Computational challenges in RTP treatment planning: setting the stage

Joe Deasy, PhD

deasyj@mskcc.org

Overview

- Treatment planning: underpinnings
  - Outcomes and models
- Treatment planning technology
  - The desirables: what we need
  - How can we get there?

Treatment planning: underpinnings
Outcomes and models

The ‘Planning Target Volume’:
add margins around suspected disease for uncertainty with respect to anatomy + geometric motion + geometrical uncertainty + possible gross disease.

Give this the full dose right out to the edge.

Also stands for ‘Poor Tradeoff Volume’

Problems with the PTV concept

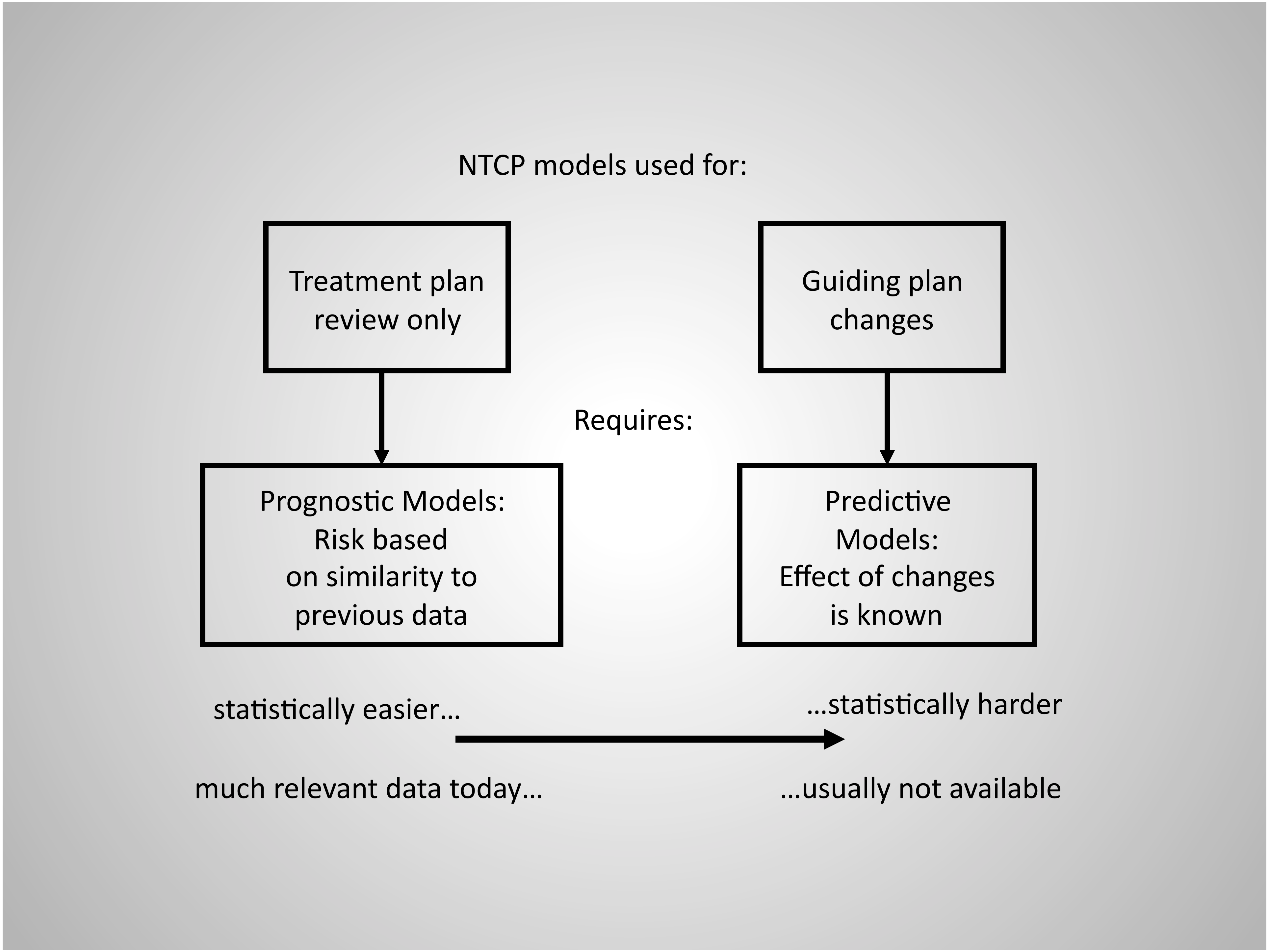
- Large shifts (very unlikely) are treated the same as small shifts (very likely)
- assumes that normal tissue volume effects are much less important than target volume coverage
- The Gaussian dose tail will always invade the PTV; so full dose requires a big field

Instead…

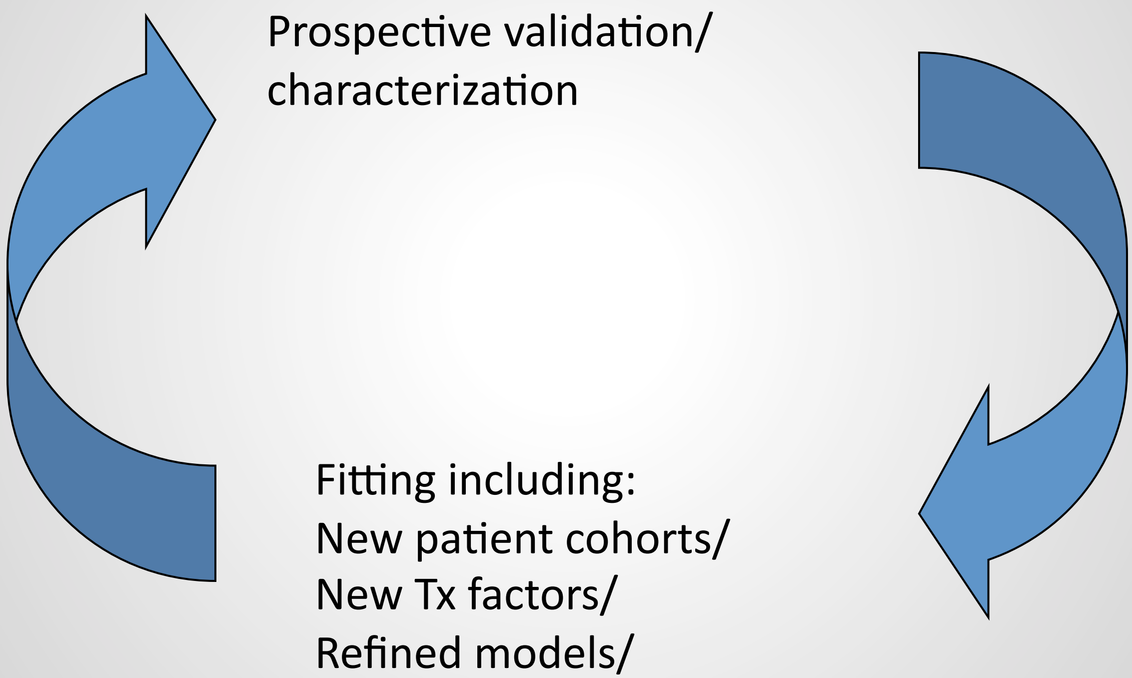
- Treatment planning needs to be driven by the impact on outcomes.
- And different treatment philosophies will handle tradeoffs between local control and toxicity differently.

Planning objective functions

- Only just emerging…
- Usually numerically uncertain
- Often have shallow slopes instead of sharp separations between risk and non-risk


NTCP models used for:
Treatment plan review only
Guiding plan changes
Requires:
Prognostic Models: Risk based on similarity to previous data
Predictive Models: Effect of changes is known
statistically easier…
…statistically harder
much relevant data today…
…usually not available

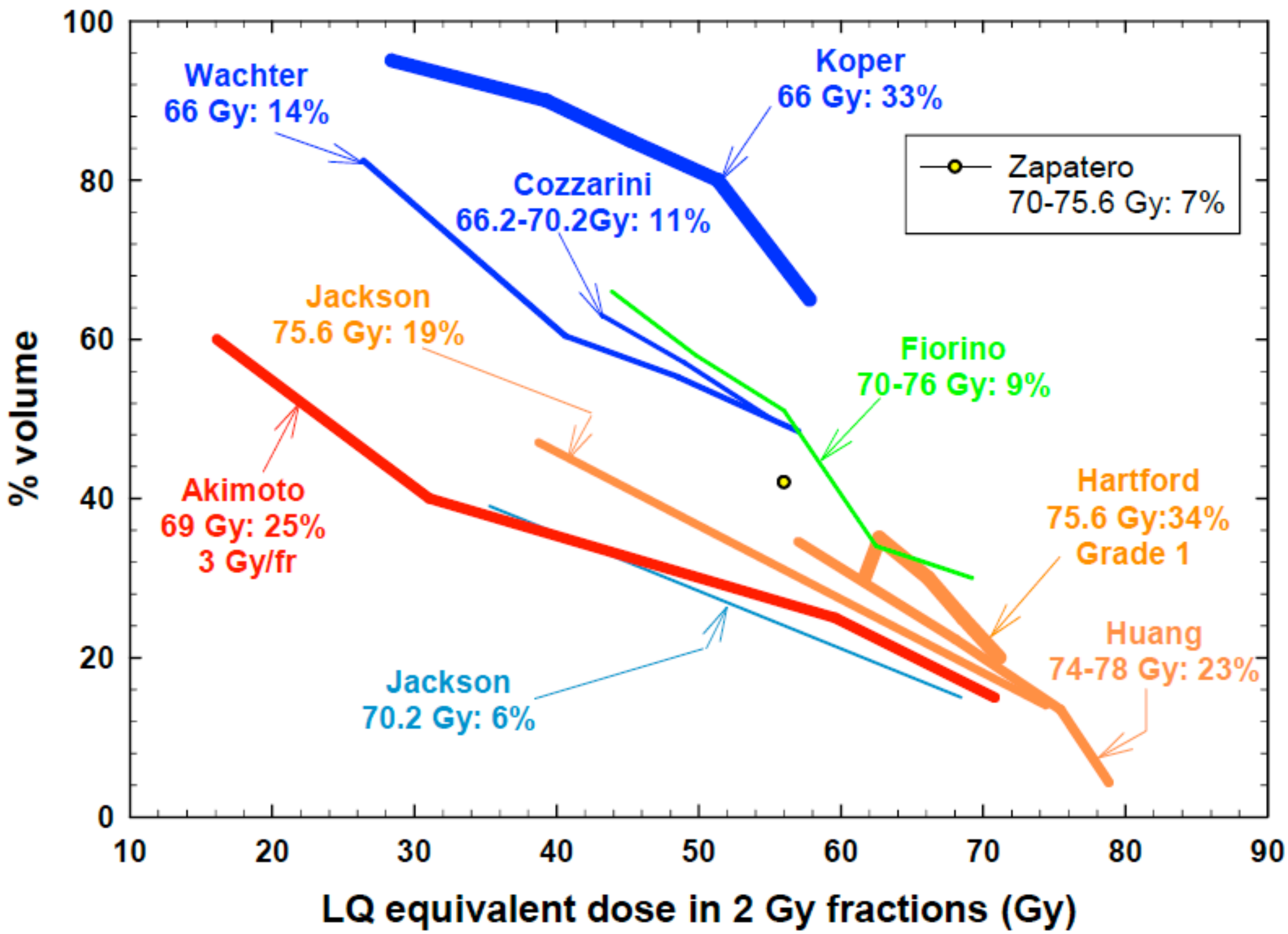
The NTCP/TCP development spiral

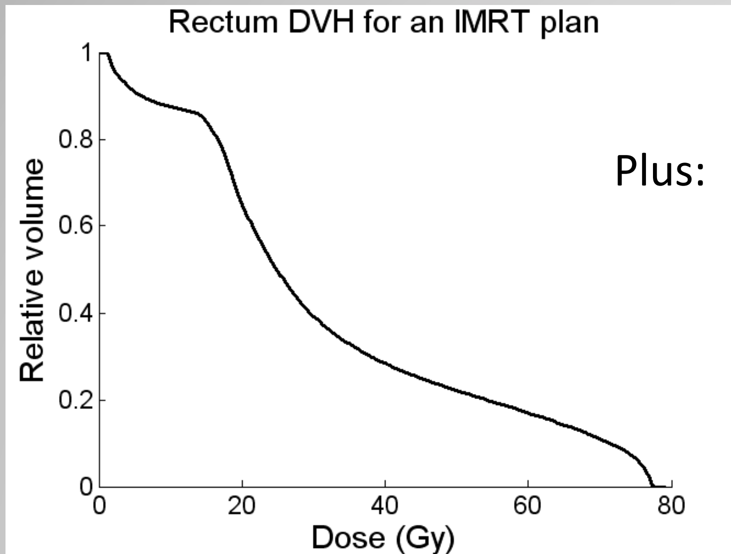


RADIATION DOSE–VOLUME EFFECTS IN RADIATION-INDUCED RECTAL INJURY

JEFF M. MICHALSKI, M.D.,* HIRAM GAY, M.D.,* ANDREW JACKSON, M.D.,† SUSAN L. TUCKER, PH.D.,‡ AND JOSEPH O. DEASY, PH.D.*

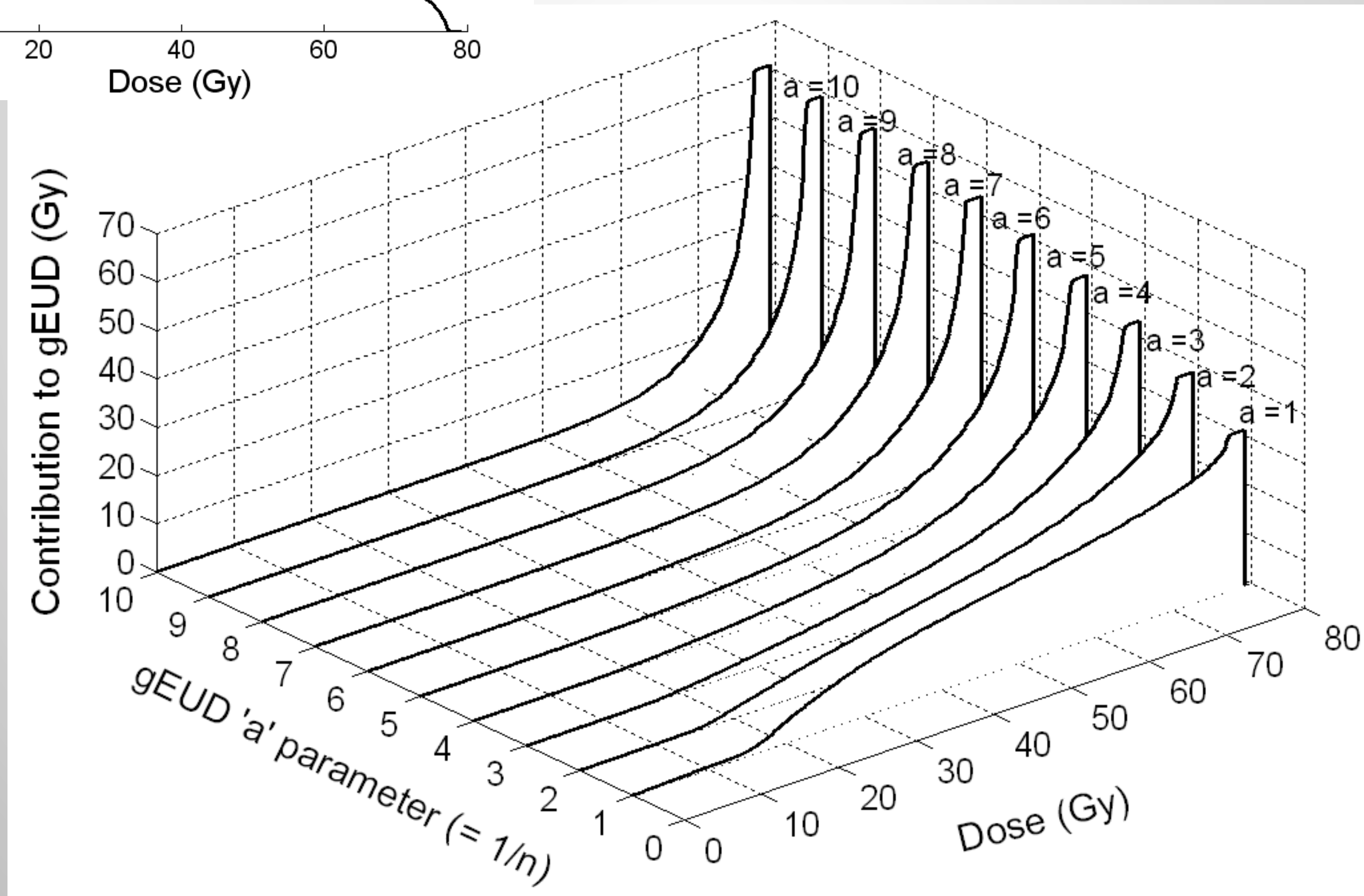
Dose-volume limits for >= grade 2 rectal toxicity with LQ corrected doses (α/β = 3 Gy)

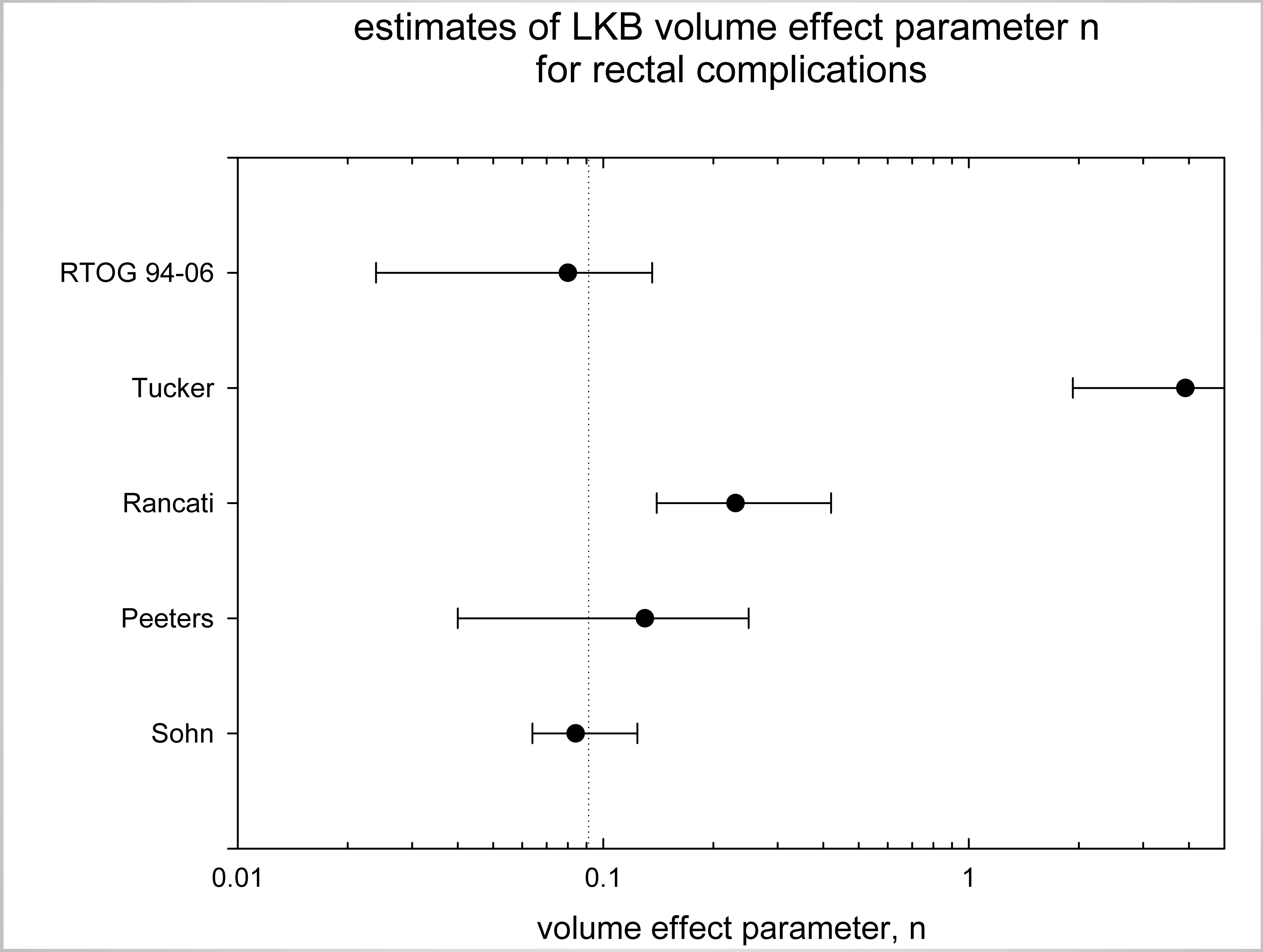




Plus: $$\text{gEUD} = \left[\left(d_1^a + d_2^a + d_3^a + \ldots + d_n^a\right)/\, N_{\text{Voxels}}\right]^{1/a}$$

Results in different relative contributions to gEUD within the DVH:



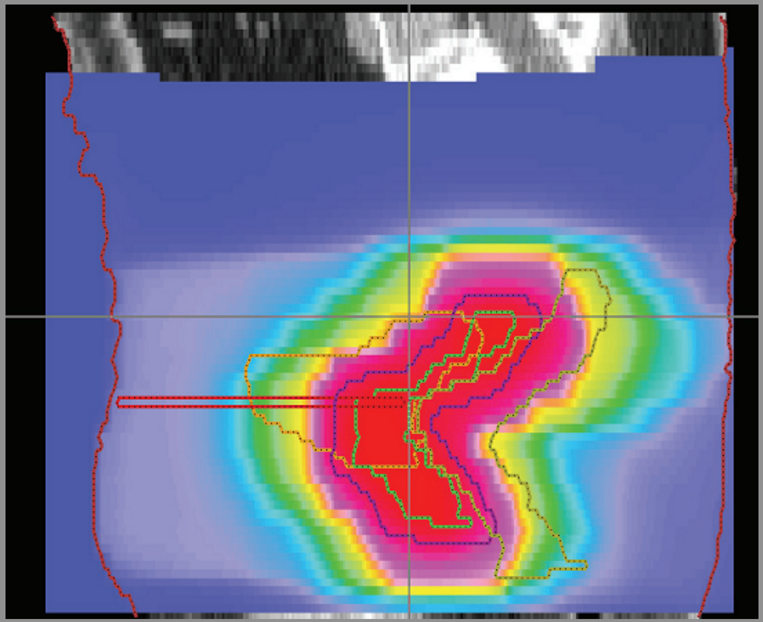


(Slide courtesy A. Jackson et al.)

(Note: a = 1/n)

Are IMRT rectal dose-volume limits a problem?

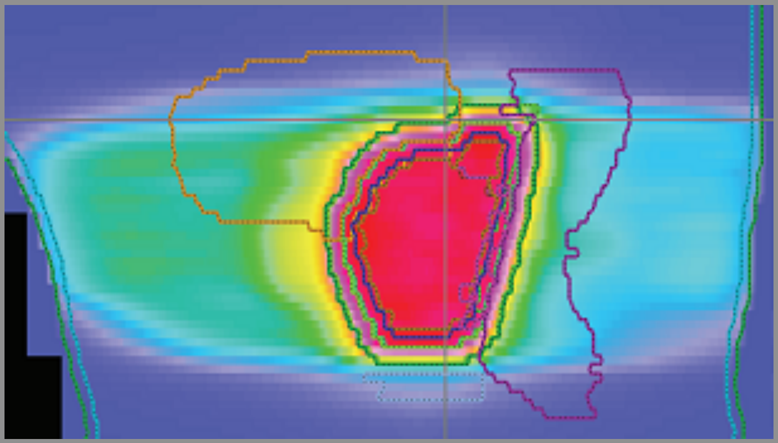
Typical 3DCRT plan (sagittal)



Rectal gEUD = 53 Gy

(a= 10)

Typical IMRT plan (sagittal)



Rectal gEUD = 24 Gy

ELSEVIER

Radiotherapy and Oncology 74 (2005) 187–195

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

Rectal and bladder motion during conformal radiotherapy after radical prostatectomy

Claudio Fiorino[a,*], Franca Foppiano[b], Paola Franzone[c], Sara Broggi[a], Pietro Castellone[a,d], Michela Marcenaro[c], Riccardo Calandrino[a], Giuseppe Sanguineti[e]

[a]*Servizio di Fisica Sanitaria, IRCCS H. S. Raffaele, Via Olgettina 60, 20132 Milano, Italy*
[b]*Unità di Fisica Medica, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*
[c]*Dipartimento di Radioterapia, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*
[d]*Dipartimento di Fisica, Università Federico II, Napoli, Italy*
[e]*Department of Radiation Oncology, University of Texas, Medical Branch Galveston, TX, USA*

Received 17 December 2003; received in revised form 7 September 2004; accepted 7 October 2004
Available online 28 October 2004

(Rad Oncol 2005)

Variation in rectal DVHs for daily Fx's

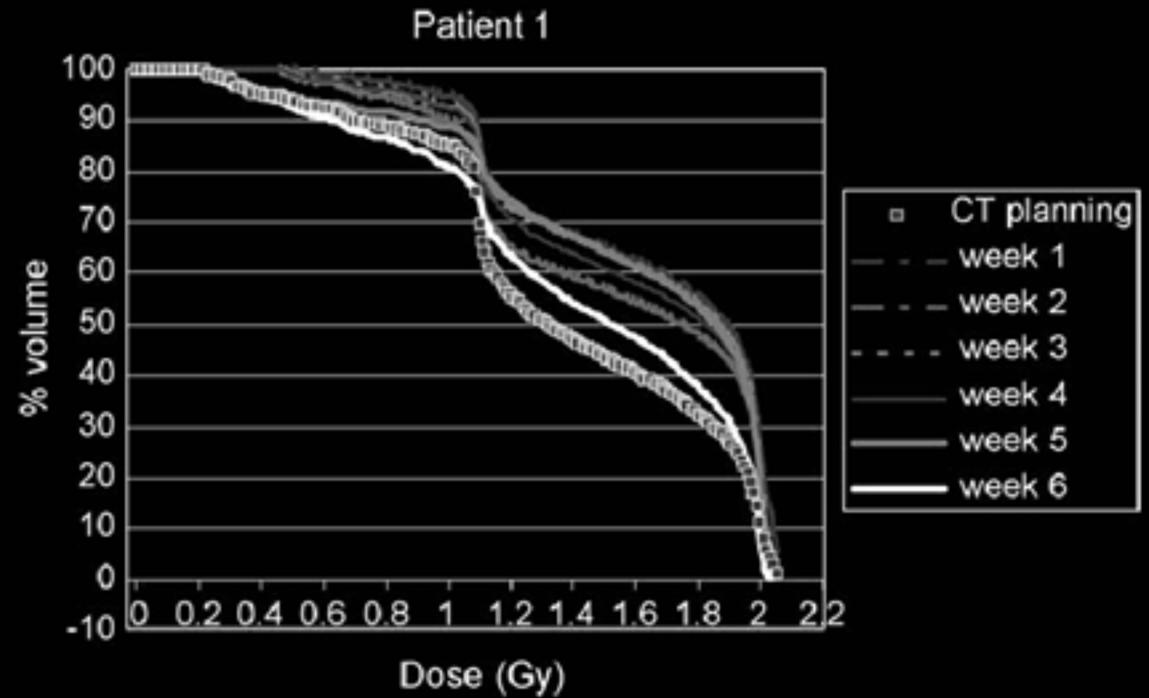


Fig. 3. Rectum DVH trend: the DVH at planning scan (CT planning) and the DVHs during the treatment (week 1…week 6) are shown for a patient with a large systematic component of the difference between planning and therapy (Patient 1).

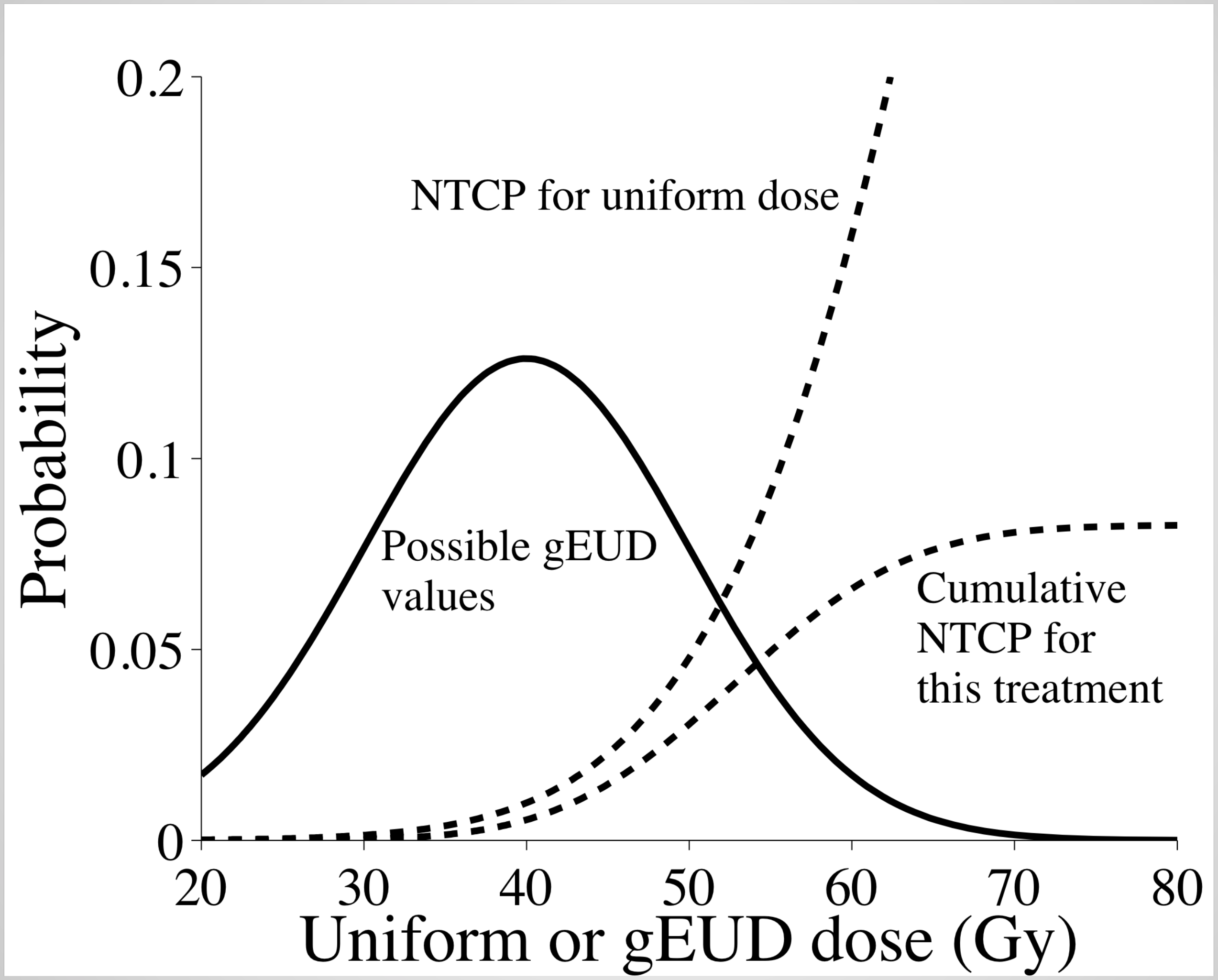

0.2
0.15
0.1
0.05
0
Probability
NTCP for uniform dose
Possible gEUD
values
Cumulative
NTCP for
this treatment
20
30
40
50
60
70
80
Uniform or gEUD dose (Gy)

Fig. 9

Acta Oncologica, 2010; 49: 1040–1044

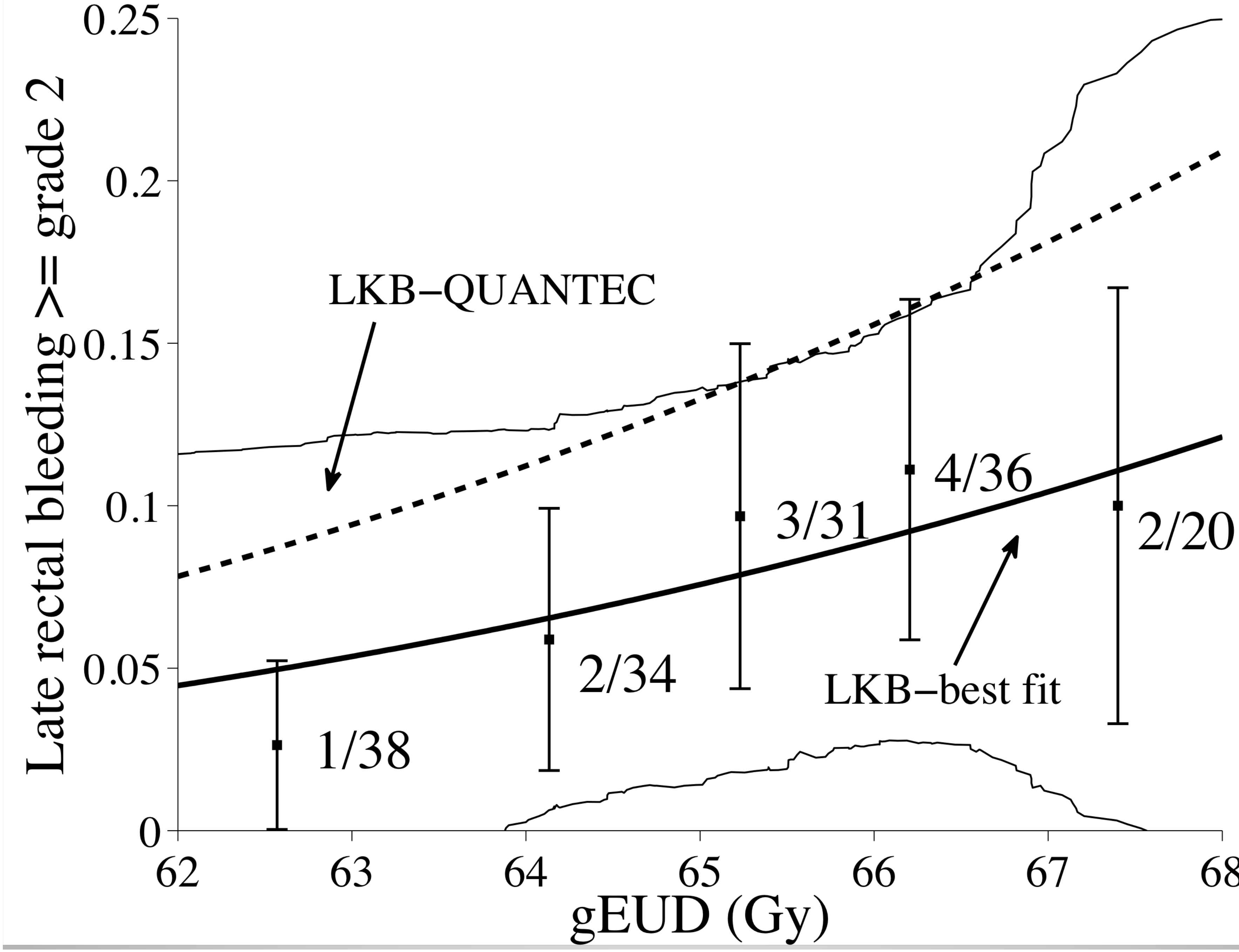
informa
healthcare

ORIGINAL ARTICLE

Normal Tissue Complication Probability (NTCP) modeling of late rectal bleeding following external beam radiotherapy for prostate cancer: A Test of the QUANTEC-recommended NTCP model

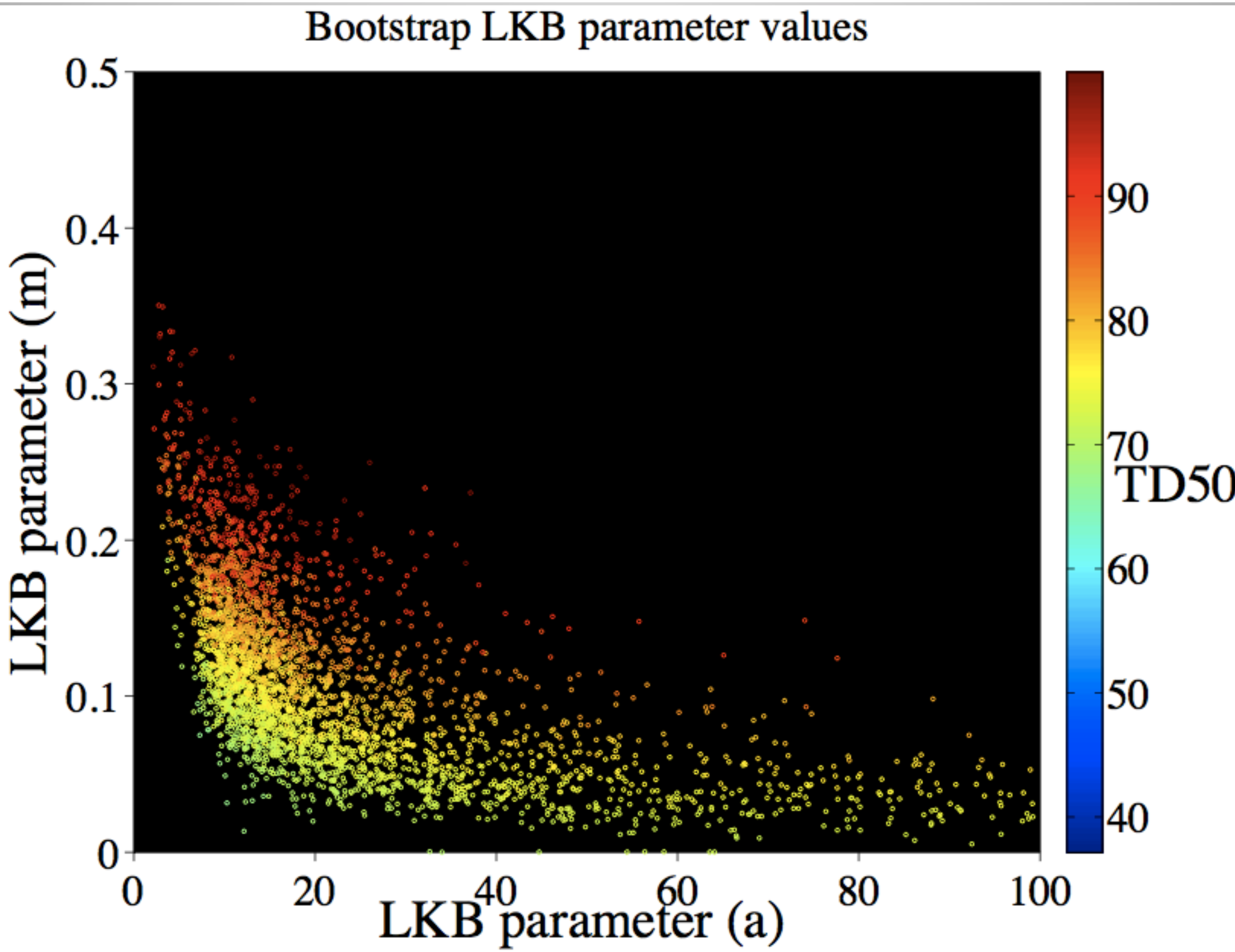
MITCHELL LIU[1], VITALI MOISEENKO[2], ALEXANDER AGRANOVICH[1], ANAND KARVAT[1], WINKLE KWAN[1], ZIAD H. SALEH[3], ADITYA A. APTE[3] & JOSEPH O. DEASY[3]

[1]Fraser Valley Centre, British Columbia Cancer Centre, Surrey, BC, Canada, [2]Vancouver Centre, British Columbia Cancer Agency, Vancouver, BC, Canada and [3]Department of Radiation Oncology and the Mallinckrodt Institute of Radiology, Washington University, St. Louis, MO

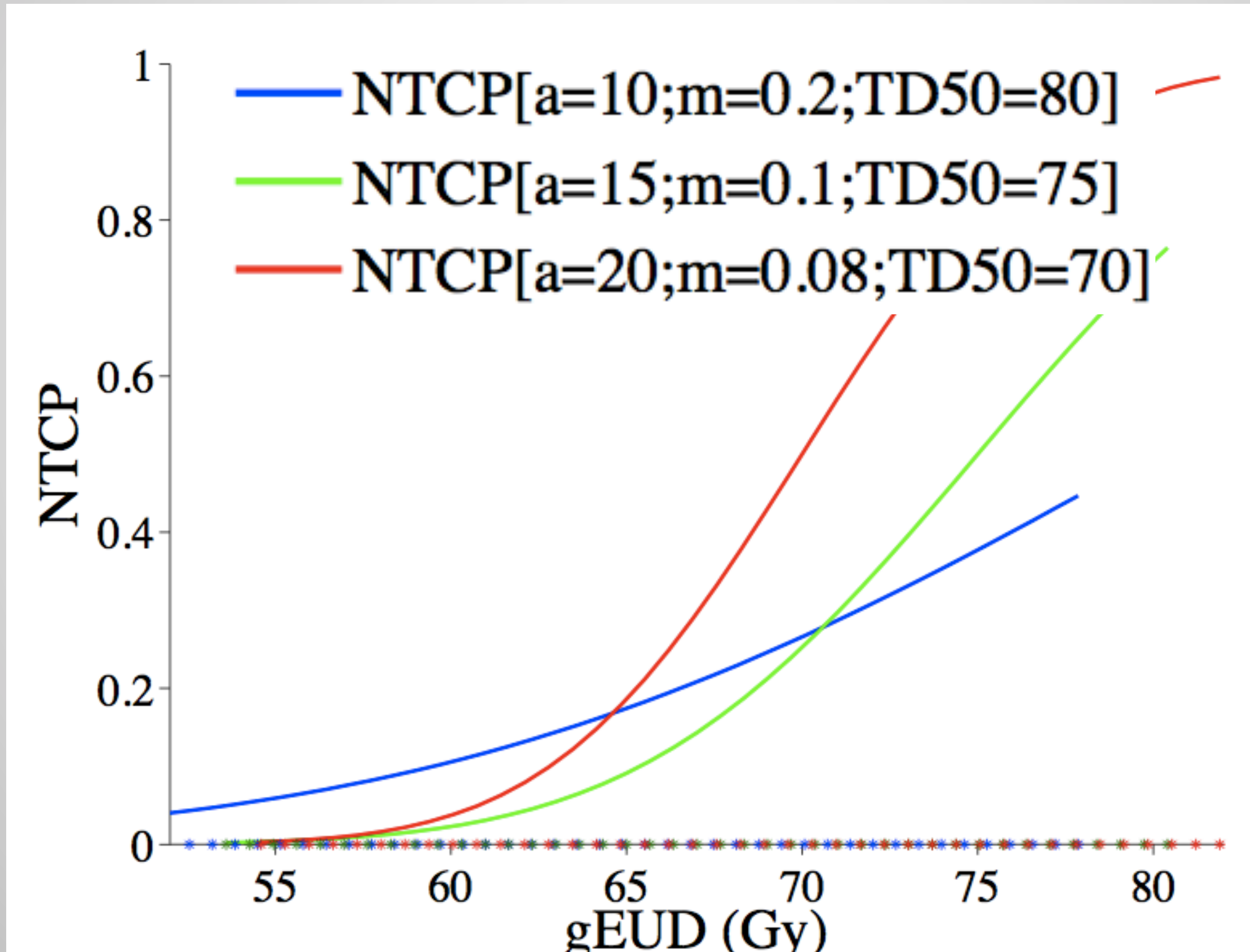


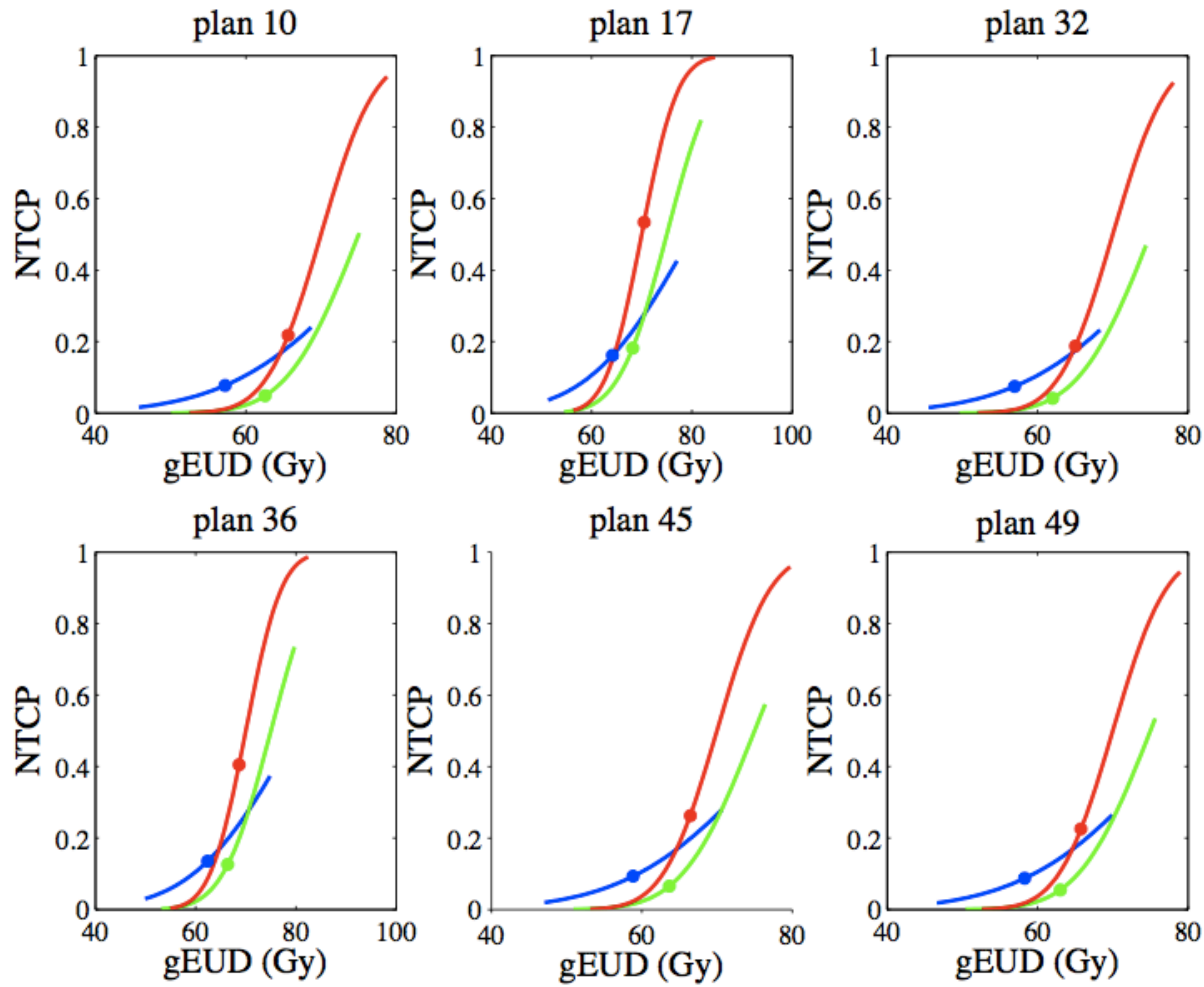
0.25
0.2
0.15
0.1
0.05
0
Late rectal bleeding >= grade 2
LKB−QUANTEC
LKB−best fit
1/38
2/34
3/31
4/36
2/20
62
63
64
65
66
67
68
gEUD (Gy)

The impact of model parameter uncertainties on NTCP predictions


Bootstrap LKB parameter values
LKB parameter (m)
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
LKB parameter (a)
90
80
70
TD50
60
50
40

What is the true model?





plan 10
plan 17
plan 32
plan 36
plan 45
plan 49
NTCP
gEUD (Gy)
0
0.2
0.4
0.6
0.8
1
40
60
80
100

Dose-volume constraints

- D*x* represents the minimum dose that at least *x*% of the volume receives
- V*x* represents the minimum (percentage) volume that receives at least *x* Gy

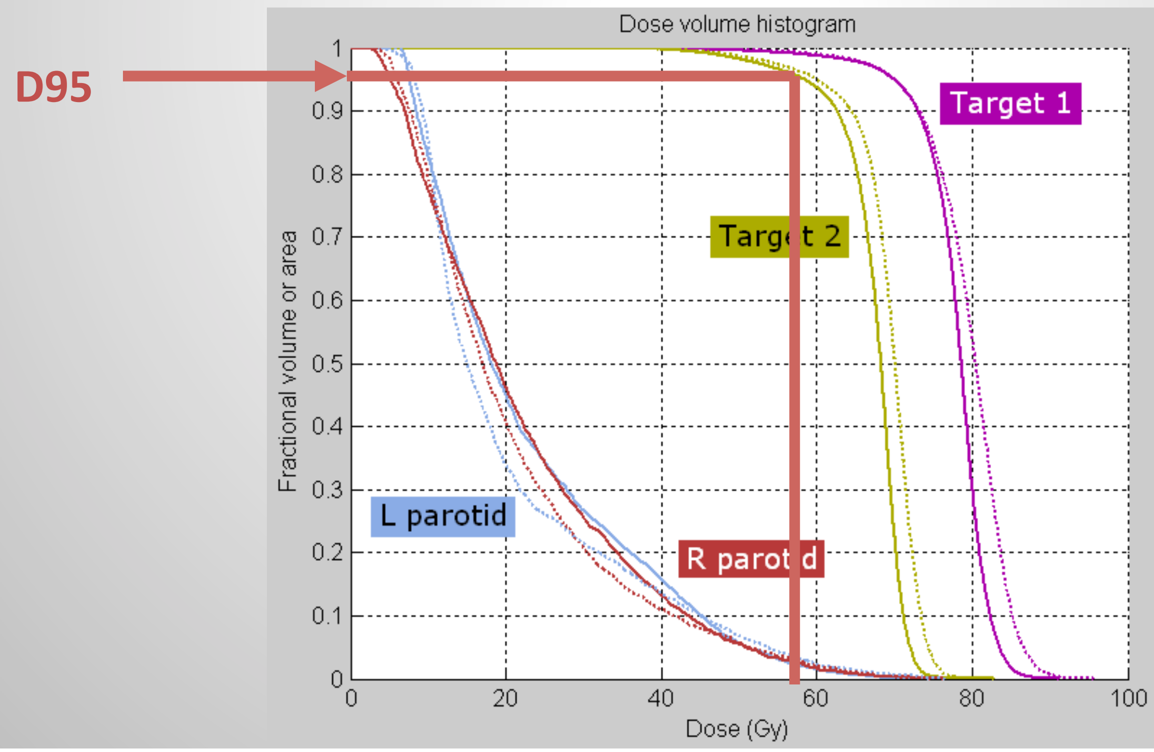
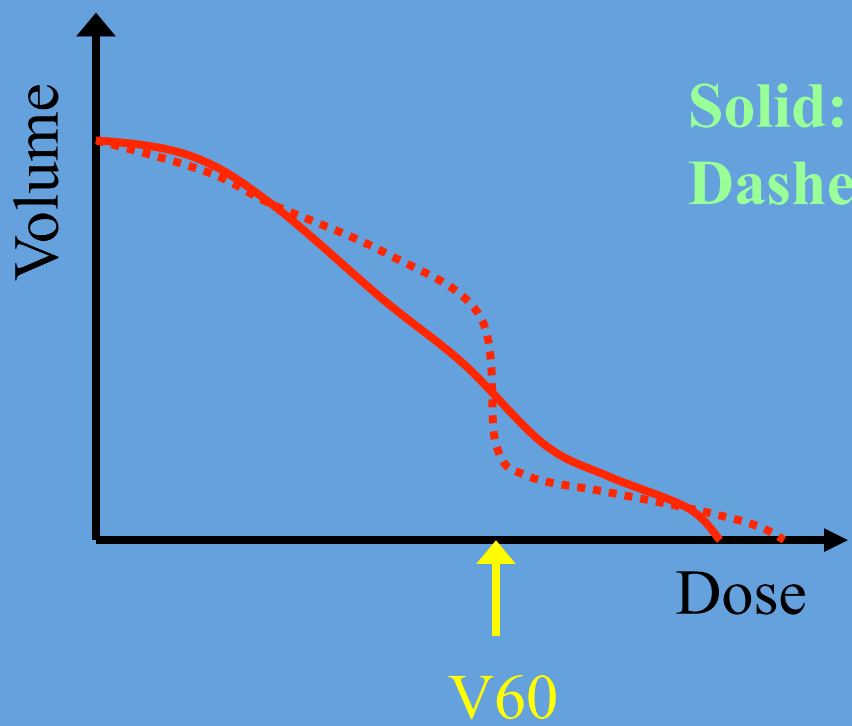


Illustration of DVH 'warping' by a dose-volume constraint



Solid: typical pre-IMRT DVH
Dashed: after 'optimization'

Big problem when single DVH pts used for optimization: pinned DVH

Additional problems with using traditional dose-volume constraints in IMRT optimization

- Non-convex
  - No guarantee of optimality with current solvers
  - Potentially slower than linear/quadratic objectives
- Difficult implementation. Must be:
  - Mixed-integer programming, or
  - Approximated

Solution: mean-tail-dose

- Definition
  - MOH*x* – mean of hottest *x*%
  - MOC*x* – mean of coldest *x*%

- Potentially more biologically relevant (smoother)
- Linear
- Convex
  - Faster
  - Guaranteed to be optimal if solution is found
- Found to correlate with traditional dose-volume metrics

- Suggested by Romeijn et al. (2003, 2006)

Solution: generalized equivalent uniform dose (gEUD)

- gEUD is the exponentially weighted dose value:

$$\text{gEUD}(\mathbf{d}, a) = \left(\frac{1}{N} \sum_{i=1}^{N} d_i^a \right)^{1/a}$$

  - d_i represents the dose to voxel i,
  - N is the number of voxels in the structure of interest, and
  - a is a variable exponent parameter.

Benefits of gEUD

- Radiobiologically relevant
  - Has parameter (a) which can be tuned to underlying data
  - Can track high doses (a large), low doses (a negative), or some average dose ($a \sim 1$)
- Convex (Choi 2002)
- Correlates well to dose-volume constraints
- Previously suggested (Niemierko 1998; Choi 2002; Wu 2002, 2003; Olafsson 2005; Thomas 2005; Chapet 2005)

Dissertation work: Determining value of replacement candidates

- Datasets of clinical treatment plans were used:
  - Lung cancer, 263 patients
  - Prostate cancer, 291 patients
- Calculated the correlation between gEUD and clinically applicable dose-volume constraints
  - Tested various values of the parameter a
  - Did the same for MOH/MOC*x* with values of *x*

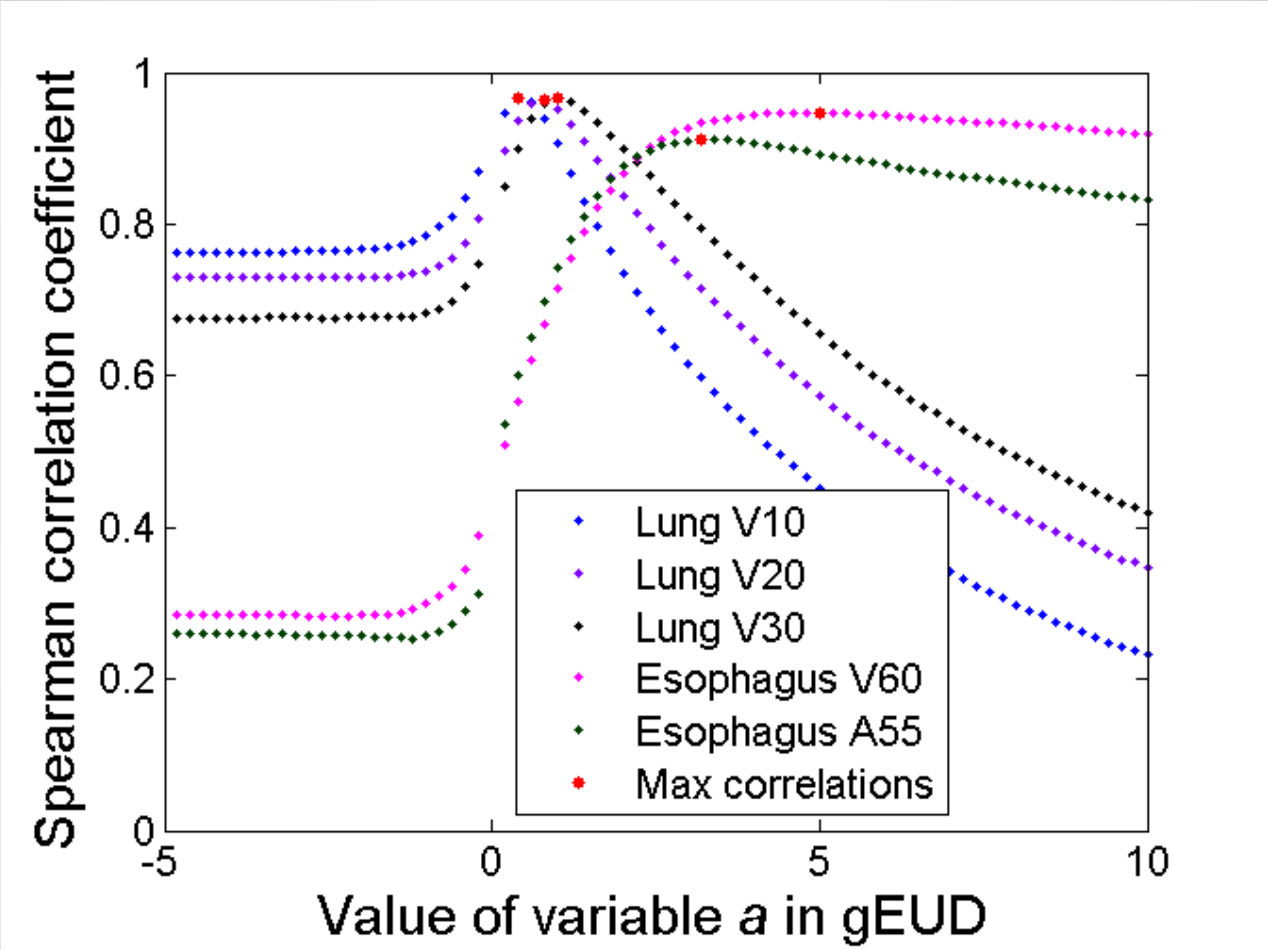
Correlations between gEUD/MOH/MOC and DV metrics

- Spearman correlation coefficients
  - All together mean: 0.94, median: 0.97, range: 0.45 to 1.00
  - gEUD mean: 0.93, median: 0.96, range: 0.45 to 1.00
  - mean-tail-dose mean: 0.95, median: 0.98, range: 0.45 to 1.00
  - The 0.45 coefficient is an outlier

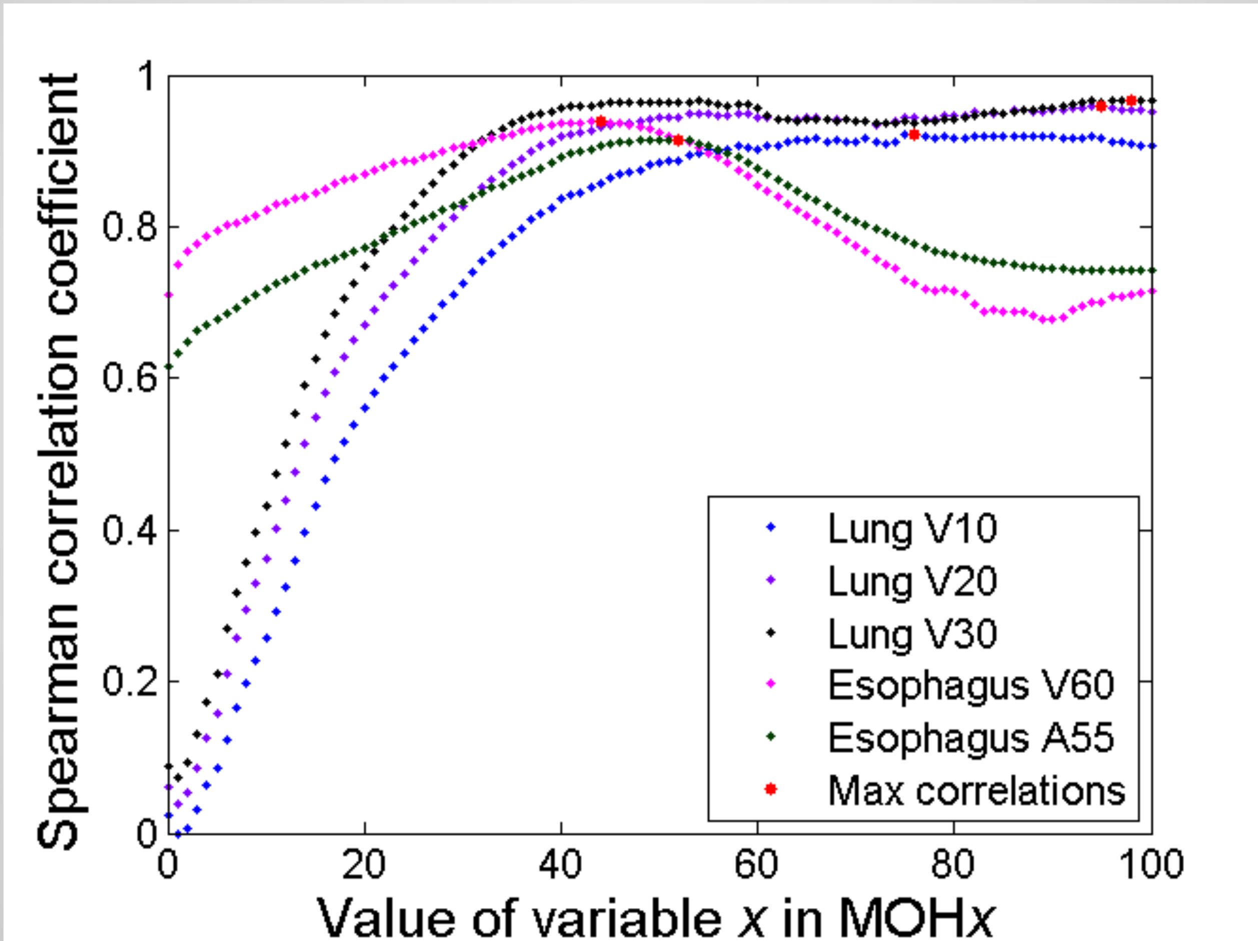
- 51 of the 60 correlations tested had a Spearman correlation coefficient greater than 0.90

- In general, mean-tail-dose had higher correlations than gEUD (27 of 30 correlations equal or greater), though gEUD and mean-tail-dose correlation coefficients were often similar.

Correlation between dose-volume metrics and gEUD



Correlation between dose-volume metrics and mean-tail-dose



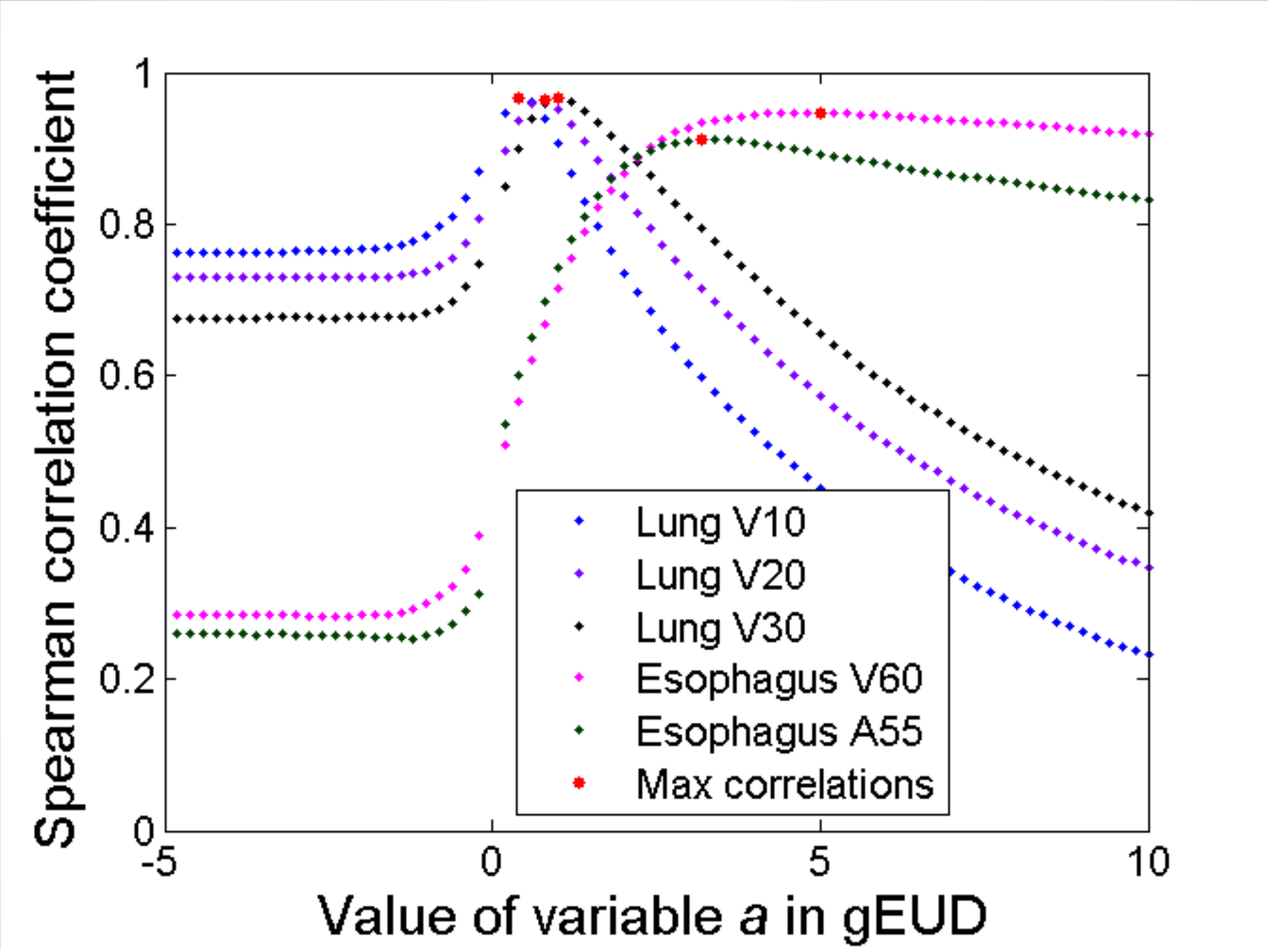
Correlations between gEUD/MOH/MOC and DV metrics

- Spearman correlation coefficients
  - All together mean: 0.94, median: 0.97, range: 0.45 to 1.00
  - gEUD mean: 0.93, median: 0.96, range: 0.45 to 1.00
  - mean-tail-dose mean: 0.95, median: 0.98, range: 0.45 to 1.00
  - The 0.45 coefficient is an outlier

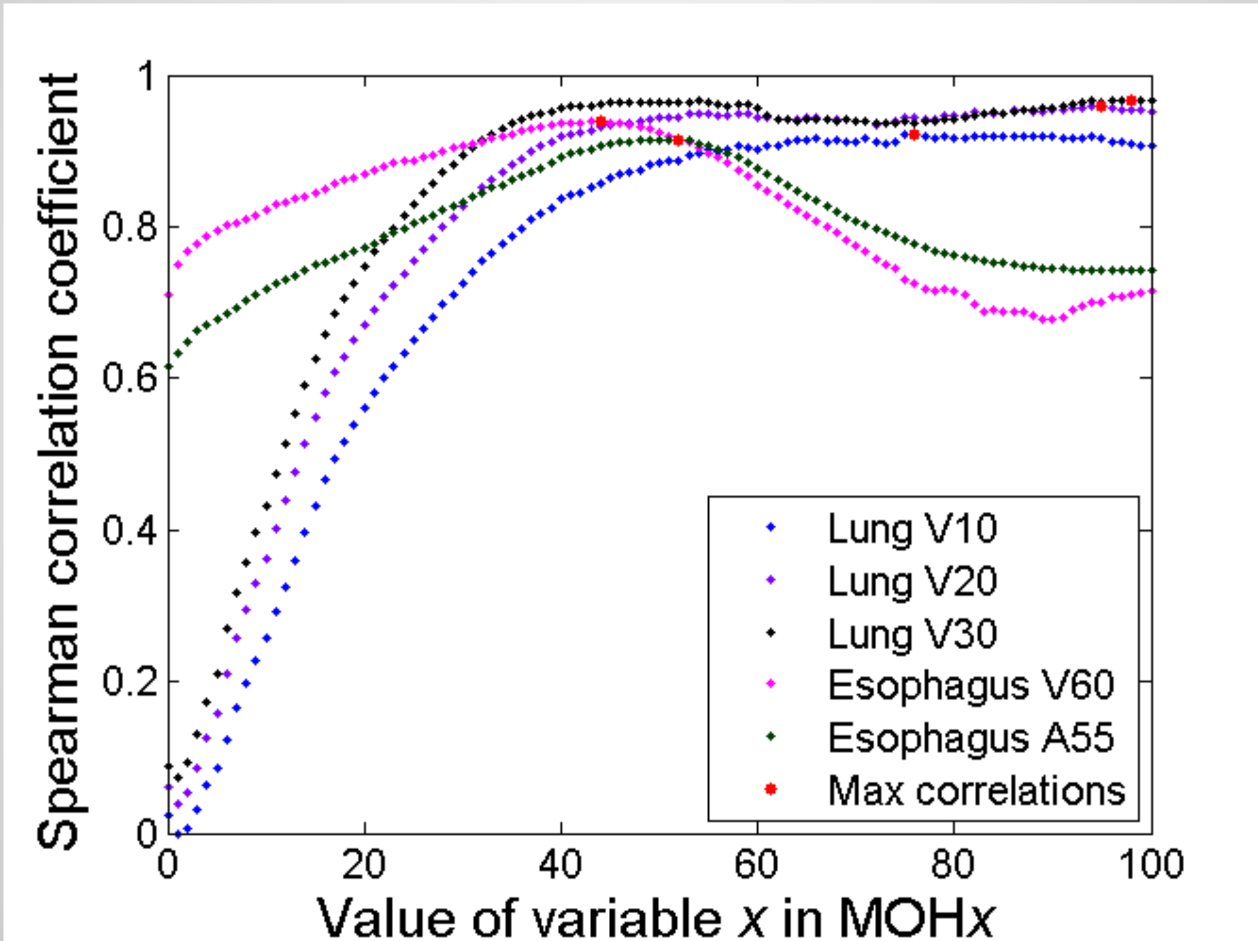
- 51 of the 60 correlations tested had a Spearman correlation coefficient greater than 0.90

- In general, mean-tail-dose had higher correlations than gEUD (27 of 30 correlations equal or greater), though gEUD and mean-tail-dose correlation coefficients were often similar.

Correlation between dose-volume metrics and gEUD



Correlation between dose-volume metrics and mean-tail-dose



What about tumor control probability?

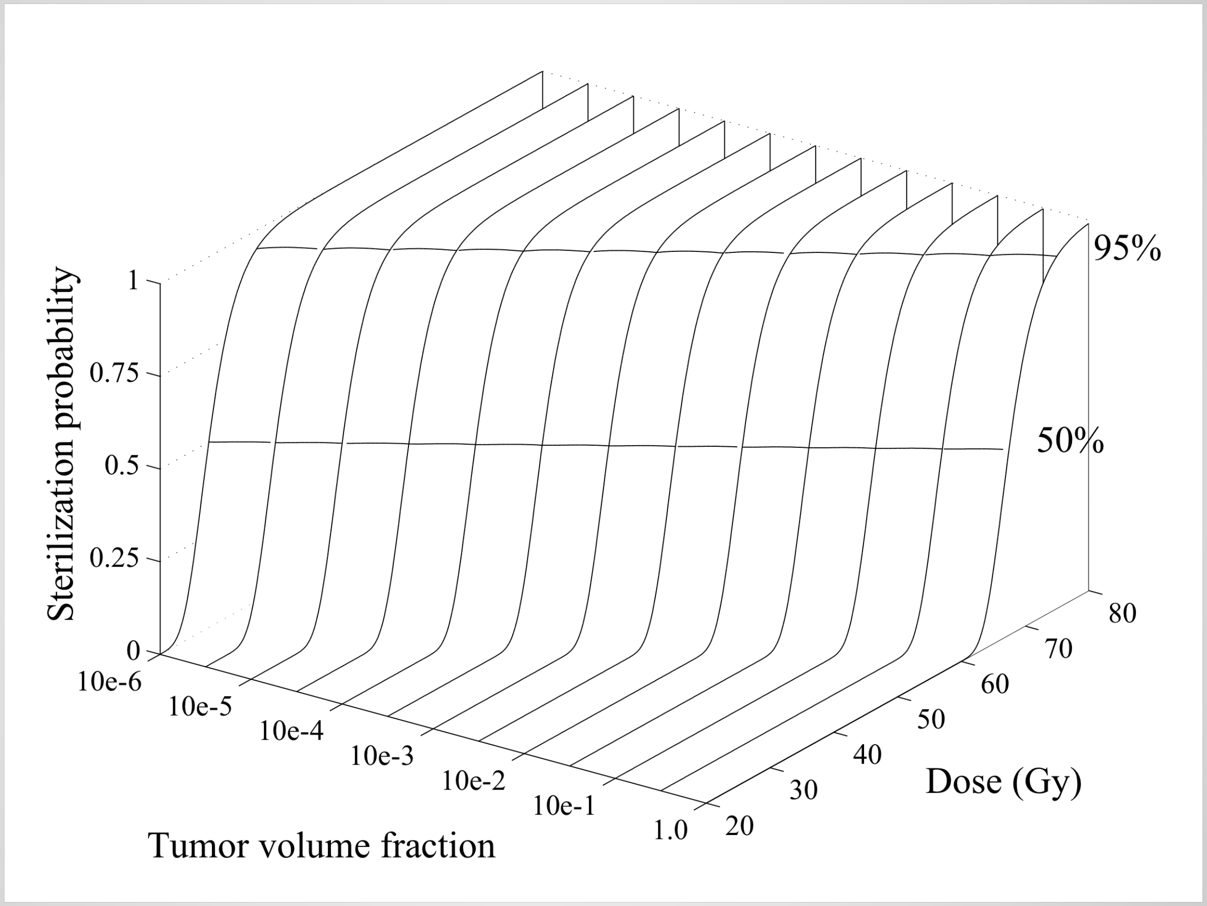
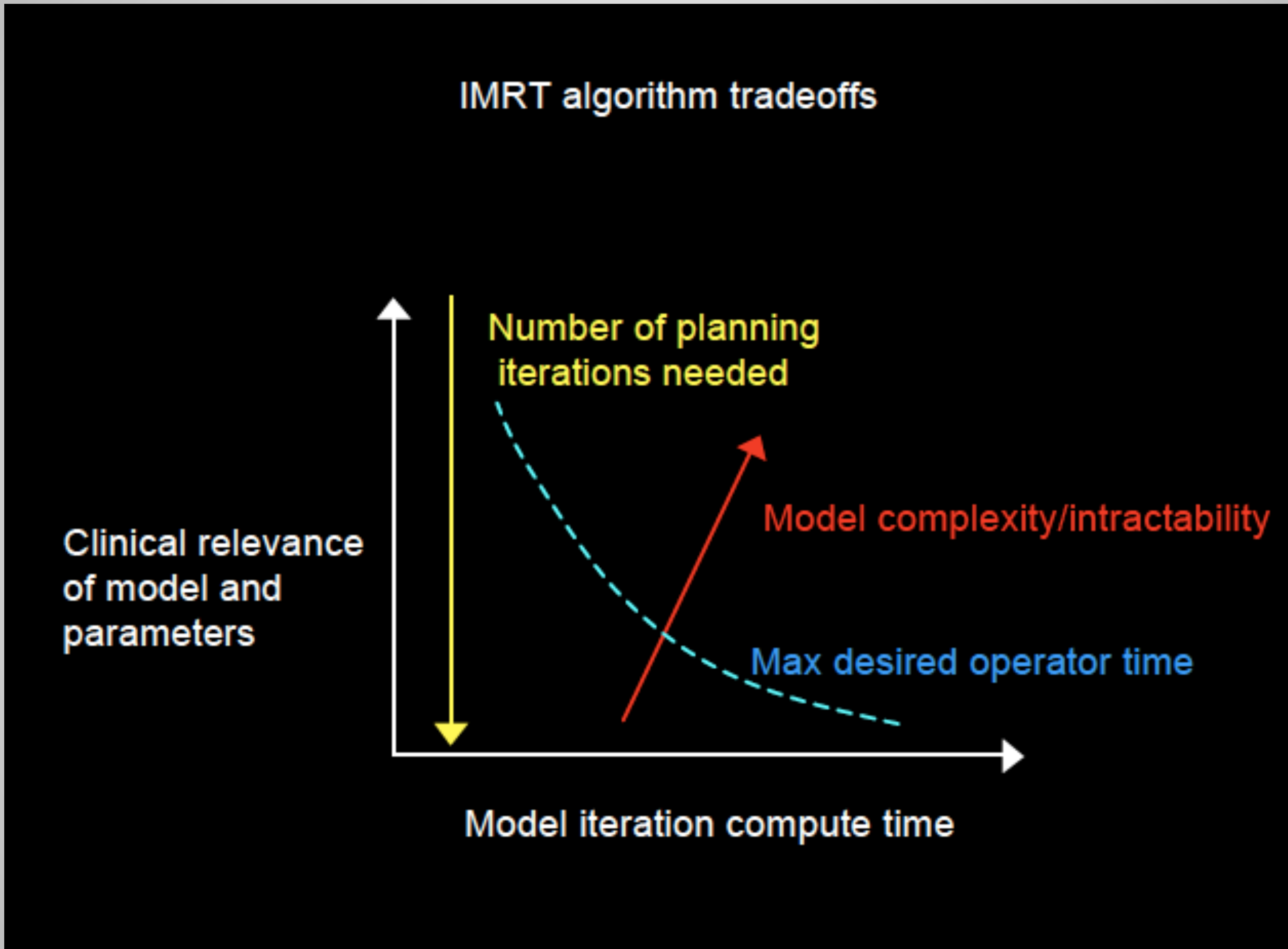

Sterilization probability
1
0.75
0.5
0.25
0
10e-6
10e-5
10e-4
10e-3
10e-2
10e-1
1.0
Tumor volume fraction
20
30
40
50
60
70
80
Dose (Gy)
95%
50%

Fig. 1

How can we get there?
The desirables: what we need

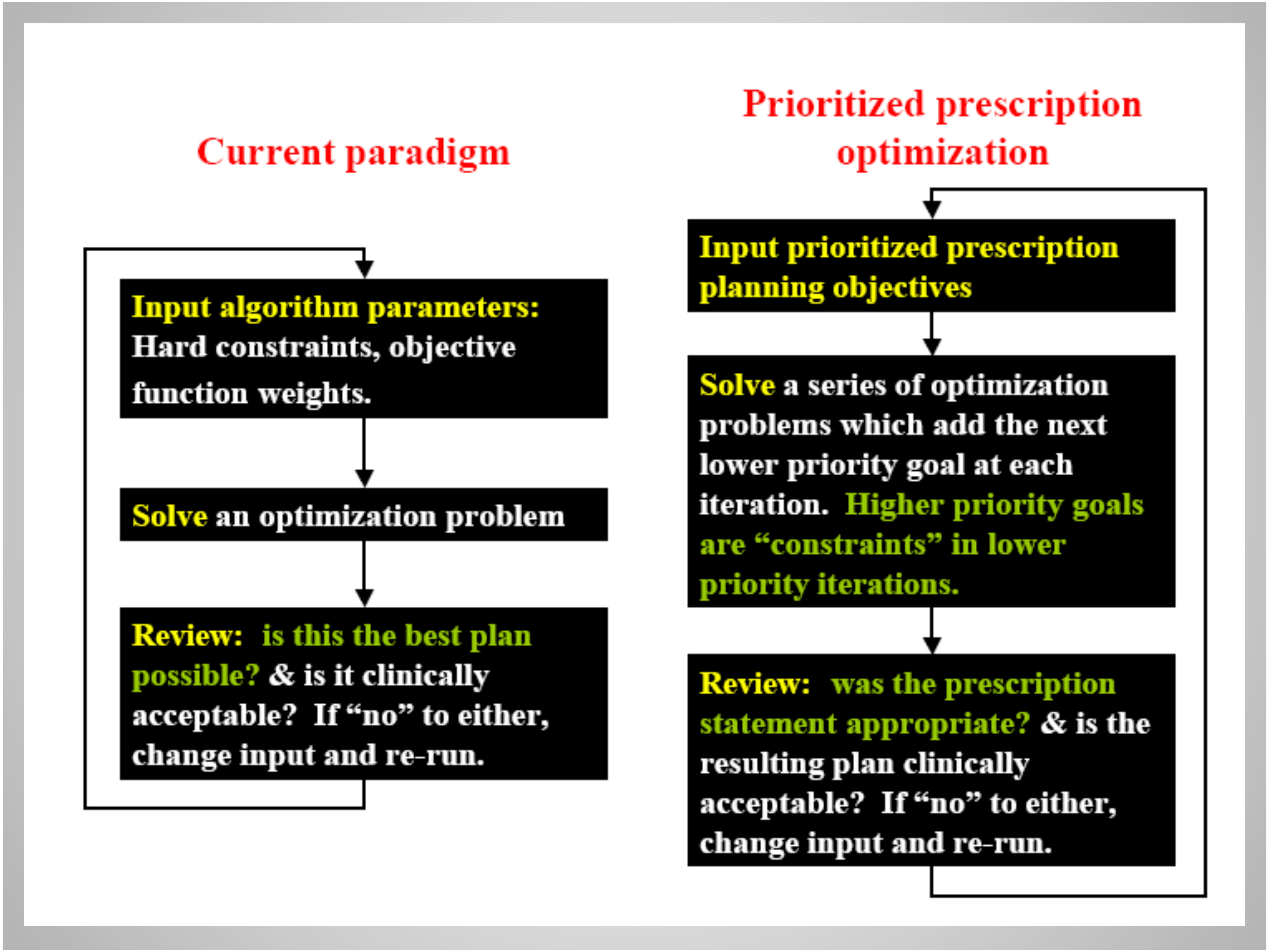
IMRT software design goals

- Clinical relevance of parameters and plan model
- Steerability of plan changes in next plan iteration or at "tweaking phase"
- Efficiency/speed of feasible solution generation in a plan iteration
- Dosimetrically faithful and delivery-time-efficient leaf segmentation
- Accuracy, likelihood of arriving at the global optimimum to within a target %.


IMRT algorithm tradeoffs
Number of planning iterations needed
Model complexity/intractability
Clinical relevance of model and parameters
Max desired operator time
Model iteration compute time

How can we get there?
Our approach

(many following slides from Vanessa Clark's dissertation with supervisor Yixin Chen)


Current paradigm
Input algorithm parameters: Hard constraints, objective function weights.
Solve an optimization problem
Review: is this the best plan possible? & is it clinically acceptable? If “no” to either, change input and re-run.
Prioritized prescription optimization
Input prioritized prescription planning objectives
Solve a series of optimization problems which add the next lower priority goal at each iteration. Higher priority goals are “constraints” in lower priority iterations.
Review: was the prescription statement appropriate? & is the resulting plan clinically acceptable? If “no” to either, change input and re-run.

Previous work using hierarchical methods for IMRT optimization

- Jee et al. (Michigan 2007)
  - Lexicographic ordering
  - Goal programming, not slip
  - Nonconvex dose metrics
  - 2 cases (1 prostate, 1 head and neck)
  - No direct clinical comparison
- Spalding et al. (Michigan 2007)
  - Lexicographic ordering, gEUD, IMRT
  - 15 pancreatic cancer cases
- Wilkens et al. (WashU 2007)
  - 6 head and neck cases
  - No direct clinical comparison

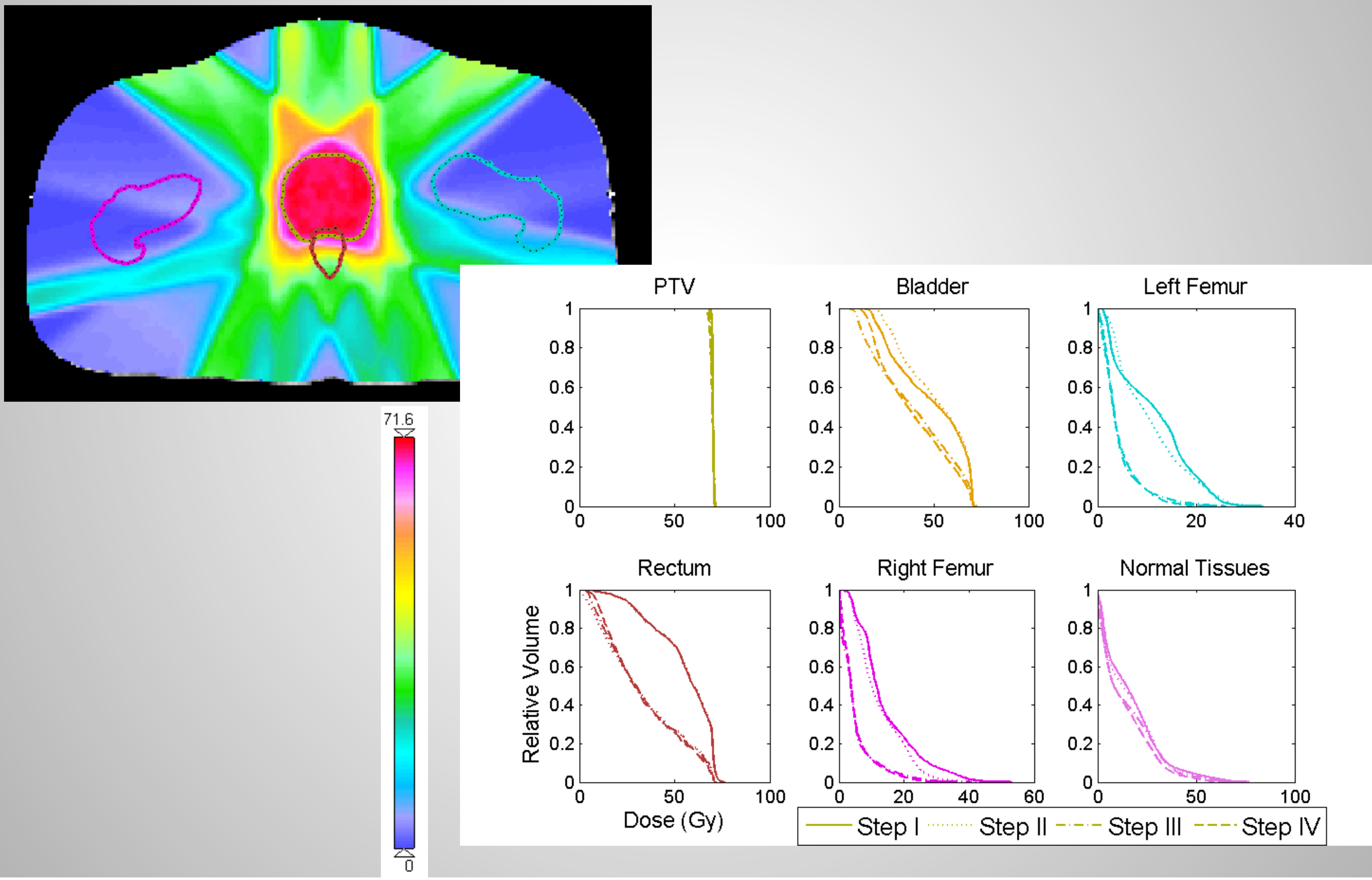
This work

- Hierarchical optimization
- 22 total prostate cases
- Convex objectives and constraints (for optimality)
- Direct clinical comparison (12 cases)
- First successful implementation of optimization for prostate using lexicographic ordering that is completely quadratic and linear (and convex)

Prioritized prescription optimization

	objectives	hard constraints
step I target coverage, high-priority OARs	minimize $F_I = \Sigma_{all\ voxels\ j} (D_j - D_{pres})^2$ and maximize D_{min} for **PTV**	• D_{max} for **rectum** • W_{max} for beam weights
step II additional OARs	minimize MOHx for **rectum**	as in step I and • max value for F_I for all targets • D_{min} and D_{max} for target as achieved in step I
step III dose falloff	minimize D_{mean} in bladder, femurs, and normal tissue	as in step II and • MOHx for rectum as achieved in step II
step IV smooth dose	minimize $\Sigma_{all\ beamlets\ i}\ w_i^2$	as in step III and • D_{mean} for bladder, femurs, and normal tissue as achieved in step III

Prostate results



Results summary

- Results appear to be comparable to clinical quality
- Average total runtime: 20 mins (prostate)

Chapter 4: Comparison of prioritized prescription optimization with current clinical results

Showed that prioritized prescription optimization is comparable to clinical methods by direct comparison

Background: Clinical comparisons

- To translate this research to use in the clinic, comparisons with existing clinical methods are necessary
  - To show validity
  - To show usefulness
  - To be accepted by clinicians
  - To have commercial companies implement it in their clinical software
- Technically challenging
- No study has previously compared using prioritized optimization techniques directly to those in the clinic

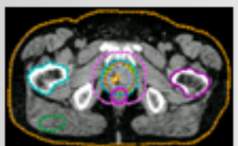
Formulation

- Based on physician preferences
- Guarantees (constraints):
  - Maximum PTV dose ≤ 75.6 Gy * 1.10
  - Rectum V65 < 17% (MOH31 < 65)
  - Rectum V40 < 35% (MOH98 < 30)
  - Bladder V65 < 25% (MOH35 < 64)
  - Bladder V40 < 50% (MOH100 < 40)
- Objectives (optimized in the following order):
  1. Maximize PTV D98 (MOC10)
  2. Minimize Rectum V65 (MOH31) & V40 (MOH98)
  3. Minimize Bladder V65 (MOH35) & V40 (MOH100)
  4. Minimize Normal Tissues mean & max dose
  5. Smoothing and minimize PTV mean dose

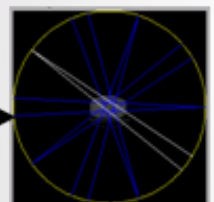
System Integration

-Technically challenging
-Broad potential impact

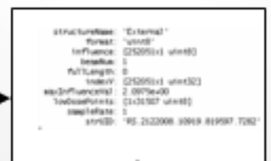
Define target and critical structures



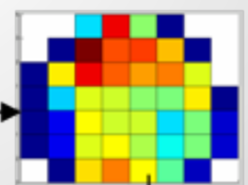
Define beam geometry and parameters



Compute beamlets using QIB

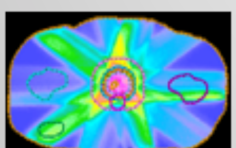


Optimize beamlet weights using priopt / Mosek



Generate deliverable leaf sequences

Recompute final dose using DPM



Experiment datasets

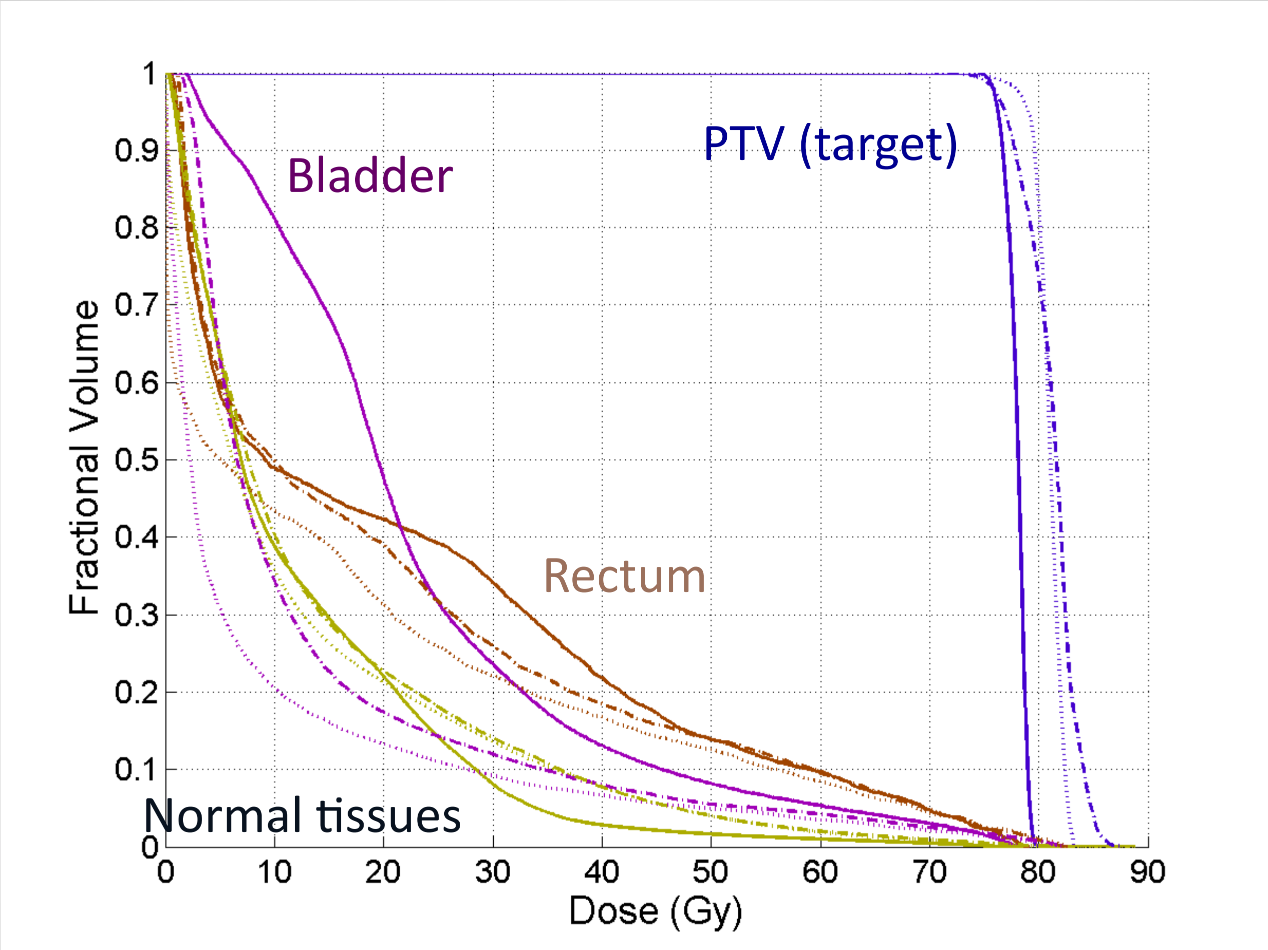
- 6 definitive prostate (3 training)
  - 75.6 Gy
- 6 postoperative prostate (2 training)
  - 64.8 Gy
  - 79.2 Gy
- Anonymized
- Compared to results calculated using Pinnacle during normal course of clinical operations

Example result

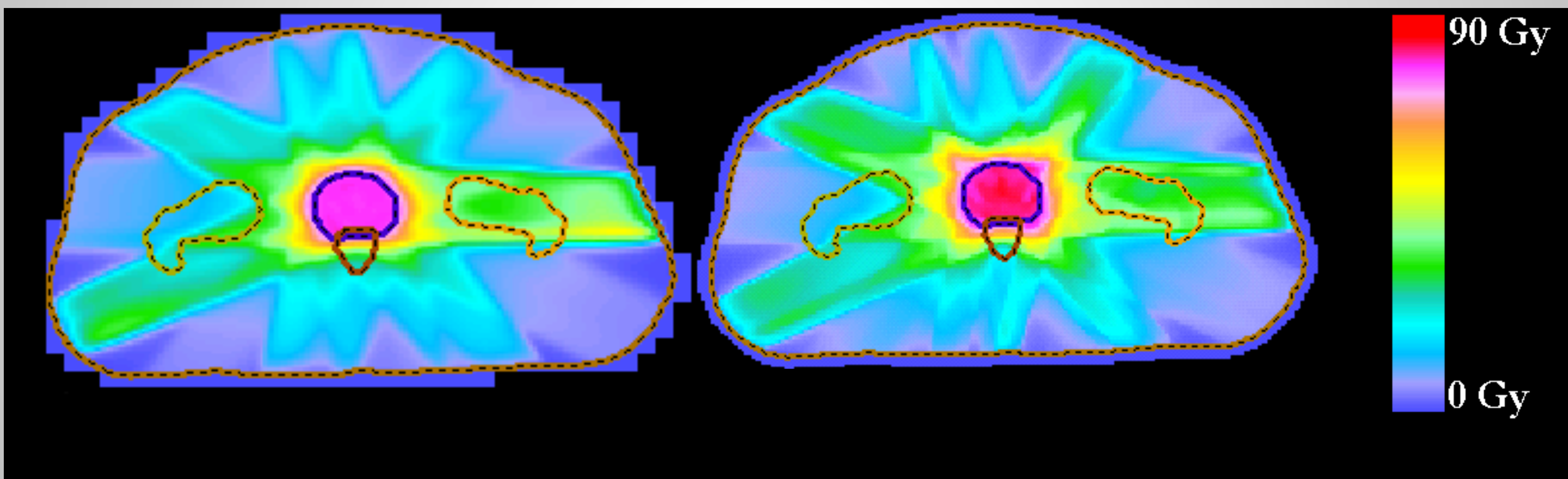
____ Clinical

.... Priopt QIB

- - - - Priopt DPM



Dose distributions for example result

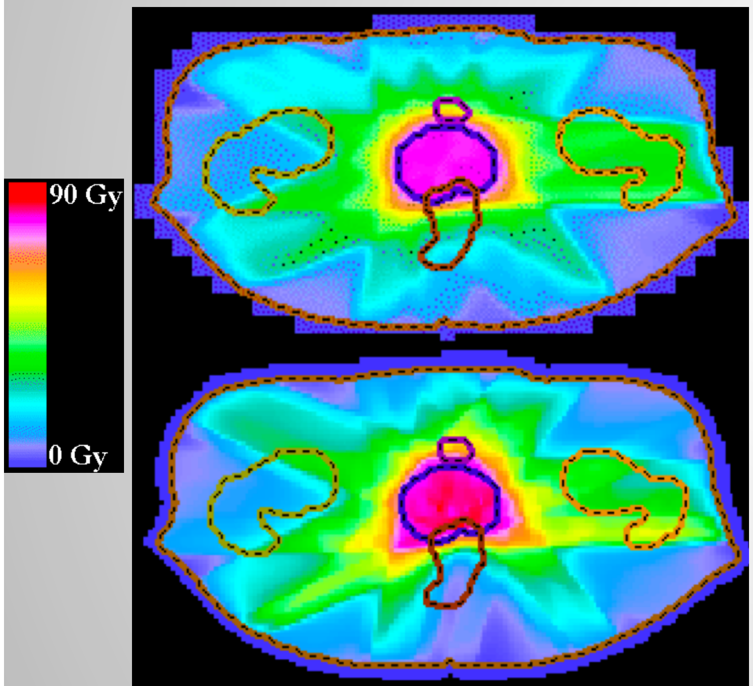


Clinical

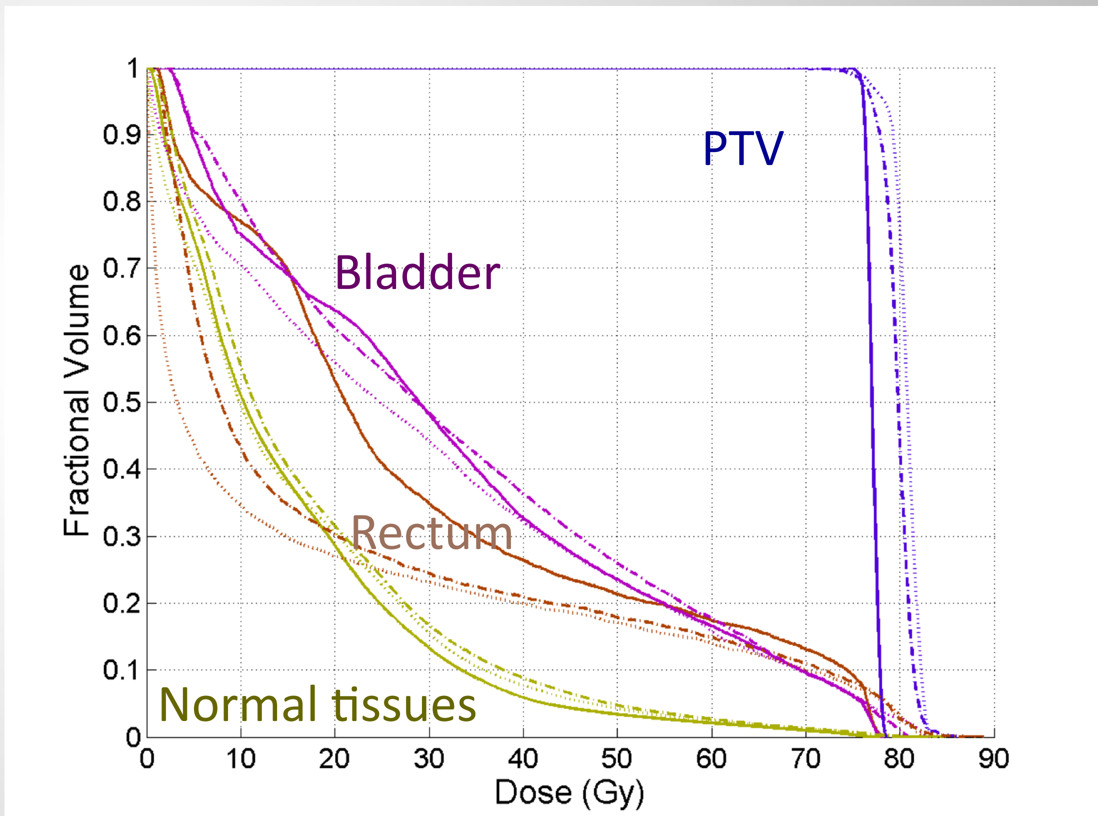
Priopt
with DPM

Priopt vs. Pinnacle for one case

Pinnacle



Priopt



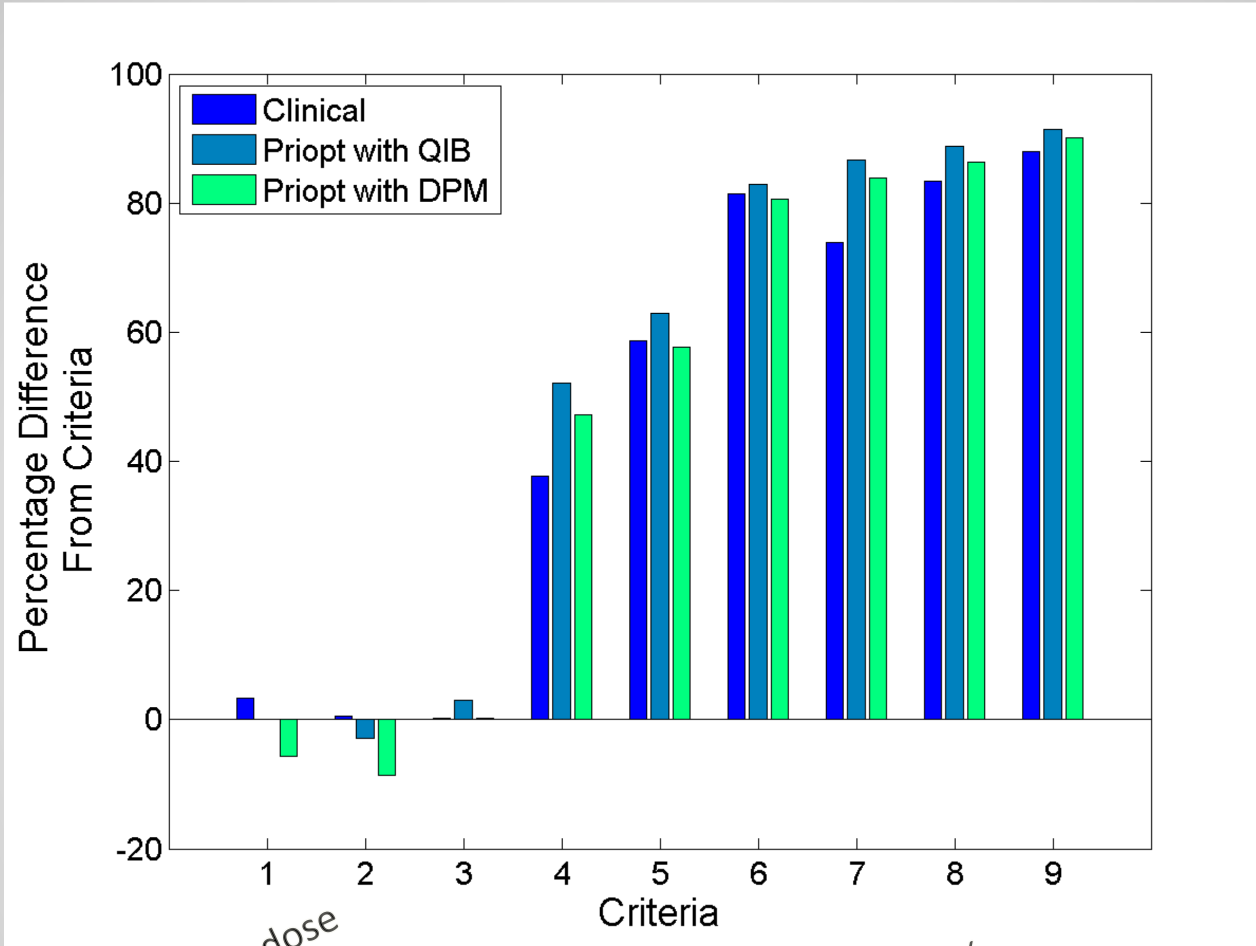
--- Pinnacle

… Priopt QIB

- - Priopt DPM final

Clinical criteria comparison

Superior



1. Target max dose < 110% pres. dose
2. Target max dose < 107% pres. dose
3. Target D98 > prescription dose
4. Rectum V40 < 35%
5. Rectum V65 < 17%
6. Rectum V70 < 25%
7. Bladder V40 < 50%
8. Bladder V65 < 25%
9. Bladder V70 < 25%

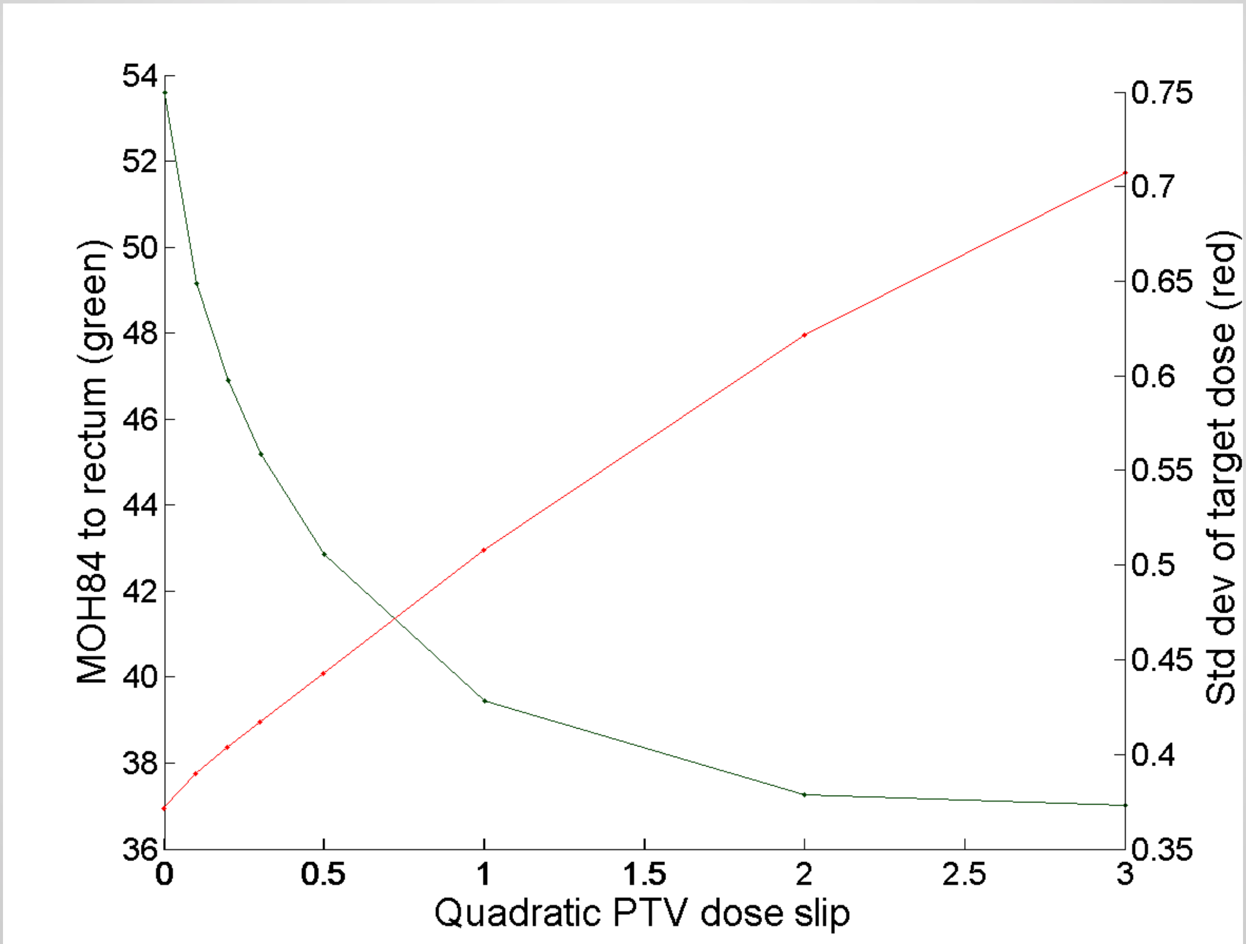
Difference between our method and clinical for all cases

	Definitive		Postoperative	
	Difference	Std Dev	Difference	Std Dev
Target max dose < 110% pres dose	11.0	4.3	9.4	2.7
Target max dose < 107% pres dose (preferred)	11.3	4.4	9.7	2.8
Target D98 > prescription dose	0.0	0.0	0.0	0.0
Rectum V40 < 35%	4.0	8.5	17.0	45.5
Rectum V65 < 17%	1.7	9.0	0.0	20.0
Rectum V70 < 25%	1.3	5.8	3.1	7.8
Bladder V40 < 50%	3.8	6.5	1.8	25.9
Bladder V65 < 25%	3.4	3.6	0.3	14.7
Bladder V70 < 25% (unspecified criteria)	4.0	3.7	4.4	12.1

The concept of ‘slip’

- Resulting dose distributions at each step may be quite similar (small search space)
- Need for expanding the possible solution space at each step
- Allow slight degradation of objective function from step to step: ‘slip’
- Variable parameter – what is best value?
- We found that a class solution works
- Automated solution may improve results

Slip tradeoff graph



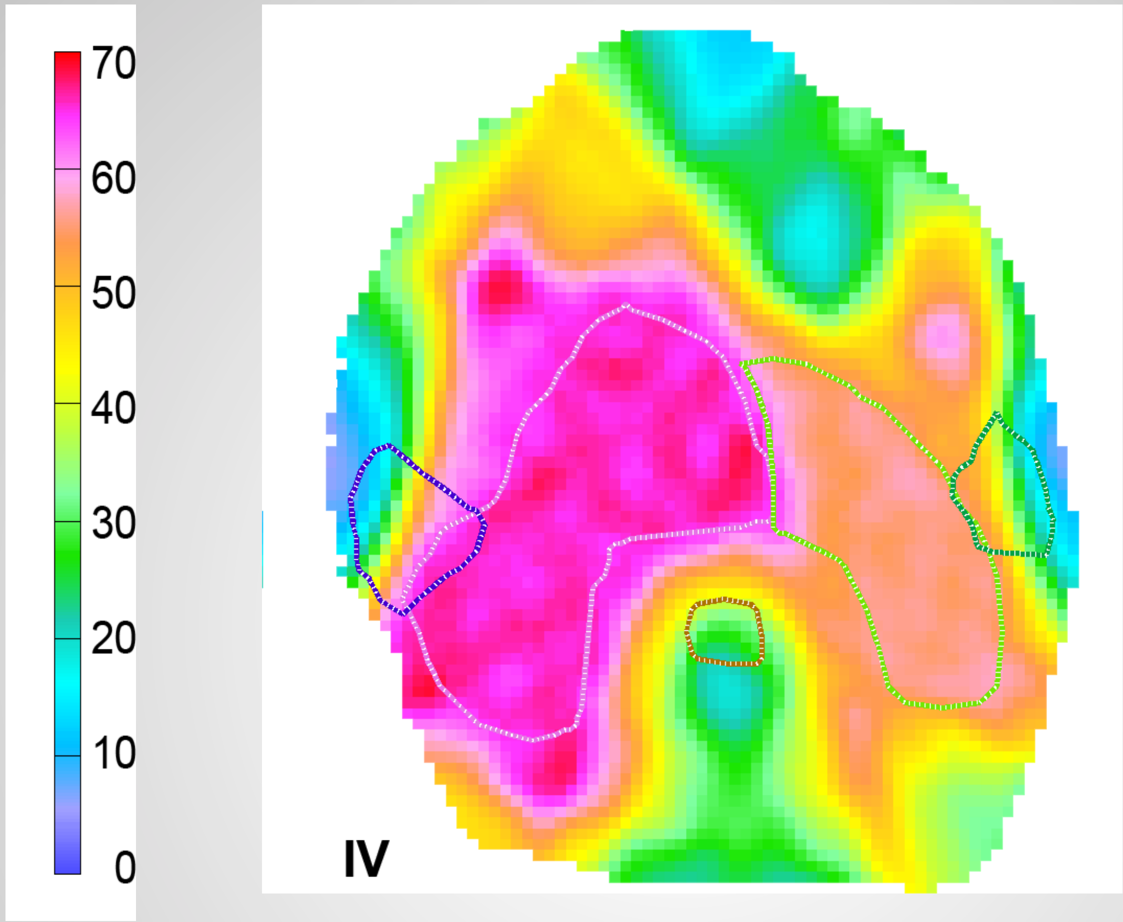
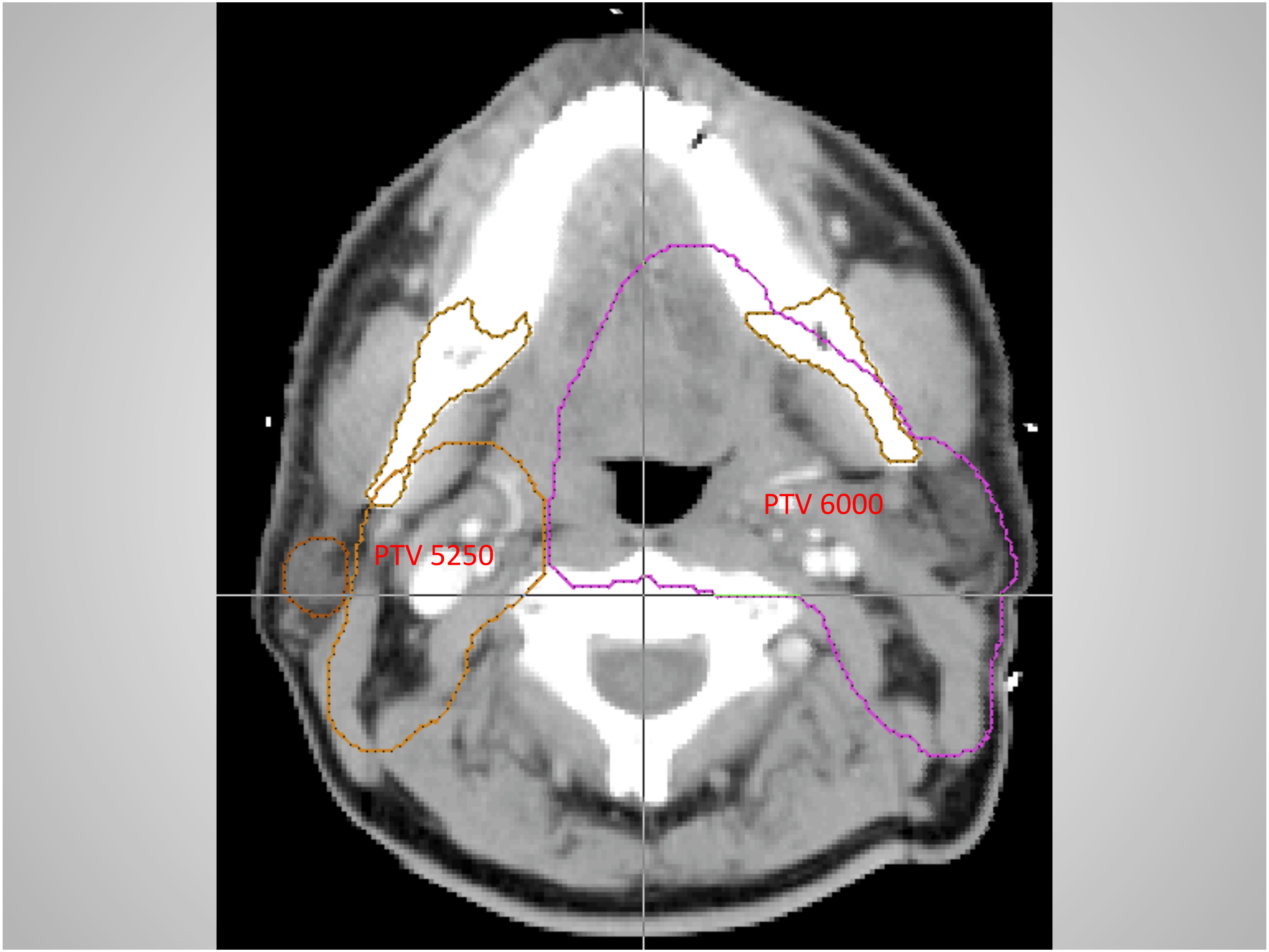


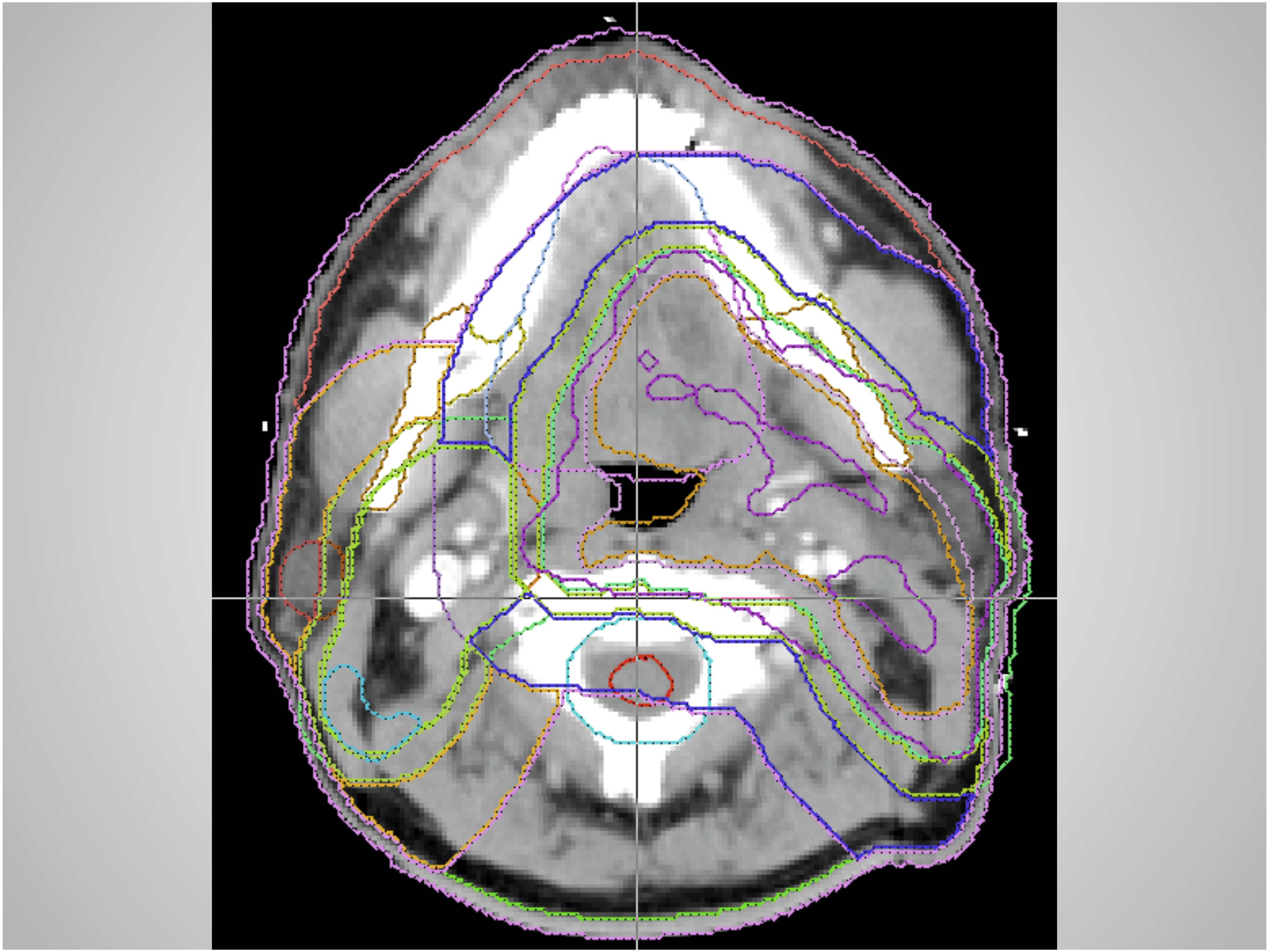
Figure 4. Transverse view of the dose distribution after step IV for a representative head and neck case. The outlined structures are (from left to right) right parotid gland, PTV1, spinal cord, PTV2, and left parotid gland. All dose values are given in Gy.

Prioritized planning within Pinnacle

Pinnacle has…

- Typical DVH constraints
- gEUD objectives
- Constrained optimization


PTV 6000
PTV 5250



Required planning objectives [1/3]

ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value	a
LTPAROT_OPT	Max EUD		1950			1	--	1
RTPAROT_OPT	Max EUD		1400			1	--	1
POST AVOID	Max Dose		4000			1	--	
2CM OUT_60	Max EUD		3200			2	--	1
2CM OUTER RIN	Max EUD		2700			1	--	1
MAND_OPT	Max EUD		2750			1	--	1
ORALCAV_OPT	Max EUD		3850			1	--	1
2CM OUT_60	Max Dose		5800			4	--	
2CM OUTER RIN	Max Dose		4600			2	--	

Required planning objectives [2/3]

ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight
PTV60_OPT	Max Dose		6150			41
PTV60_OPT	Min Dose		6150			25
INNER RING 60	Min Dose		6150			65
5MM OUT RING	Max Dose		6000			1
PTV5250_OPT	Min Dose		5400			10
PTV5250_OPT	Max Dose		5600			33
5MM OUT RING	Max Dose		5250			5
SHOULDER AVO	Max Dose		1900			1
CORD + MARGIN	Max Dose		4150			35

Required planning objectives [3/3]

ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value	a
OUTER BODY RI	Max Dose		4500			2	--	
OUTER BODY RI	Max EUD		800			2	--	1
LARYNX_OPT	Max EUD		4200			1	--	1
ESOPH_OPT	Max EUD		2000			1	--	1
5MM OUT RING	Max EUD		5300			3	--	1
AVOID STREAK	Max EUD		4000			3	--	1
AVOID STREAK	Max Dose		5000			1	--	
6900 (DMPO)_1	Max Dose		6150			10	--	
PTV60_OPT	Uniform Dose		6150			1	--	
NEED 52	Min Dose		5400			1	--	
6000 (DMPO)_1	Max Dose		6150			55	--	
PTV5250_OPT	Max DVH		5700	4		10	--	
INN RING 5250	Min Dose		5400			15	--	

PriOpt, Step 1

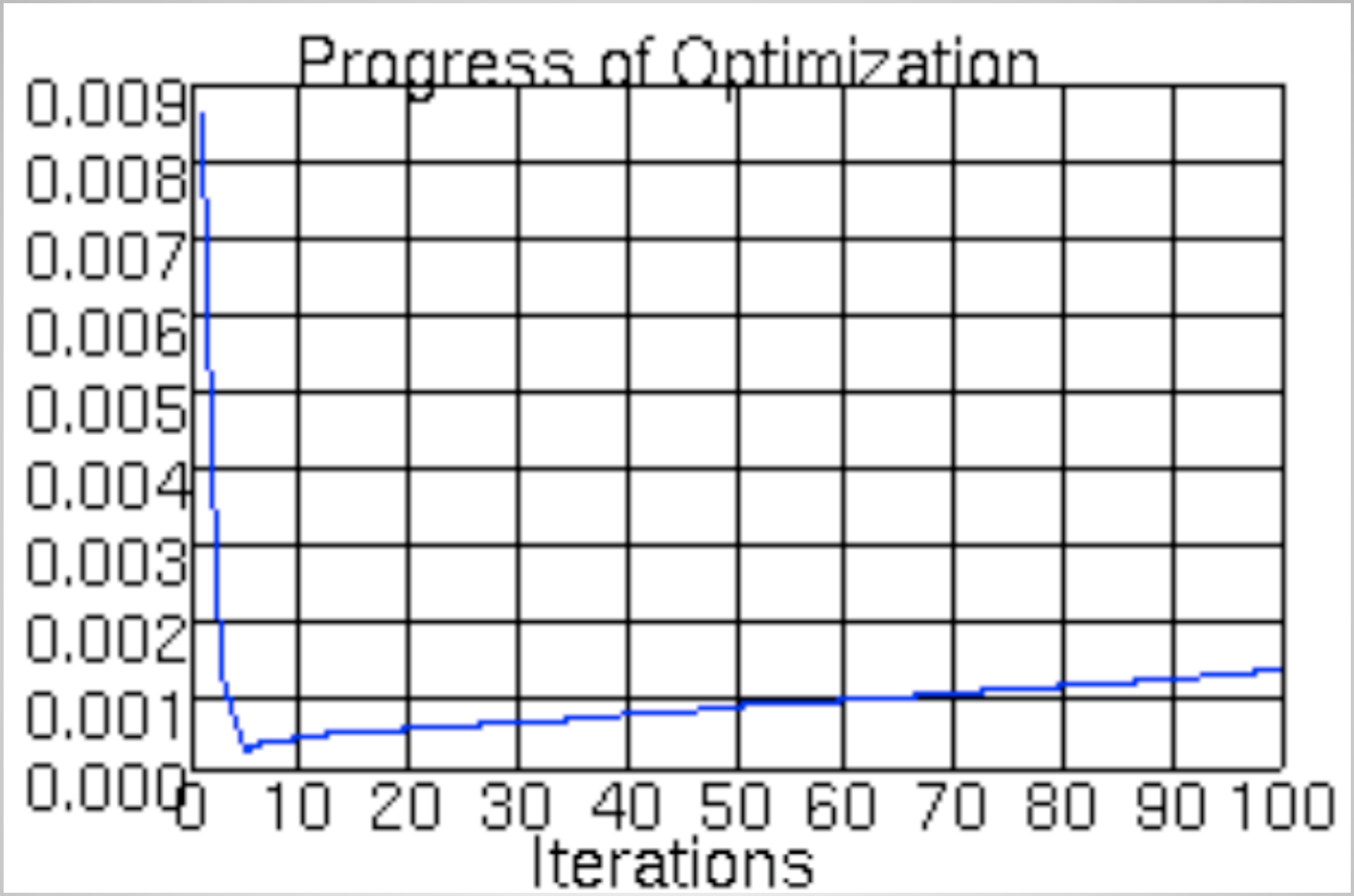
ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value	a
CORD	Max Dose	☑	4500				--	
BRAINSTEM	Max Dose	☑	5000				--	
PTV 6000	Min DVH	☐	6000	98		1	--	
PTV 5250	Min DVH	☐	5250	98		1	--	
2CM OUT_60	Max EUD	☐	4500			1	--	10

PriOpt, Step 2

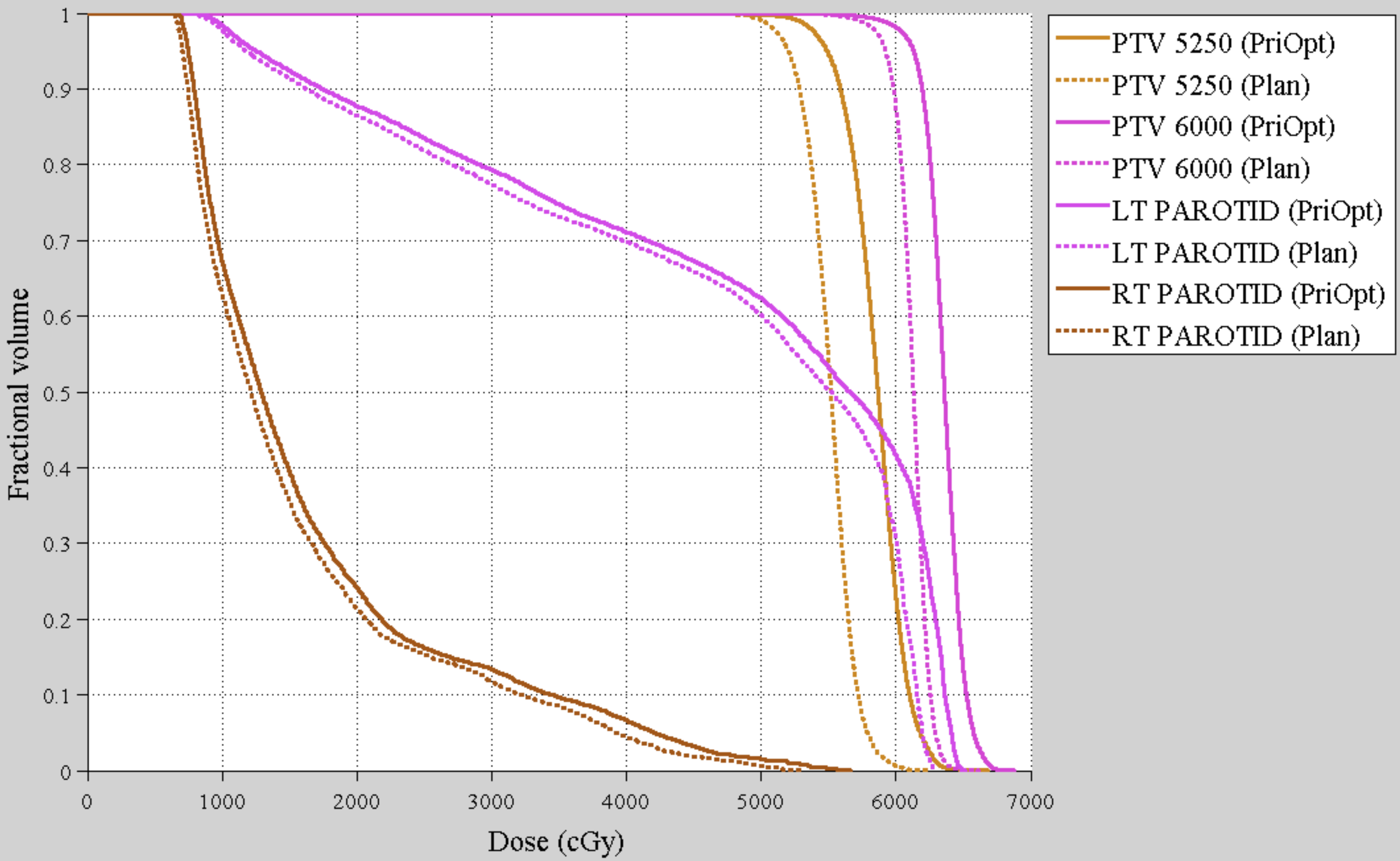
ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value	a	gEUD
CORD	Max Dose	✓	4500				1.30191e−07		
BRAINSTEM	Max Dose	✓	5000				2.43115e−09		
PTV 6000	Min Dose	✓	5580				8.78213e−07		
PTV 5250	Min Dose	✓	4950				1.19567e−07		
2CM OUT_60	Max EUD	✓	4600				1.23133e−07	10	4603.61
LT PAROTID	Max EUD		4000			1	0.00270102	1	4464.85
RT PAROTID	Max EUD		1200			1	4.14136e−05	1	1217.27

PriOpt, Step 3 (last step)

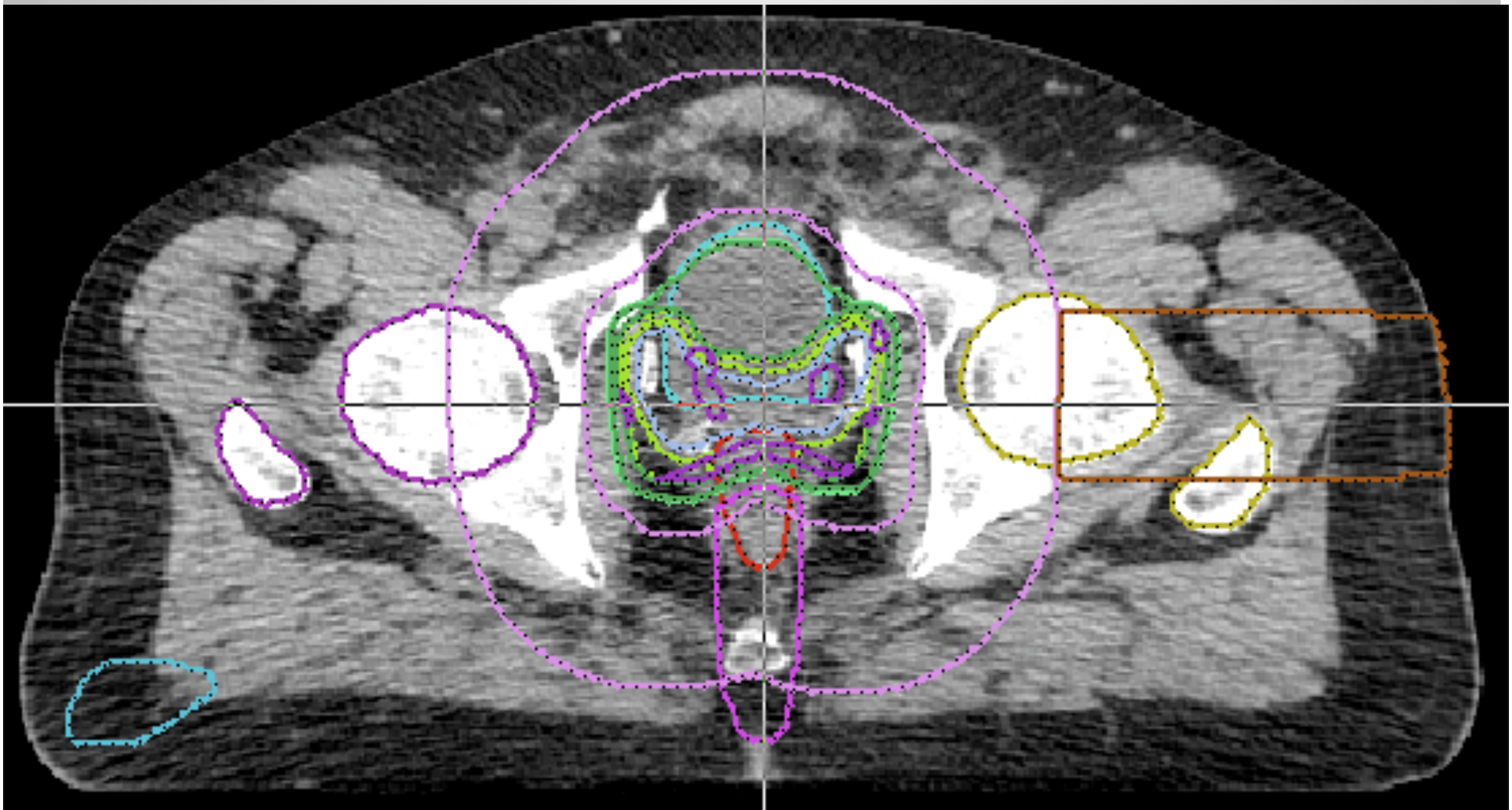
ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value	a
CORD	Max Dose	✓	4500				--	
BRAINSTEM	Max Dose	✓	5000				--	
PTV 6000	Min Dose	✓	5580				--	
PTV 5250	Min Dose	✓	4950				--	
2CM OUT_60	Max EUD	✓	4600				--	10
LT PAROTID	Max EUD	✓	4500				--	1
RT PAROTID	Max EUD	✓	1250				--	1
2CM OUT_60	Max EUD		3200			1	--	2
PTV 5250	Target EUD		5250			1	--	1
PTV 6000	Target EUD		6000			1	--	1


Progress of Optimization
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
0 10 20 30 40 50 60 70 80 90 100
Iterations

Slow!



Fractional volume
Dose (cGy)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
1000
2000
3000
4000
5000
6000
7000
PTV 5250 (PriOpt)
PTV 5250 (Plan)
PTV 6000 (PriOpt)
PTV 6000 (Plan)
LT PAROTID (PriOpt)
LT PAROTID (Plan)
RT PAROTID (PriOpt)
RT PAROTID (Plan)

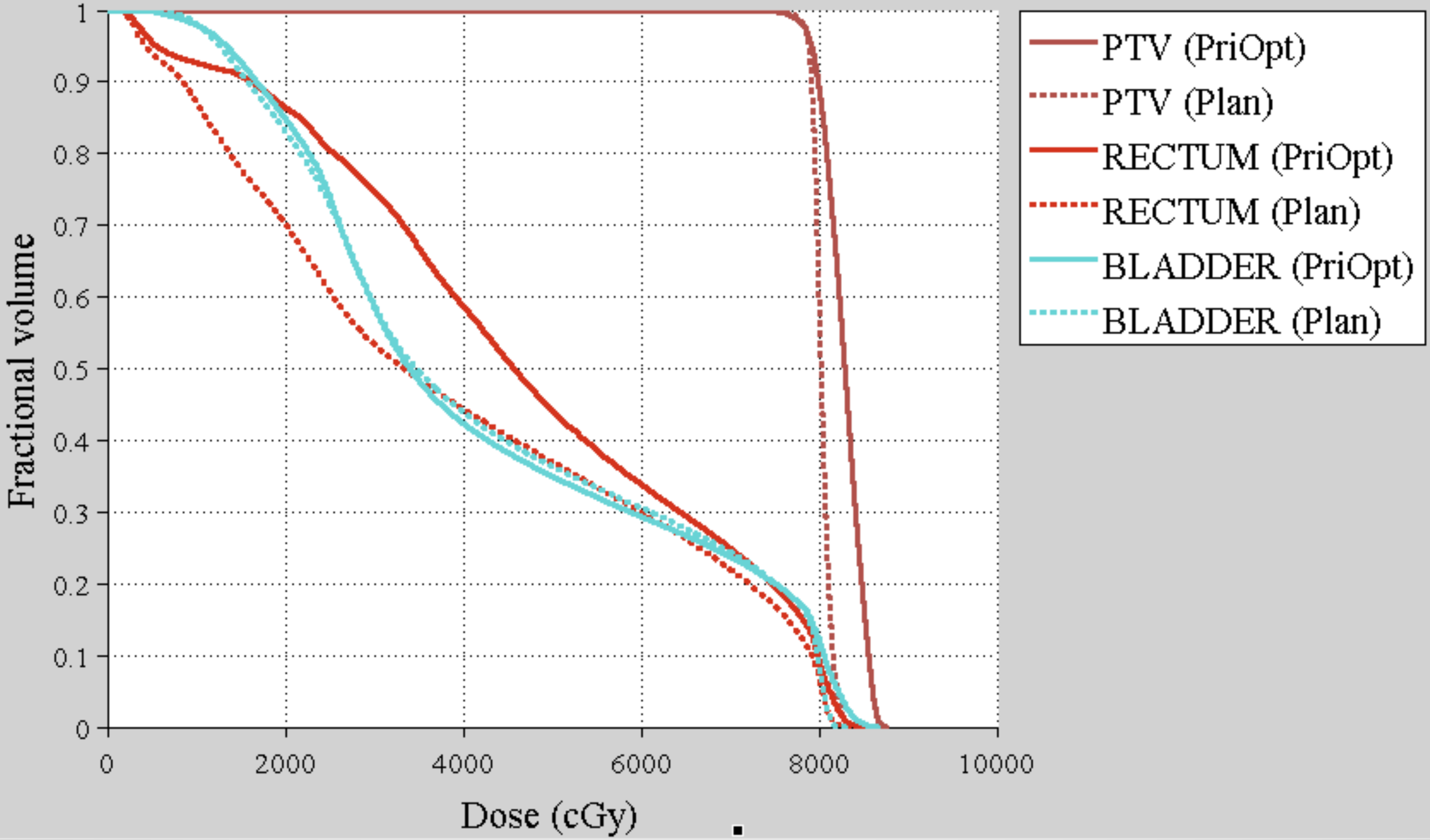


Prostate objectives

ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value	a
LTPAROT_OPT	Max EUD		1950			1	--	1
RTPAROT_OPT	Max EUD		1400			1	--	1
POST AVOID	Max Dose		4000			1	--	
2CM OUT_60	Max EUD		3200			2	--	1
2CM OUTER RIN	Max EUD		2700			1	--	1
MAND_OPT	Max EUD		2750			1	--	1
ORALCAV_OPT	Max EUD		3850			1	--	1
2CM OUT_60	Max Dose		5800			4	--	
2CM OUTER RIN	Max Dose		4600			2	--	
OUTSIDE RING 1	Max Dose		6175			1		
PTV	Max Dose		8662			1		
PTV	Min Dose		7875			1		

Prostate PriOpt Step 3 (final step)

ROI	Type	Constrain	Target cGy	% Volume	% Variation	Weight	Objective Value	a
OUTSIDE RING 1	Max DVH	✓	6175	2			--	
PTV	Max Dose	✓	8662				--	
PTV	Min DVH	✓	7875	98			--	
RECTUM	Max EUD	✓	6180				--	5
BLADDER	Max EUD	✓	6180				--	5
OUTSIDE RING 1	Max EUD	☐	2000			1	--	2
OUTSIDE RING 3	Max EUD	☐	5000			1	--	10
extern_minus_ptv	Max Dose	✓	4500				--	



PTV (PriOpt)
PTV (Plan)
RECTUM (PriOpt)
RECTUM (Plan)
BLADDER (PriOpt)
BLADDER (Plan)
Fractional volume
Dose (cGy)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
2000
4000
6000
8000
10000

Issues

- Can be slow
- Automation (scripting) may be hampered by the need to keep the objective function from 'blowing up'. That is, objectives shouldn't be too far off what was available from earlier steps.

Problems with ‘PriOpt’

- What if there could be a BIG gain in a lower priority outcome for a small loss in a higher priority outcome?
- …the urge to make small changes (‘tweaking’)
- Speed…