Computational challenges in intensity modulated radiation therapy treatment planning

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Collaborators

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- Jan Wilkens, PhD
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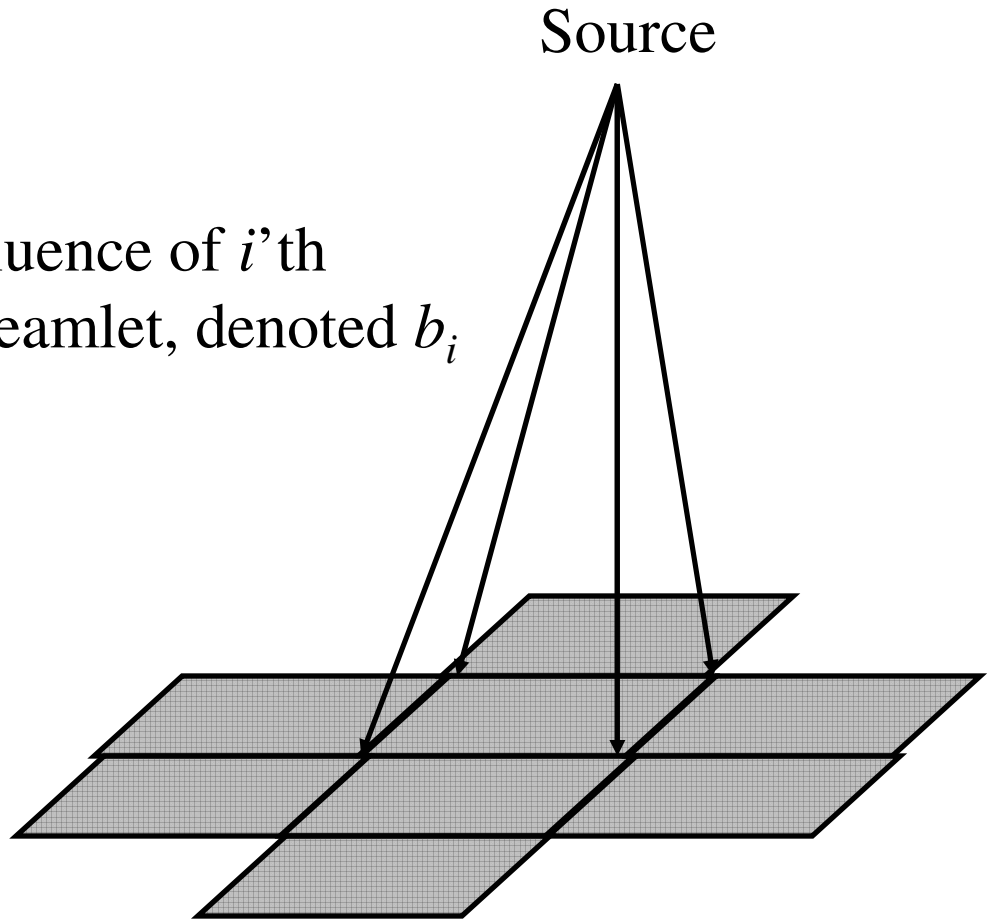
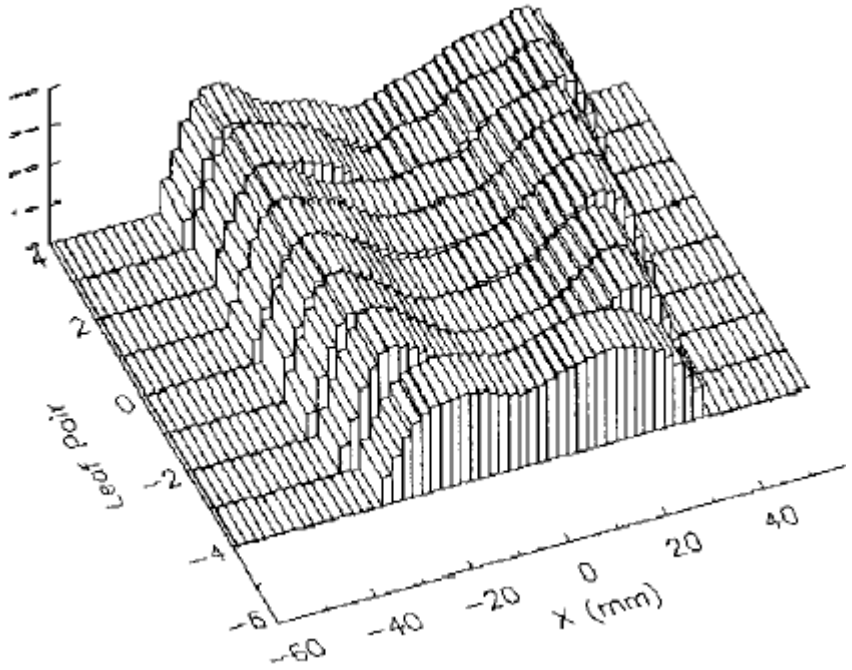
Preface: the current paradigm

A Pencil beam or *beamlet*



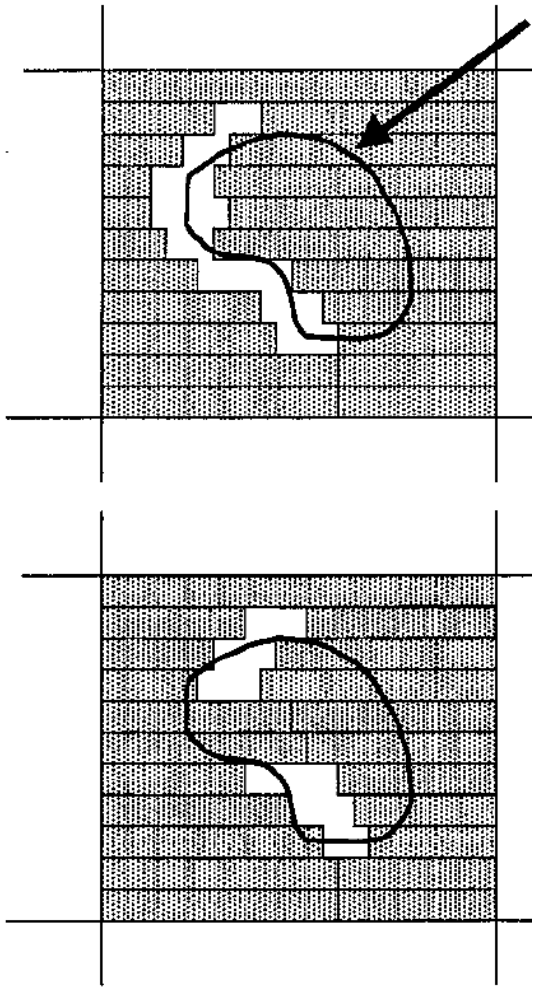
Optimization of beamlet fluence weights results in a 'fluence map' for each treatment head position

Fluence map example
(a map of the b_i's)



(From: Chui *et al.*, *Medical Physics* (2001) **28**:2441-2449.)

An IMRT dose distribution is constructed from a superposition of open static fields of variable fluence

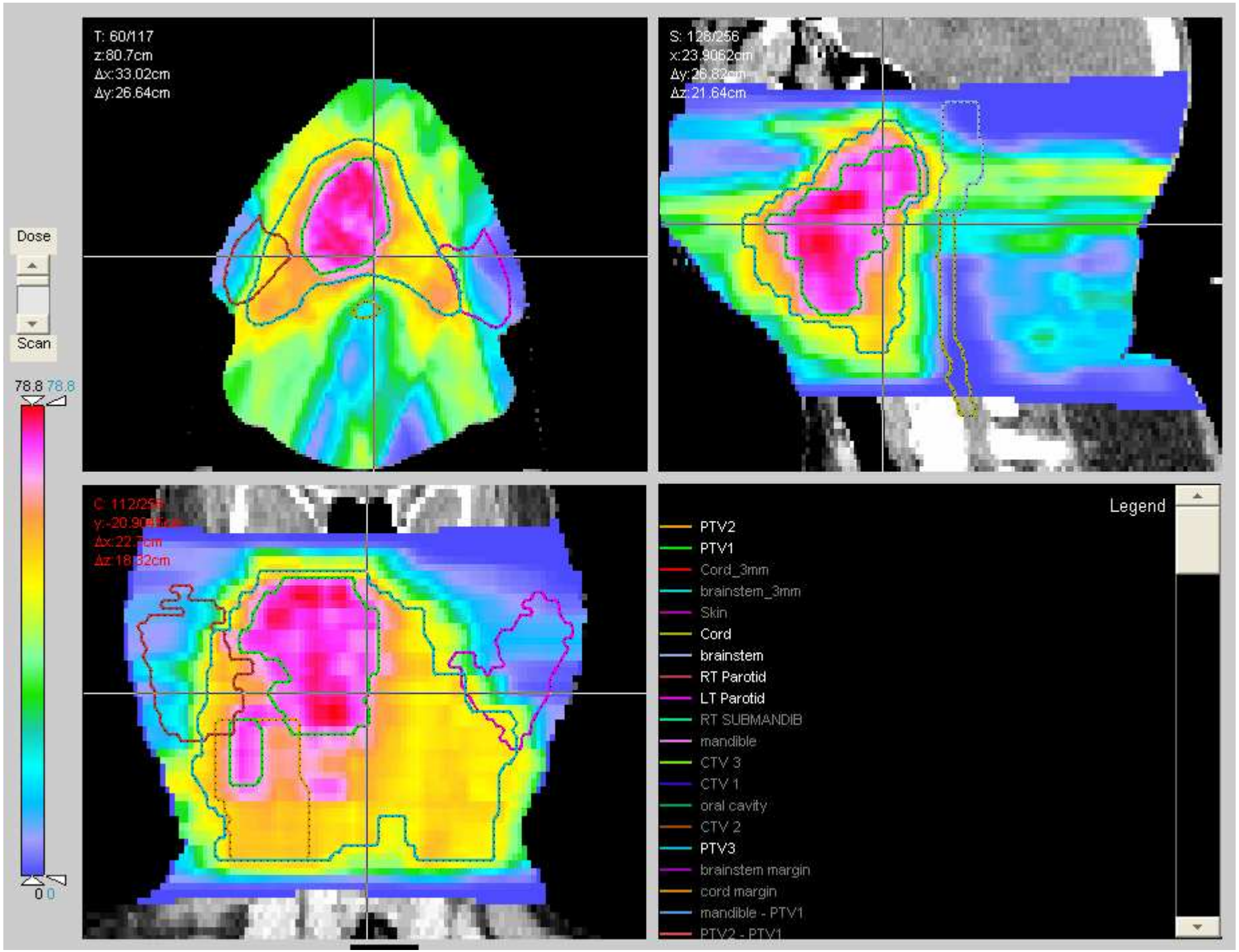


Beam's Eye View of target volume

First delivered field "segment"

Second segment.

(From: Kung and Chen, *Medical Physics* (2000) **27**:1617-1622.)


T: 60/117
z:80.7cm
Δx:33.02cm
Δy:26.64cm
S: 126/256
x:23.9062cm
Δy:26.82cm
Δz:21.64cm
Dose
Scan
78.8 78.8
0 0
Legend
PTV2
PTV1
Cord_3mm
brainstem_3mm
Skin
Cord
brainstem
RT Parotid
LT Parotid
RT SUBMANDIB
mandible
CTV 3
CTV 1
oral cavity
CTV 2
PTV3
brainstem margin
cord margin
mandible - PTV1
PTV2 - PTV1

Basic IMRTP approaches

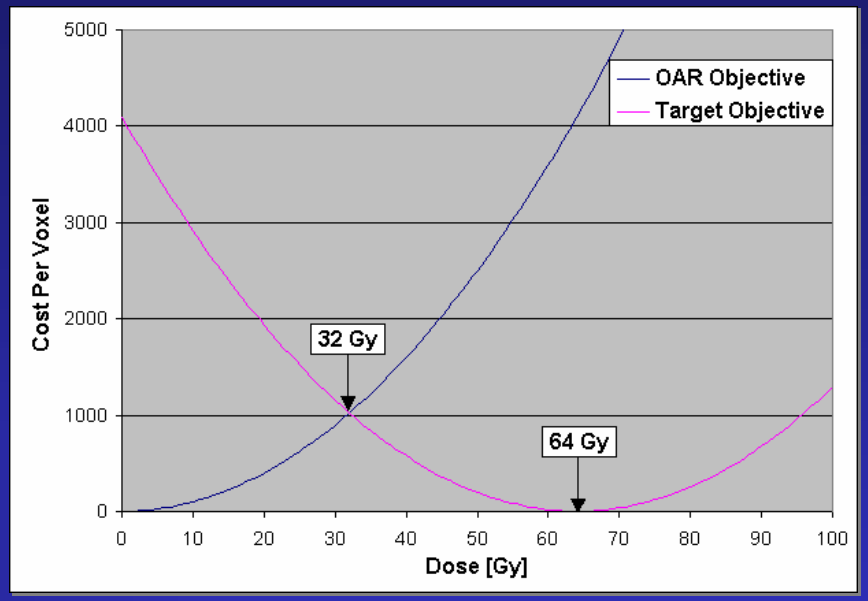
(most common by far)

The ‘objective function’

- Typically, the objective function is a sum of terms, some of which represent normal tissue structures and one or more terms represents the target.
  - This is called a ‘linear sum objective function’
  - The different terms have different multiplying weights (constants) in front, representing relative importance

Linearly weighted objective functions

- Individual terms (or goal functions) are added to comprise the objective function.
- Typically, each anatomy structure of importance has one or more goal terms.
- Goals are evaluated for each voxel contained in a structure.



Graph of cost per voxel vs. dose

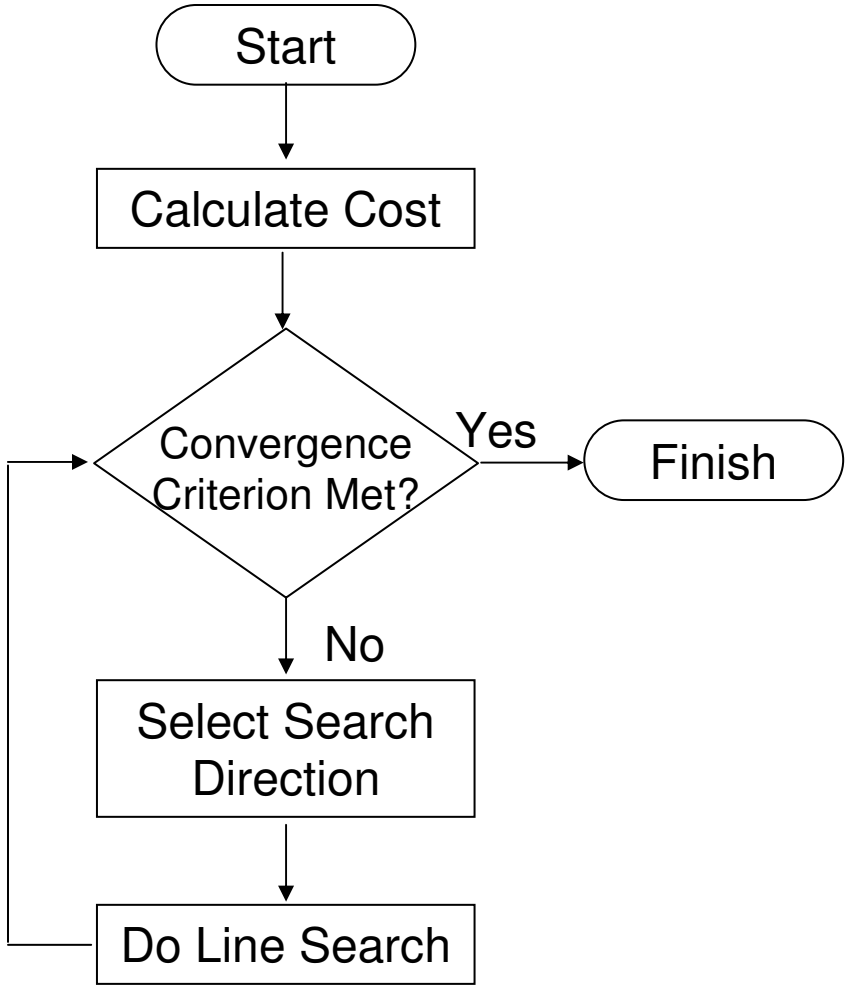
$$F = w_{\text{OAR}} \sum_{i=1}^{n} (D_i - 0)^2 + w_{\text{Target}} \sum_{j=1}^{m} (D_j - 64)^2$$

Objective for an OAR of n voxels

Objective for a target of m voxels

Iterative solution

- Start with a set of initial beamlet weights.
- Search along a series of directions in beamlet weight space.
- Stop when
  - cost is zero
  - cost not improved
  - fixed number of iterations exceeded
- When done, beamlet weights are ‘optimized.’



A ‘state of the art’ IMRT treatment planning system...

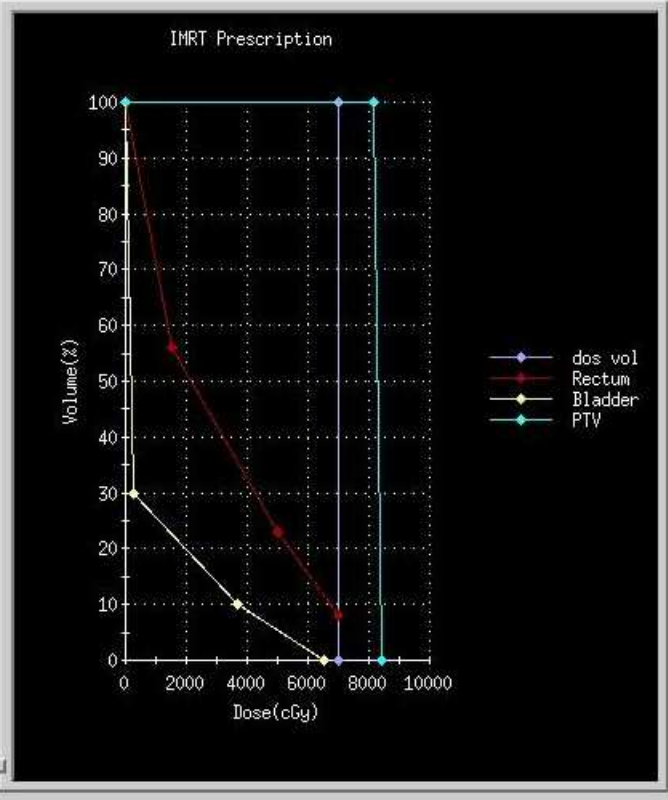
- Accepts constraints
  - Max dose
  - Min dose
  - Dose-volume constraints: no more than x% of an organ can receive y% dose (e.g., “V20 can be no larger than...”).
- Tries to match or exceed goal DVH parameters
  - for target volumes
  - for normal tissues

The CMS XiO Prescription Page

IMRT Prescription

IMRT Prescription

Structure	Type	Rank	Objective	Dose(cGy)	Volume(%)	Weight	Power	Status
LT Femur	OAR	12	Maximum	4600	0	30	2.0	Off
RT Femur	OAR	12	Maximum	4600	0	30	2.0	Off
PREVIEW	OAR	12						
Seminal Vesicle	OAR	12						
CTV1	OAR	12						
dos vol	OAR	12	Maximum	7000	0	30	2.0	On
Penile Bulb	OAR	12						
Skin	OAR	12	Maximum	5000	0	5	2.0	Off
Rectum	OAR	2	Dose Volume	1500	56	75	2.0	On
			Dose Volume	5000	23	75	2.0	On
			Dose Volume	7000	8	75	2.0	On
Bladder	OAR	3	Dose Volume	250	30	30	2.0	On
			Dose Volume	3700	10	30	2.0	On
			Maximum	6500	0	30	2.0	On
Prostate	OAR	7						
PTV	Target	1	Minimum	8150	100	300	2.0	On
			Maximum	8400	0	300	2.0	On



OK CANCEL

The weight paradox: hard-to-control tradeoffs and the lack of clear priorities

- Normal tissue weights should be large enough so the mathematical engine tries to reduce dose to those structures
- Target weights should be much larger than normal tissue weights so that good target coverage is not compromised...but...
- There is no perfect compromise
  - Very high target weights: engine neglects normal tissues
  - Not very high target weights: engine does not preserve target dose characteristics

State-of-the-art workflow: "Are we finished yet?"

Physician: "*Here is what I'd like.*"

Later....Dosimetrist: "*I tried it, and tried to fix it. Here it is.*"

Physician thinks "*Is that the best they can do?*" Says: "*How busy are you? Can you try to improve this part?*"

Dosimetrist: "*Pretty busy. But I'll try if you want me to.*"

Thus, current IMRT systems are highly inefficient, and lead to planning iterations with no clear guidelines for establishing that a ‘clinically superior’ plan cannot be achieved.

IMRT planning challenges

1. Lack of scientific comparisons
2. Incorporating accurate dose calculations
3. Mastering the ‘data-glut’
4. Controlling dose distribution characteristics & tradeoffs
5. Making tradeoffs responsive to outcomes models

Challenge #1: Lack of scientific comparisons

IMRT optimization and operations research: facilitating operations research approaches in IMRT

J Deasy*[1], E Lee[2], M Langer[3], T Bortfeld[4], Y Zhang[5], H Liu[6], R Mohan[6], R Ahuja[7], J Dempsey[7], A Pollack[8], J Rosenman[9], A Eisbruch[10], R Rardin[11], J Purdy[1], K Zakarian[1], J Alaly[1]

(1) Washington Univ, Saint Louis, MO, (2) Georgia Inst Tech and Emory Univ, Atlanta, GA, (3) Indiana Univ, Indianapolis, IN, (4) Massachusetts General Hospital, Boston, MA, (5) Rice University, Houston, TX, (6) UT M.D. Anderson Cancer Center, Houston, TX, (7) University of Florida, Gainesville, FL, (8) Fox Chase Cancer Center, Philadelphia, PA, (9) Univ of North Carolina, Chapel Hill, NC, (10) Univ Michigan, Ann Arbor, MI, (11) Purdue Univ, W. Lafayette, IN,

(Deasy et al., Annals Op Res, In press)

Motivation I

- Many IMRT treatment planning algorithms, but…
- Few comparisons
- Tools for comparison and common data access are missing
- Common datasets are missing
- Few (no?) comparisons of techniques.

Motivation II

- Many optimization experts in the field of Operations Research
- No access to radiotherapy datasets
- Little interaction with the field of radiotherapy

ORART: Operations Research Applications in Radiation Therapy

- NCI/NSF jointly sponsored workshop, Feb. 2002
  - 10 physicians, 10 physicists, 10 optimization/operations research experts
  - Proceedings posted on the web.
- Optimization in Radiation Therapy meeting (Palta, Dempsey, Lee, Jan. 2003.)
- ORART Collaborative Working Group (NCI/NSF funded)
  - "ORART Toolbox" for sharing treatment planning data
  - ORART Test-suite data sets

Approach

- Construct common collaboratory framework: graphical and analytical plan review tools.
- Provide a common approach to generating test beamlet dosimetry data.
- Compile common benchmark suite of anonymized patient plans and IMRT prescription challenges.
- All publicly available and open-source.

Components

- CERR for plan review and analysis (common data format)
- Extensions to CERR to produce common beamlet dosimetry (ORART Toolbox)
- Treatment planning data exported in RTOG or DICOM format, converted to CERR format

CERR: A Computational Environment for Radiotherapy Research

- Matlab-based
  - Cross-platform
- RTOG format-based
  - Self-describing format
- Open-source
- Freely available via webpage: http://radium.wustl.edu/cerr

Successful imports from

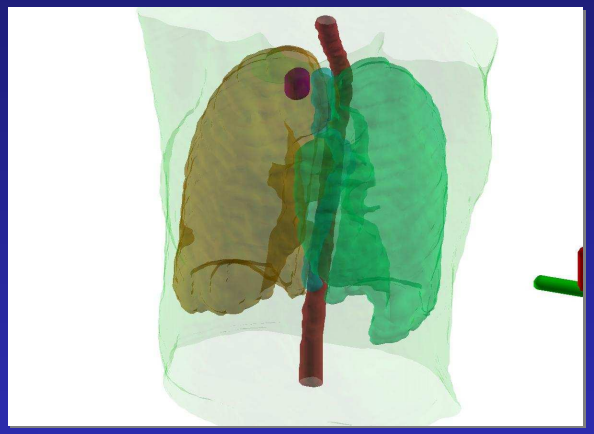
- CMS Focus (RTOG)
- Pinnacle (RTOG)
- TMS Helax (RTOG)
- Helios (DICOM)
- …Many other systems

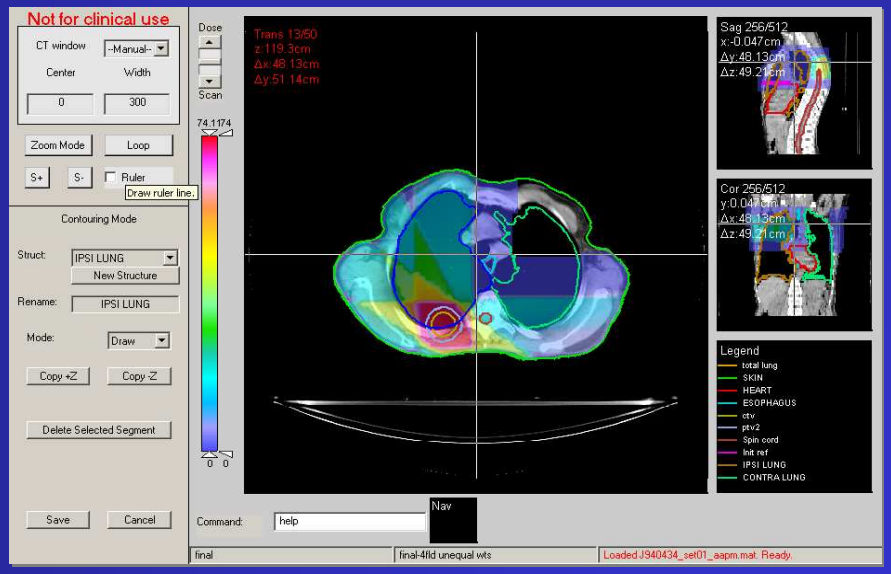
CERR: current major components

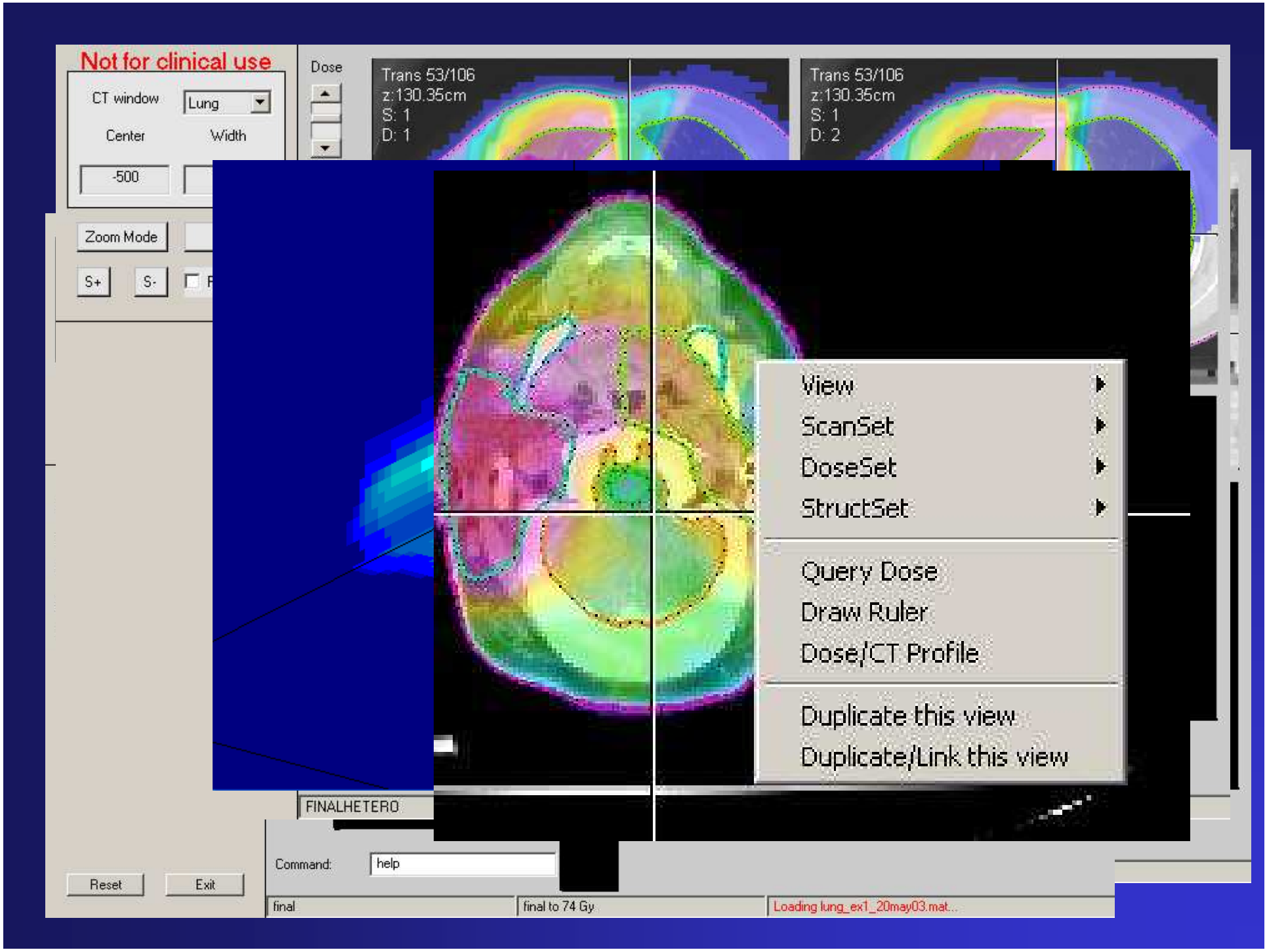
- Version 3 (in beta test)
- Can handle many CT sets
- Can import PET/MRI
- Transverse, coronal, sagittal slice viewers
- DVH calculation and display
- Contouring/re-contouring tools
- Plan metric comparison tools
- Dose comparison tools
- IMRT beamlet calculations

Computational Environment for Radiotherapy Research (CERR)

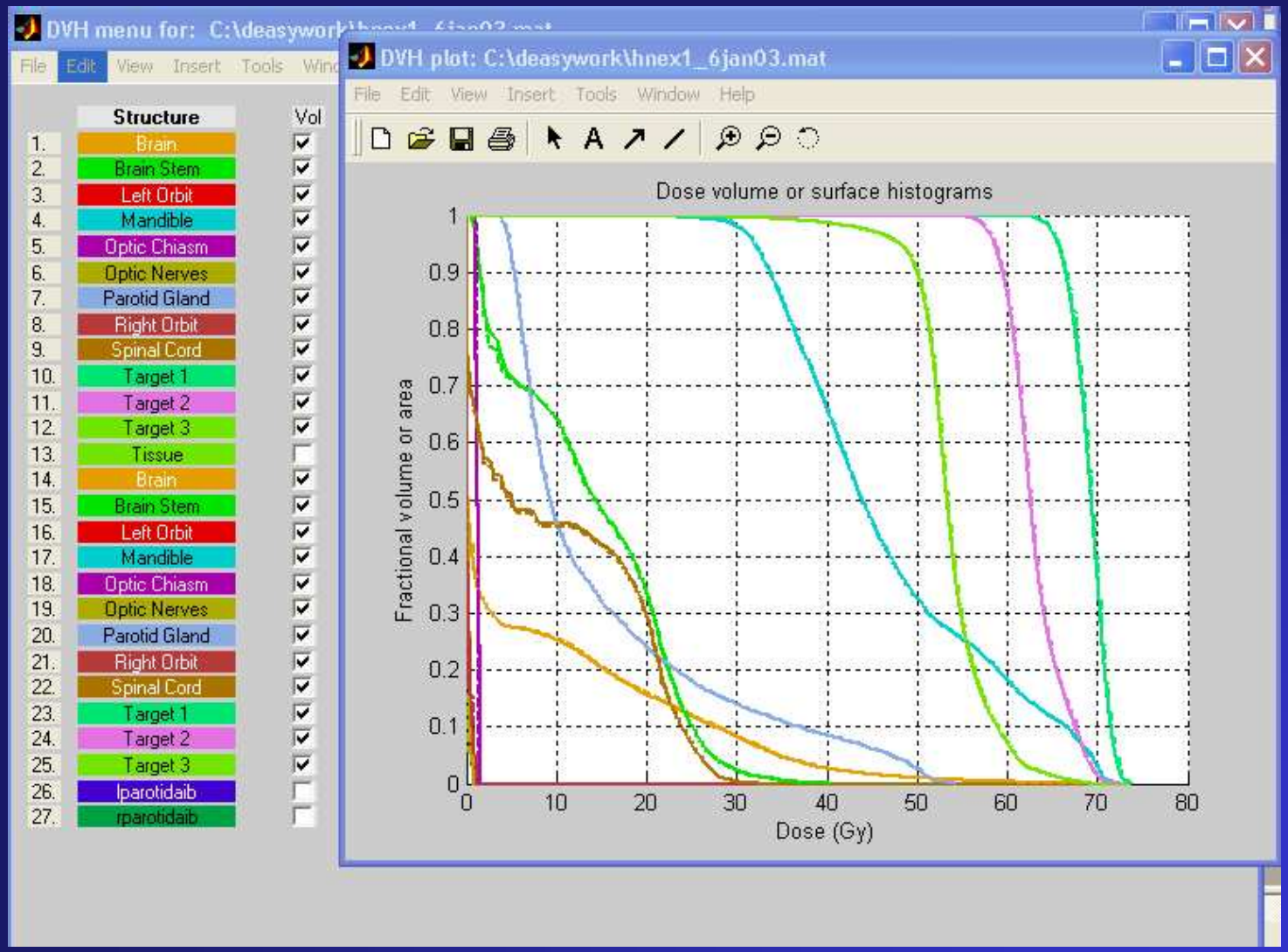
- 3-D plans exported from planning systems, archived, and converted to CERR format
- Matlab-based
- Freely available from http://radium.wustl.edu/cerr






Not for clinical use
CT window
Lung
Center
Width
-500
Zoom Mode
S+
S-
Dose
Trans 53/106
z:130.35cm
S: 1
D: 1
Trans 53/106
z:130.35cm
S: 1
D: 2
View
ScanSet
DoseSet
StructSet
Query Dose
Draw Ruler
Dose/CT Profile
Duplicate this view
Duplicate/Link this view
FINALHETERO
Command:
help
Reset
Exit
final
final to 74 Gy
Loading lung_ex1_20may03.mat...

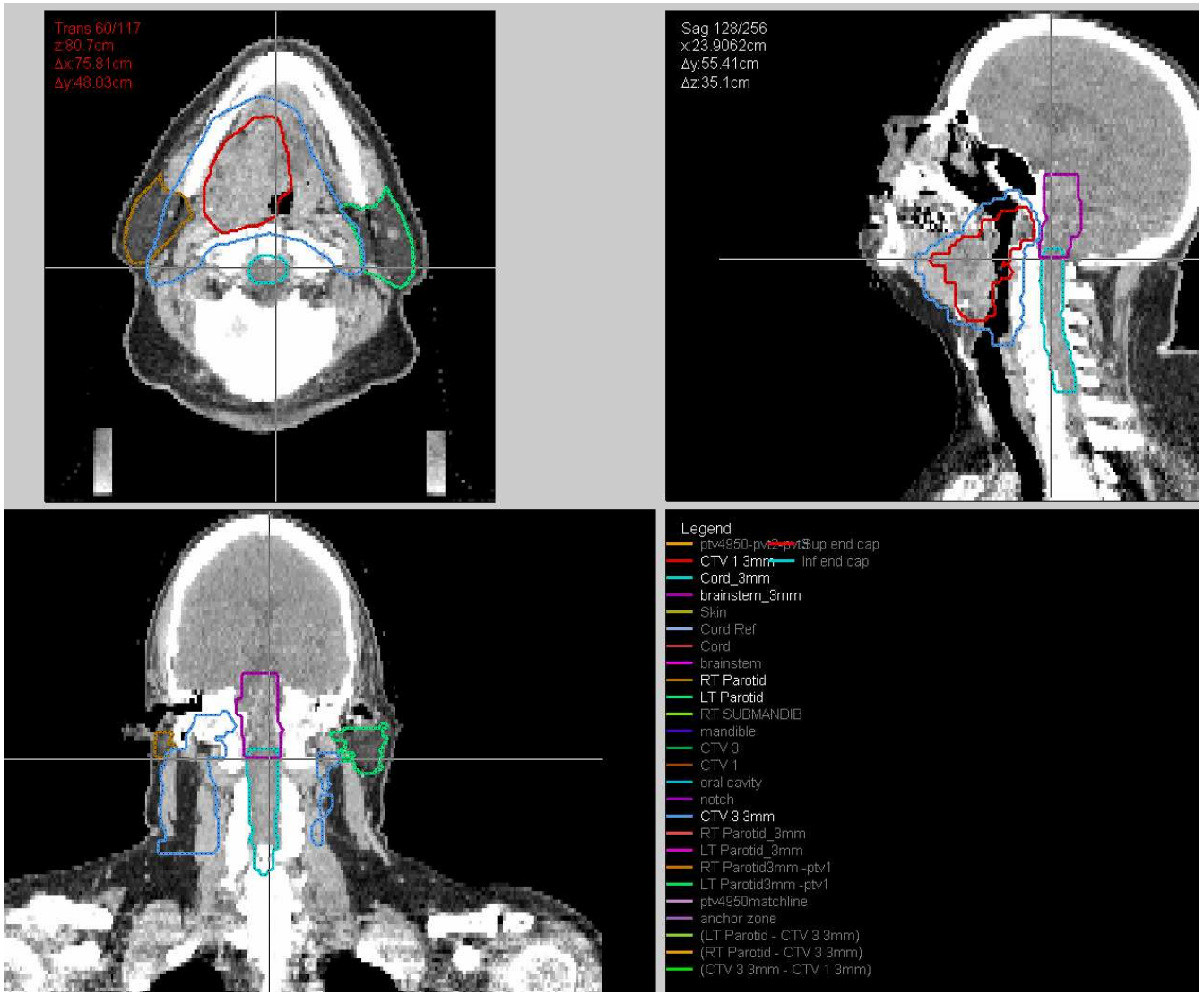
Recomputed DVHs generally the same to within RMSE of 1%



CERR

- Has been downloaded nearly 1,000 times in the last year by users from 37 different countries
- Is used by clinical trial QA physicists in Sweden, UK, Japan, US, Netherlands.
- Is used by optimization researchers.
- E.g., PMH project by Tim Craig et al. to compute probabilistically desirable target volumes.

This figures shows the three target volumes: ‘CTV 1 3mm’, ‘CTV 2 3mm’, and ‘CTV 3 3mm’.

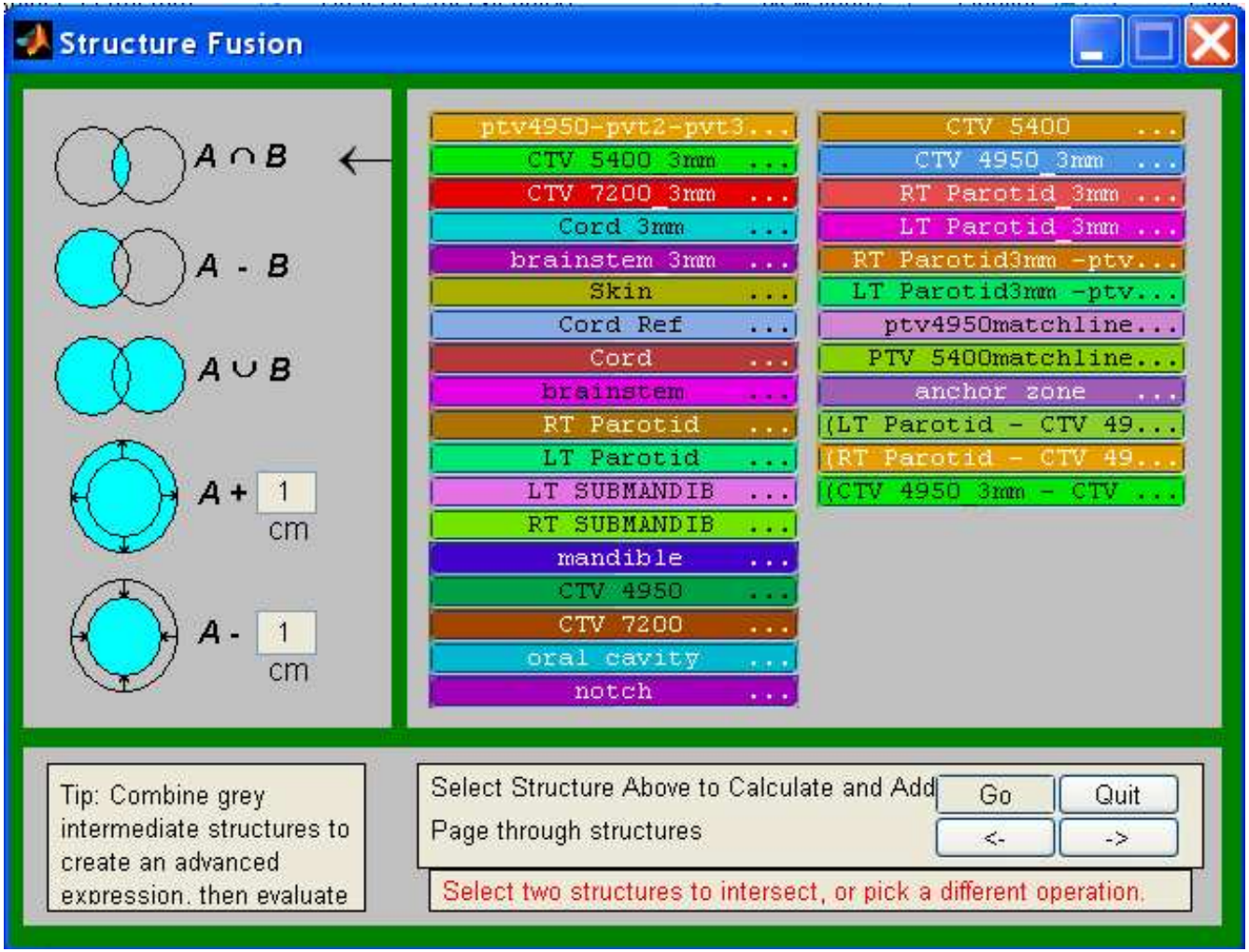


Prescription (Eisbruch)

- The prescription for this case was adapted from detailed suggestions by Avi Eisbruch:
- 72 Gy to the CTV 1 3mm structure.
- 64 Gy to the CTV 2 3mm structure,
- 60 Gy to the CTV 3 3mm structure.
- The mean dose to the parotid glands should be held as low as possible,
- but not at the expense of an adequate target dose distribution. Preferably, one parotid gland at least should be held below 26 Gy.
- The mean dose to the oral cavity should be held as low as possible, but not at the expense of an adequate target dose distribution.

- The mandible should receive no more than 70 Gy max dose.
- The max to the cord should be 45 Gy (hard constraint),
- The max to the cord_3mm should be 50 Gy (hard constraint),
- The max to the brainstem (brainstem) should be 54 Gy (hard constraint).
- The max to the brainstem expansion (brainstem_3mm) should be 58 Gy (hard constraint).
- An adequate target dose distribution will have:
  - Min 93% of prescribed dose
  - Max <115%
- Of course, it is impossible not to have heterogeneities near the integrated boost volume.

You can easily derive new structures using the structure fusion tool, under the structures menu (‘Derive new structure’).



IMRT beamlet generation: the ORART toolbox

- Software routines giving Matlab/CERR users access to beamlet dosimetry.
- Based on written CWG specification.
- Integrated with CERR.
- Generation of beamlet data
- Dosimetry data access within Matlab
- Multiple output formats (binary and ASCII-based).

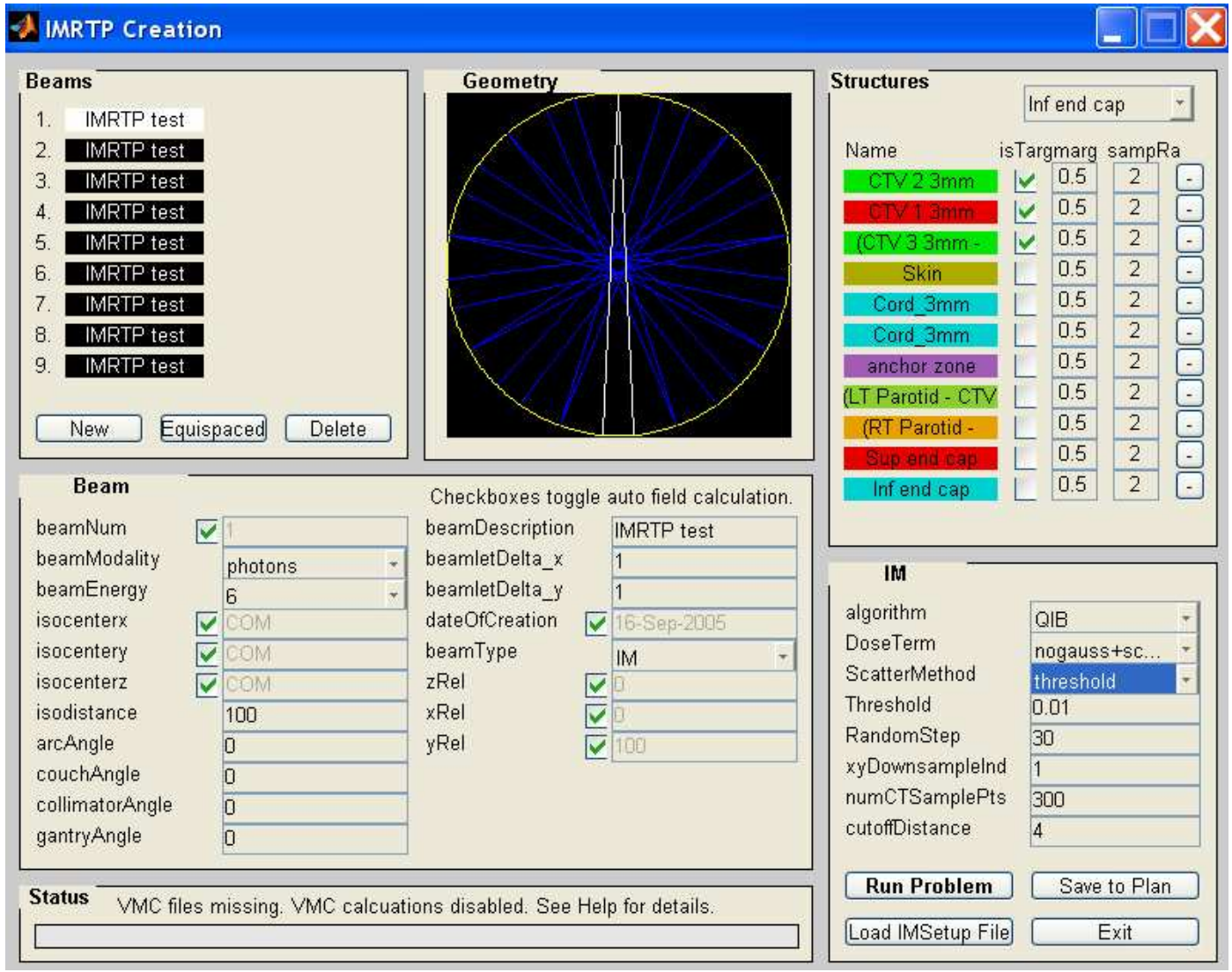
Facilitating operations research activity in radiation therapy

- Operations researchers typically start with a matrix description of the problem.
- In our case:

$$d_i = \sum_{j=1}^{\text{Num beamlets}} A_{i,j} w_j .$$

- Much, much faster than iteratively recomputing dose

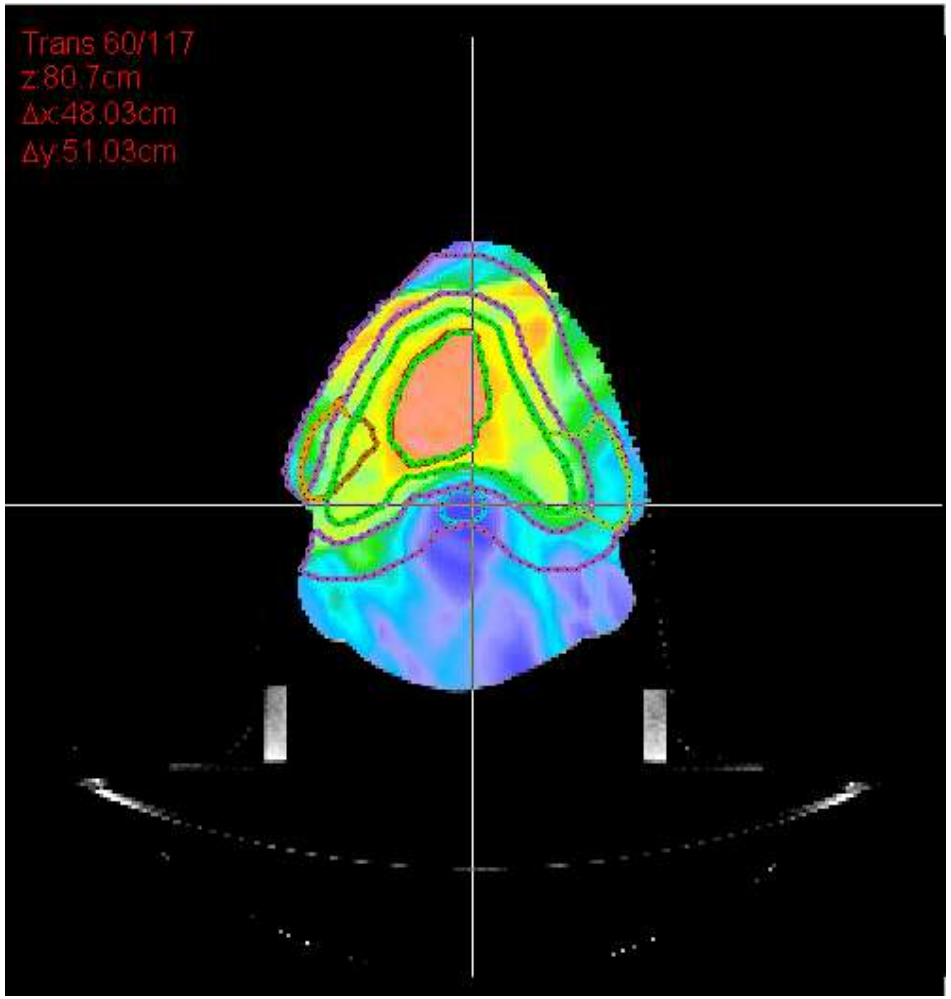
‘influence matrix’


IMRTP Creation
Beams
1. IMRTP test
2. IMRTP test
3. IMRTP test
4. IMRTP test
5. IMRTP test
6. IMRTP test
7. IMRTP test
8. IMRTP test
9. IMRTP test
New
Equispaced
Delete
Geometry
Structures
Inf end cap
Name
isTarg
marg
sampRa
CTV 2 3mm
CTV 1 3mm
(CTV 3 3mm -
Skin
Cord_3mm
Cord_3mm
anchor zone
(LT Parotid - CTV
(RT Parotid -
Sup end cap
Inf end cap
Beam
Checkboxes toggle auto field calculation.
beamNum
beamModality
photons
beamEnergy
isocenterx
isocentery
isocenterz
isodistance
arcAngle
couchAngle
collimatorAngle
gantryAngle
beamDescription
IMRTP test
beamletDelta_x
beamletDelta_y
dateOfCreation
16-Sep-2005
beamType
IM
zRel
xRel
yRel
IM
algorithm
QIB
DoseTerm
nogauss+sc...
ScatterMethod
threshold
Threshold
RandomStep
xyDownsampleInd
numCTSamplePts
cutoffDistance
Run Problem
Save to Plan
Load IMSetup File
Exit
Status
VMC files missing. VMC calcuations disabled. See Help for details.

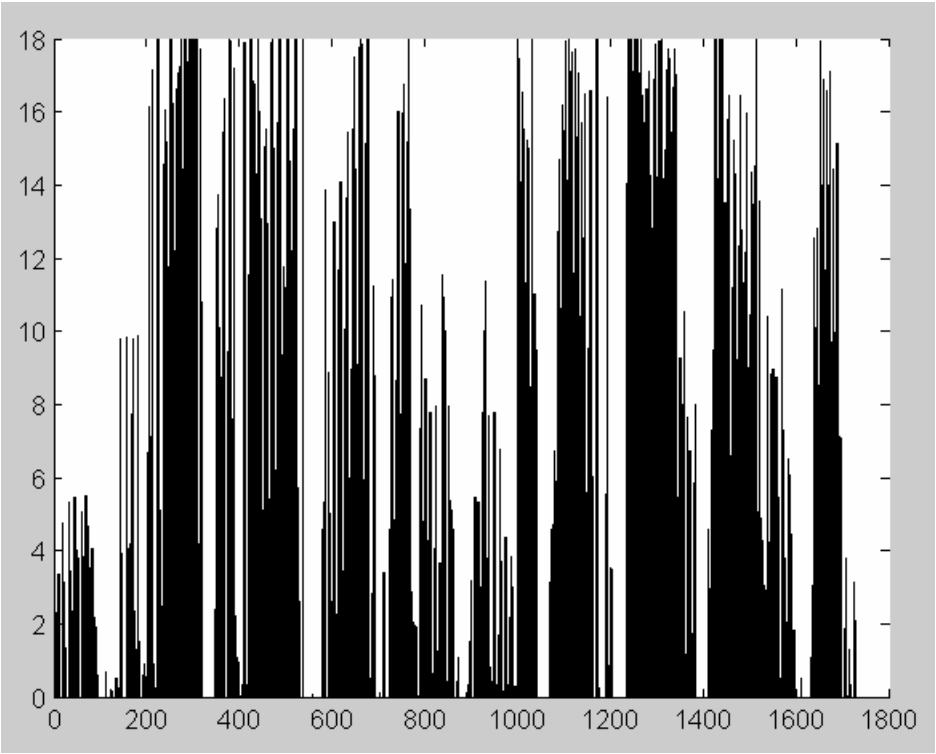
Access to beamlet data in Matlab

```
>> doseNum = 1; structNum = 11; beamletNum = 1;
>> planC{12}{doseNum}.IMDosimetry.beamlets(structNum,beamletNum)
ans =
      structureName: 'Target 1'
             format: 'uint8'
          influence: [1907x1 uint8]
         fullLength: 8054
             indexV: [1907x1 uint32]
    maxInfluenceVal: 0.0396
         sampleRate: 2
            beamNum: 1
```

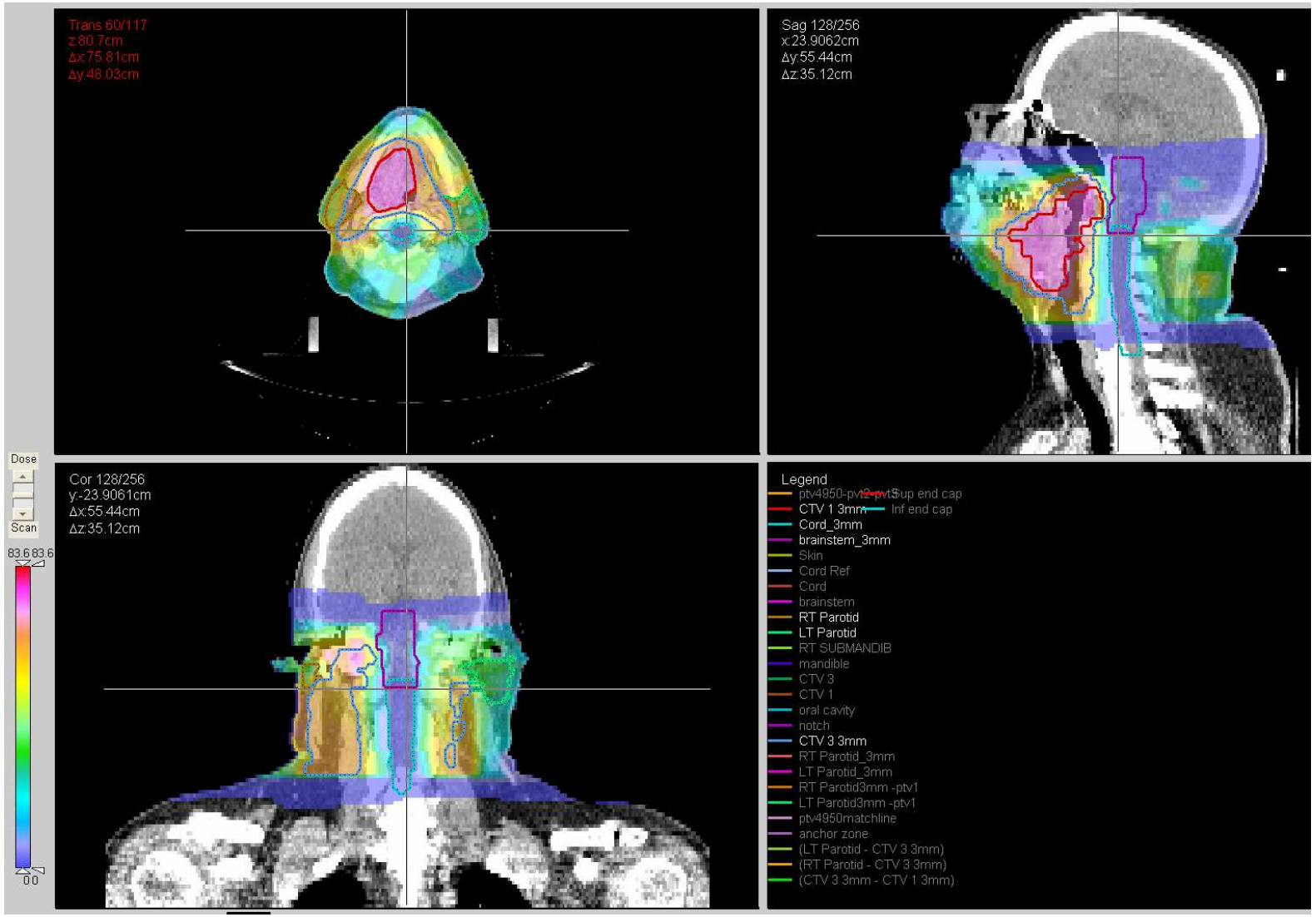
The green target is the CTV 3 3mm. Other structures created included left and right parotids minus the CTV 3 3mm, as I gave the CTV priority.



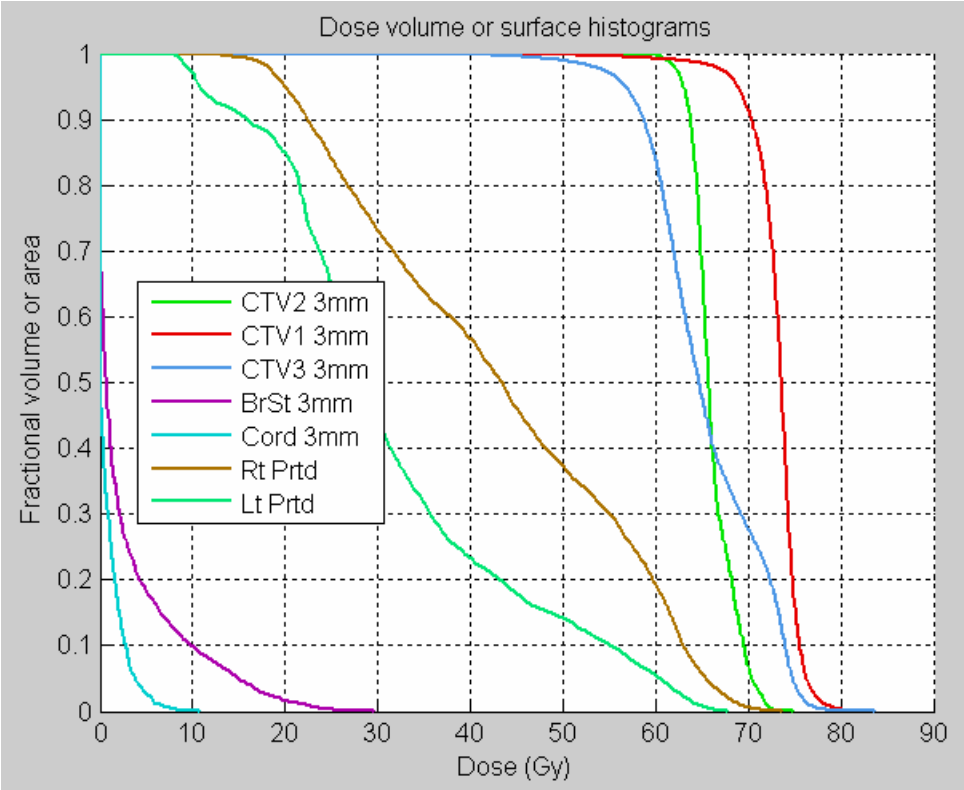
Simple quadratic programming example of beam weights



Obviously there are some relatively hot regions outside the ‘CTV 3 3mm’ (the anchor zone weight perhaps could be increased). The max dose is 83.6 Gy.



Here are the DVHs. Not that great, but it's something to beat up on.
In particular the most spared parotid still gets about 28 Gy mean dose.



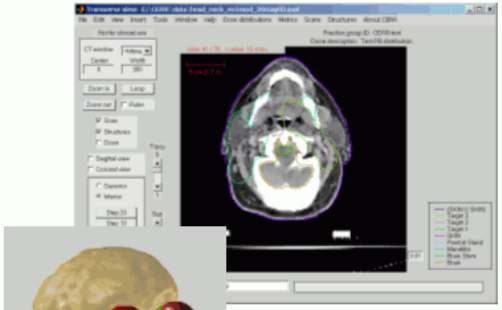

```
----------------------
Structure is:  CTV 2 3mm
Mean dose is:  66.2172
Total volume is:  67.2685 cubic cm.
Max dose is:  74.95
Min dose is:  56.75
----------------------
----------------------
Structure is:  CTV 1 3mm
Mean dose is:  73.2006
Total volume is:  177.7989 cubic cm.
Max dose is:  83.65
Min dose is:  40.55
----------------------
----------------------
Structure is:  CTV 3 3mm
Mean dose is:  65.5884
Total volume is:  717.1912 cubic cm.
Max dose is:  83.65
Min dose is:  26.95
----------------------
```

```
----------------------
Structure is:  brainstem_3mm
Mean dose is:  2.9353
Total volume is:  40.5941 cubic cm.
Max dose is:  29.55
Min dose is:  0.05
----------------------
----------------------
Structure is:  Cord_3mm
Mean dose is:  0.89611
Total volume is:  26.5168 cubic cm.
Max dose is:  10.85
Min dose is:  0.05
----------------------
```

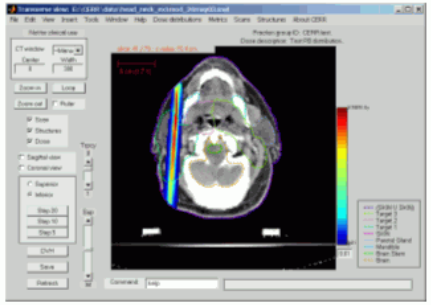
The ORART benchmark 'paradigm'

1

Treatment planning example
from the ORART test set (CERR)



2 Beamlet dosimetry
(ORART Toolbox)



3

Optimization algorithm

(third-party)

Pooled results from other
investigators/planning systems

Results

4 Comparisons and conclusions

Current weaknesses

- Lack of built-in leaf sequencing.
- Lack of ability to re-export CT and contour data into commercial treatment planning system. (But we almost have this capability now.)

The goal: "scientific" comparisons of IMRT optimization research results

That is, fair comparisons of IMRT treatment planning results, from multiple investigators, using standard realistic patient datasets

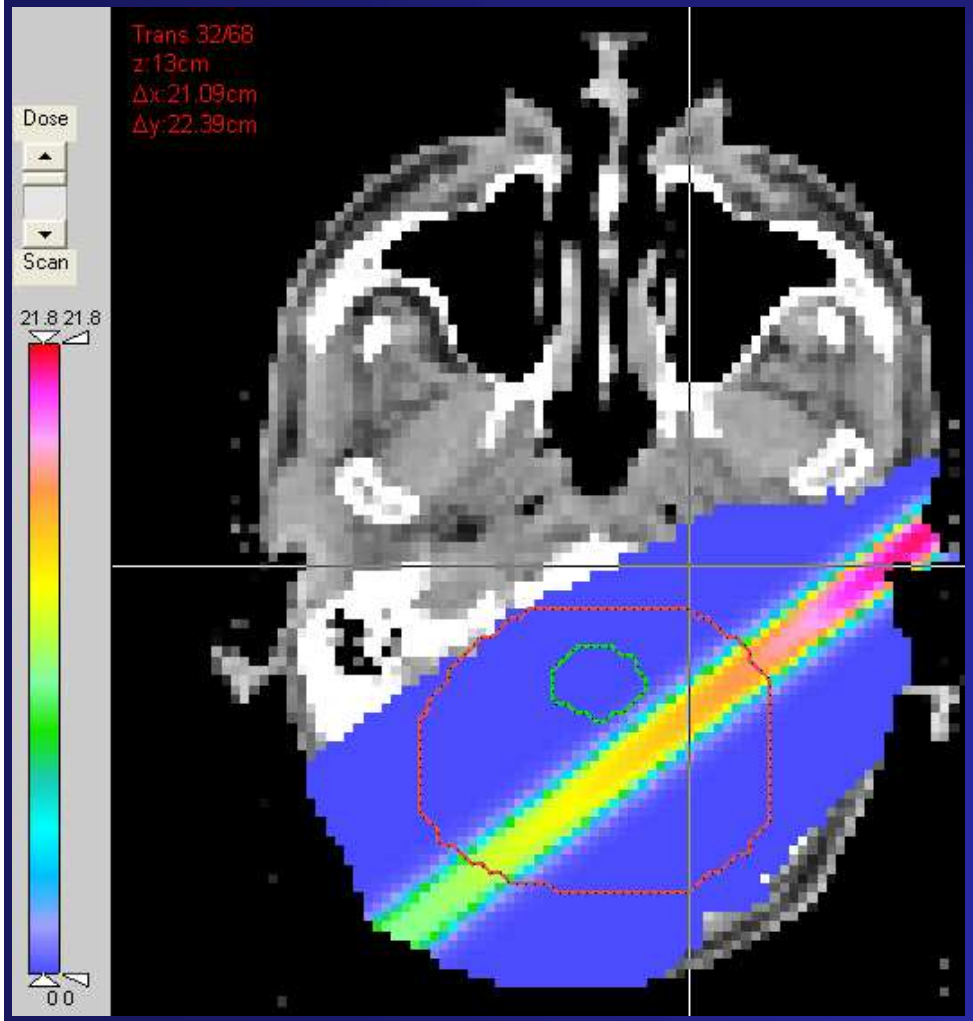
Challenge #2: Incorporating accurate dose calculations

The problem of scatter tails

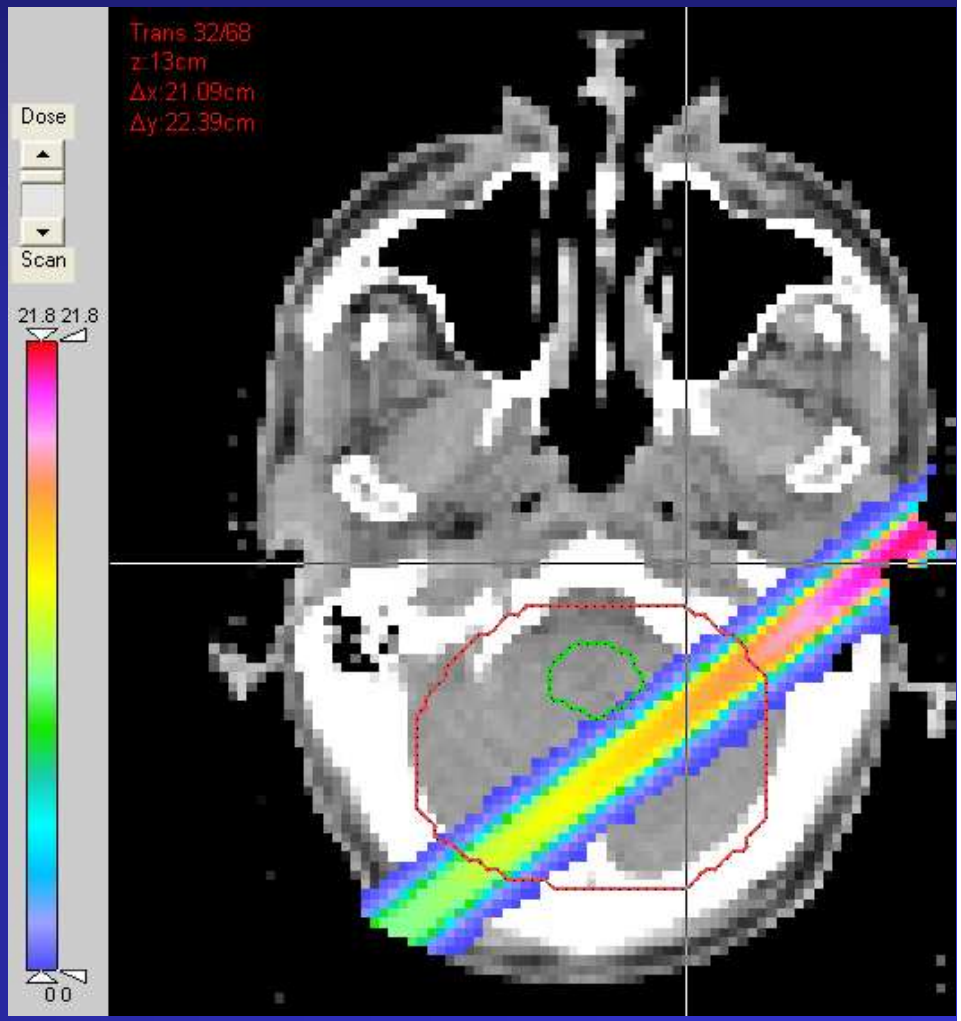
- The scatter tails of beamlets take up most of the non-zero volume of the influence matrices
- But they contribute little to the ability to shape dose
- Yet it is important to factor in the influence of scatter…
- So how do we do it?

Beamlets are usually simplified for the optimization phase

Beamlet with 4 cm tail



Beamlet with 1 cm tail



The Iterative scatter correction method

- Estimate the scatter dose using full dose (primary plus scatter) beamlet matrices and best current estimate of beam weights.
- Adjust prescription dose, on a voxel by voxel basis, to reflect the expected scatter contribution.
- Solve for optimal beam weights using primary-only beamlet matrices.
- Recompute full dose using stored beamlets.
- If full dose is close enough to prescription, terminate; otherwise go to step 1.
- Typically, two iterations are sufficient.

(Zakarian et al., ASTRO 2004; also MSKCC)

Challenge #3: Mastering the ‘data-glut’

Approach: use adaptive gridding of dose points (El Naqa, et al., unpublished)

Key element is shortest distance to critical structures

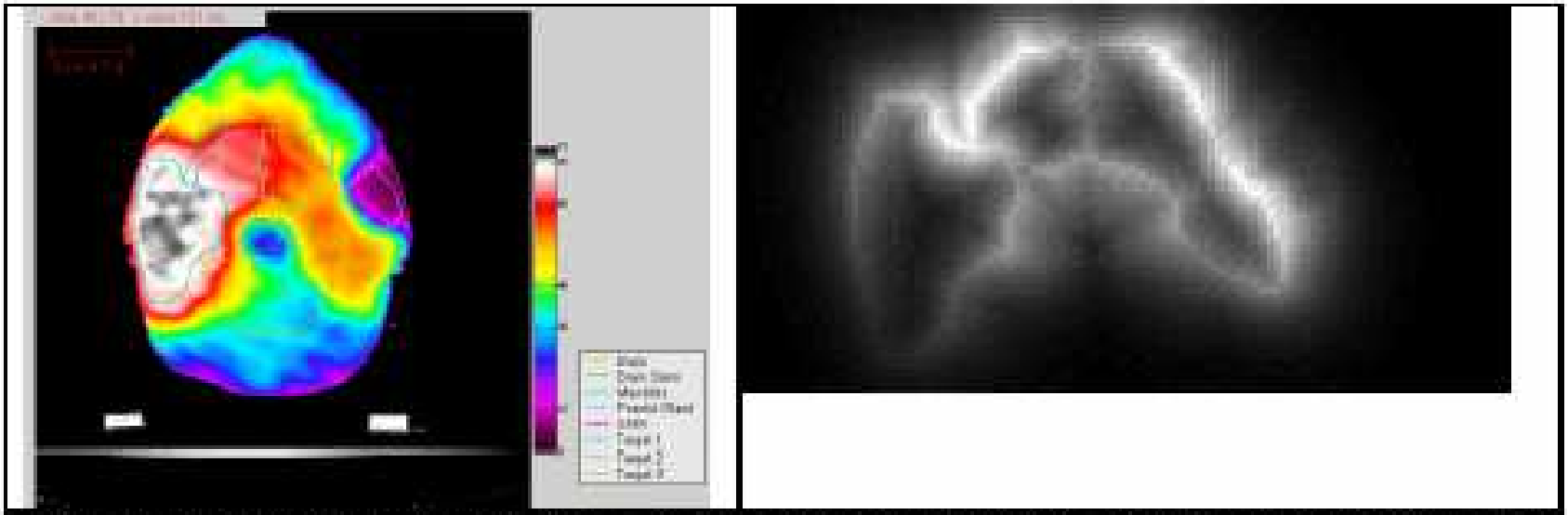
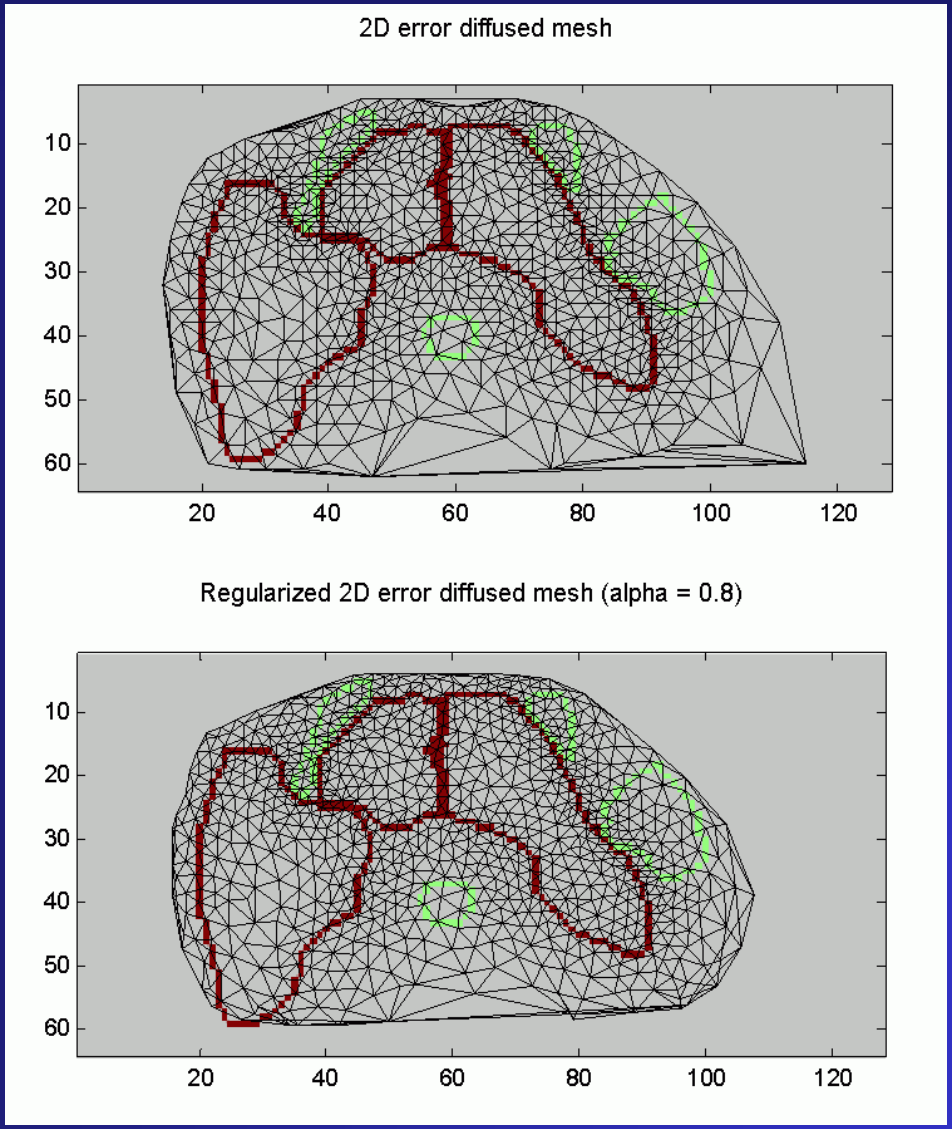


Figure 1: Left: Treatment plan slice, showing target volumes and critical structure (brain stem) position. Right: the distance transform (lesser of distance to nearest target and critical structure).

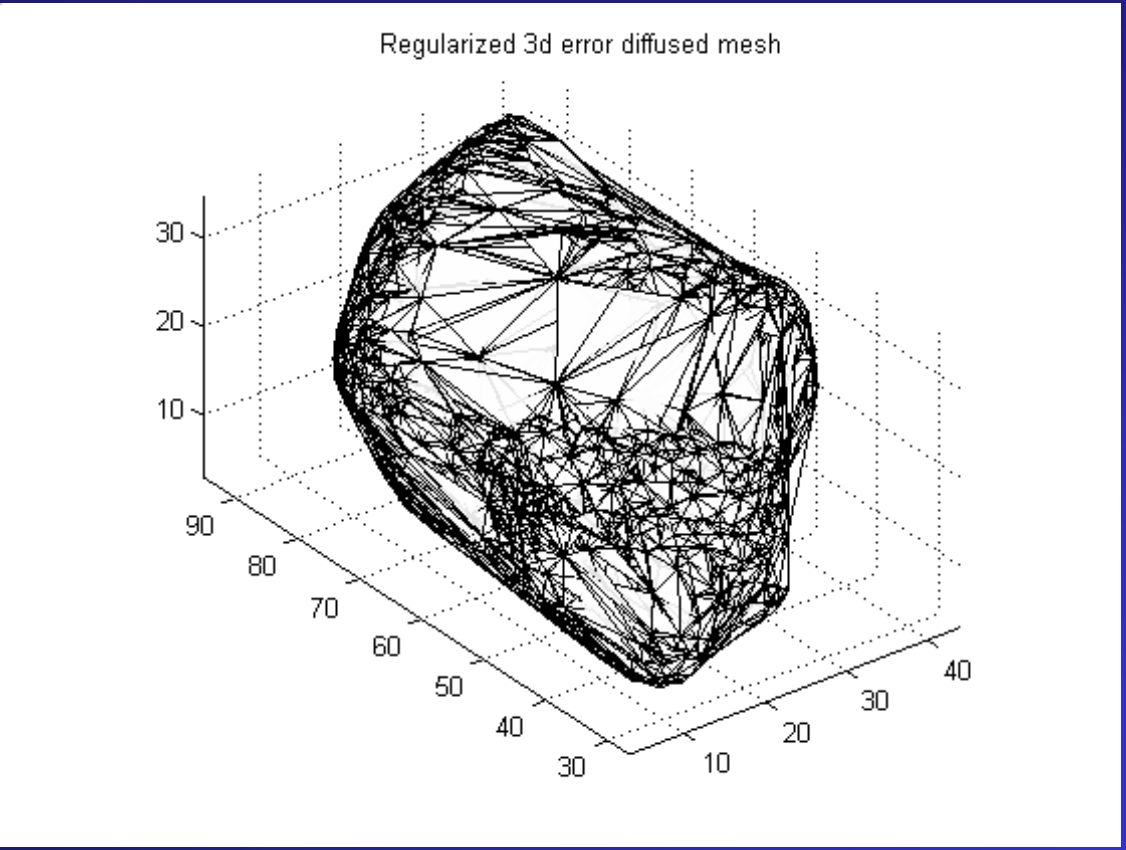
Adaptive grid generation

- STEP 1: The contours are extracted. Gridding is more aggressive near the more significant structures. A weighted distance transform is used to generate the feature map
- STEP 2: Generate mesh. Floyd-Steinberg error diffusion algorithm, modified to include dithering.
- STEP 3: Delaunay triangulation is used to generate the mesh structure.
- STEP 4: refinement by a regularized Laplacian (second derivative) smoothing,

2D error-diffused method



Extension to 3-D



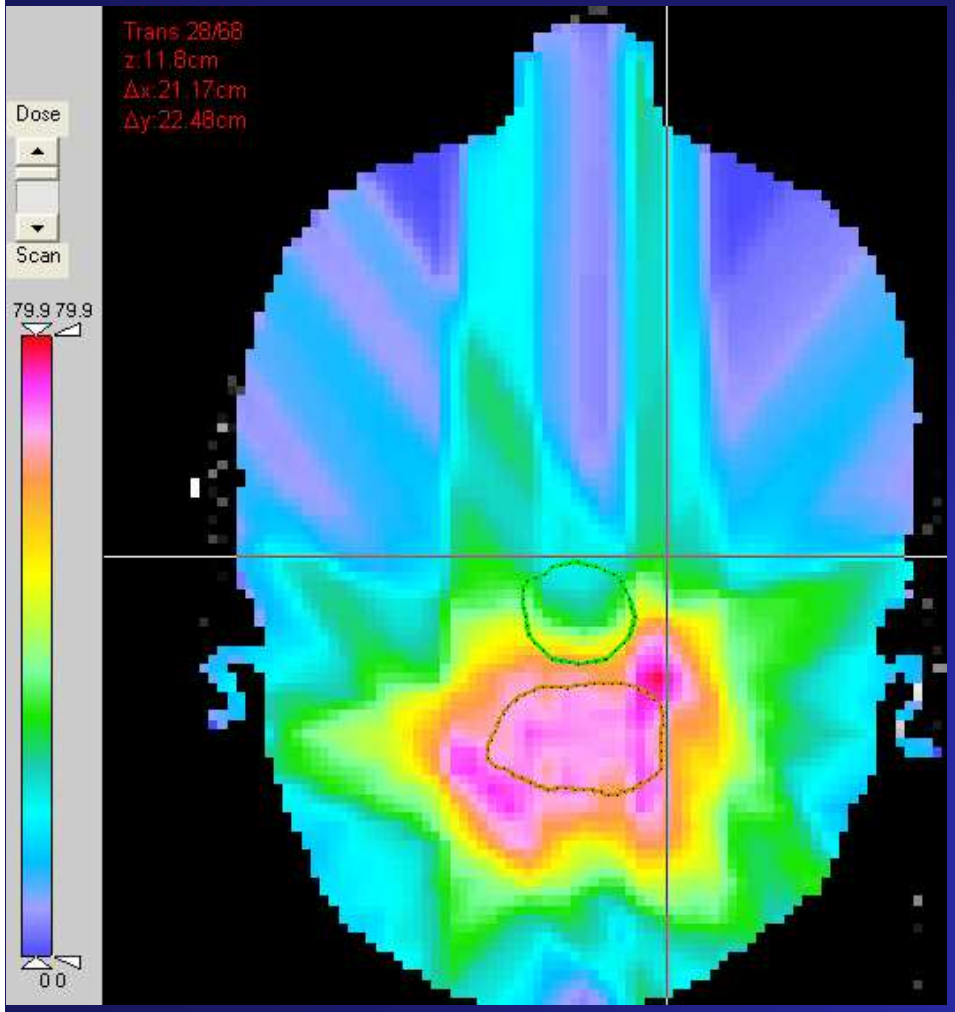
Other approaches

- Use coarse gridding on a regular grid for some structures
- Adaptive coalescing of voxels in old NOMOS planning system
- Aggressively cutoff beamlet low fluence contributions
- Randomly keep only some beamlet elements (DKFZ proposal)

Challenge #4: Controlling dose distribution characteristics & tradeoffs

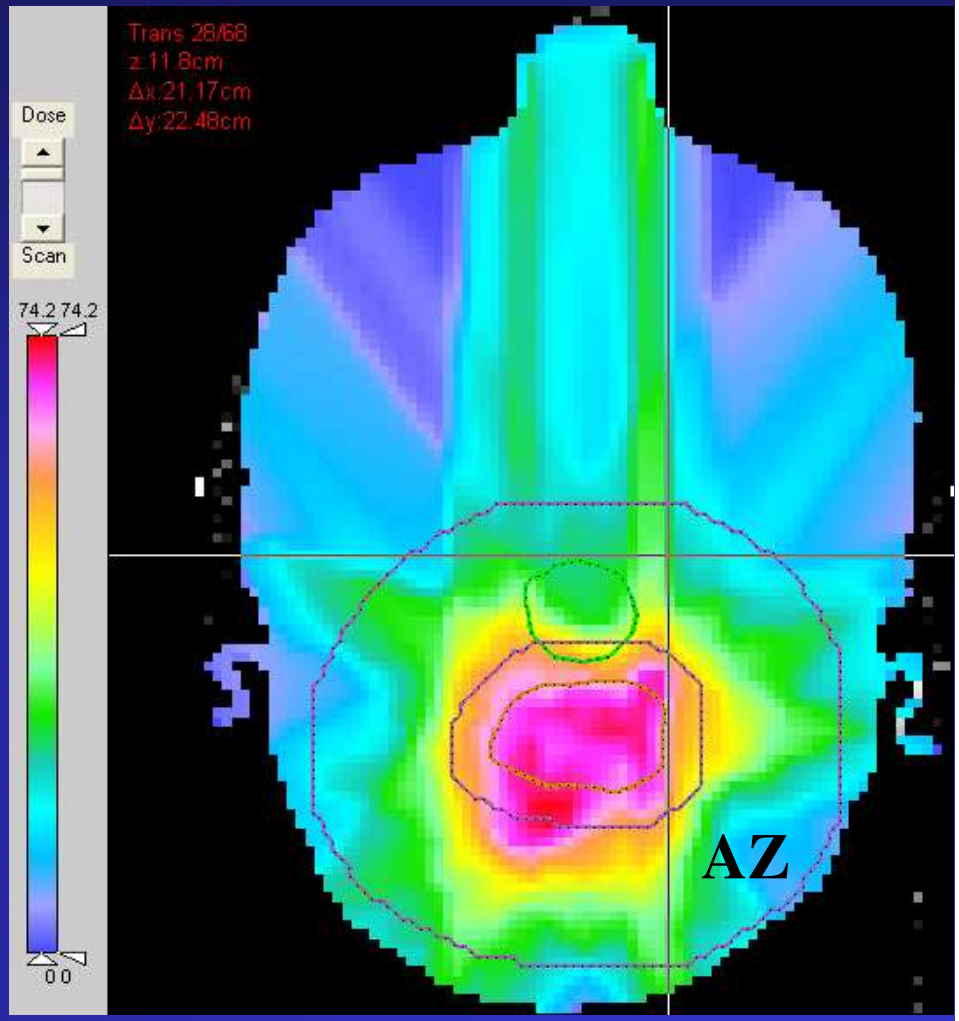
Controlling dose falloff: the Anchor zone method

No anchor zone



Hot spot outside target goes up to 80 Gy.

Anchor zone



Hot spot outside target 74 Gy

The weight paradox: hard-to-control tradeoffs and the lack of clear priorities

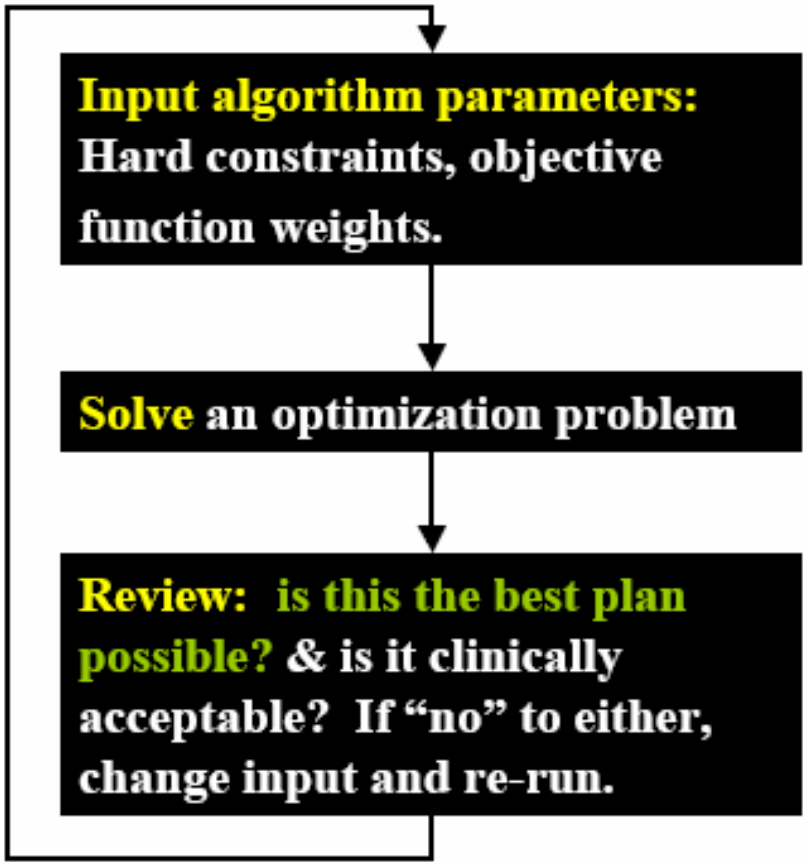
- Normal tissue weights should be large enough so the mathematical engine tries to reduce dose to those structures
- Target weights should be much larger than normal tissue weights so that good target coverage is not compromised...but...
- There is no perfect compromise
  - Very high target weights: engine neglects normal tissues
  - Not very high target weights: engine does not preserve target dose characteristics

Interim conclusion

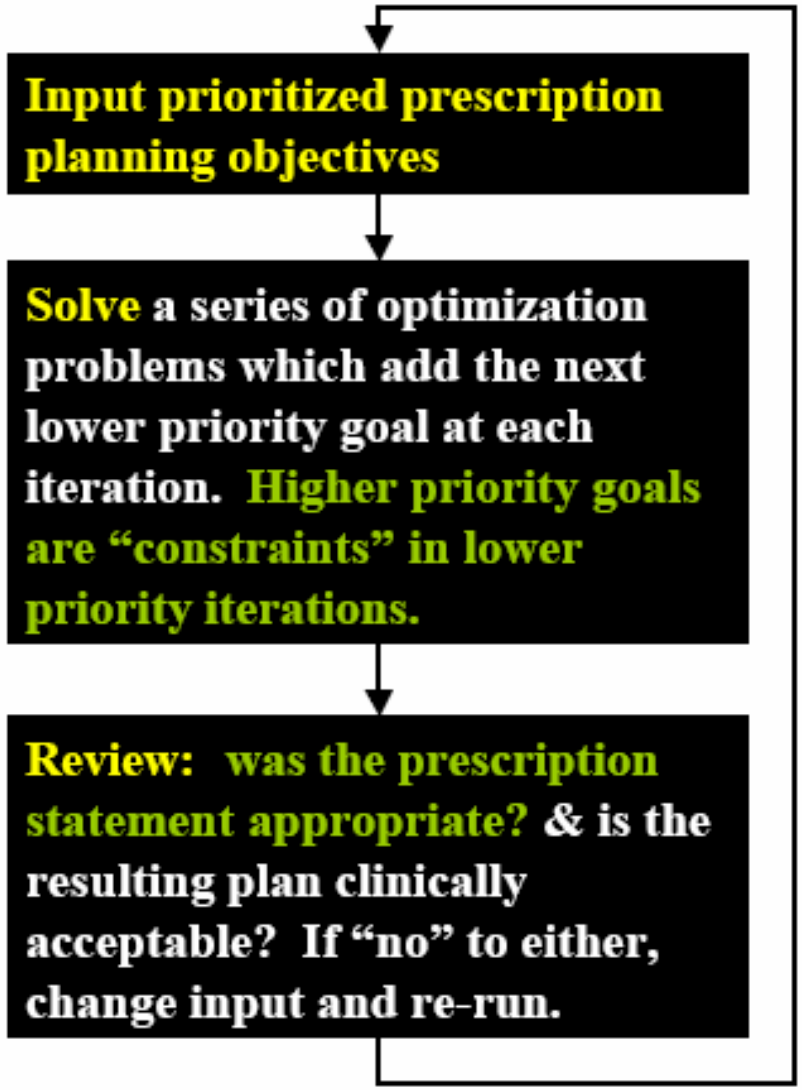
- The efficient control and use of linearly weighted objective functions is problematic
- We need a new paradigm with more control over tradeoffs…

Approach: prioritize the prescription goals ('Prioritized prescription goal planning')

Current paradigm



Prioritized prescription optimization



	objectives	constraints
step 1 target coverage, cardinal OARs	minimize $F_1=\Sigma_{\text{all voxels j}}\,(D_j - D_{pres})^2$ and maximize D_{min} for all targets	• D_{max} for spinal cord, brainstem, cord+3mm, brainstem+3mm, mandible, and hotspot zone
step 2 additional OARs	minimize D_{mean} for parotid glands and oral cavity	as in step 1 and • max value for F_1 for all targets • min value for D_{min} for all targets • max value for D_{max} for all targets as achieved in step 1
step 3 dose falloff	minimize D_{mean} in anchor zone, cord, brainstem and mandible	as in step 2 and • max value for D_{mean} for parotid glands and oral cavity as achieved in step 2

anchor zone = (Union of targets + 5cm) – (Union of targets + 0.5cm)

hotspot zone = skin – (Union of targets + 0.5cm)

prescription

- PTV1: 72 Gy
- PTV2: 54 Gy
- PTV3: 49.5 Gy

Maximum doses:

spinal cord	45 Gy
spinal cord + 3mm	50 Gy
brainstem	54 Gy
brainstem + 3mm	58 Gy
mandible – PTV1	70 Gy
hotspot zone	50 Gy

slip factor

no slip: then step 2 and step 3 yield the same solution as in step 1

ð introduce slipfactor 1+s (here: s=0.2) for the dose variance in the targets
(i.e. ~10% in standard deviation)

for all targets (i=1..3):

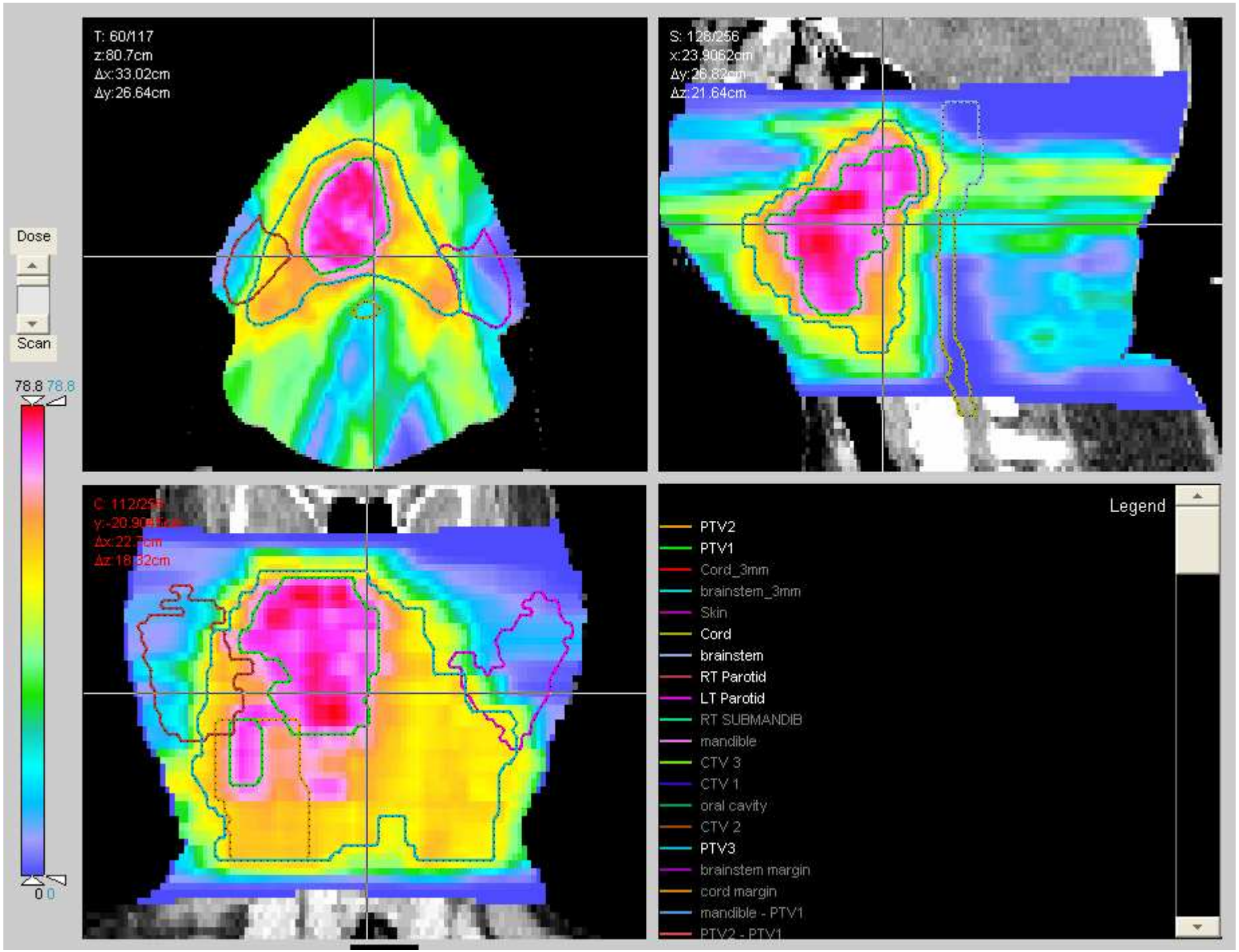
objective function: $F_i=\Sigma_{\text{all voxels } j} (D_j - D_{pres})^2 / \#\text{voxels}$

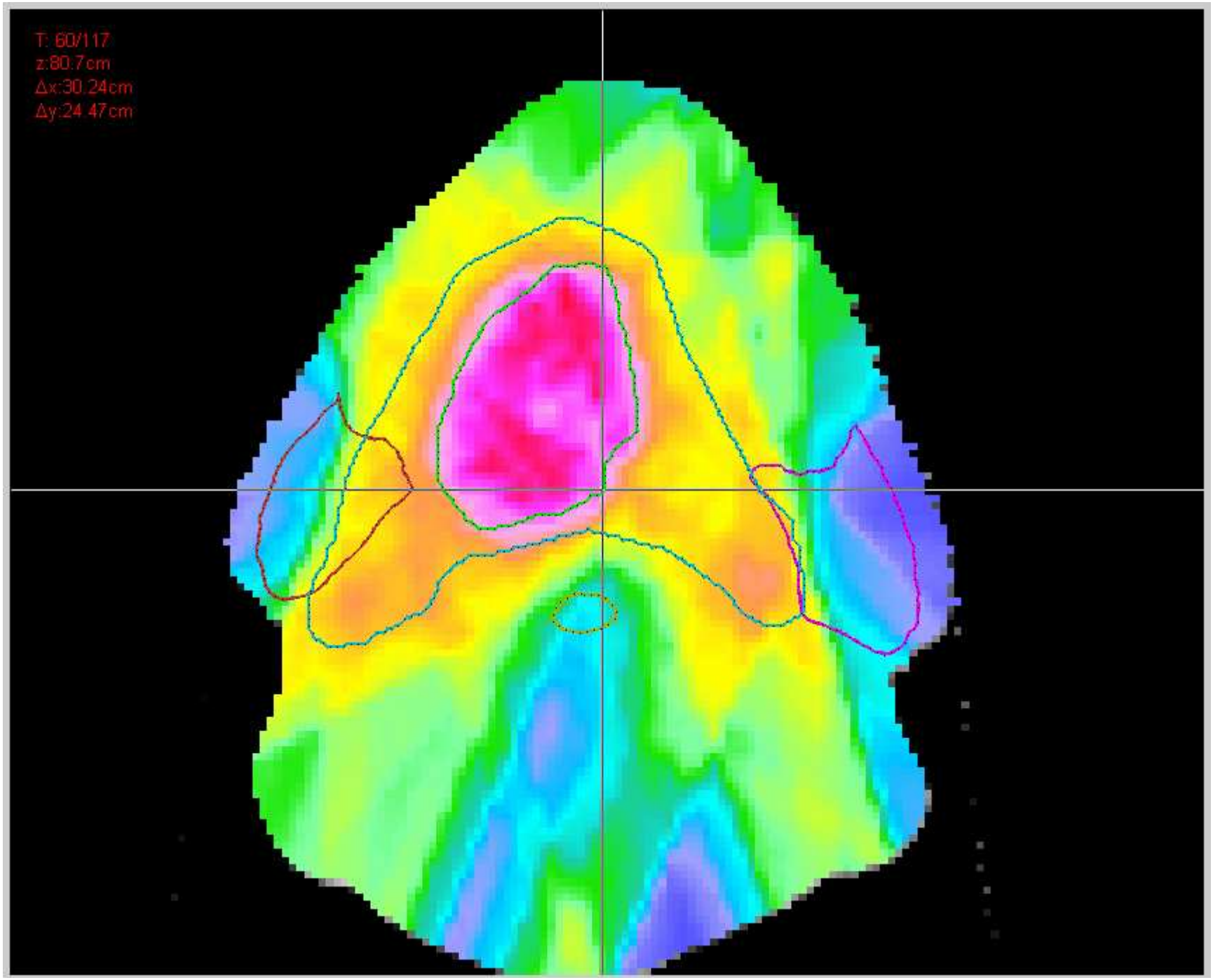
objective value after step 1: $F_i(1)$

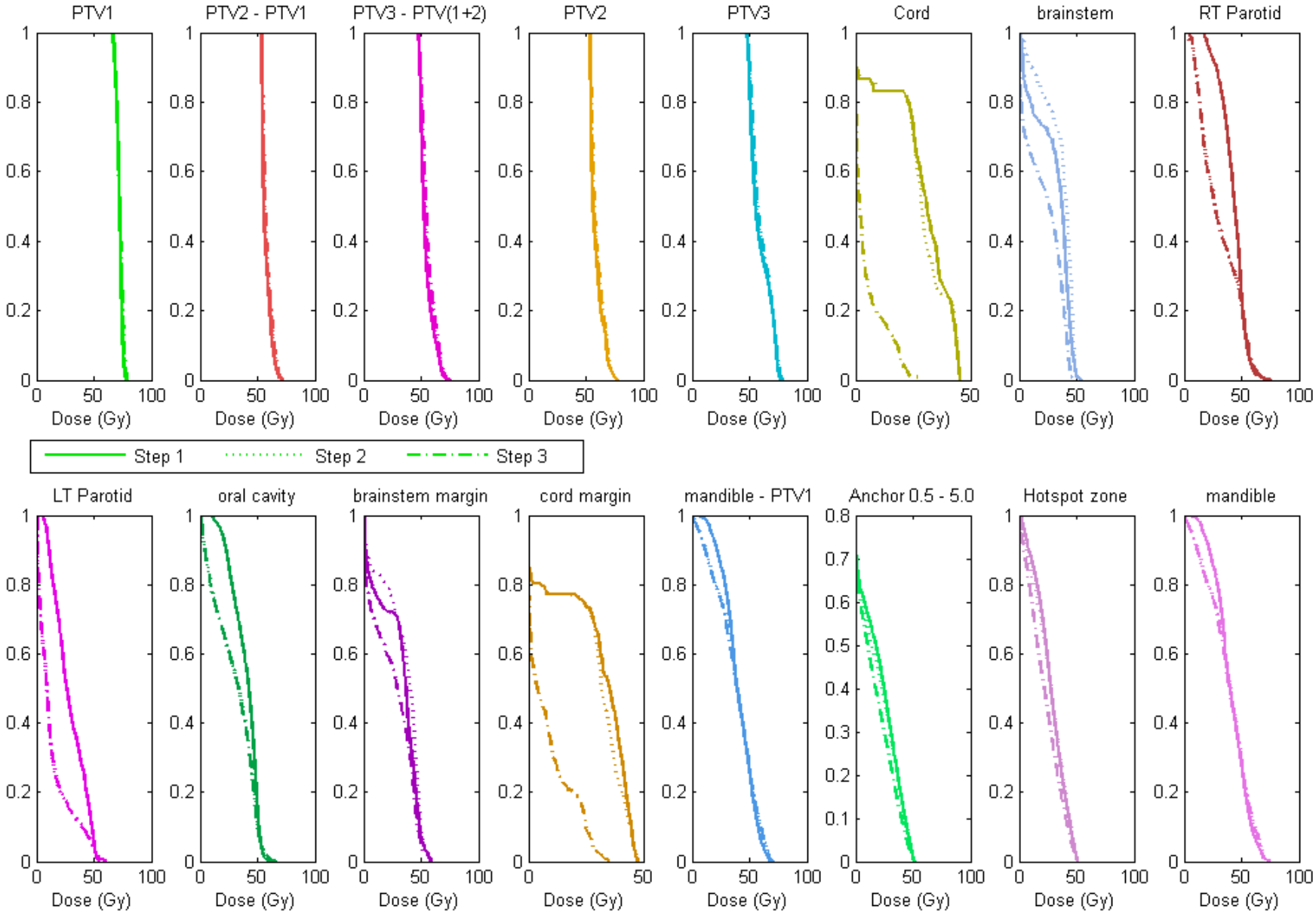
constraint in step 2: $F_i \le (1+s) F_i(1)$

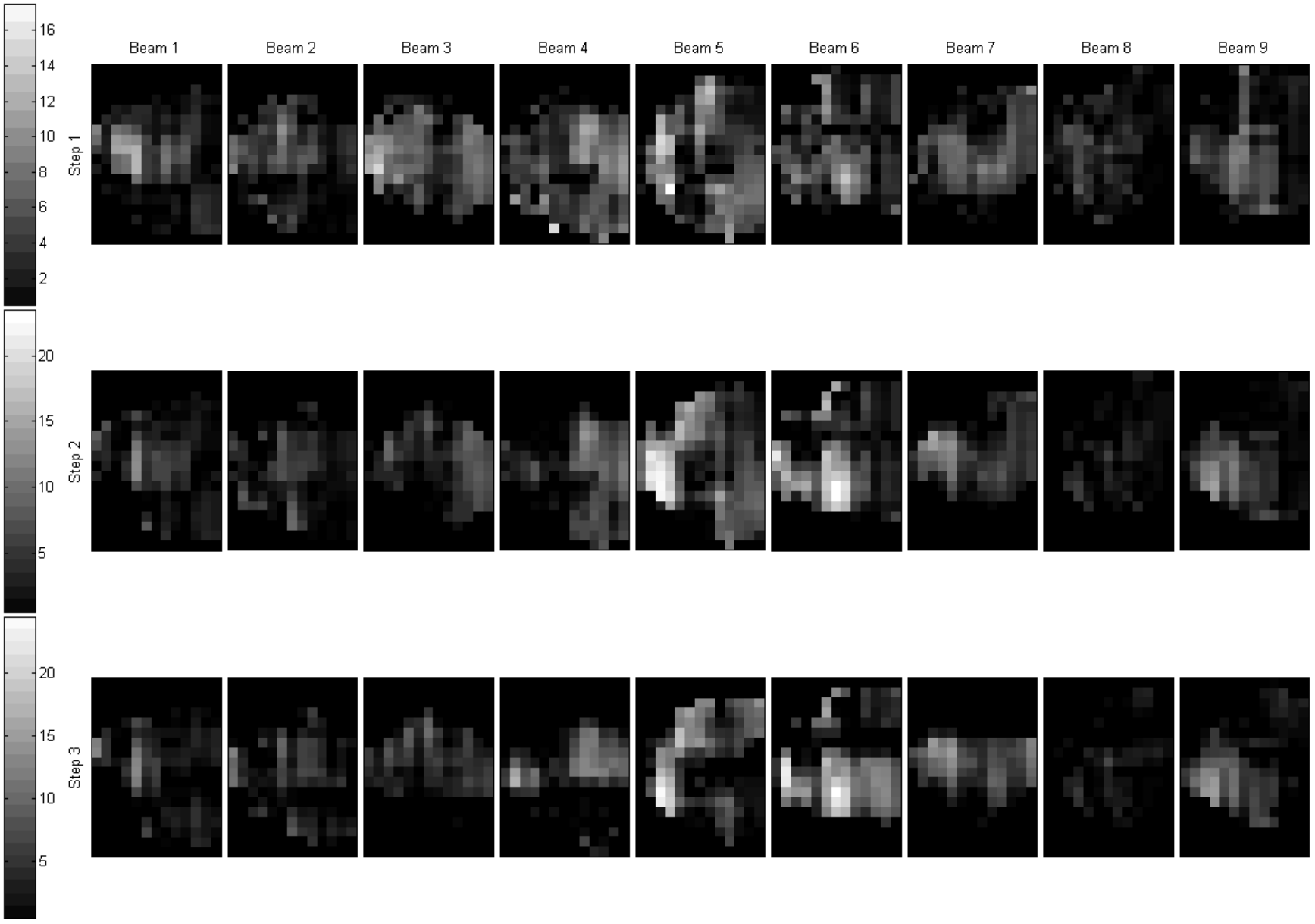
constraint in step 3: $F_i \le (1+s)^2 F_i(1)$

all other constraints: no slip


T: 60/117
z:80.7cm
Δx:33.02cm
Δy:26.64cm
S: 126/256
x:23.9062cm
Δy:26.82cm
Δz:21.64cm
Dose
Scan
78.8 78.8
0 0
Legend
PTV2
PTV1
Cord_3mm
brainstem_3mm
Skin
Cord
brainstem
RT Parotid
LT Parotid
RT SUBMANDIB
mandible
CTV 3
CTV 1
oral cavity
CTV 2
PTV3
brainstem margin
cord margin
mandible - PTV1
PTV2 - PTV1


T: 60/117
z:80.7cm
Δx:30.24cm
Δy:24.47cm

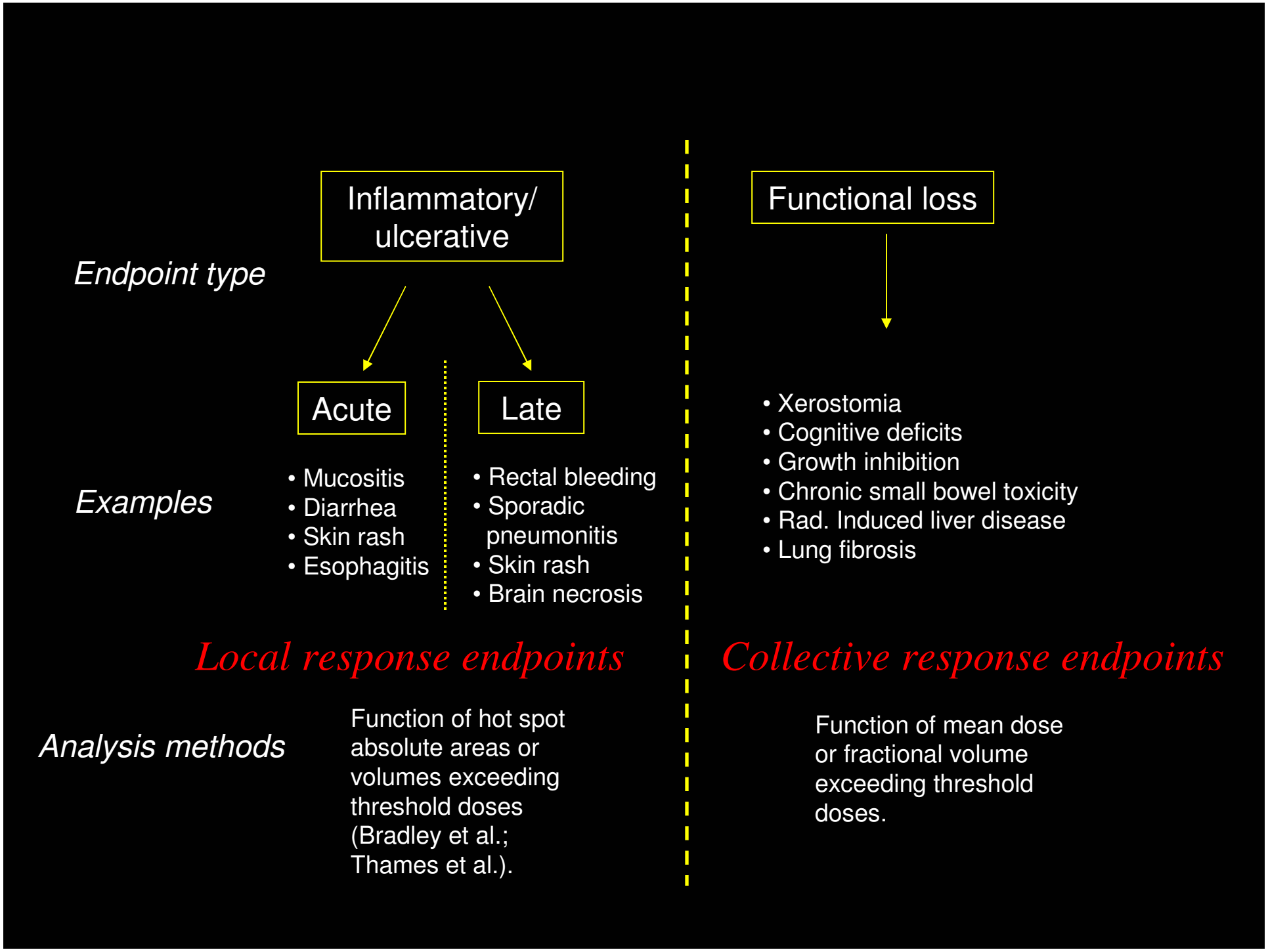

PTV1
PTV2 - PTV1
PTV3 - PTV(1+2)
PTV2
PTV3
Cord
brainstem
RT Parotid
Dose (Gy)
Step 1
Step 2
Step 3
LT Parotid
oral cavity
brainstem margin
cord margin
mandible - PTV1
Anchor 0.5 - 5.0
Hotspot zone
mandible


Beam 1
Beam 2
Beam 3
Beam 4
Beam 5
Beam 6
Beam 7
Beam 8
Beam 9
Step 1
Step 2
Step 3
16
14
12
10
8
6
4
2
20
15
10
5
20
15
10
5

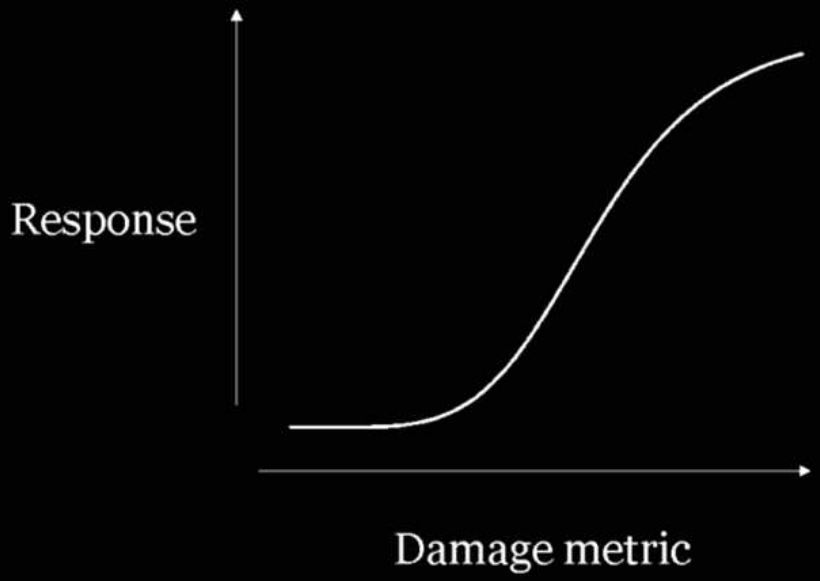
Challenge #5: Making tradeoffs responsive to outcomes models

But what do these simple equations have to do with outcomes?

Can we use prescription goals which are more likely to be related to outcomes?


Endpoint type
Inflammatory/ ulcerative
Functional loss
Acute
Late
Examples
• Mucositis
• Diarrhea
• Skin rash
• Esophagitis
• Rectal bleeding
• Sporadic pneumonitis
• Skin rash
• Brain necrosis
• Xerostomia
• Cognitive deficits
• Growth inhibition
• Chronic small bowel toxicity
• Rad. Induced liver disease
• Lung fibrosis
Local response endpoints
Collective response endpoints
Analysis methods
Function of hot spot absolute areas or volumes exceeding threshold doses (Bradley et al.; Thames et al.).
Function of mean dose or fractional volume exceeding threshold doses.

Elements of the "standard" NTCP volume effect model: EUD and LKB



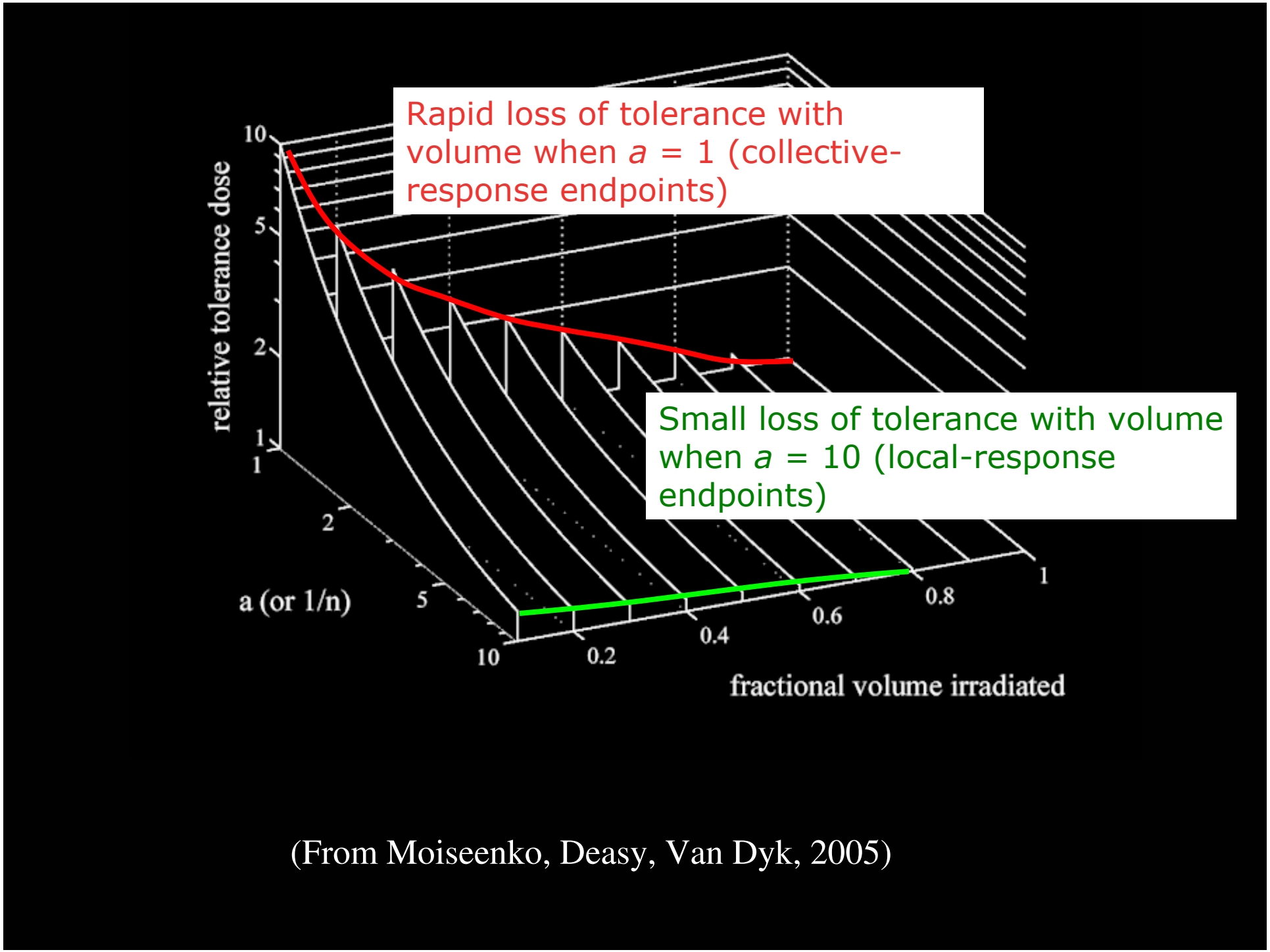
- Sigmoidal dose response curve, parameters include
  - Slope parameter
  - TD50 parameter (tolerance dose for 50% response)
- Equivalent uniform dose equation. Typically a power-law (Lyman-Kutcher-Burman, Mohan, Niemierko, NKI)

Generalized Equivalent Uniform Dose is just a power-law weighted average of the dose

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

$$= \left(\frac{1}{N} \sum_{i=1}^{N} d_i \left(d_i^{a-1} \right) \right)^{1/a}$$

'a' is the localizing parameter.



(From Moiseenko, Deasy, Van Dyk, 2005)

Can gEUD replace dose-volume metrics?

Structure	Dose-volume endpoint	*a* for highest correlation	Spearman correlation
Lung	V10	0.4	0.9655
Lung	V20	0.8	0.9628
Lung	V30	1.0	0.9660
Esophagus	V55	3.2	0.9171
Rectum	V40	1.2	0.9475
Rectum	V65	6.0	0.8301
Bladder	V40	1.0	0.9665
Bladder	V65	6.2	0.8824
Lung PTV	D95	-7.8	0.9350
Prostate PTV	D95	-29.0	0.9931

Table 1. Values of *a* (gEUD variable parameter) that had the highest correlation with various dose-volume endpoints, along with the Spearman rank correlation coefficient. All associated p-values were negligible ($<10^{-6}$).

(Clark et al., unpublished)

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The situation may be a bit better than that, because…

- Correlation between gEUD and outcome may be as good as for dose-volume constraints and outcome
- Example: gEUD(a = 3.2) has as good a Spearman's correlation with severe acute esophagitis as do DV constraints (0.42).

gEUD used to drive treatment planning

- May often be useful for driving treatment planning for normal tissue or target objectives.
- Cannot completely replace the concept of tolerance based on a small, defined volume, irradiated to a high dose (ulcerative lesions).
- 'Upper-mean-tail' functions may be better for that.
  - Mean of the hottest x% of a volume.
  - Is a linear function
  - Cannot preserve linearity if we go to min of hottest x%
  - Idea needs to be tested against outcomes datasets

Concluding thoughts

- IMRTP planning can be made to be much more automated, responsive to clinical goals, and dosimetrically reliable.
- IMRTP research can benefit greatly by using shared benchmark test cases