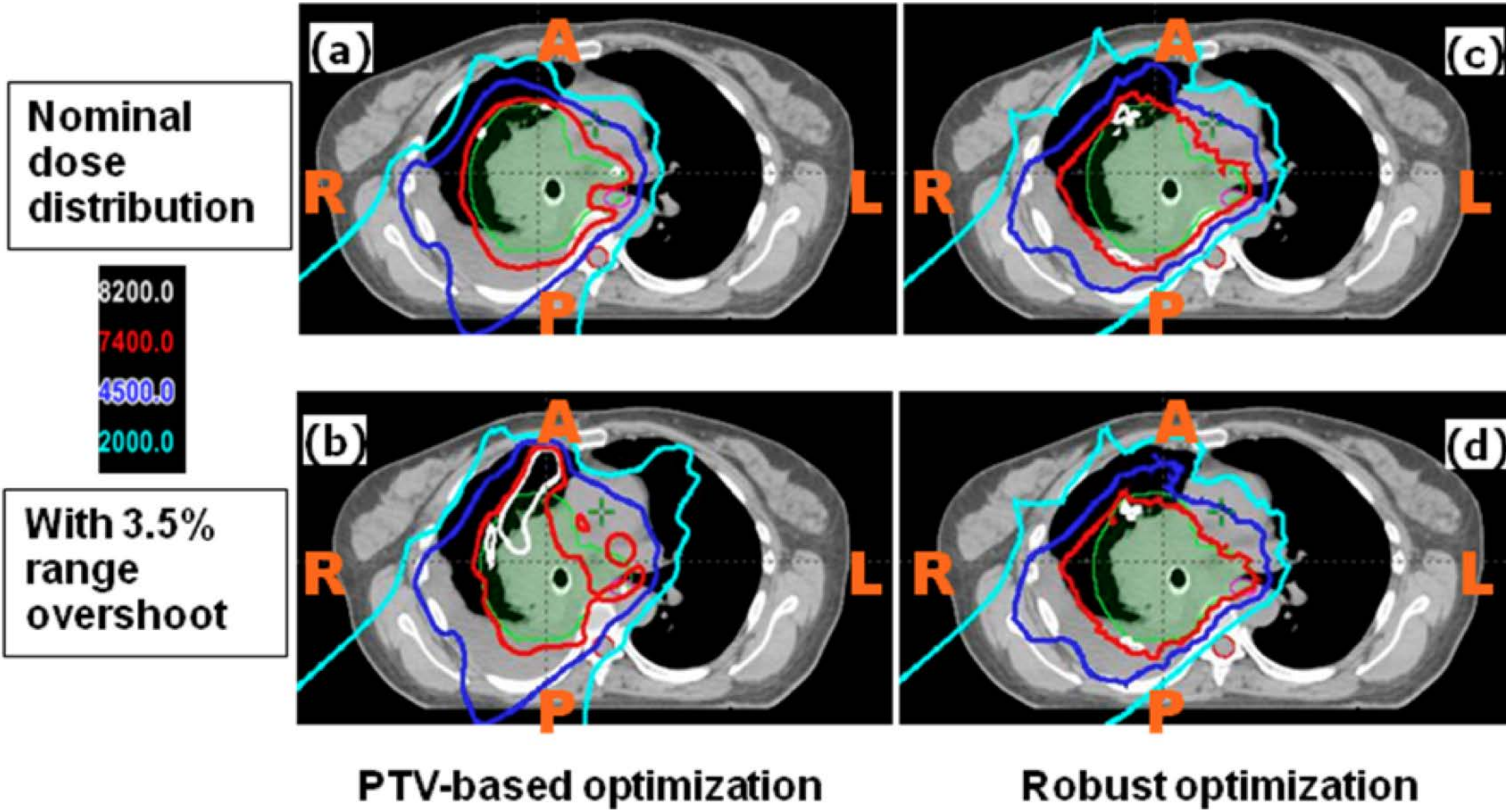
74 GyR could be designed for this patient using IMPT with MLD=17 GyR.

Zhang, Liu and Mohan


CTV
IMRT
Volume (normalized)
Dose (Gy)
CTV
PSPT
Volume (normalized)
Dose (Gy)
CTV
IMPT
Volume (normalized)
Dose (Gy)
Lung
Volume (normalized)
Dose (Gy)
Lung
Volume (normalized)
Dose (Gy)
Lung
Volume (normalized)
Dose (Gy)
Cord
Volume (normalized)
Dose (Gy)
Cord
Volume (normalized)
Dose (Gy)
Cord
Volume (normalized)
Dose (Gy)

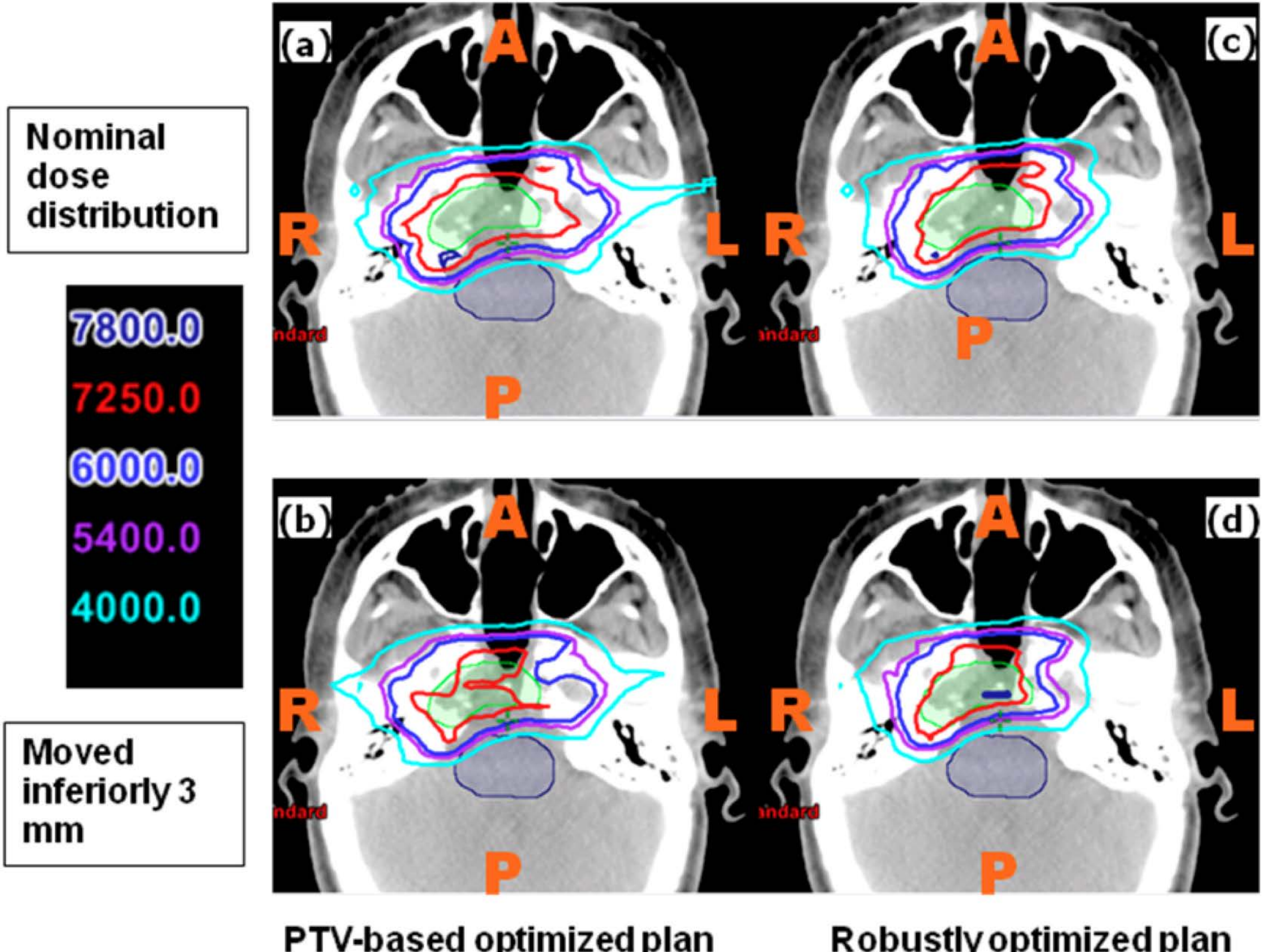


Liu, Zhang and Mohan

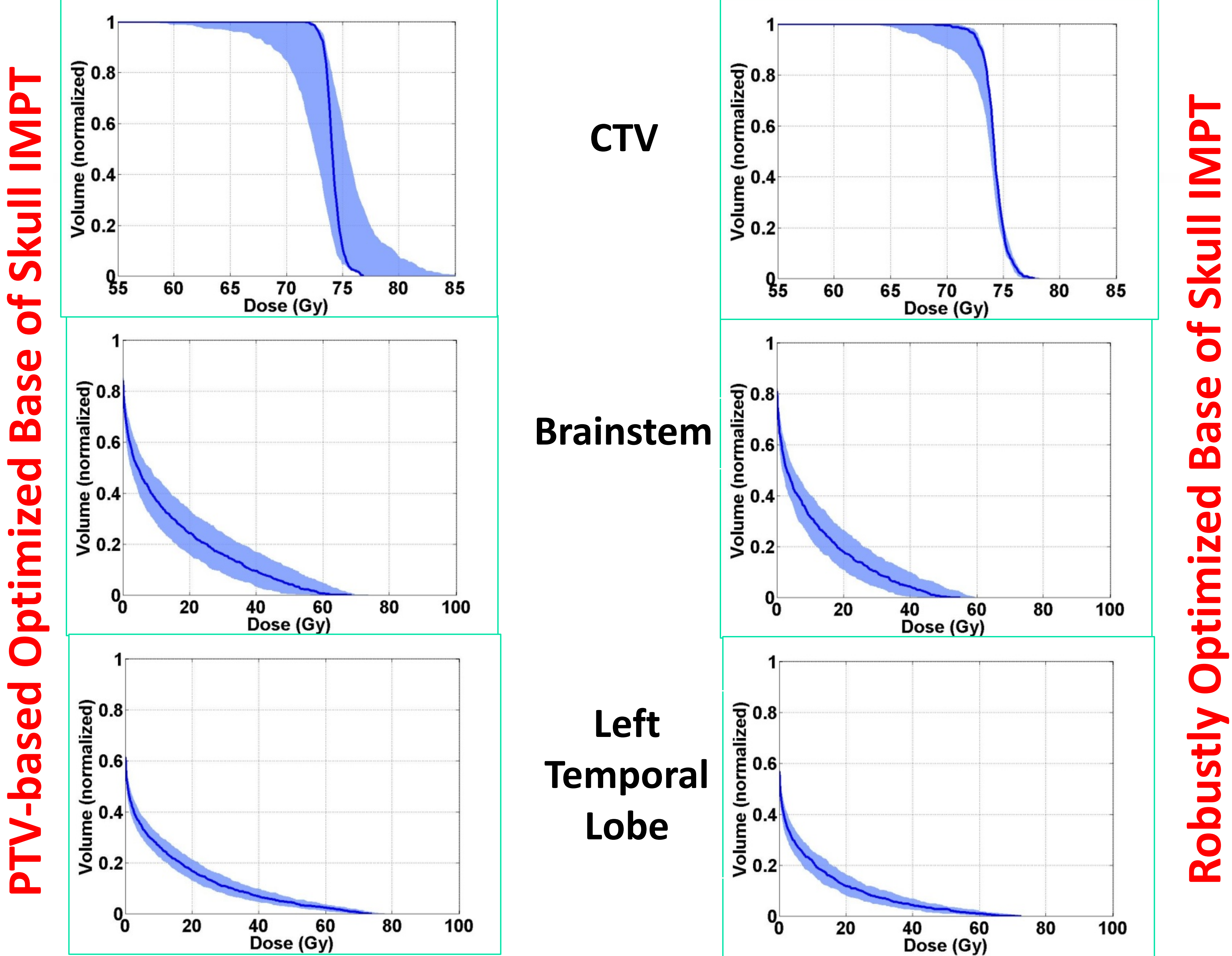

Nominal dose distribution
8200.0
7400.0
4500.0
2000.0
With 3.5% range overshoot
(a)
(b)
(c)
(d)
A
P
R
L
PTV-based optimization
Robust optimization

Voxel-by-Voxel
Worst Case Robust Optimization

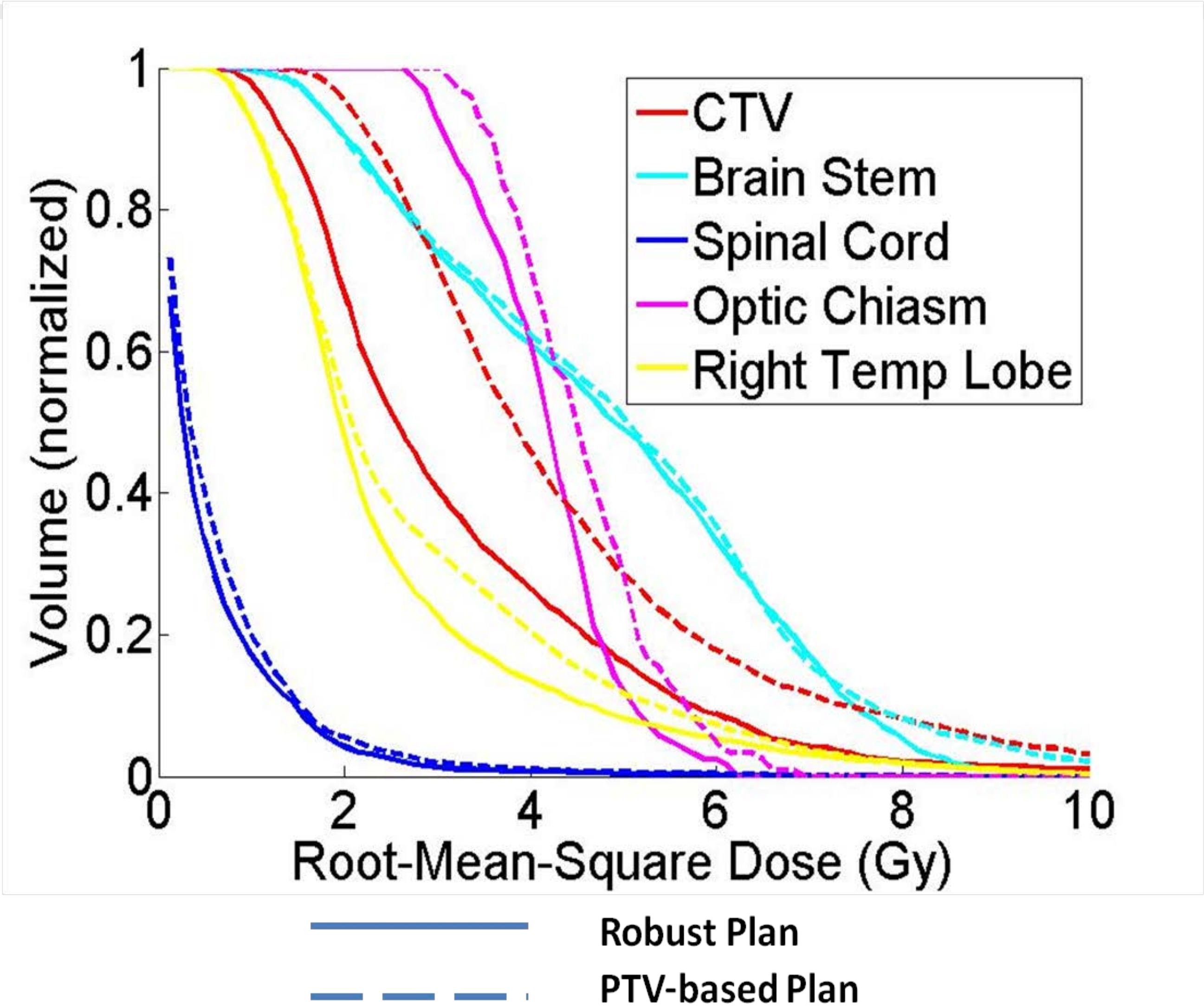
A Base of Skull Example



Nominal dose distribution
7800.0
7250.0
6000.0
5400.0
4000.0
Moved inferiorly 3 mm
(a)
(b)
(c)
(d)
A
P
R
L
PTV-based optimized plan
Robustly optimized plan

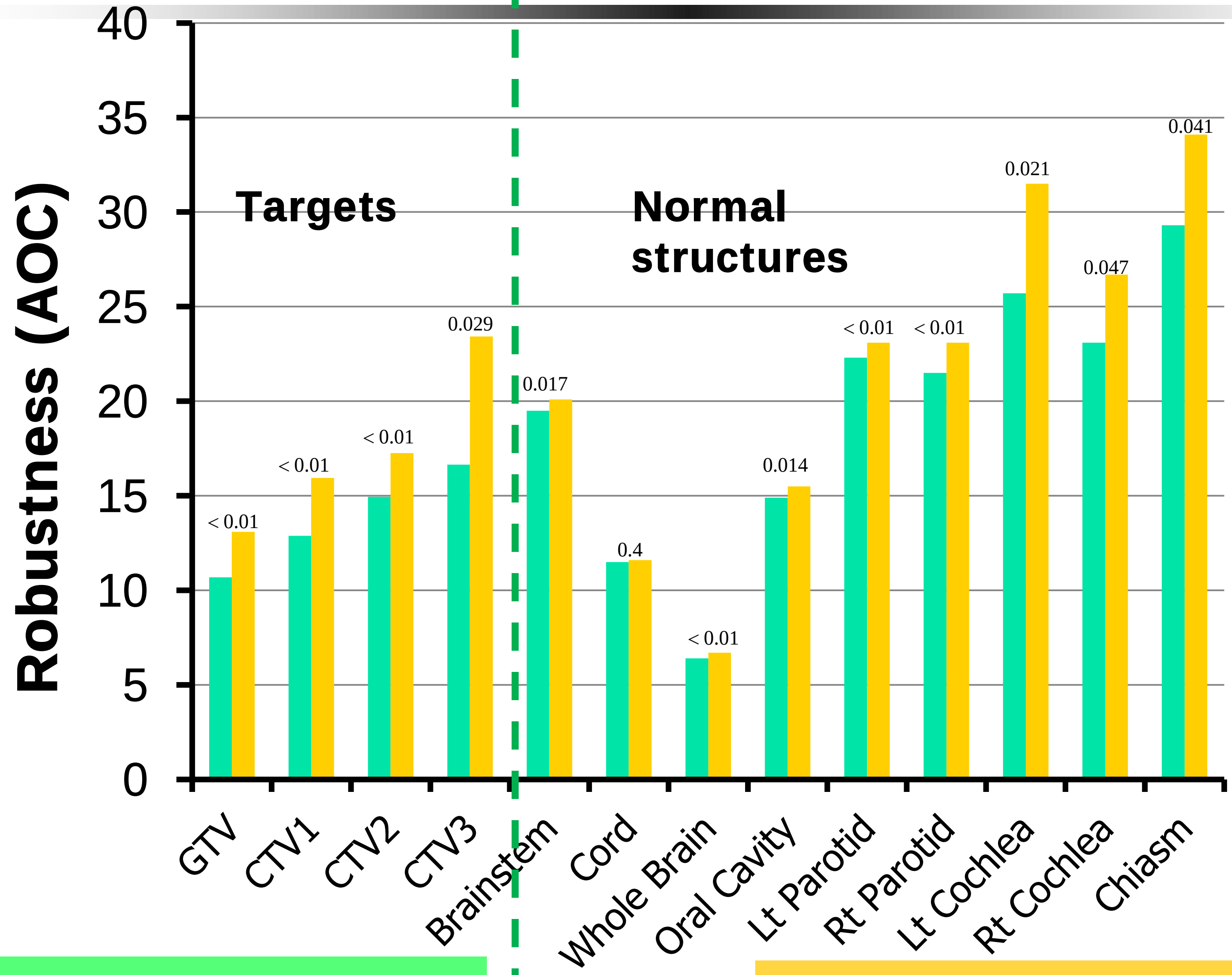

PTV-based Optimized Base of Skull IMPT
Robustly Optimized Base of Skull IMPT
CTV
Brainstem
Left Temporal Lobe
Volume (normalized)
Dose (Gy)

Area under an RMSD-Volume Histogram (RVH) curve may be a good metric of plan robustness



Liu, et al

H&N IMPT Robust Optimization - 10 patient planning study

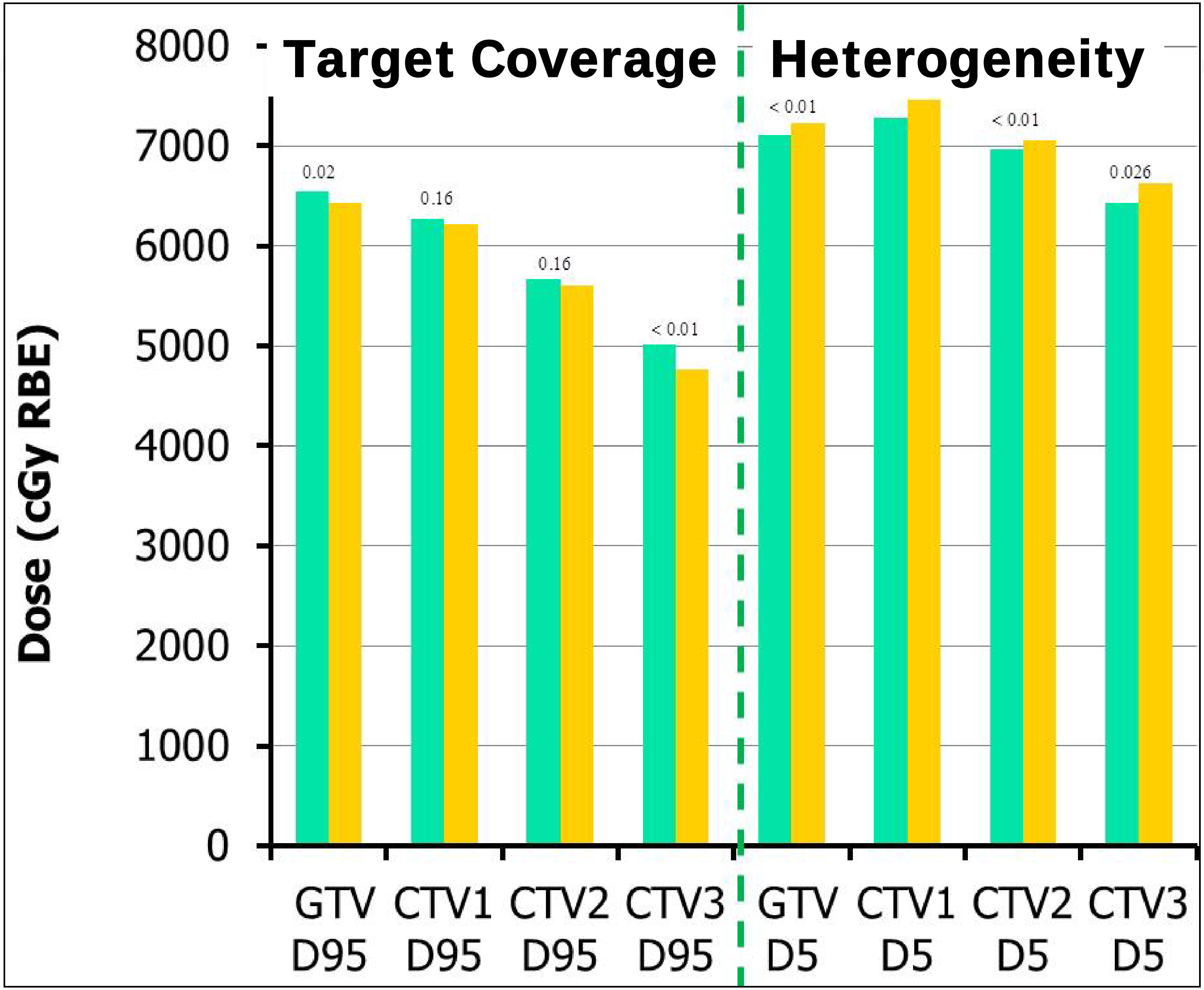


Robust Optimization

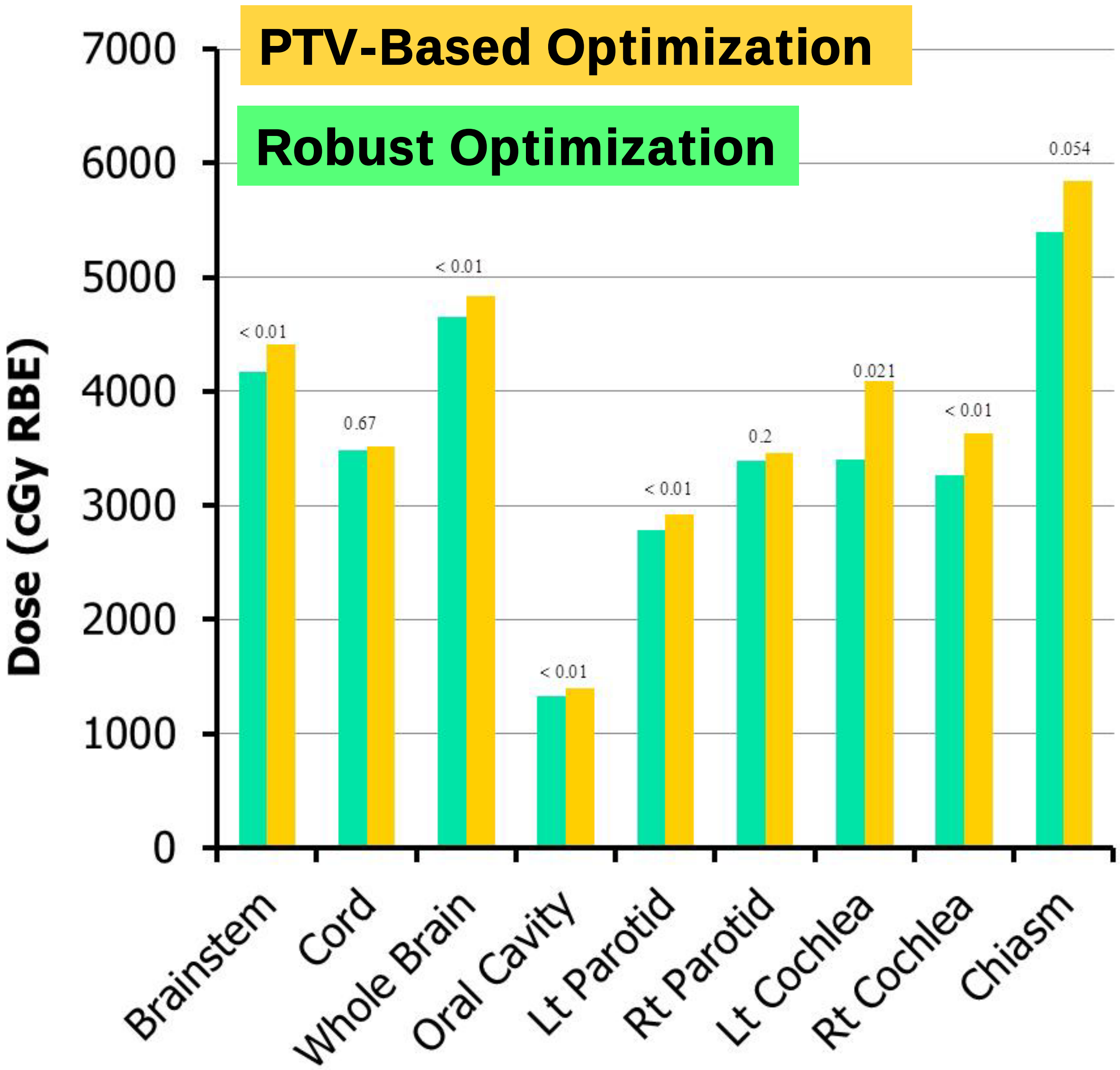
PTV-Based Optimization

Robust Optimization

PTV-Based Optimization



Normal Tissue Sparing



Why Does Robust Optimization Lead to Superior Robustness AND Superior Quality?

Other Factors That Affect IMPT Robustness

- Number of beams
- Spot sizes,
- Energy spacing
- Spot density

Where we are ...

- Significant progress made in understanding of the issues
- Approaches to robust optimization have been developed
- Only set up and range uncertainties considered

What more needs to be done ...

- Comparative effectiveness of alternative approaches to robust optimization
- Consideration of intra-fractional and inter-fractional anatomy variations
- Incorporation of RBE uncertainties
- Quantitative criteria of robustness and threshold of acceptable robustness
- ...

Acknowledgements

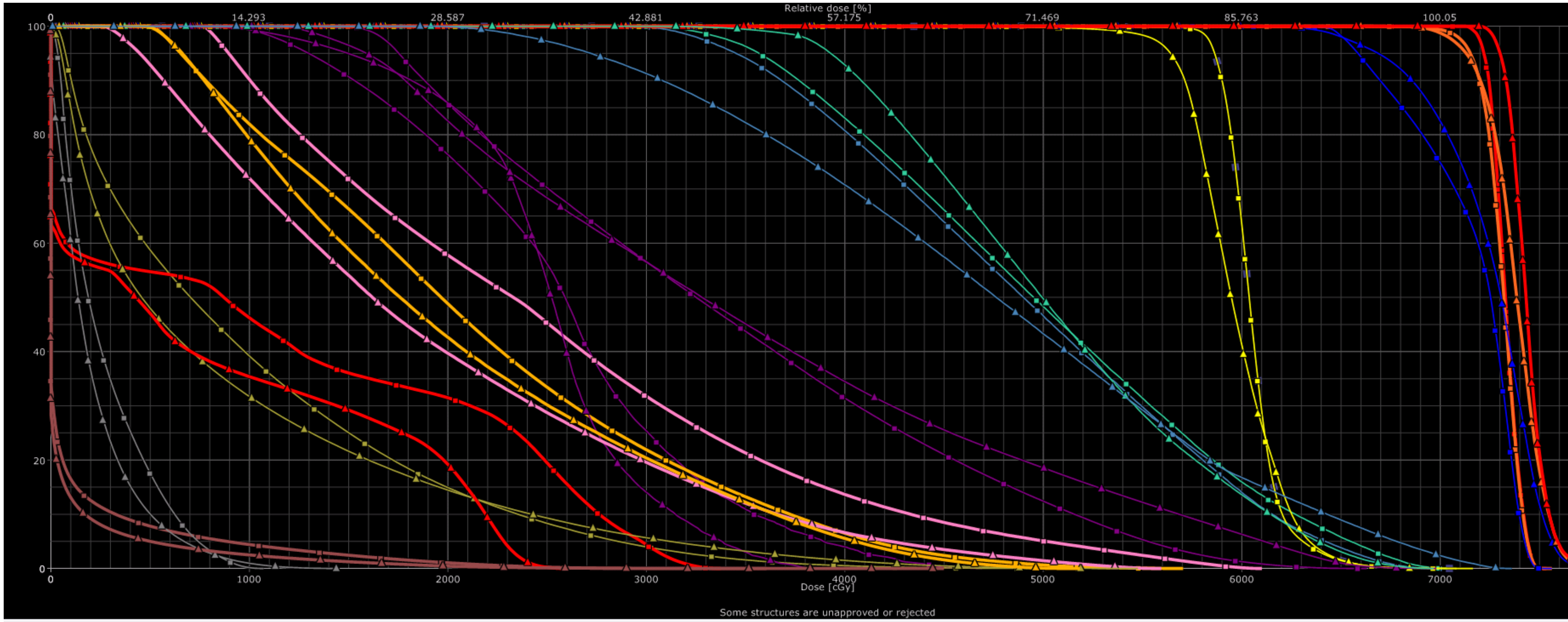
- Wei Liu
- Xiaodong Zhang
- Wenhua Cao
- Shuaiping Ge
- Maryam Zaghian
- Tony Lomax
- Jan Unkelbach

Thank You

Summary

- A robustly optimized plan was generated using in-house system for patient David (1033946)
- The plan was imported into Eclipse to have the final dose calculations.
- The robustly optimized plan has worse target coverage (mainly CTV57) than clinically approved plan in nominal scenario (shown in Eclipse) but has better coverage in the worst case scenario using robust analysis.
- The robustly optimized plan is more robust for target coverage.
- The robustly optimized plan also achieved better normal tissue sparing for majority OARs such as parotids, oral cavity.
- The worse CTV coverage of CTV57 are mainly due to the two different dose calculation algorithms used for in-house system and Eclipse.

DVH comparison between robust plan (triangle) and clinical approved plan (square)

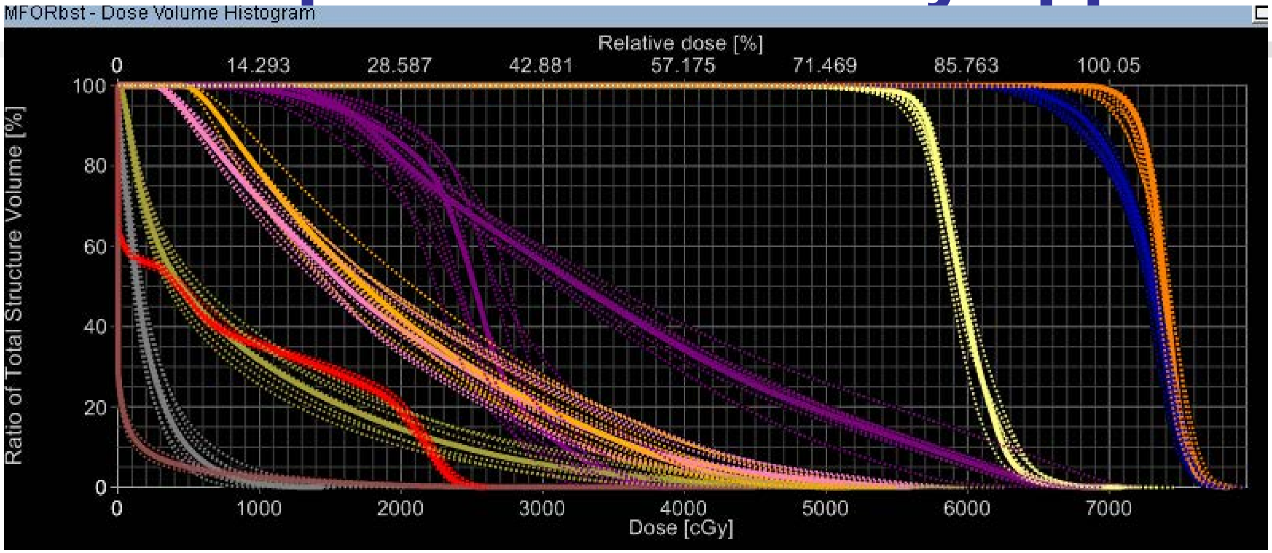


Selection | Registration | Contouring | Field Setup | Plan Evaluation

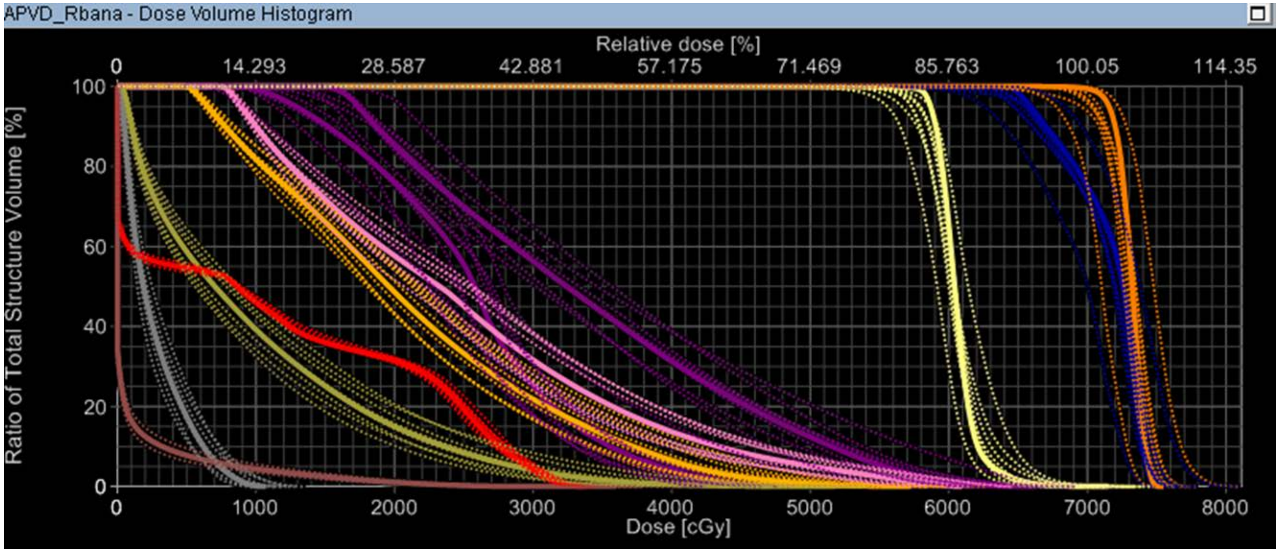
Fields | Dose Prescription | Dose Statistics | Plan Sum

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		Whole Brain	Unapproved	MFORbst	BOT_70CGE	1522.6	100.0	100.0	0.0	4501.8	82.1
☑		Whole Brain	Unapproved	APVD_SJF	BOT_70CGE	1522.6	100.0	100.0	0.0	3605.5	124.7
☑		Brain Stem	Unapproved	MFORbst	BOT_70CGE	25.0	100.0	100.0	0.0	1449.9	206.5
☑		Brain Stem	Unapproved	APVD_SJF	BOT_70CGE	25.0	100.0	100.0	4.4	1075.8	269.0
☑		Spinal Cord	Unapproved	MFORbst	BOT_70CGE	27.6	100.0	100.2	0.0	2593.5	799.7
☑		Oral Cavity	Unapproved	MFORbst	BOT_70CGE	204.0	100.0	100.0	0.0	5478.7	892.3
☑		Oral Cavity	Unapproved	APVD_SJF	BOT_70CGE	204.0	100.0	100.0	0.0	5207.4	987.8
☑		Spinal Cord	Unapproved	APVD_SJF	BOT_70CGE	27.6	100.0	100.2	0.0	3376.0	1112.8
☑		Lt Parotid	Unapproved	MFORbst	BOT_70CGE	24.3	100.0	100.0	242.0	5596.8	1904.3
☑		Rt Parotid	Unapproved	MFORbst	BOT_70CGE	27.0	100.0	100.0	475.7	5187.4	1999.4
☑		Rt Parotid	Unapproved	APVD_SJF	BOT_70CGE	27.0	100.0	100.0	487.0	5708.8	2120.8
☑		Lt Parotid	Unapproved	APVD_SJF	BOT_70CGE	24.3	100.0	100.0	724.6	6102.9	2495.0
☑		Esophagus	Unapproved	MFORbst	BOT_70CGE	1.6	100.0	100.3	754.6	3919.0	2496.7
☑		Esophagus	Unapproved	APVD_SJF	BOT_70CGE	1.6	100.0	100.3	861.0	4692.1	2558.4

Comparing of DVH and DVH bands for robustly optimized plan and clinically approved plan

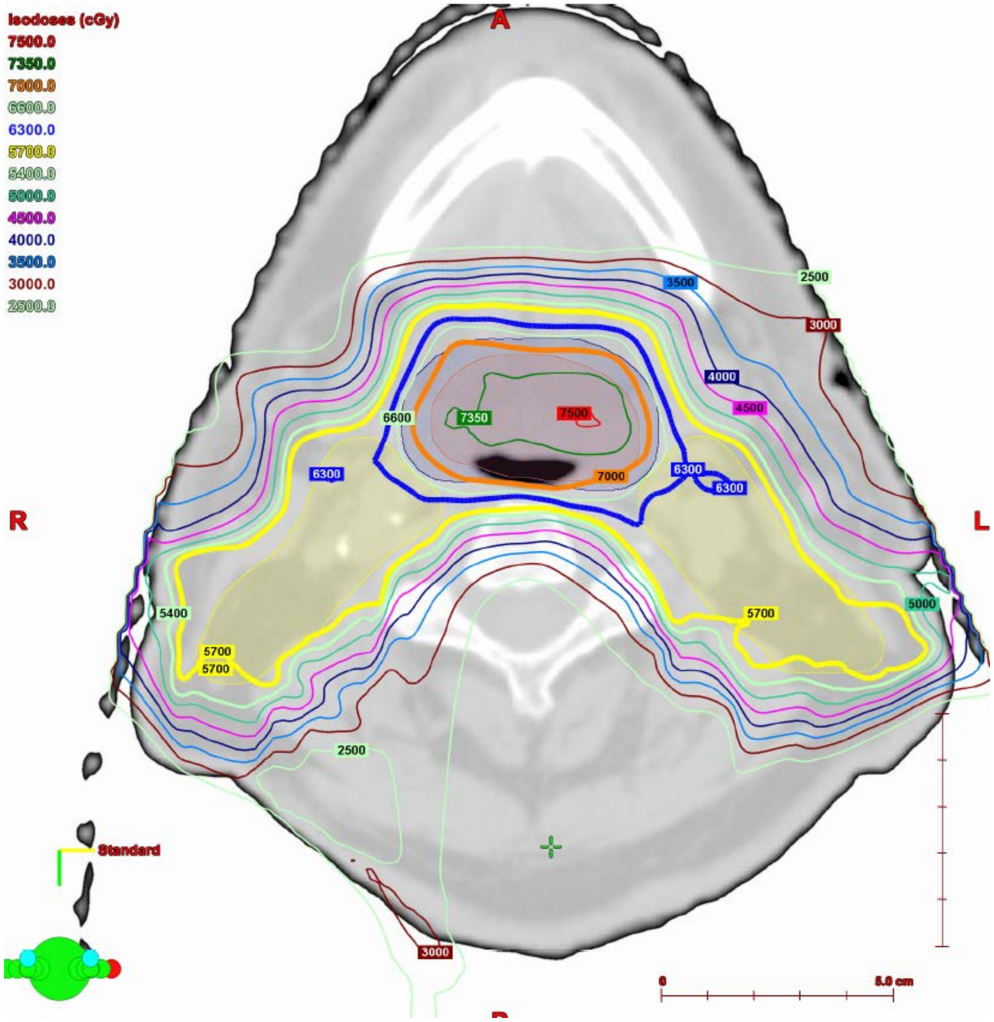


Robustly optimized plan

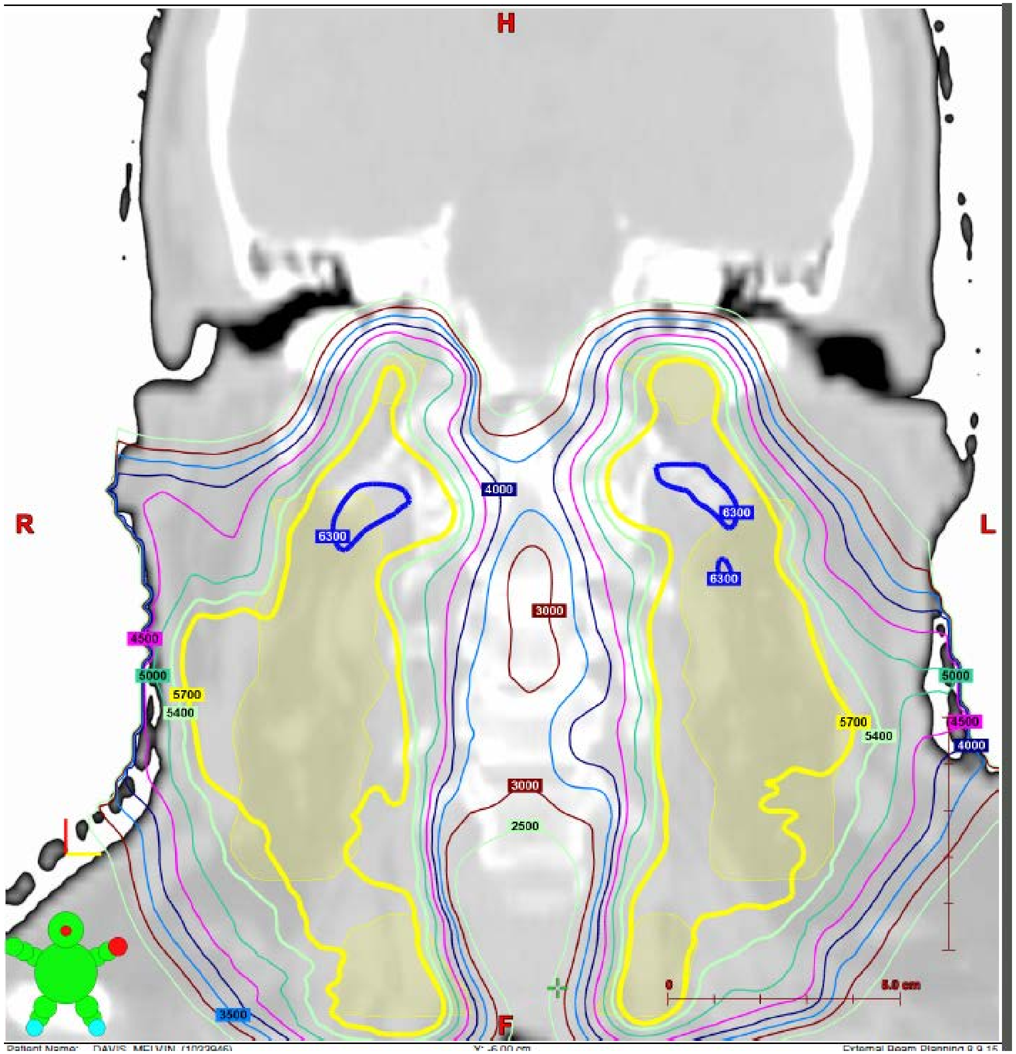


Clinically approved plan

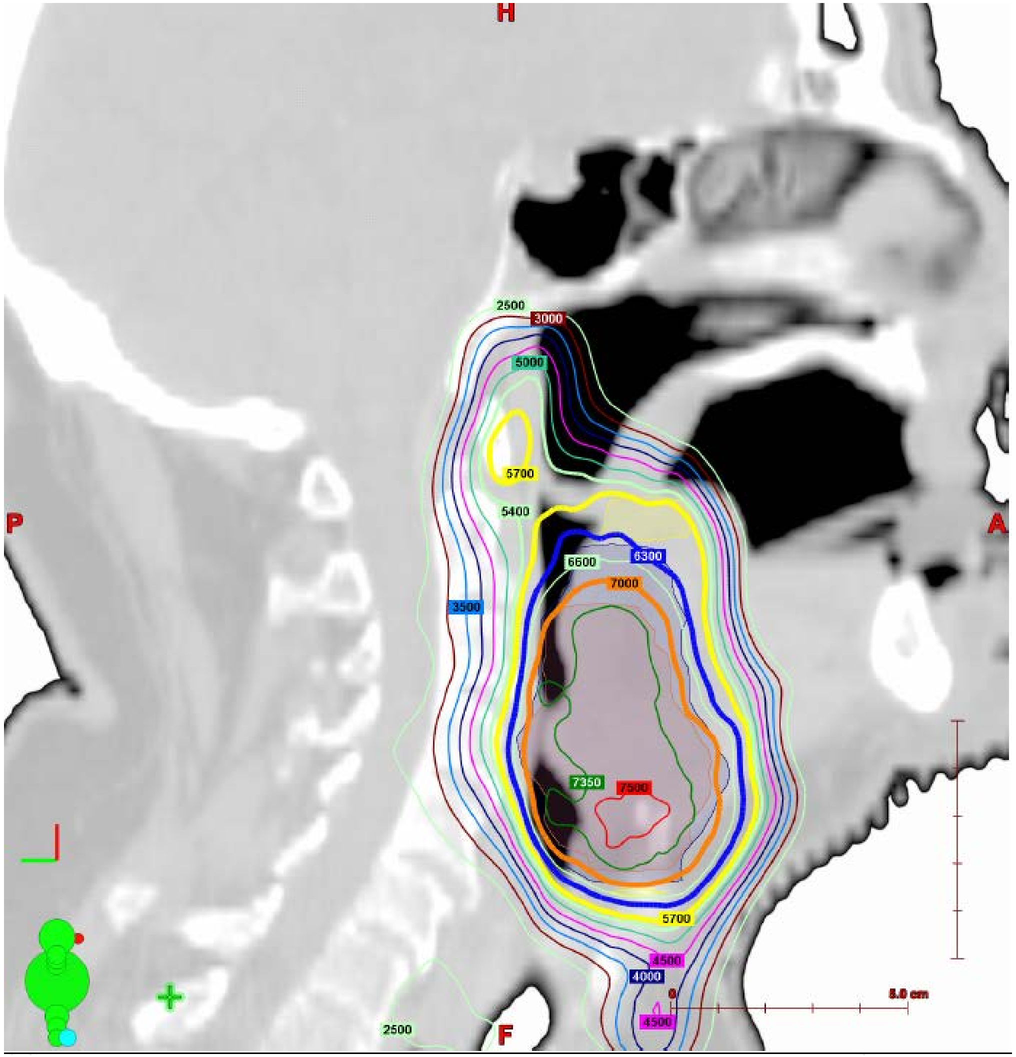
Dose Distributions for robustly optimized plan



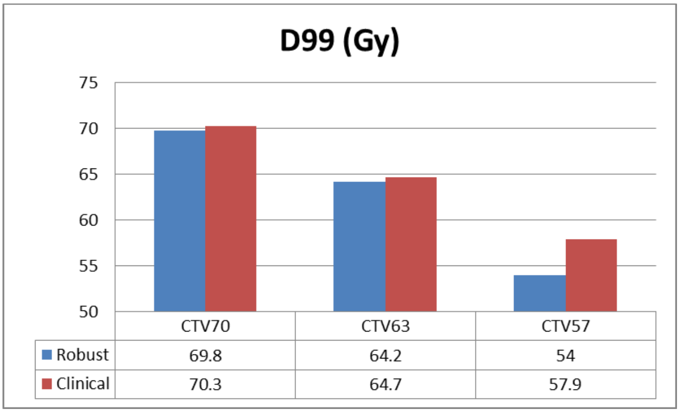
Dose Distributions for robustly optimized plan

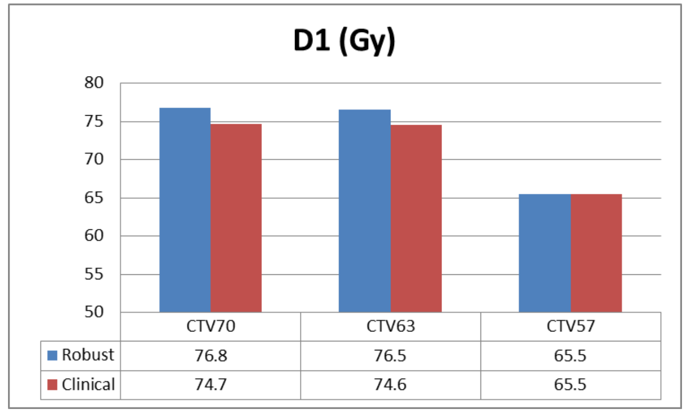


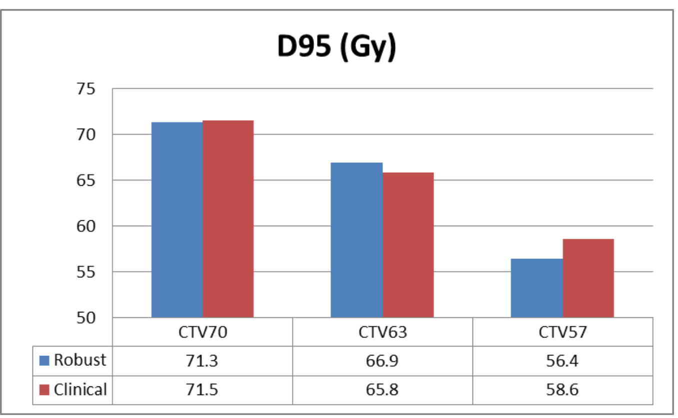
Dose Distributions for robustly optimized plan

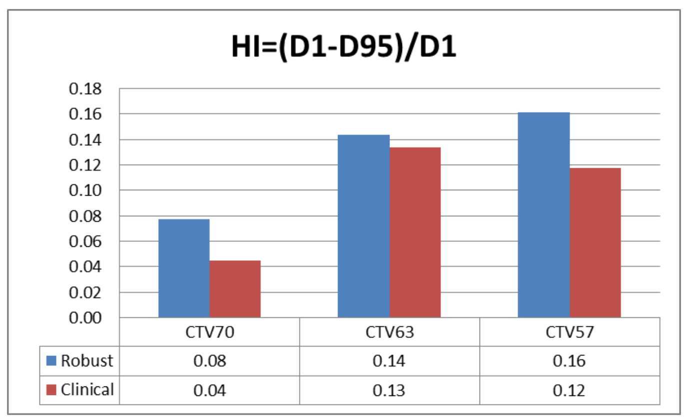


Target Coverage







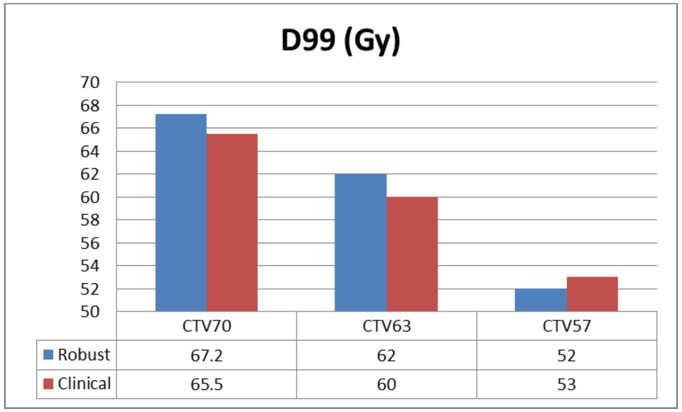


- **The robust plan has slight worse coverage in terms of D99 and D95 for CTV70, CTV63 and CTV57**
- **The robust plan is more heterogeneous as indicated by the HI index and D1**

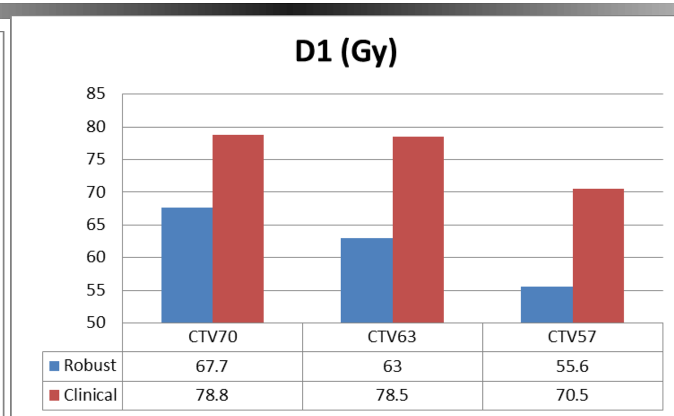
The larger, the better for

The smaller, the better for D1 and

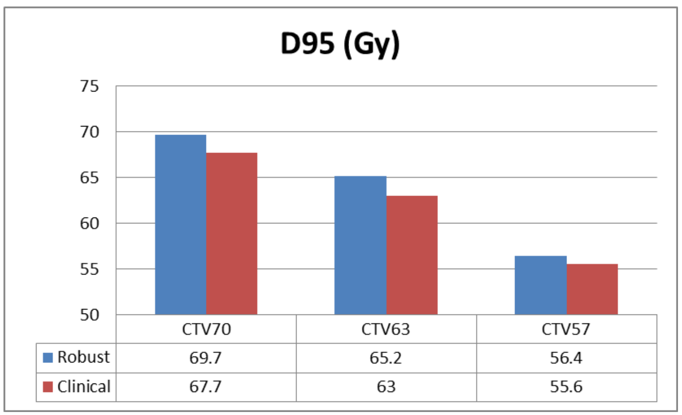
Target Robustness (1)



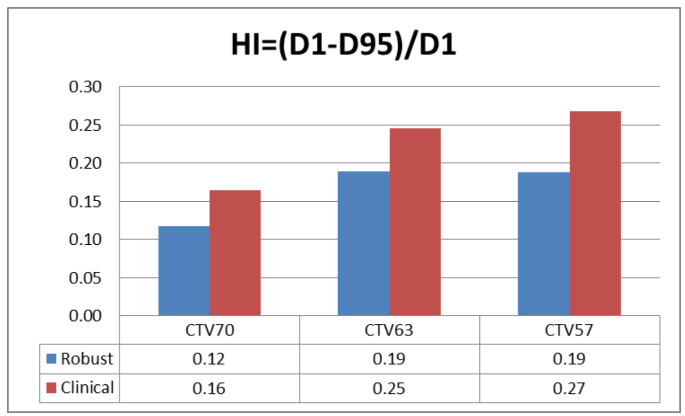
	CTV70	CTV63	CTV57
Robust	67.2	62	52
Clinical	65.5	60	53



	CTV70	CTV63	CTV57
Robust	67.7	63	55.6
Clinical	78.8	78.5	70.5



	CTV70	CTV63	CTV57
Robust	69.7	65.2	56.4
Clinical	67.7	63	55.6



	CTV70	CTV63	CTV57
Robust	0.12	0.19	0.19
Clinical	0.16	0.25	0.27

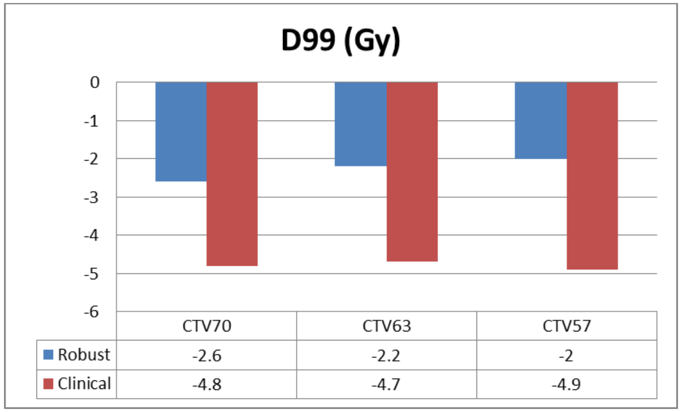
The robust plan has better coverage in terms of D99 and D95 for CTV70, CTV63 and CTV57 in worst case scenarios

The robust plan is more homogeneous as indicated by the HI index and D1 in worst case scenarios

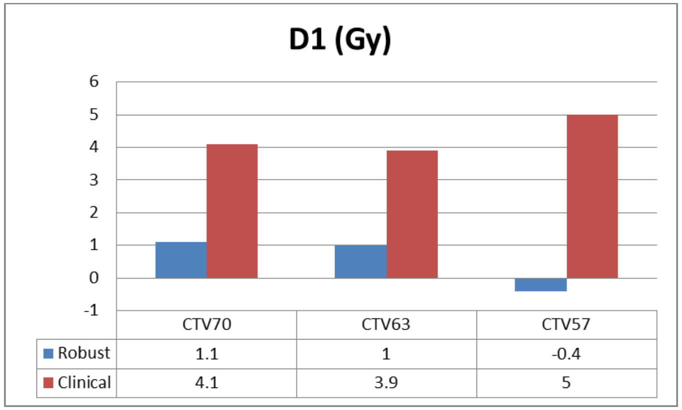
The larger, the better for D99 and D95

The smaller, the better for D1 and HI

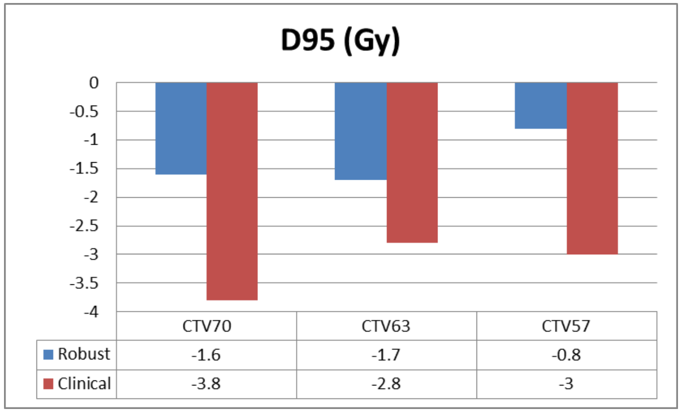
Target Robustness: variations of D99, D95, D1 and HI



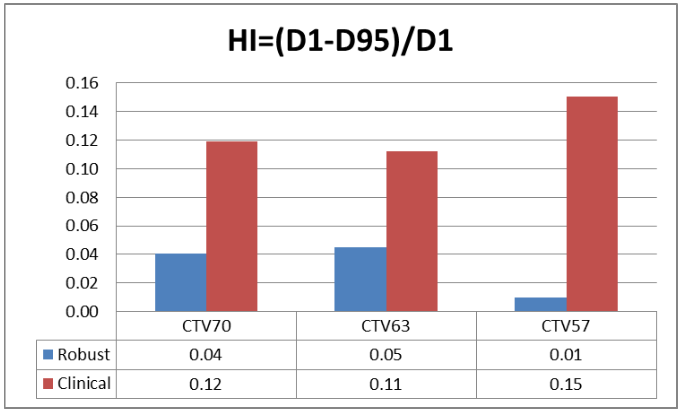
	CTV70	CTV63	CTV57
Robust	-2.6	-2.2	-2
Clinical	-4.8	-4.7	-4.9



	CTV70	CTV63	CTV57
Robust	1.1	1	-0.4
Clinical	4.1	3.9	5



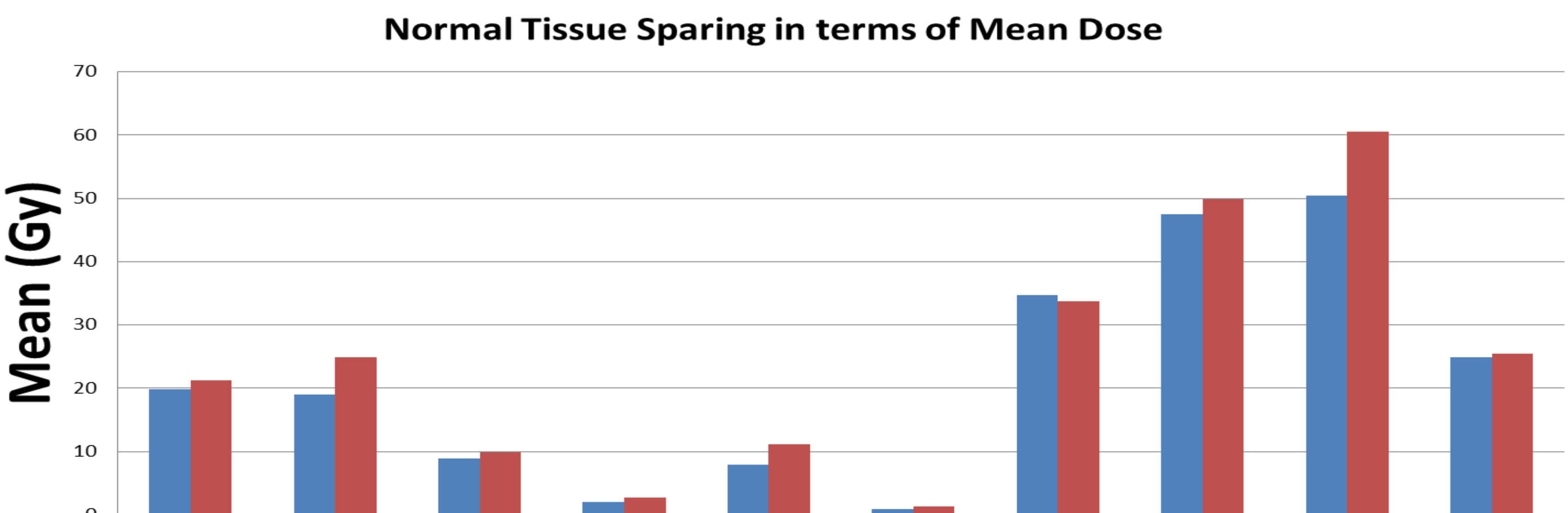
	CTV70	CTV63	CTV57
Robust	-1.6	-1.7	-0.8
Clinical	-3.8	-2.8	-3



	CTV70	CTV63	CTV57
Robust	0.04	0.05	0.01
Clinical	0.12	0.11	0.15

- **The robust plan has narrower variations between worst case and nominal variations for the D99, D95, D1 and HI**

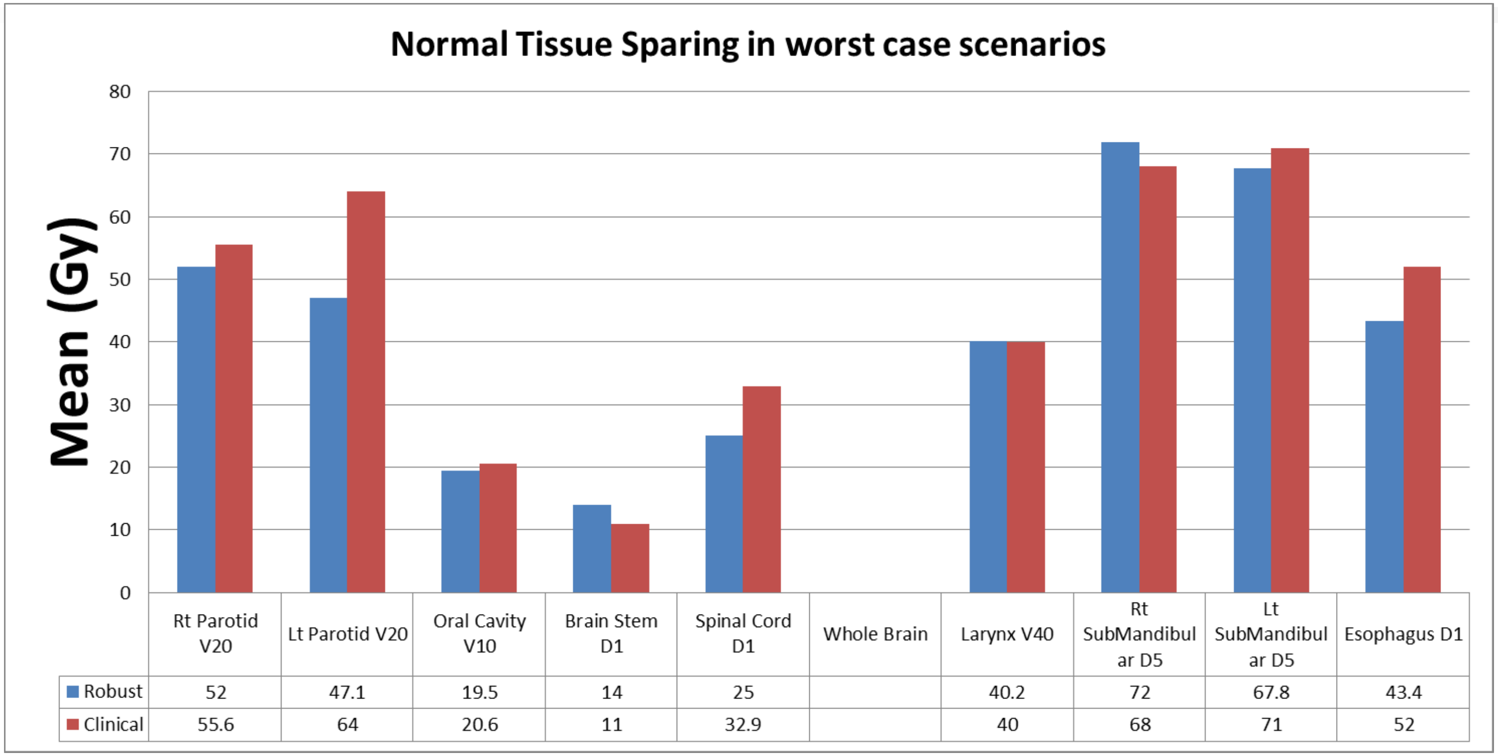
Critical Organ Sparing



	Rt Parotid	Lt Parotid	Oral Cavity	Brain Stem	Spinal Cord	Whole Brain	Larynx	Rt SubMandibular	Lt SubMandibular	Esophagus
Robust	19.9	19	8.91	2.04	7.95	0.82	34.7	47.5	50.5	24.9
Clinical	21.2	24.9	9.9	2.68	11.09	1.25	33.8	49.9	60.6	25.5

- **The robust plan achieved the better normal tissue sparing in terms of mean dose except for larynx which is 0.9 Gy higher than clincal plan.**

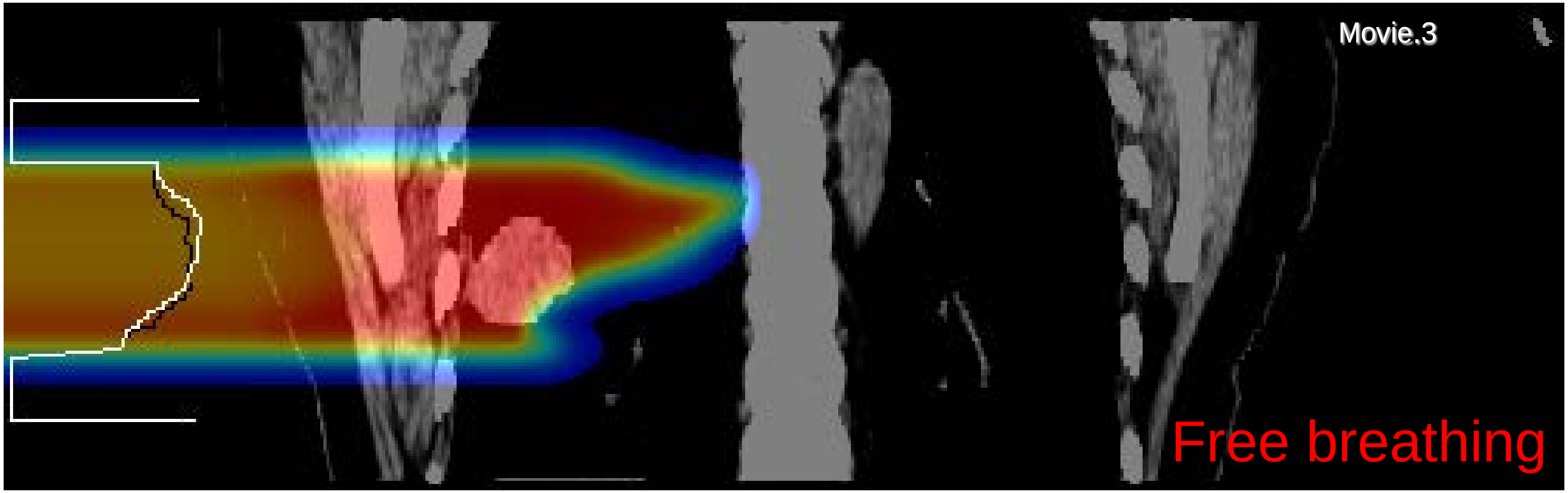
Clinical Organ Sparing in worst case scenarios

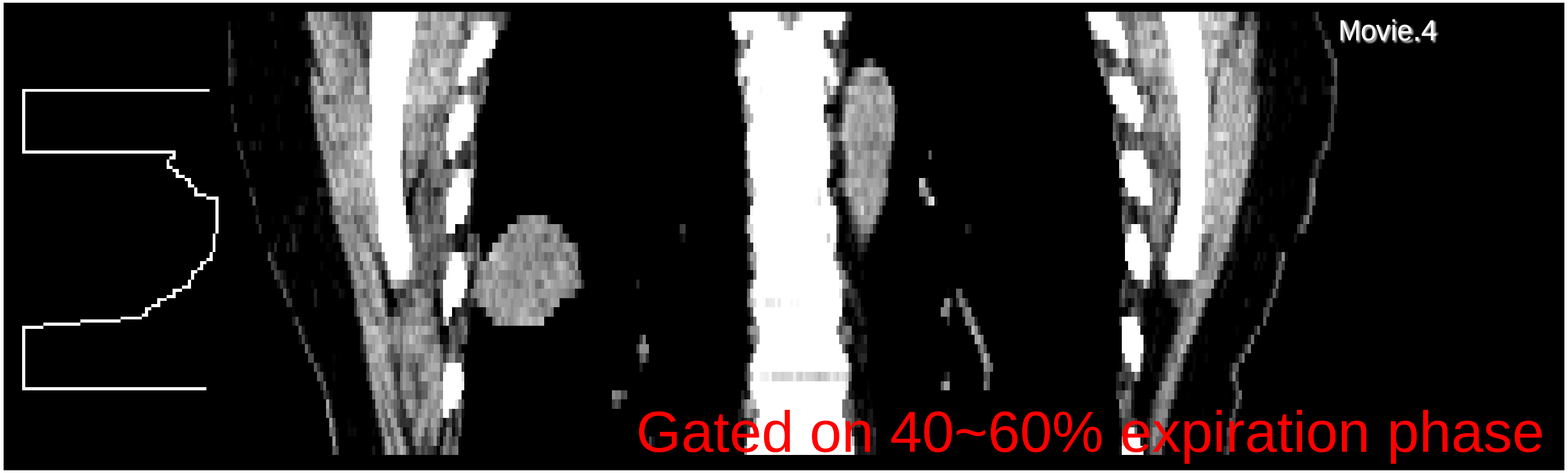


	Rt Parotid V20	Lt Parotid V20	Oral Cavity V10	Brain Stem D1	Spinal Cord D1	Whole Brain	Larynx V40	Rt SubMandibular D5	Lt SubMandibular D5	Esophagus D1
Robust	52	47.1	19.5	14	25		40.2	72	67.8	43.4
Clinical	55.6	64	20.6	11	32.9		40	68	71	52

- **In worst case scenarios, the robust plan achieves better normal tissue sparing except Brain Stem which both plans are well below tolerance and Rt SubMandibular.**

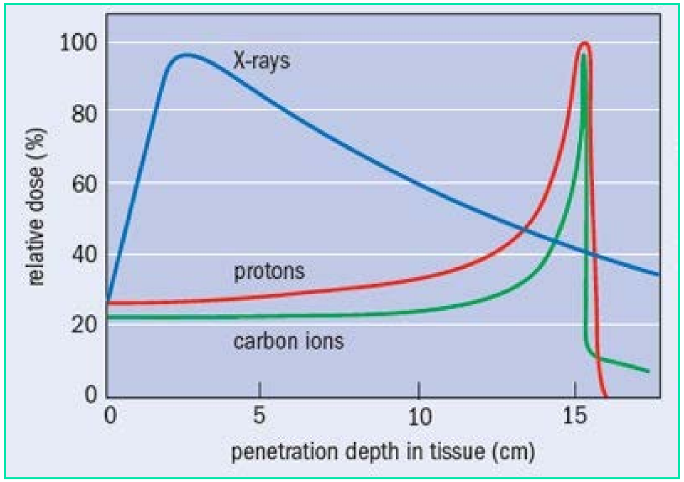
Not accountable for with PTV margins

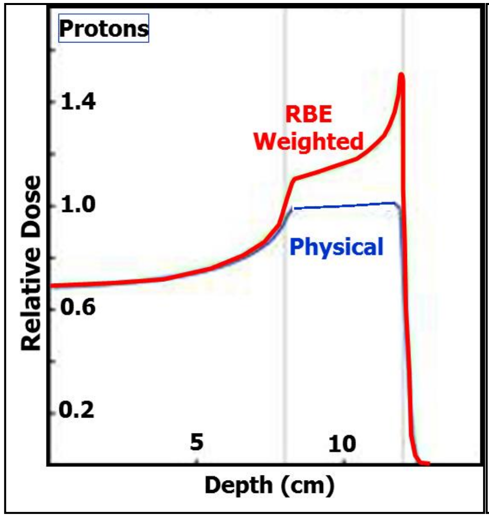


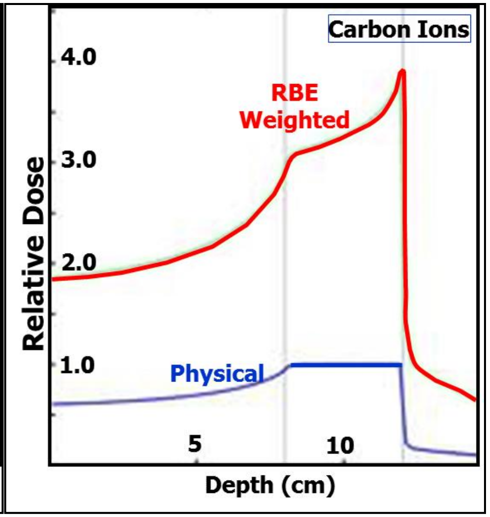


Tsunashima

Rationale for Particle Therapy

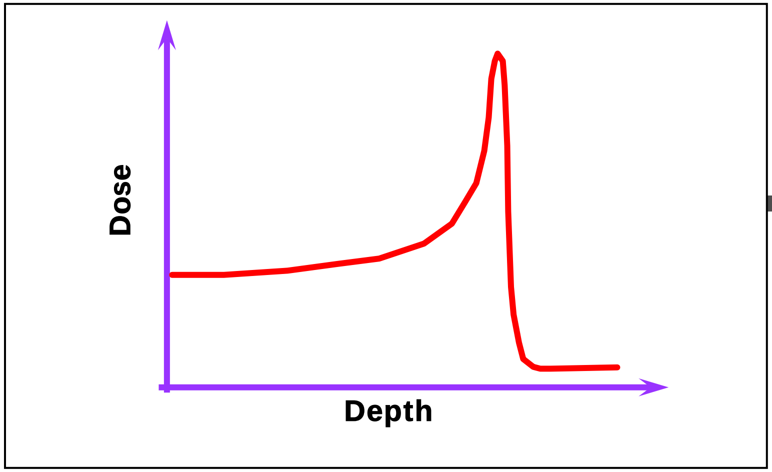


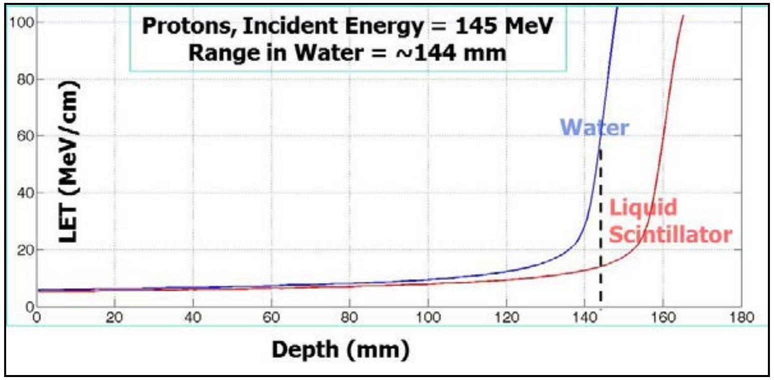


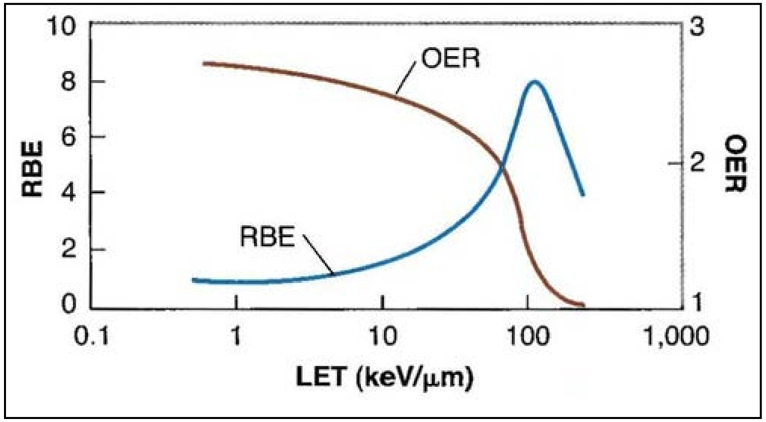


- Physical properties
  - Low dose at the entrance
  - Low or no dose beyond the range
- Biological properties
  - Higher relative biological effectiveness (RBE)
  - Lower oxygen enhancement ratio

Particles - Sources of their Strength







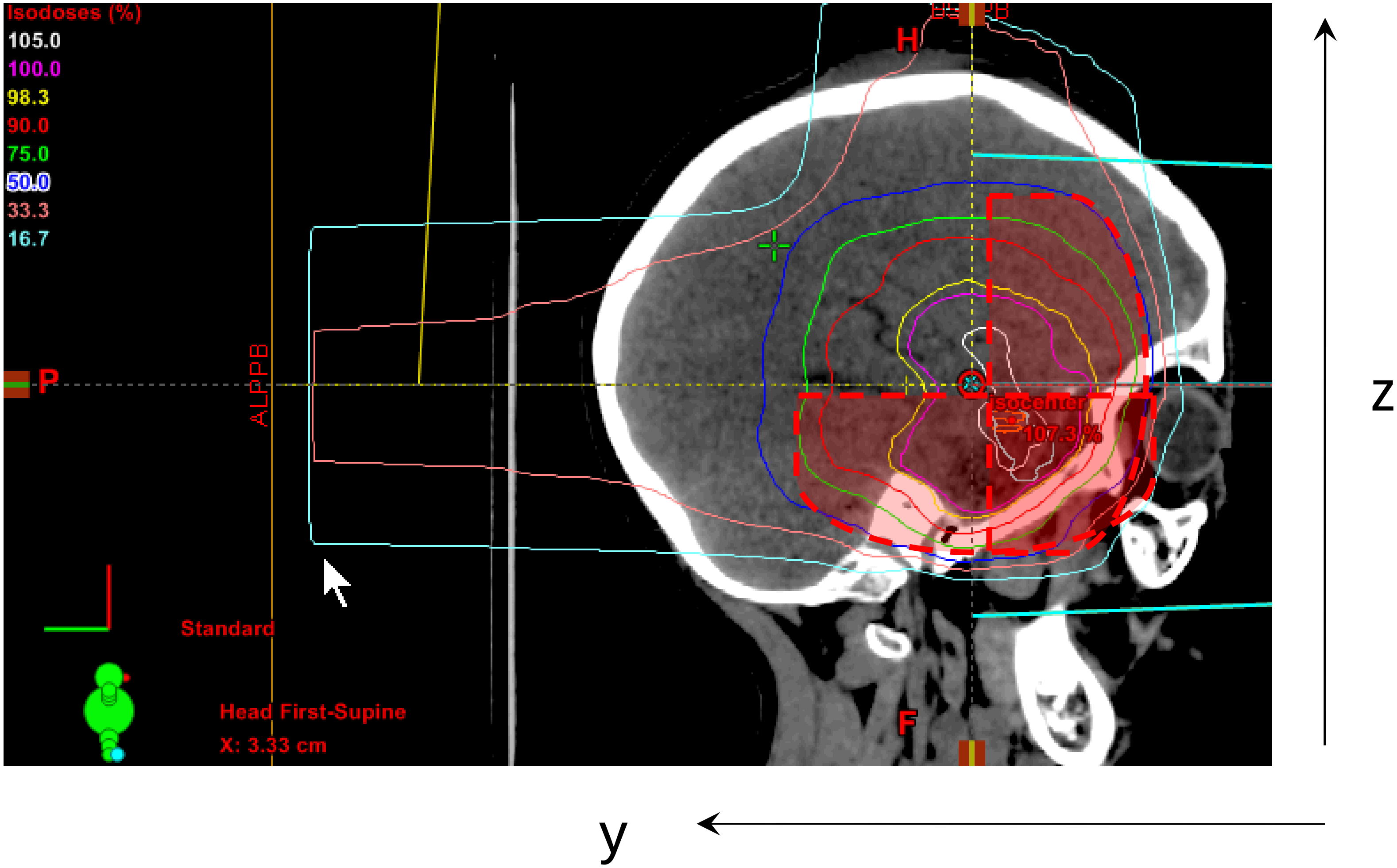
- Particles loose energy continuously as they penetrate the medium
- Linear energy transfer (LET) increases as they slow down
  - Most energy deposited near the end of the range
  - Have a finite range – they stop
- Biological effectiveness is a function LET, so it increases correspondingly

Radiobiological Effectiveness of Protons

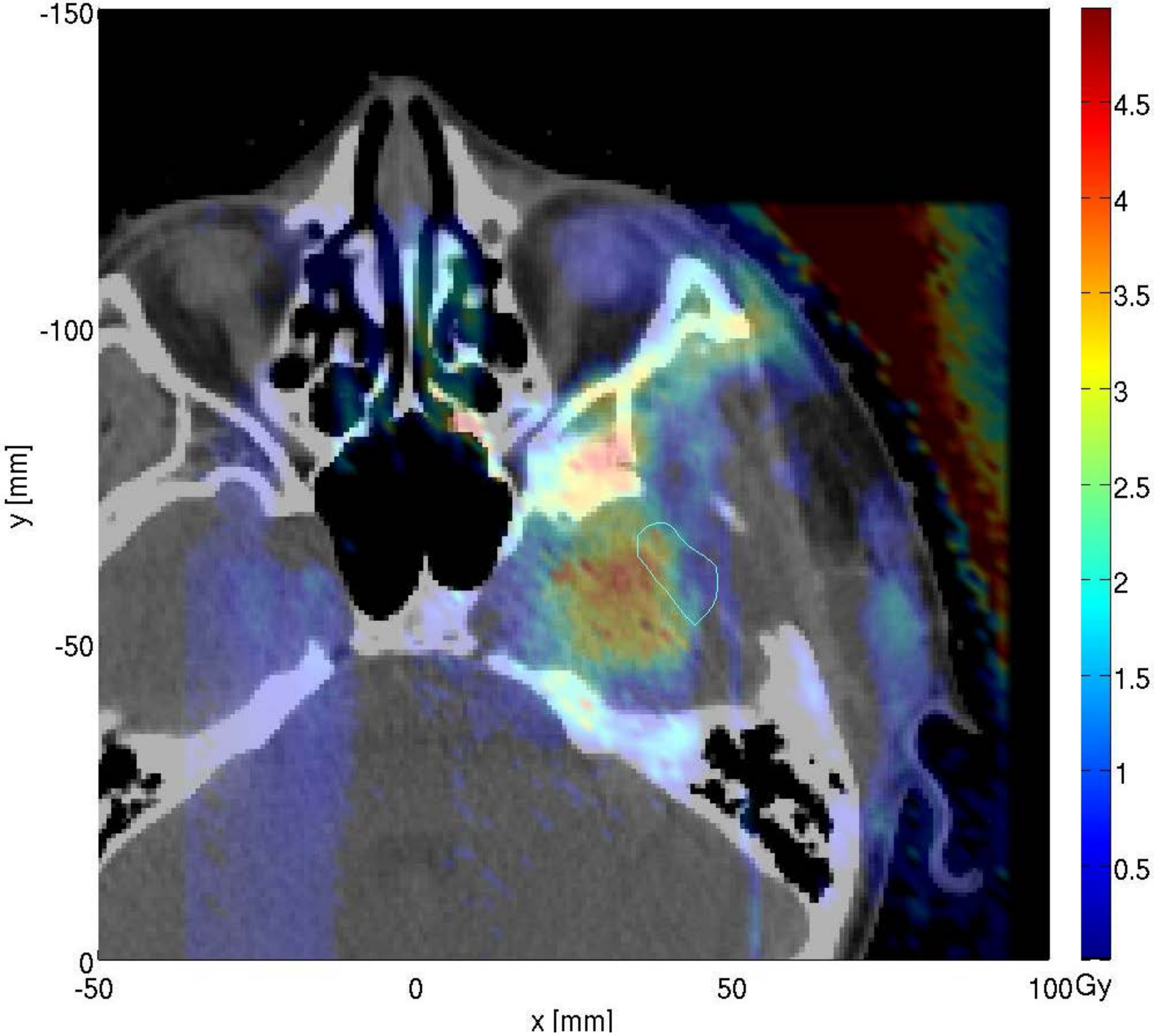
- Proton RBE is assumed to be 1.1
- Claim: Clinical data do not suggest that RBE is different from 1.1
- In reality, RBE is a complex function of
  - Energy (LET)
  - Dose per fraction
  - Tissue/cell type, alpha/beta ratio
  - End point
- Another claim: Proton RBE is high in very narrow region and, thus inconsequential

Variable RBE-Weighted Dose Effect for a CNS Patient

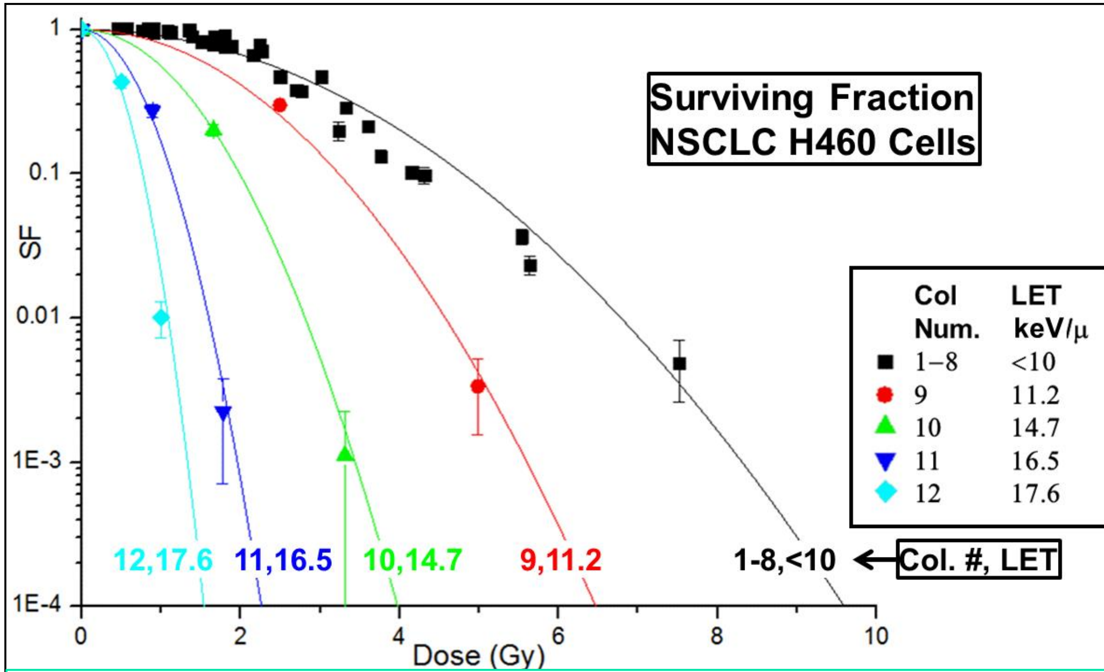
13 year old male with malignant meningioma

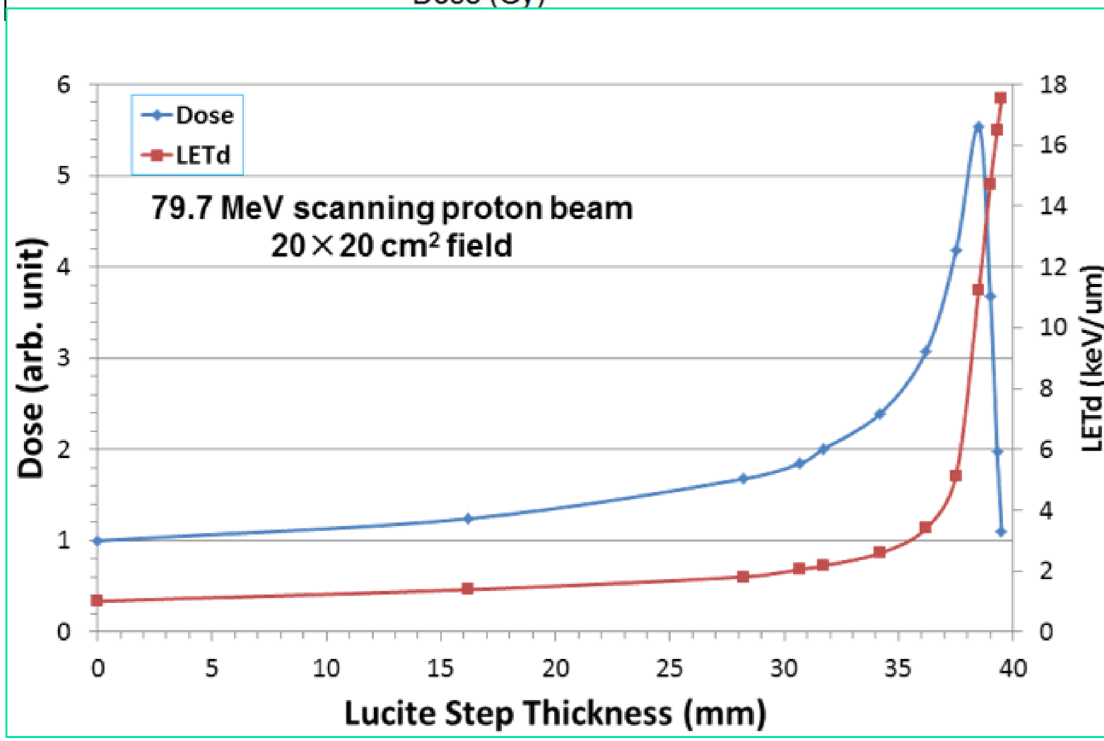


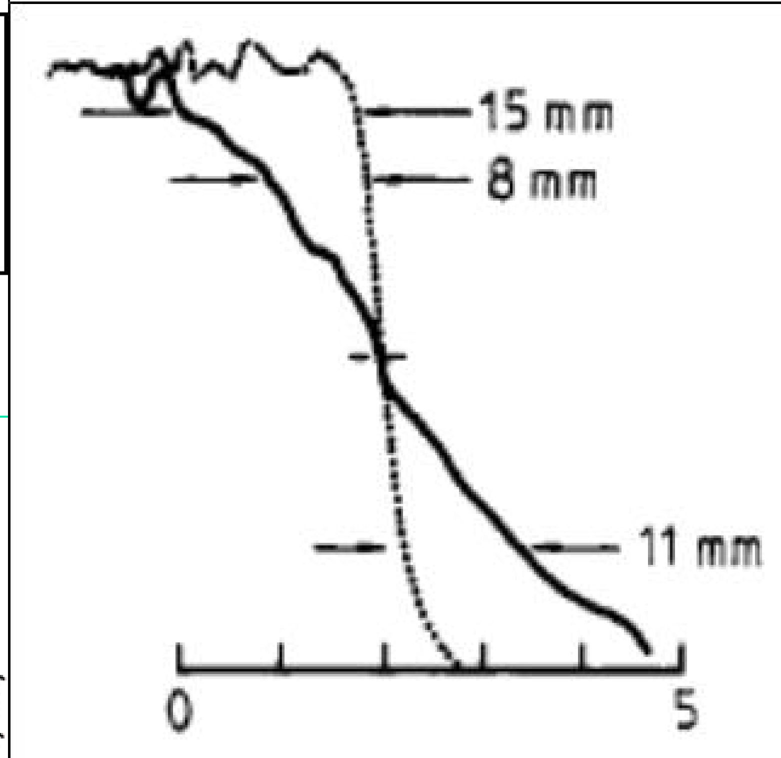
Possible Effect of Variable RBE-Weighted Dose - Brain Necrosis in CNS Patients



RBE of Protons







Urie, et al, Phys. Med. Biol., 1986, Vol. 31, No. 1, 1-15.

So …

WYS ≠ WYG

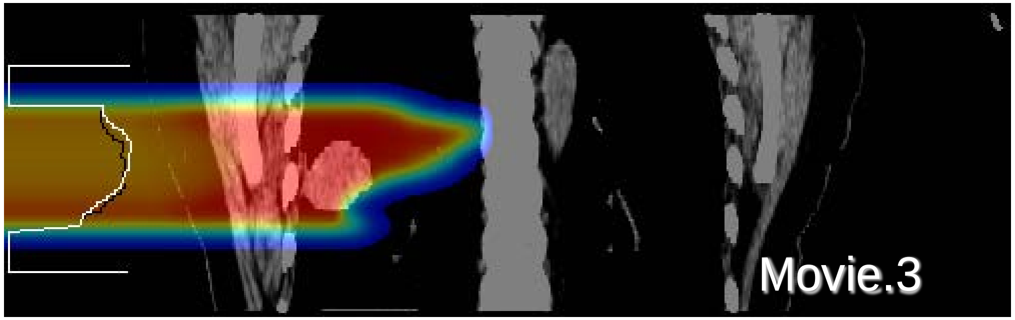
Final Words

- Particle therapy is the future of RT
- Despite considerable superiority on paper of particle therapy (vs. photon therapy), evidence of superiority of particle therapy in clinical practice so far is unclear
- It is essential to understand the underlying physical, biological and clinical reasons for such lack of evidence through case-by-case and population-based analyses of clinical data

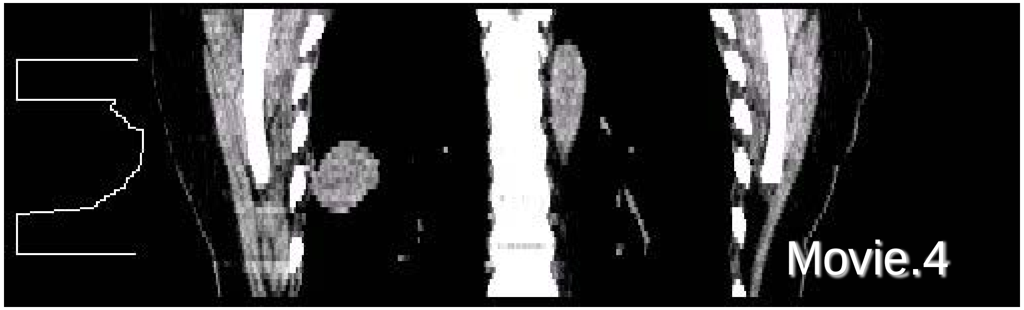
Final Words

- Particle therapy is more complex, more vulnerable to physical and biological uncertainties
- Particle therapy is more costly
- Enormous opportunities for additional R&D to
  - Minimize uncertainties and their impact
  - Improve understanding of biology of particles
  - Identify optimum particle(s)
  - Reduce the cost of particle therapy
- Engineers, computer scientists, physicists, etc. in India can play an important role in many of these areas

Free Breathing and Gated PSPT Plans



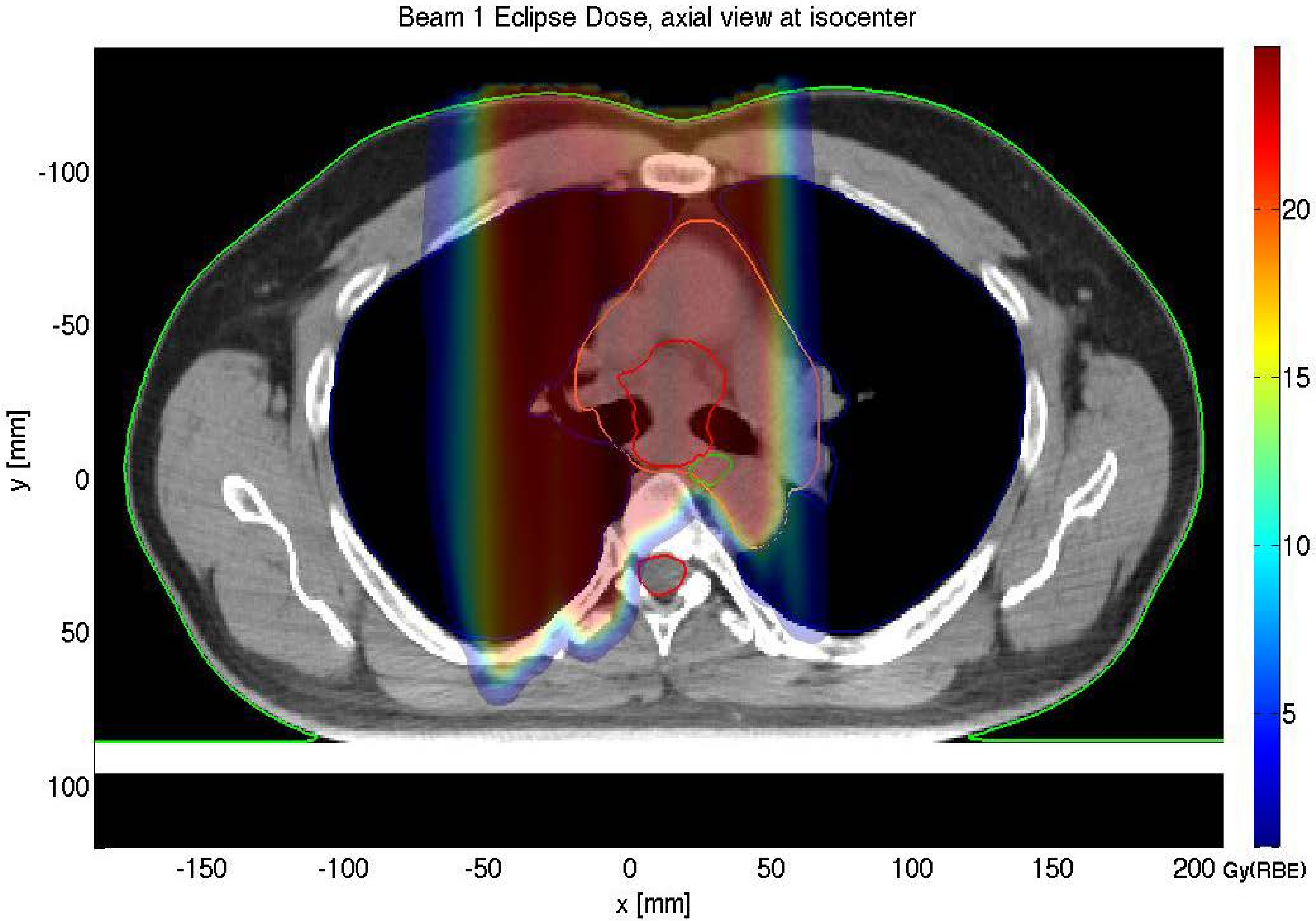
Non gated: Free breathing



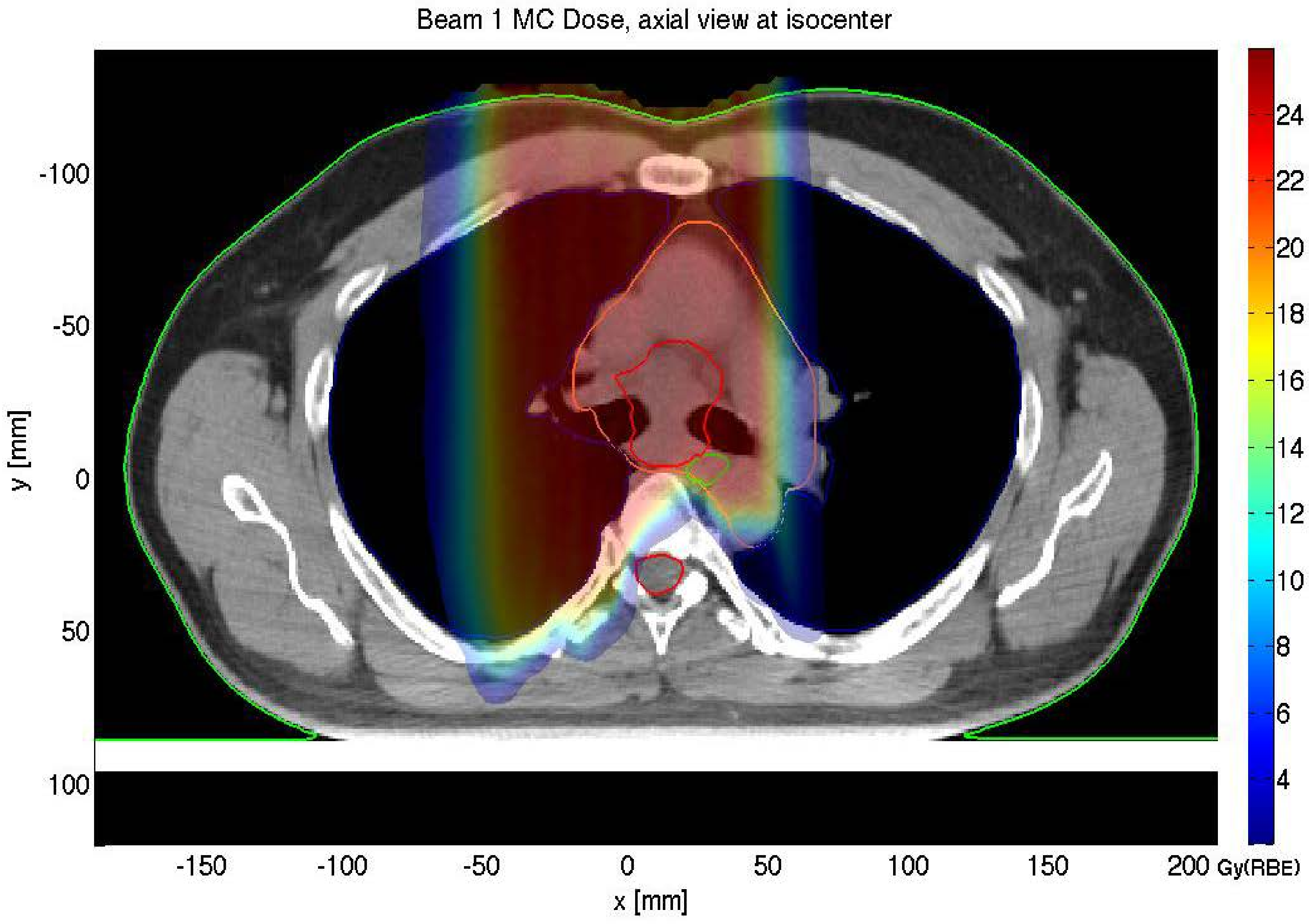
Gated on 40~60% expiration phase

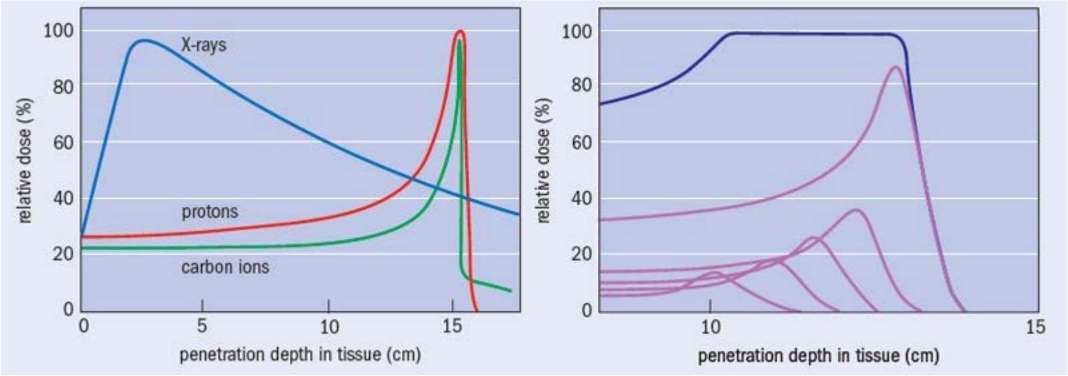
(Yoshikazu Tsunashima)

Eclipse Dose for Beam 1



MC Dose for Beam 1

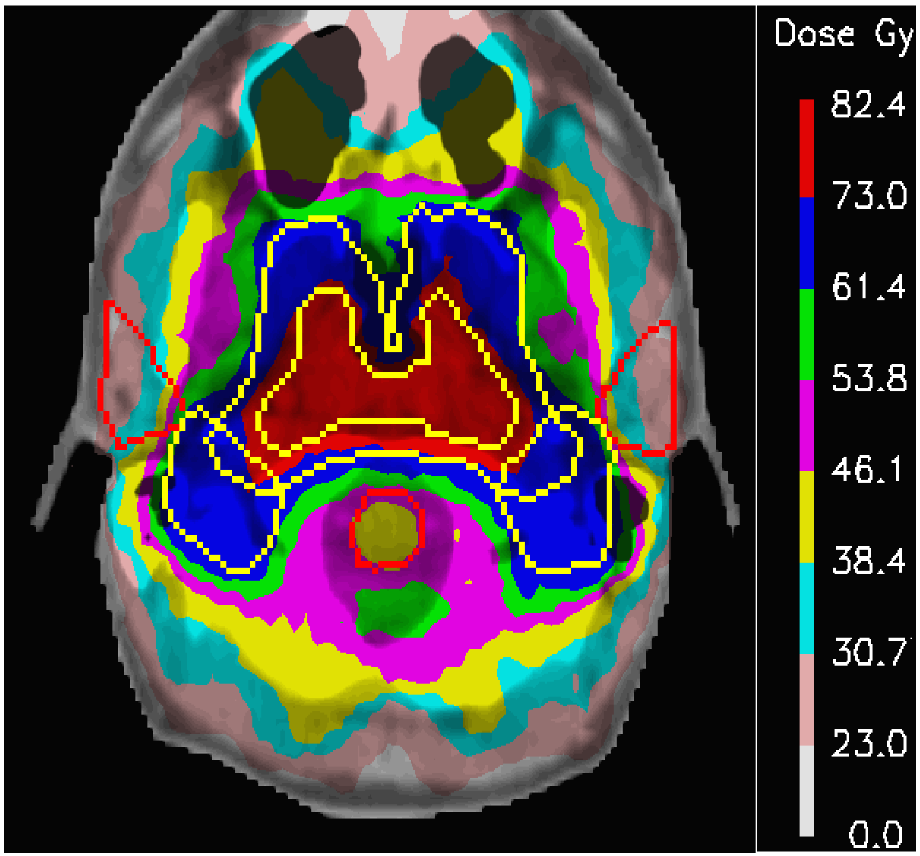




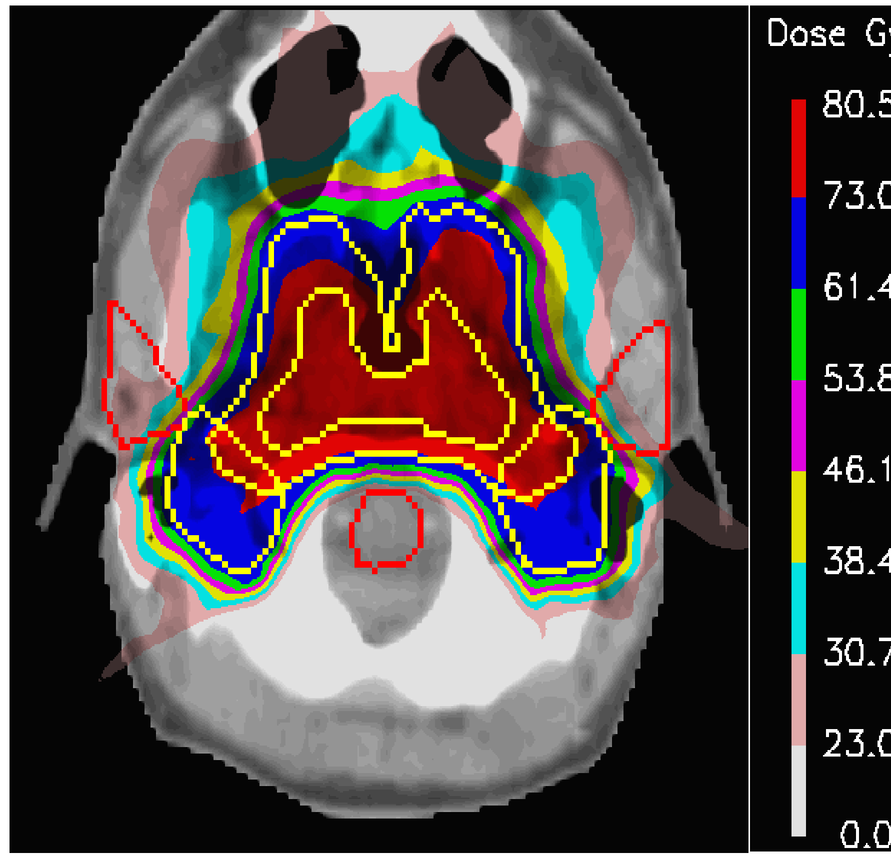
100
80
60
40
20
0
relative dose (%)
X-rays
protons
carbon ions
0
5
10
15
penetration depth in tissue (cm)
100
80
60
40
20
0
relative dose (%)
10
15
penetration depth in tissue (cm)

Nasopharynx Treatment Plans
IMRT vs. IMPT

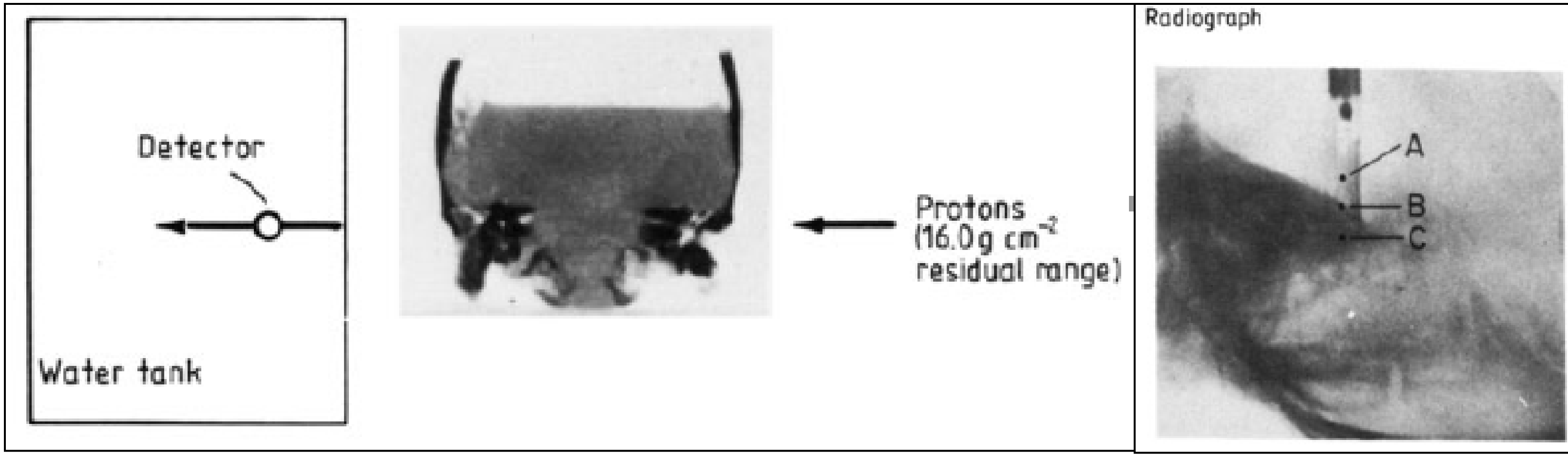
IMRT

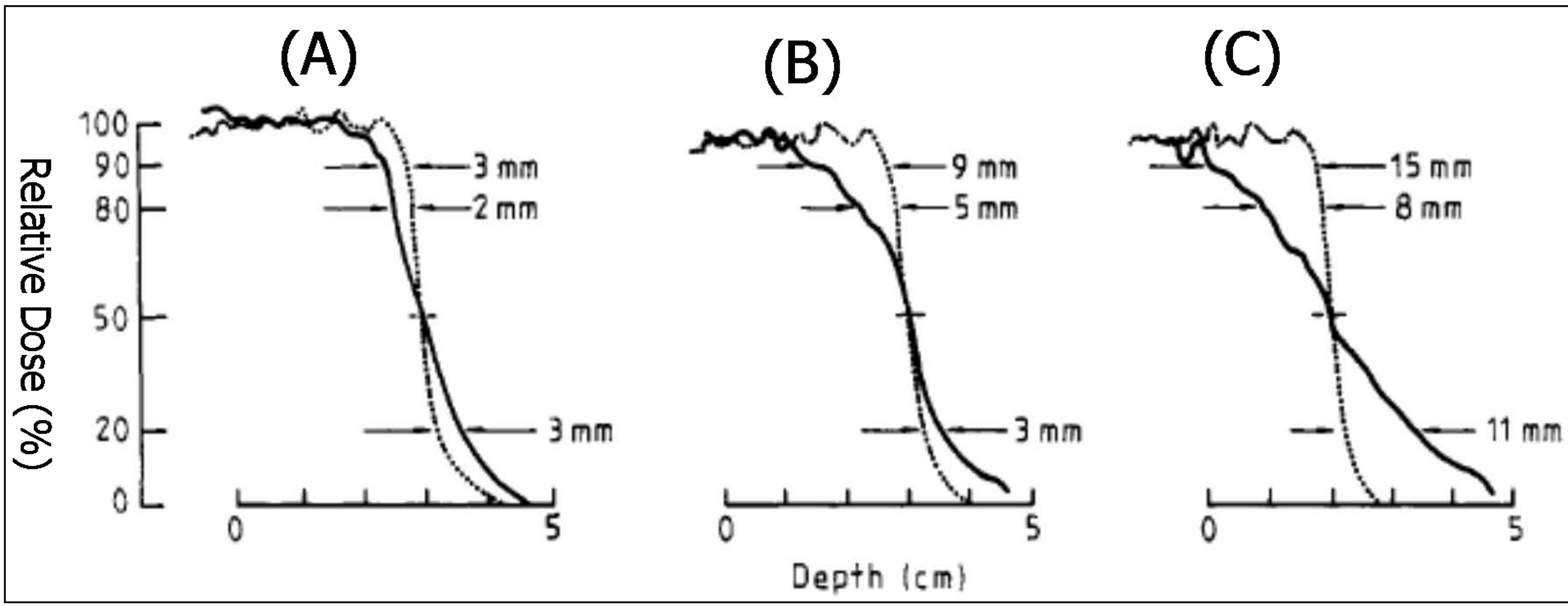


IMPT



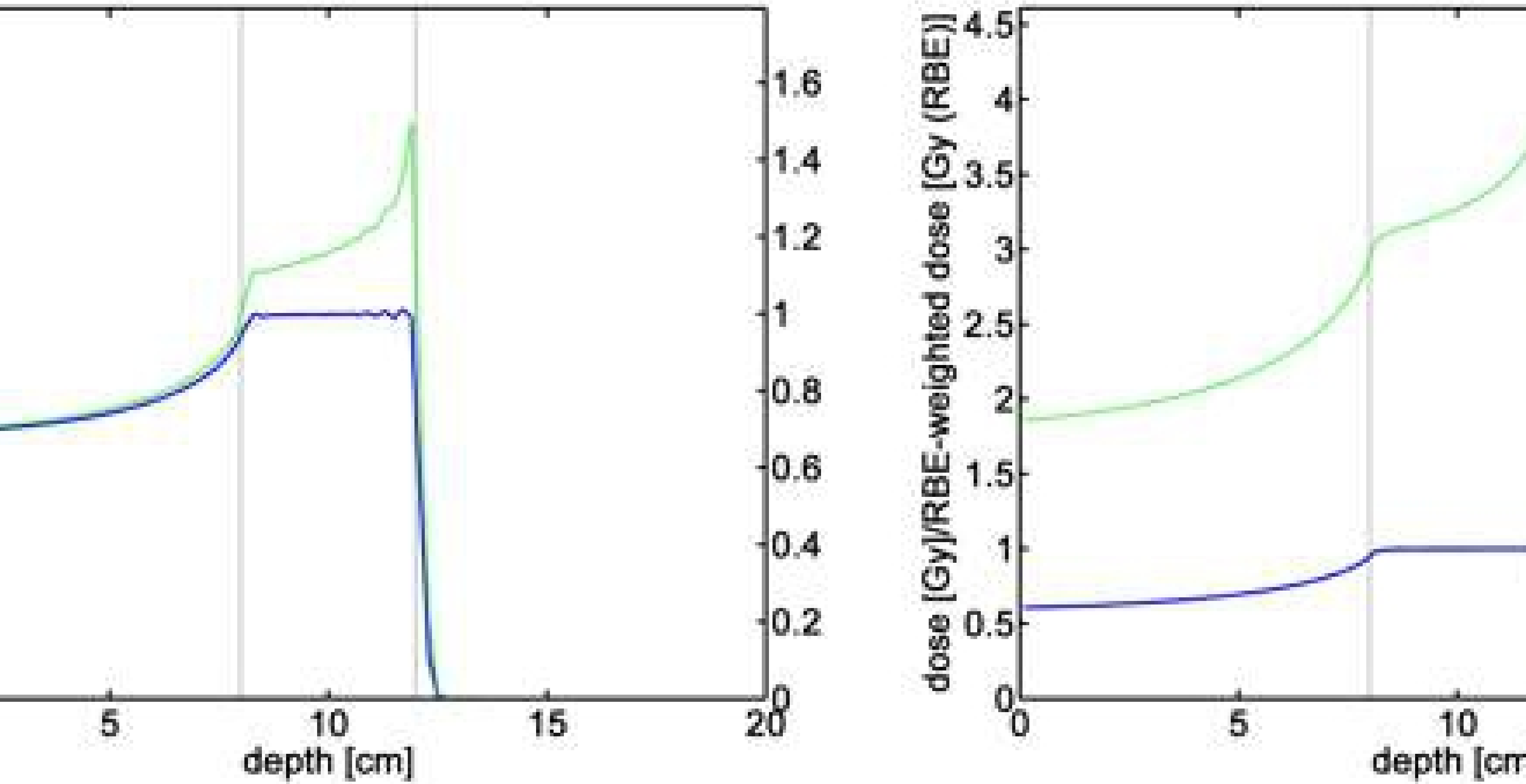
Lomax - PSI, Smith - MGH



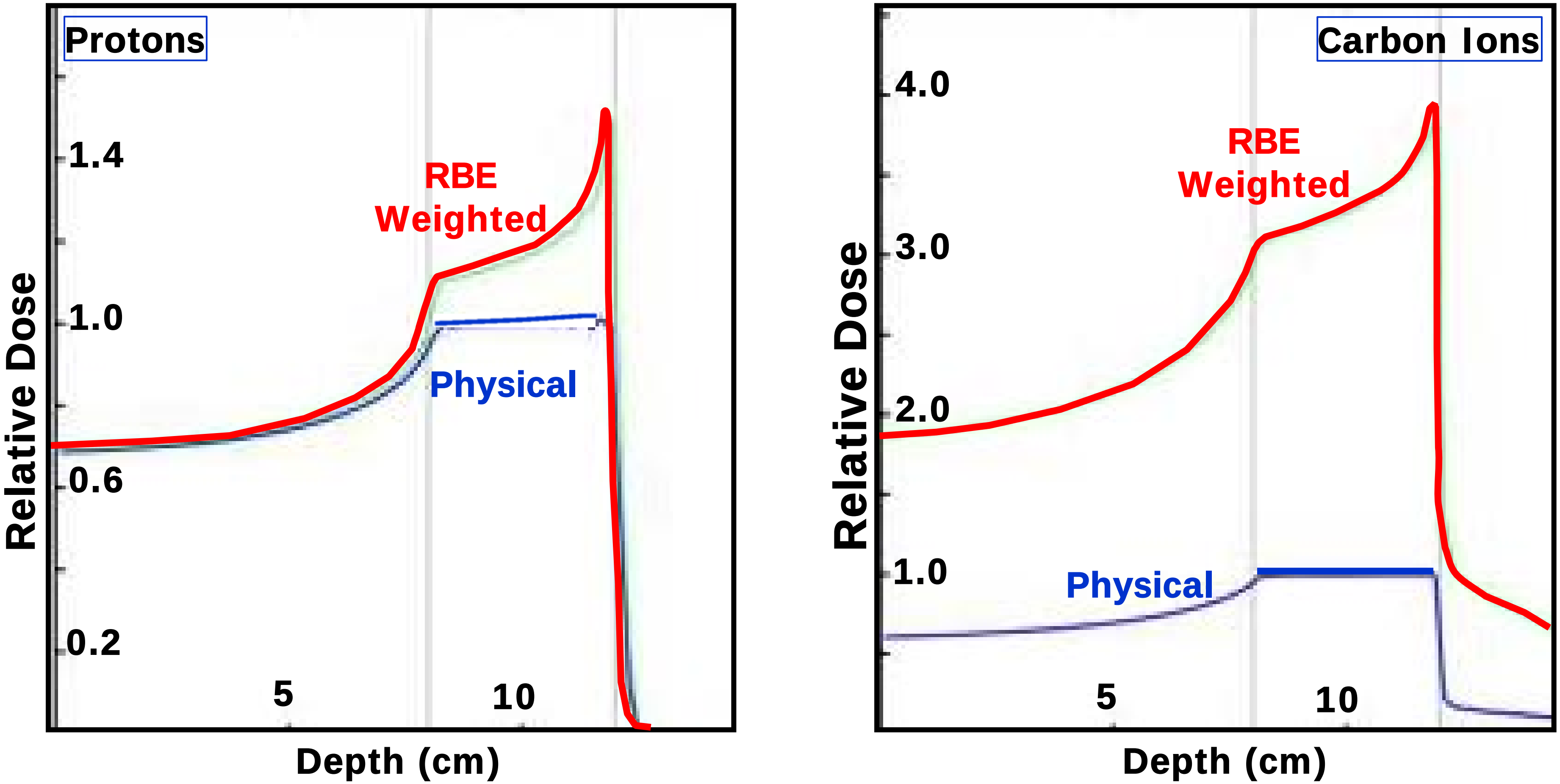


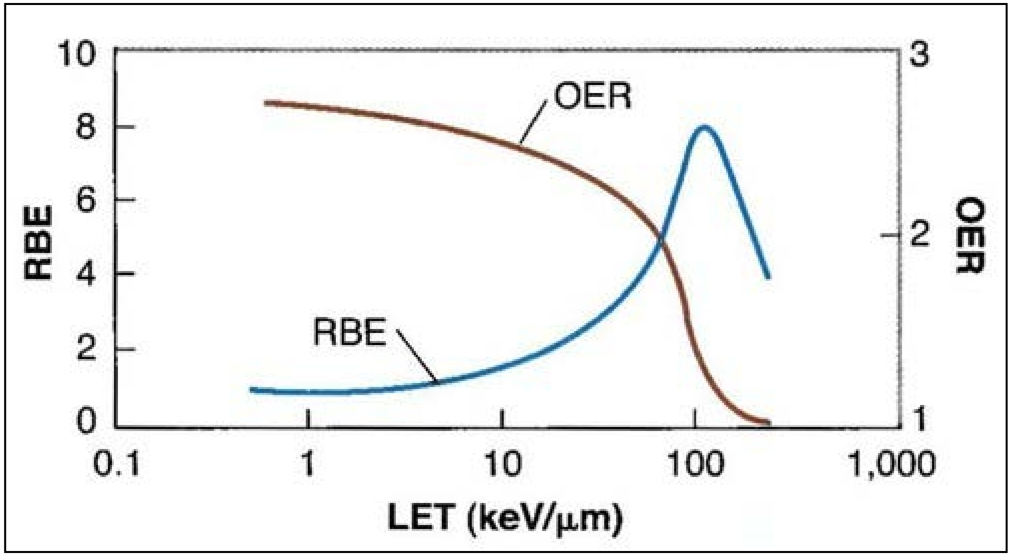
Protons Through Base of Skull: 90 to 20 % fall of increases from 6 to 32 mm

Urie, et al, Phys. Med. Biol., 1986, Vol. 31, No. 1, 1-15.

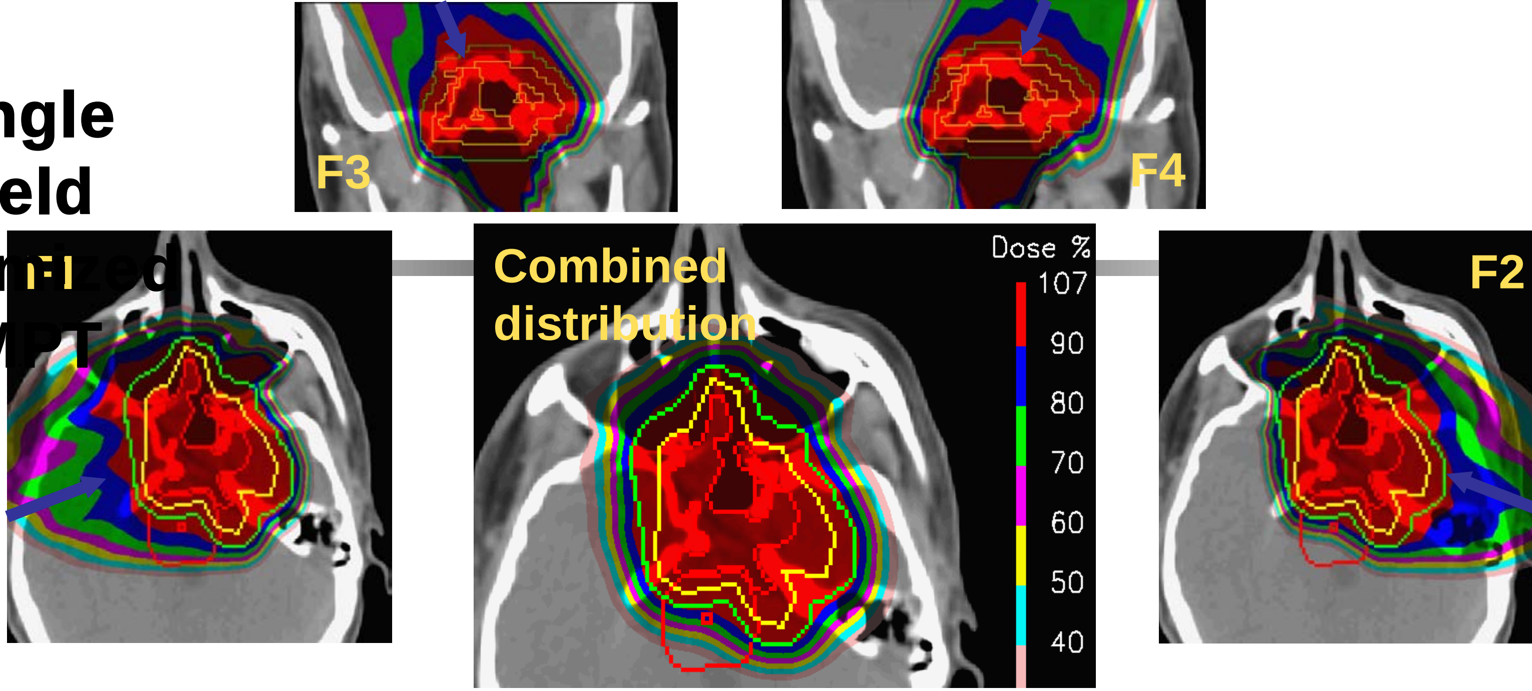


1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
5
10
15
20
depth [cm]
dose [Gy]/RBE-weighted dose [Gy (RBE)]
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
5
10

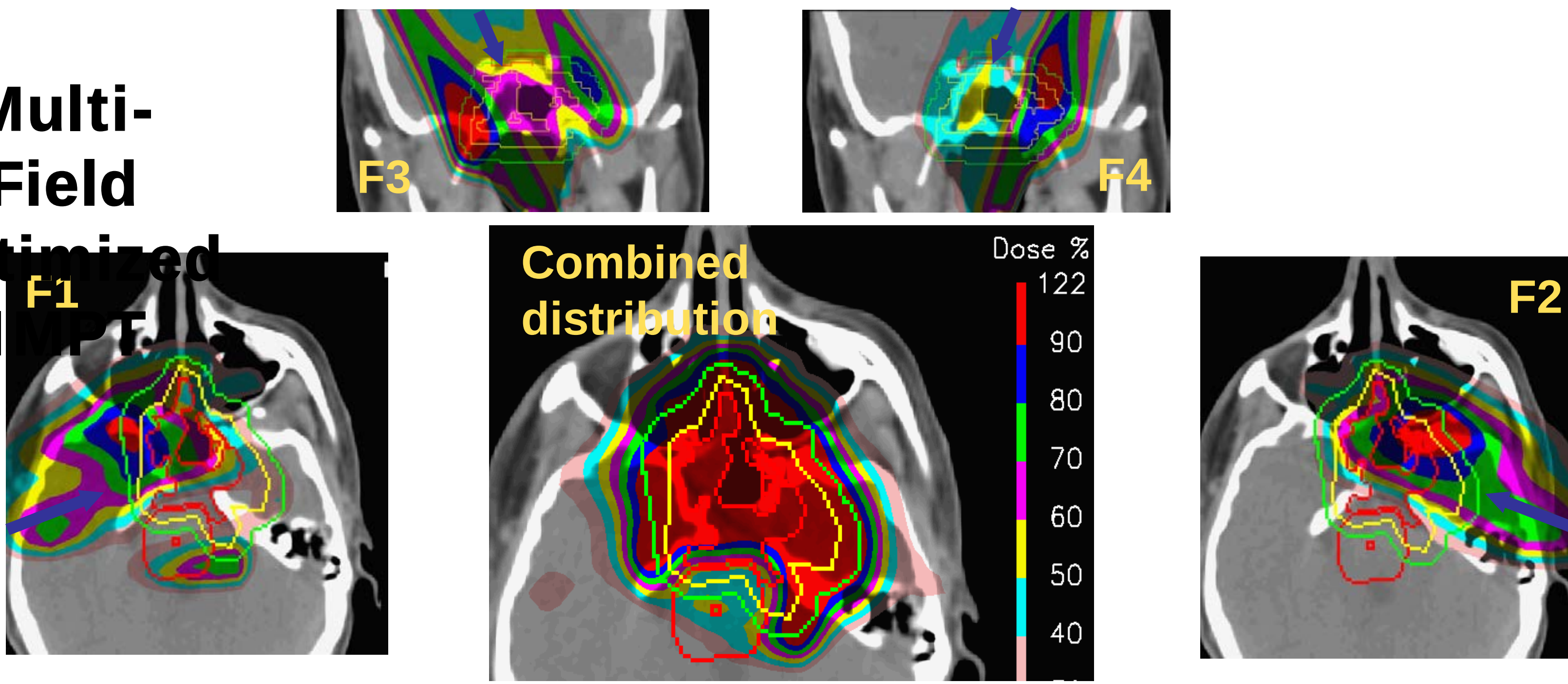

Protons
RBE
Weighted
Physical
Relative Dose
1.4
1.0
0.6
0.2
5
10
Depth (cm)
Carbon Ions
RBE
Weighted
Physical
Relative Dose
4.0
3.0
2.0
1.0
5
10
Depth (cm)

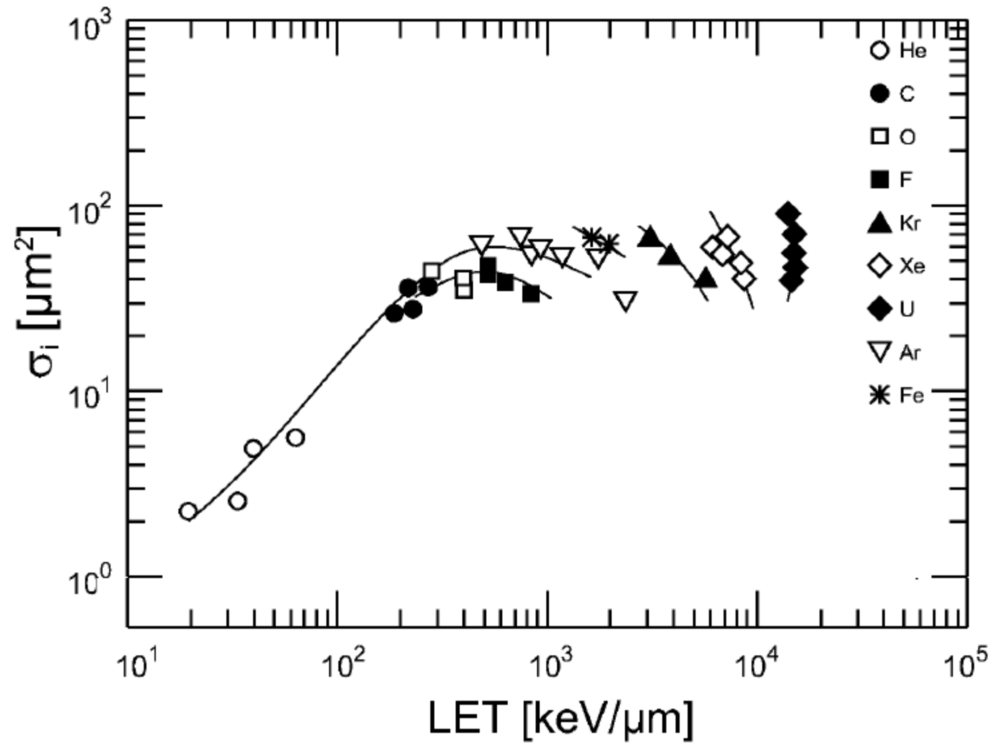

10
8
6
4
2
0
RBE
3
2
1
OER
OER
RBE
0.1
1
10
100
1,000
LET (keV/μm)

Single Field Optimized IMPT



Multi-Field Optimized IMPT

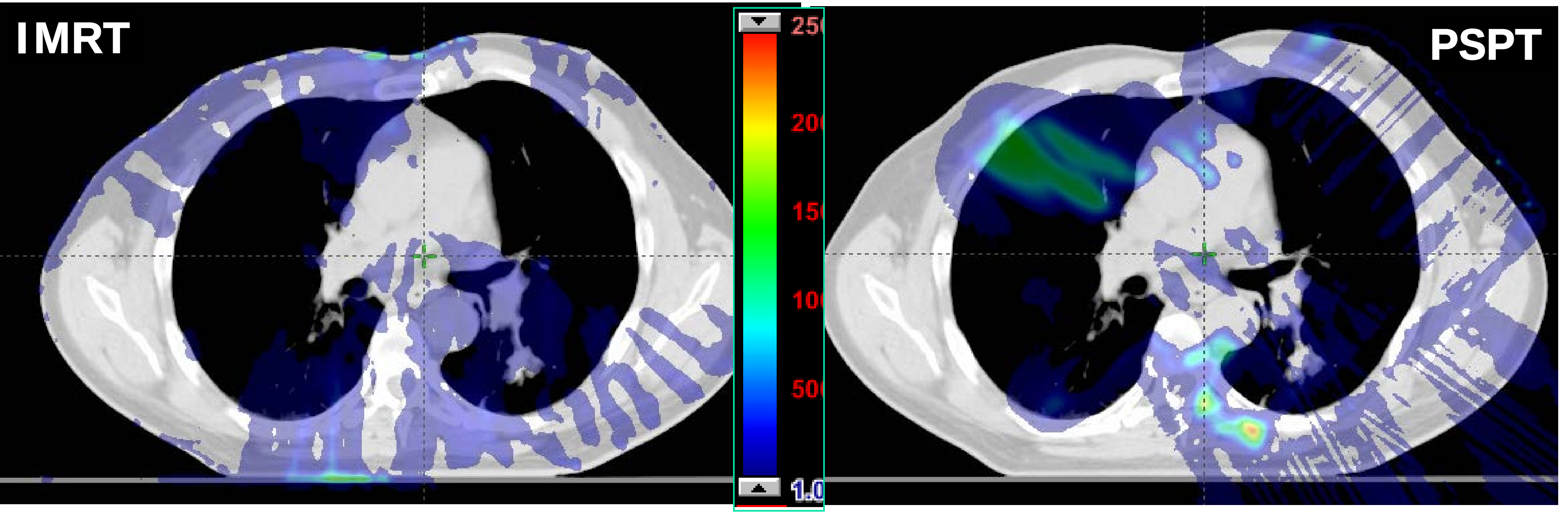


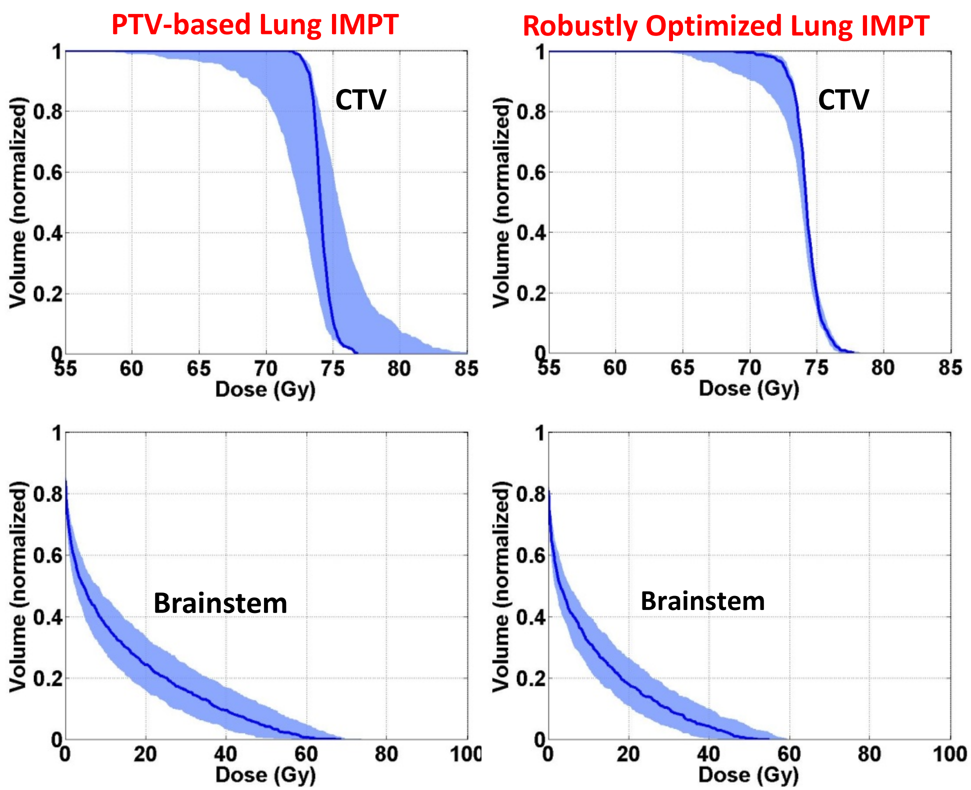


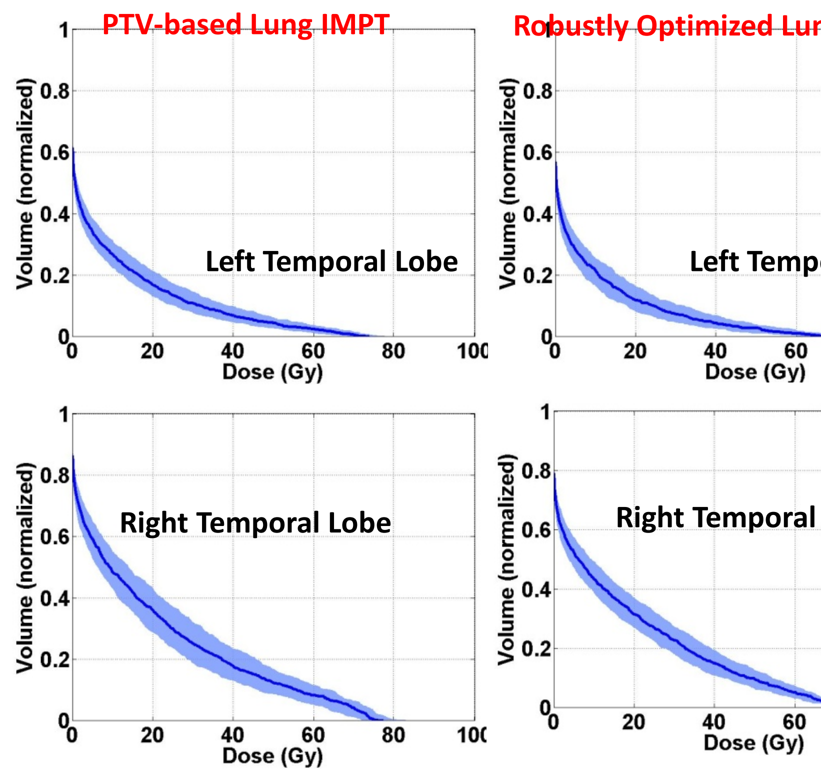
10^3
10^2
10^1
10^0
σ_i [μm^2]
10^1
10^2
10^3
10^4
10^5
LET [keV/μm]
He
C
O
F
Kr
Xe
U
Ar
Fe

Effect of Motion of IMRT vs. PSPT
4D - Static Dose Distributions

- Motion < 5 mm
- For photons – Difference < Less 5 Gy (RBE)
- For protons –
  - Difference ~ 10 Gy contralateral lung
  - Difference ~ 15 Gy near spine & ribs

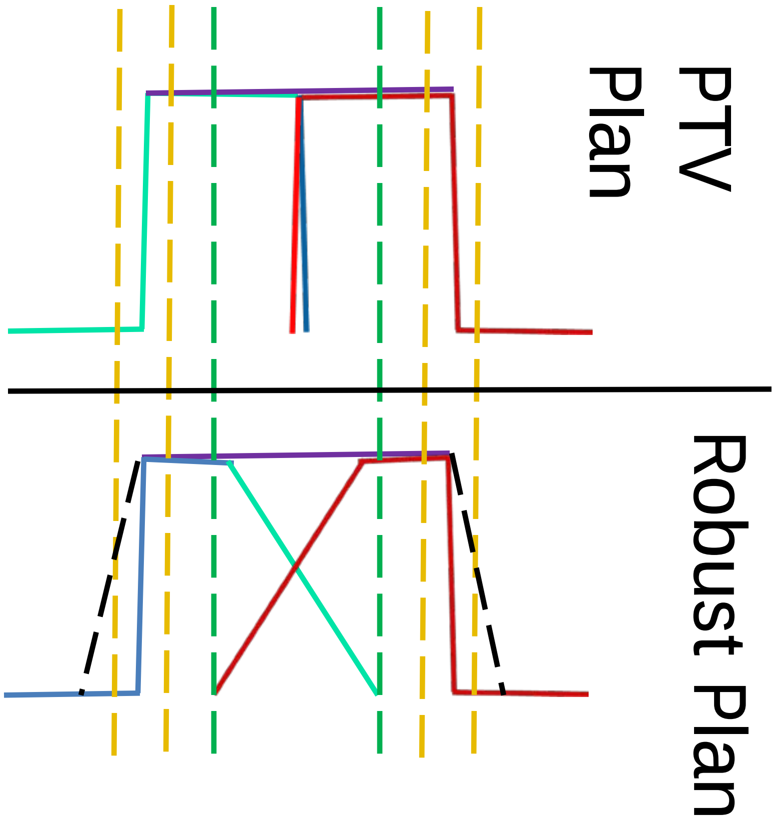



PTV-based Lung IMPT
Robustly Optimized Lung IMPT
CTV
CTV
Brainstem
Brainstem
Volume (normalized)
Dose (Gy)


PTV-based Lung IMPT
Left Temporal Lobe
Right Temporal Lobe
Volume (normalized)
Dose (Gy)

Why robust optimization leads to more robust plans?*

- **Robust optimization considerably reduces high dose gradients within each individual field, which helps improve the plan robustness.** *This mechanism mostly happens within the targets (between the green dash lines)*
- **Robust optimization leads to a dose distribution, which can be perturbed to follow the change of anatomy. This helps to improve the plan robustness while maintaining**



*(1) *Liu et al.*, Med. Phys. 39(6):3089-4001, 6/2012