Achieving What-You-See-Is-What-You-Get in Proton Therapy

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Making Cancer History®

How much <u>trust</u> do we have

- In what we see on a treatment plan (dose distributions and DVHs)
- In the dose delivered to the CTV and normal structures
- In the biological effectiveness of dose distributions in tumors and normal tissues
- In the estimation of response as function of dose distributions
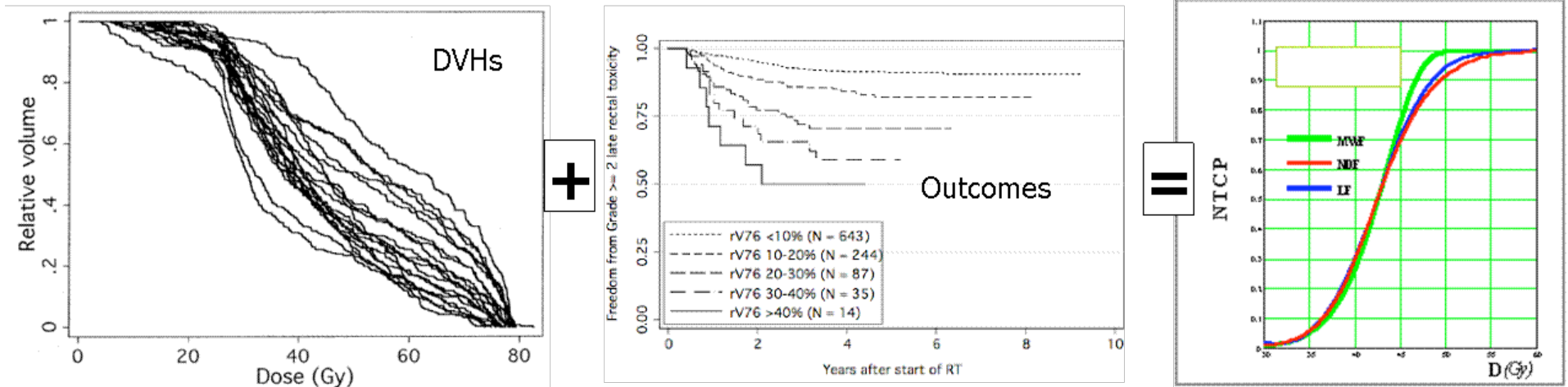
Soares, JAMA 2005: "Evaluation of New Treatments in Radiation Oncology - Are They Better Than Standard Treatments?"

- **Data on 12734 patients from 57 RTOG randomized trials between 1968-2002 were evaluated**

- **"No substantive differences between experimental and conventional treatments"**

- **"Innovations were as likely as standard treatments to be successful"**

- **Why?**
  - **Equipoise**
  - **Large error bars**

Proton beam therapy – Do we need the randomized trials and can we do them? Editorial (Glimelius and Montelius 2007, *Radiother Oncol* 83 (2):105-9)

- **Reviewed proton clinical literature**
- **Question: Why is the evidence in favor of protons so weak that despite decades of experience with protons?**
- **Considering the demonstrated superiority of proton vs. photon dose distributions [on treatment plans] why is the evidence not clear?**
- **Reasons cited:**
  - **Limited number of trials**
  - **Inability to conduct high quality trials at proton facilities intended for physics research**
- **Could it also be that error bars are large?**

In photon therapy ...

- **R&D and studies over the decades have helped to gradually**
  - **reduce margins**
  - **improve confidence in margins**
  - **and improve confidence in dose distributions and their relationship to outcomes**
- **Can that confidence be extended to protons**
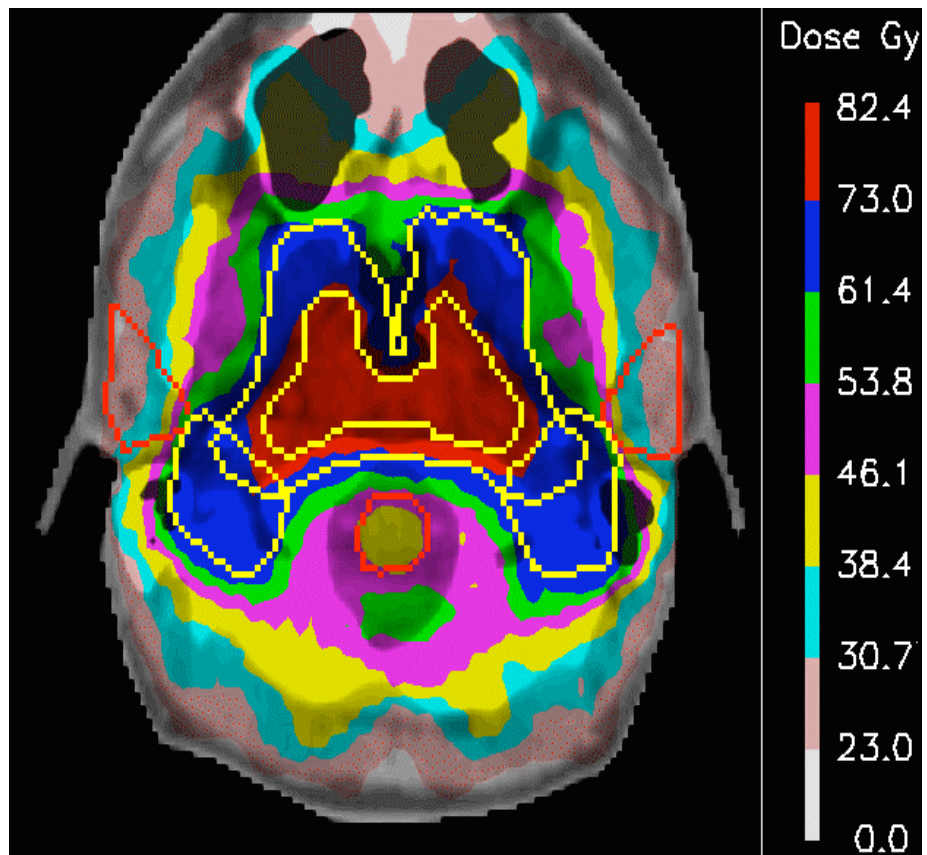

(a)   (b)   (c)
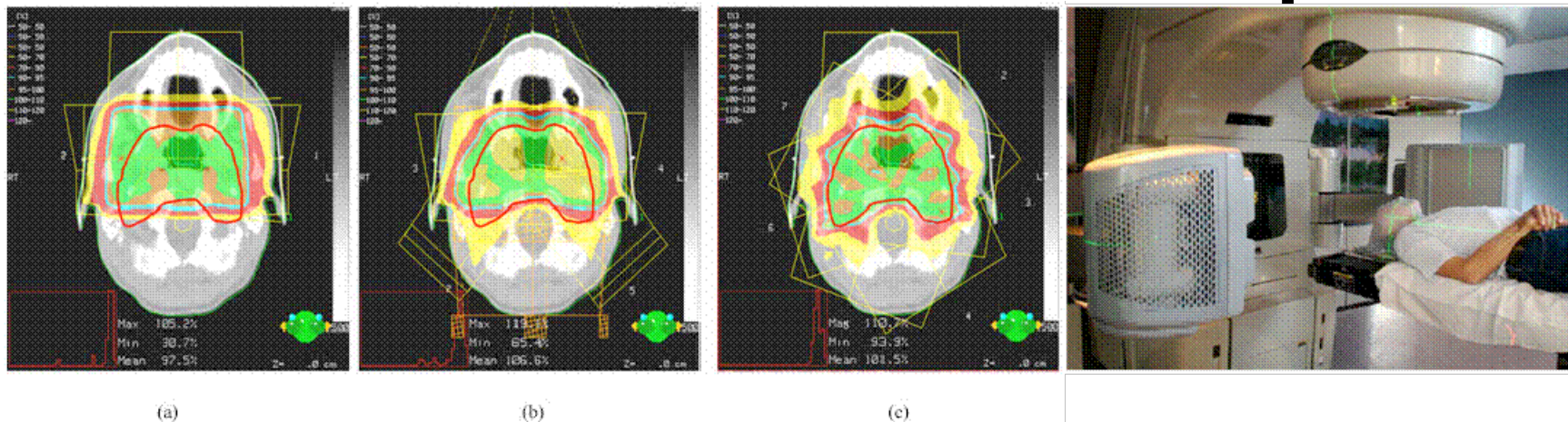
In Proton Therapy ...

- **Is what you see on a proton treatment plan be significantly different from what the actually patient gets?**

- **What are the probable causes?**

- **What are the consequences (site and, possibly, patient specific)?**

- **How can we achieve WYS $\cong$ WYG?**
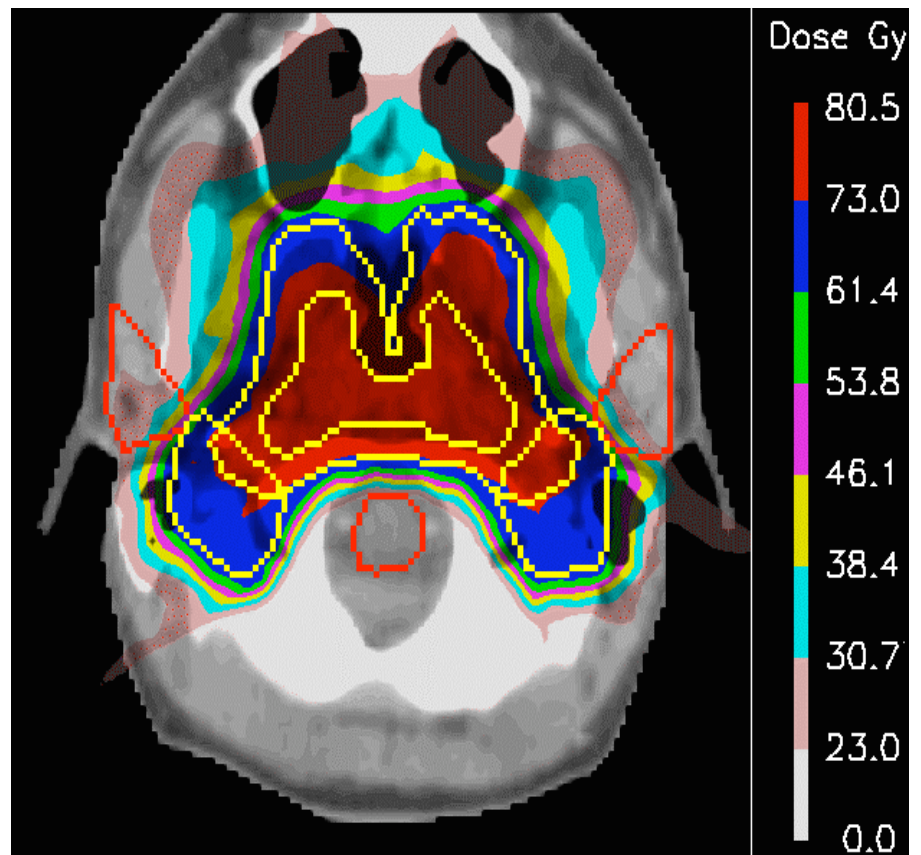
- **How can we verify that WYS $\cong$ WYG?**

What You See
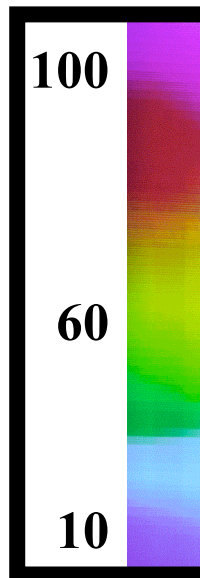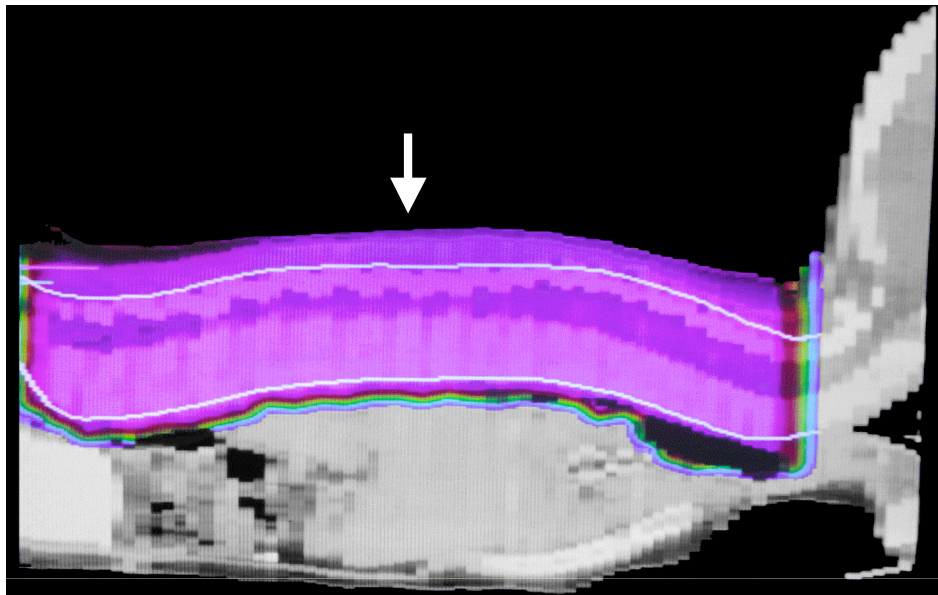
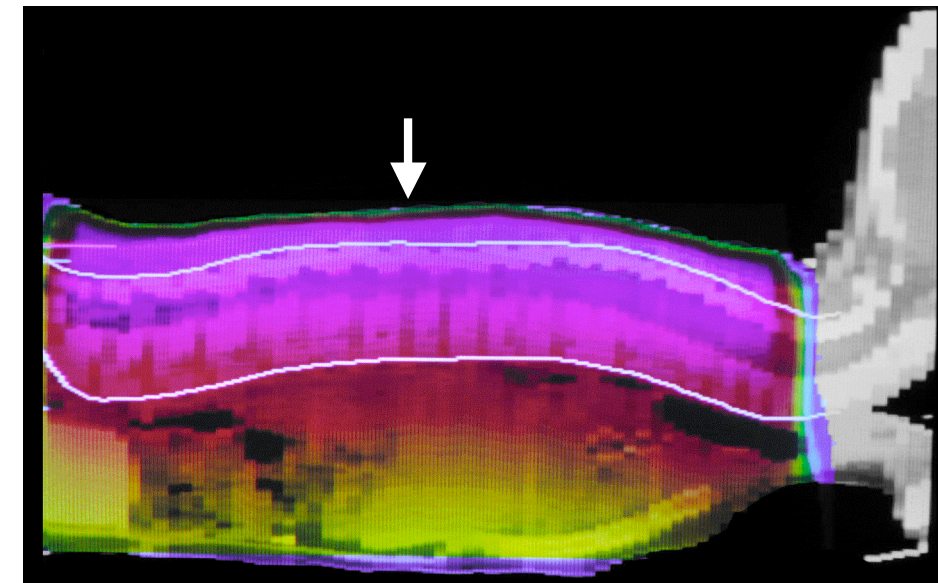# Nasopharynx Treatment Plans Photons vs. Protons
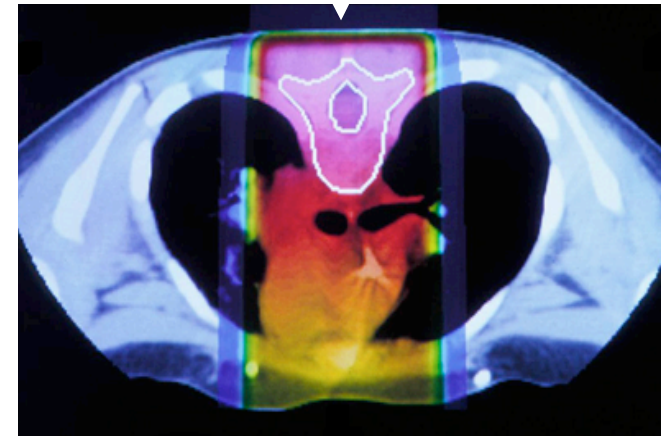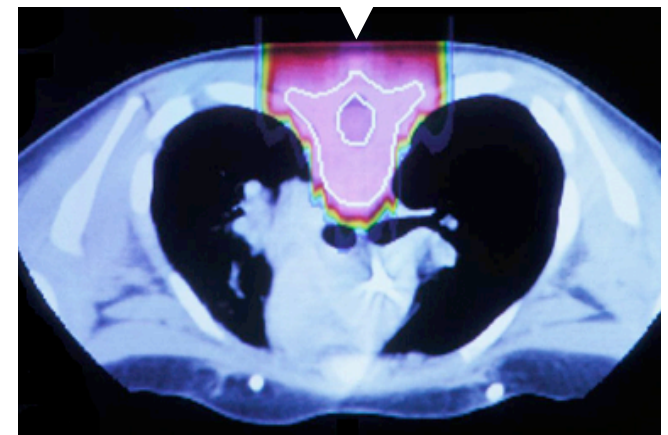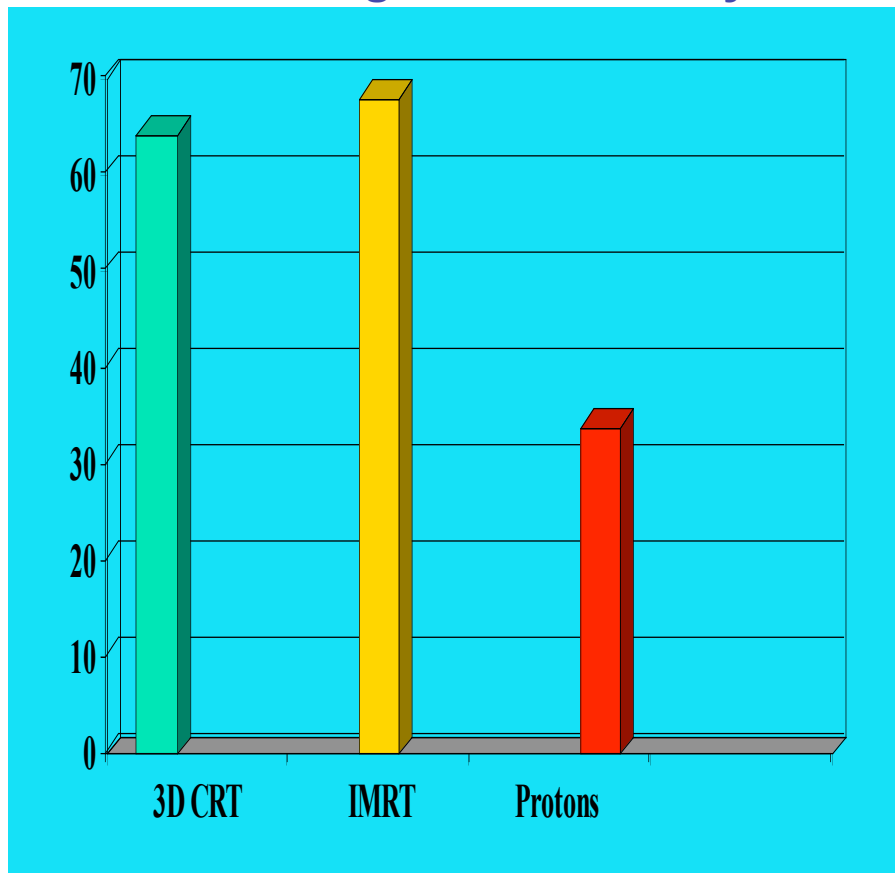

Lomax - PSI

MEDULLOBLASTOMA

PHOTONS

PROTONS

100
60
10

Adams – MGH (via Smith)

NSCLC Proton Therapy at MDACC – Treatment Related Pneumonitis

All Degrees of Severity — bar chart (values 0–70): 3D CRT, IMRT, Protons

>= Grade 3 — bar chart (values 0–35): 3D CRT, IMRT, Protons

Cox
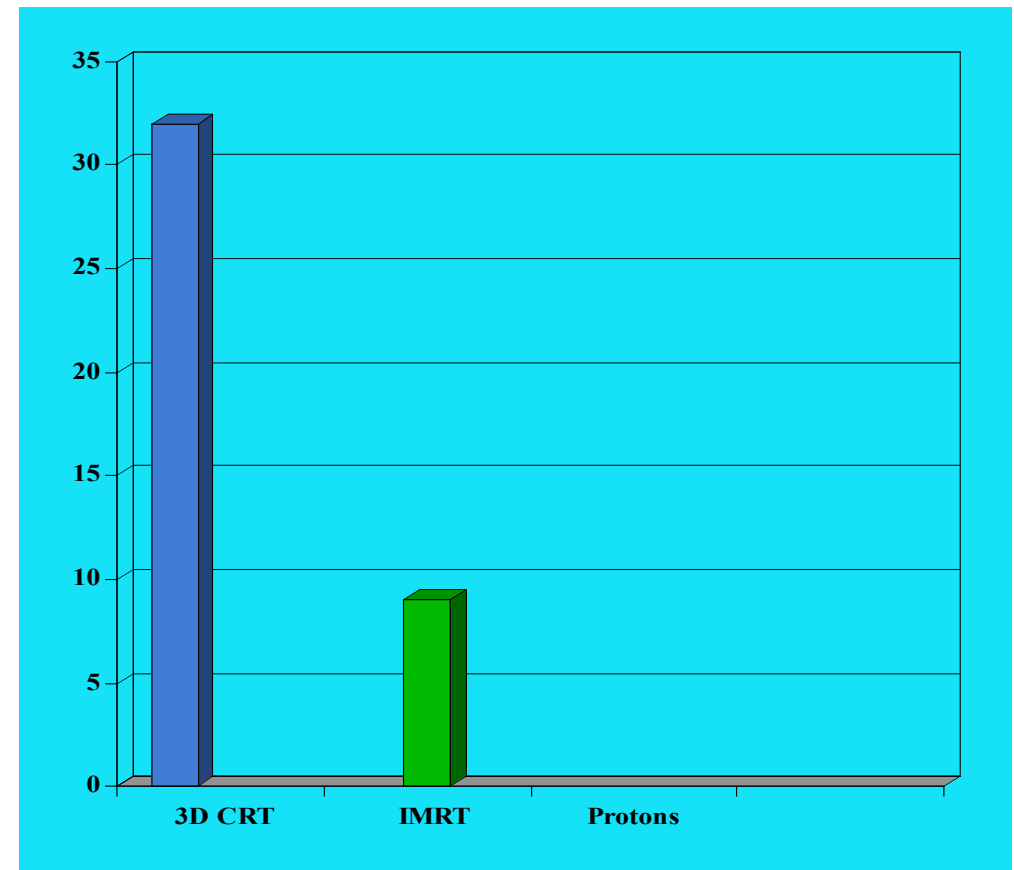
Protons Have Great Potential

Further R&D is needed:

To improve understanding of physical, biological and clinical aspects of PT and to improve technology

Need to conduct trials to test proton therapy's efficacy

Magical Protons? – Goitein IJROBP 70, 2008
## "a few notes of caution"

- **"Perception that proton technology is mature is wrong."**
  - **"Insufficient importance being given to achieving sharp proton beam penumbra ..."**
  - **"... margins are quite substantial, especially in lung ..."**
  - **Organ motion**
  - **Inhomogeneities**
  - **...**

WYS ≠ WYG Necessarily

- **Why?**
  - **High sensitivity of protons to motion, positioning variability and anatomic changes and other uncertainties**
  - **Degradation of proton range (distal edge)**
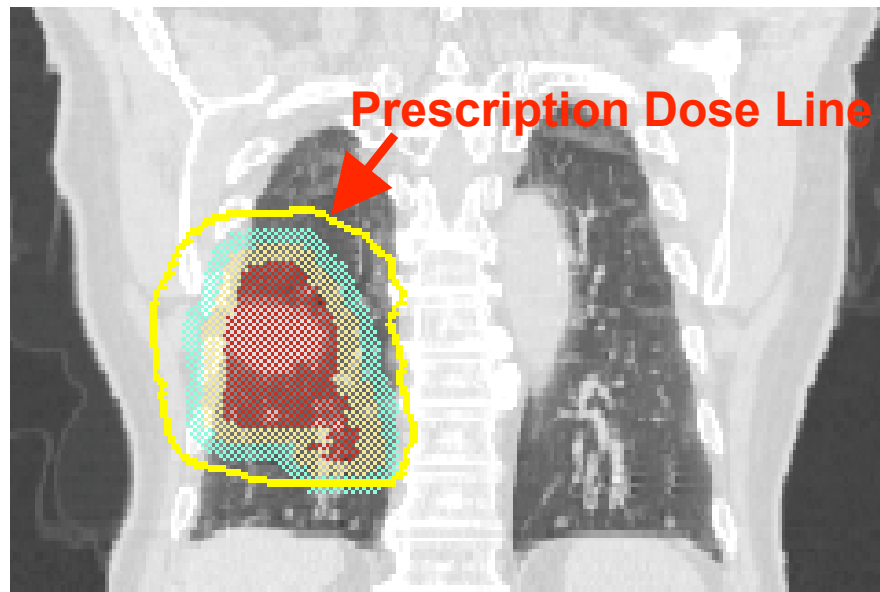 - **Approximations of dose calculation methods**
  - **...**
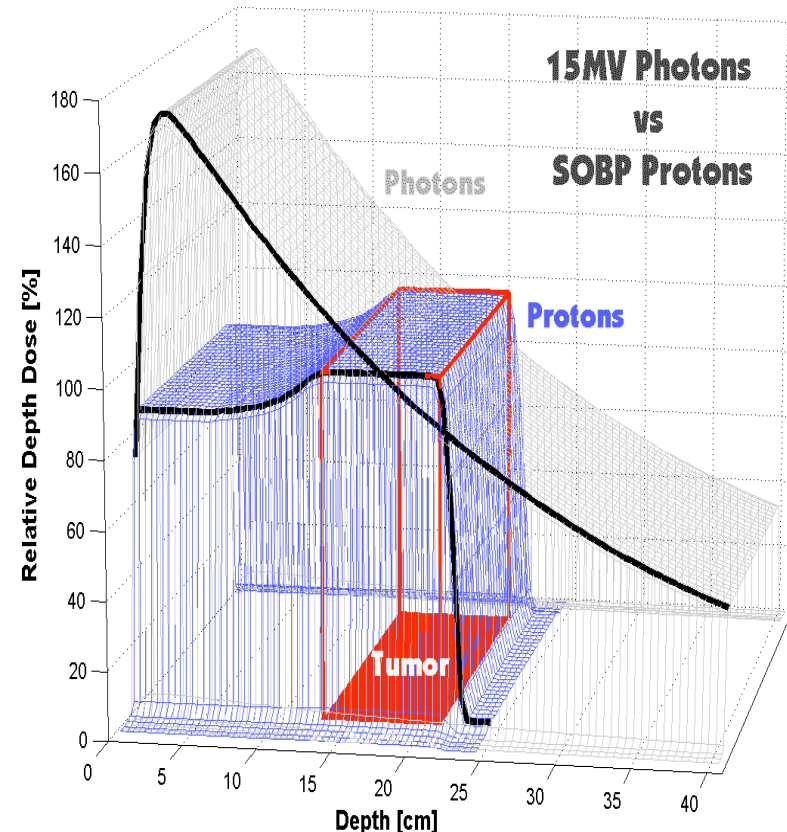
Don't we have the similar issues with photons?

- **Yes, but …**
- **Protons**
  - **Have finite range**
  - **Are charged**
  - **Are more sensitive to perturbations**

Intra- and Inter-Fractional Changes

An example

Impact of Respiratory Motion on Proton Dose Distributions

Prescription Dose Line

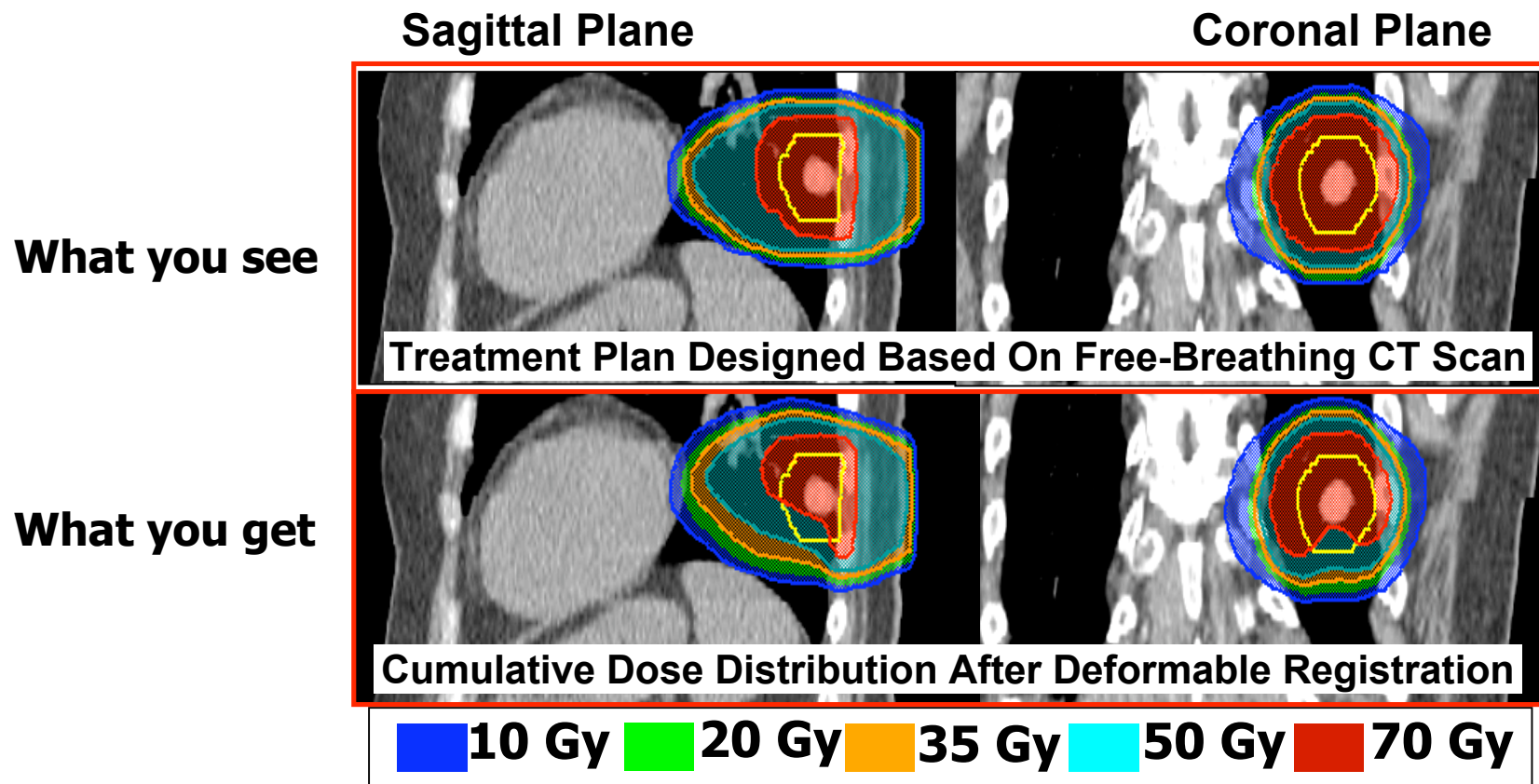Treatment planned based on single free-breathing CT image (perceived dose distribution)
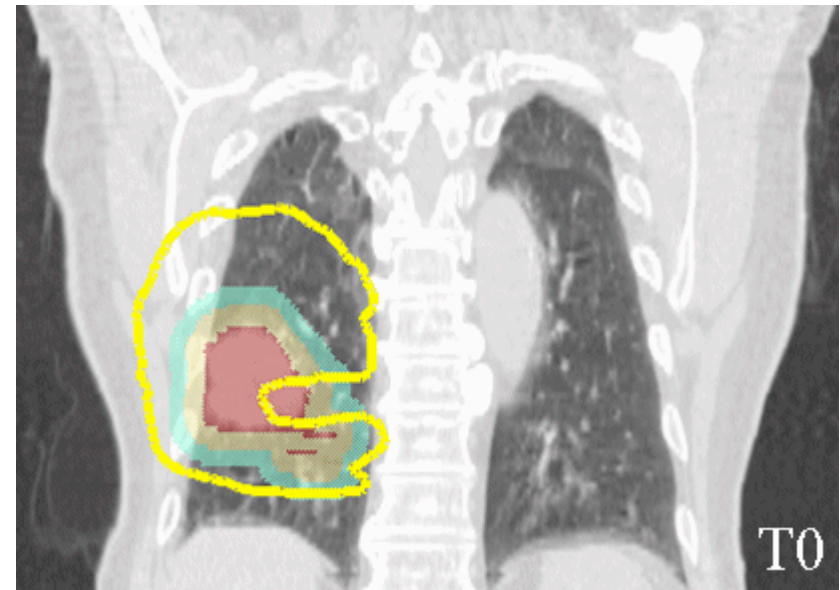
The same treatment plan calculated on 10 phases of the 4D CT image

Dong

Impact of Intra-Fractional Motion Cumulative

Impact of Intra-Fractional Motion – Current Solution

Proton Plan with Smearing and Compensator Designed to cover the Range of Motion
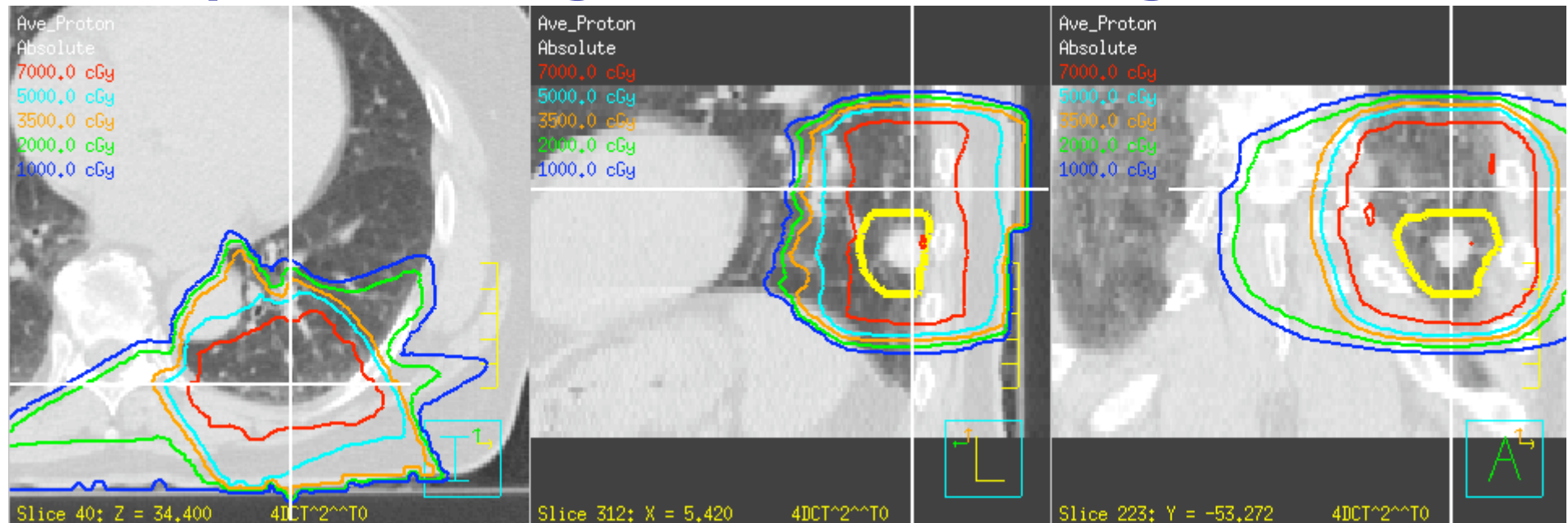
| 10 Gy | 20 Gy | 35 Gy | 50 Gy | 70 Gy |

Zhang, Dong, et al MDACC

Inter-Fractional Variations

Proton: 3 beams plan

Solution: Repeat Imaging and Adaptive Replanning

63.000
20.000
10.000

IMRT: 7 beams plan

Zhang

Original Plan

After Two weeks of Radiotherapy
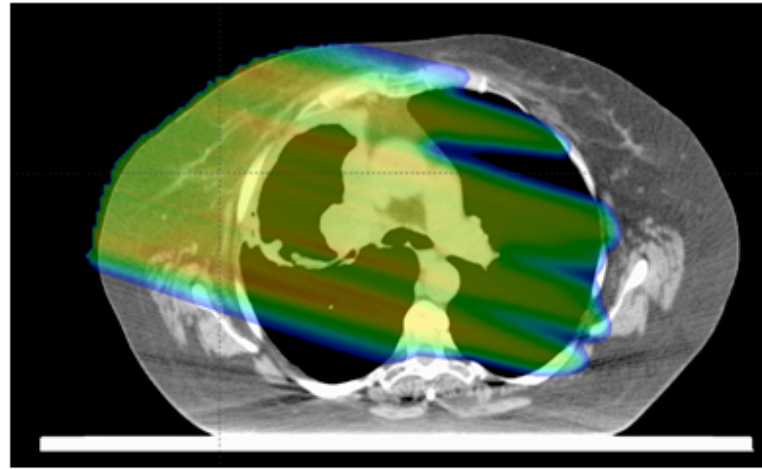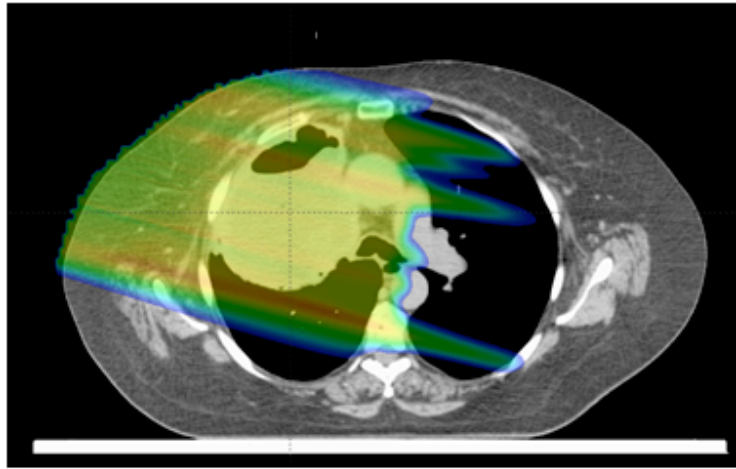
Fig.2 Comparison of dose distribution from single RAO field before and after tumor shrinkage as detected during third week of treatment. (This patient experienced the most dramatic tumor shrinkage).

Amos, *et al.* Poster at PTCOG 46, 2007
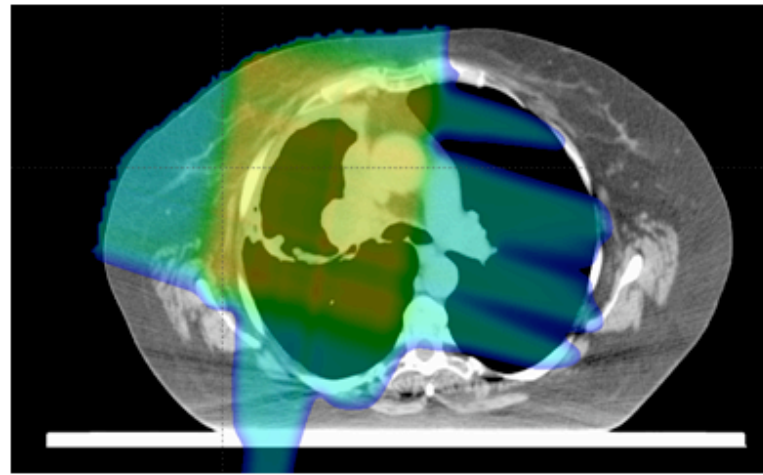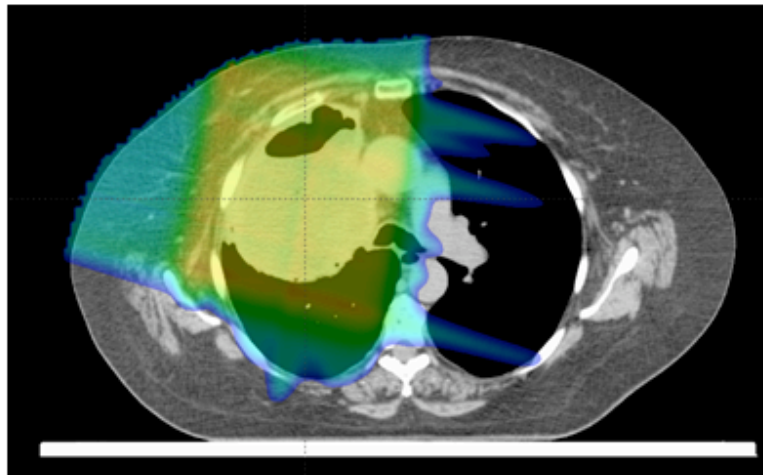
Fig.3 Comparison of total dose distribution before and after tumor shrinkage. (Same patient as Fig.2)

Inhomogeneities

Distal Edge Degradation Caused By Heterogeneities

Heterogeneity

$E(t_1) = E(t_2)$

$E(t_1) > E(t_2)$

t_1

t_2

A

B

Detector

Water tank

Protons
(16.0g cm^{-2}
residual range)

Radiograph

A
B
C

(A)

100
90
80

50

20

0

0   5

3 mm
2 mm

3 mm

(B)

0   5

9 mm
5 mm

3 mm

(C)

0   5

15 mm
8 mm

11 mm

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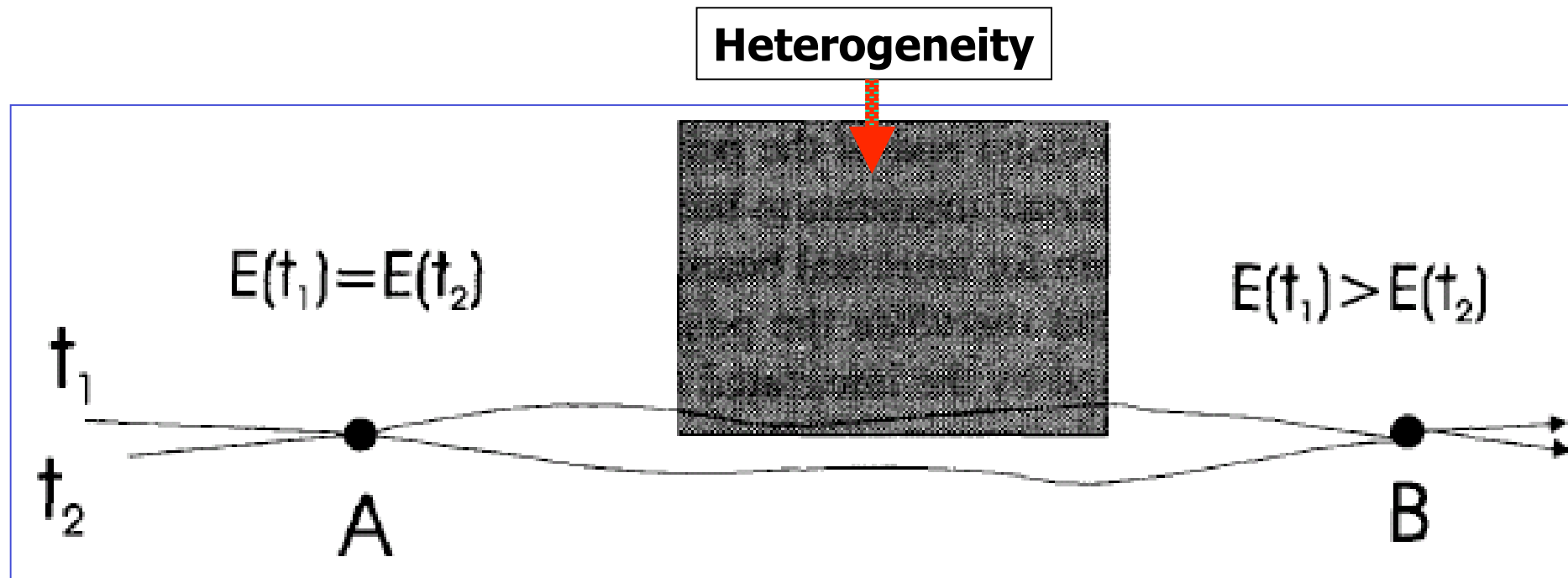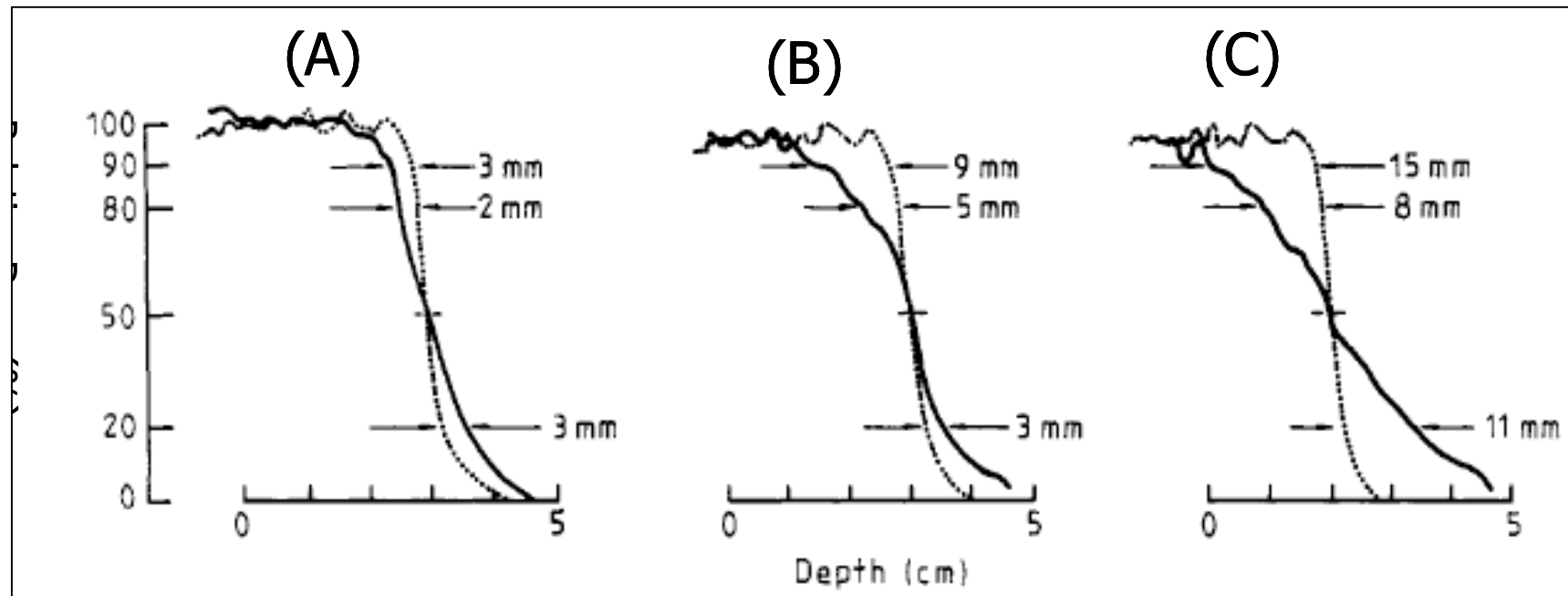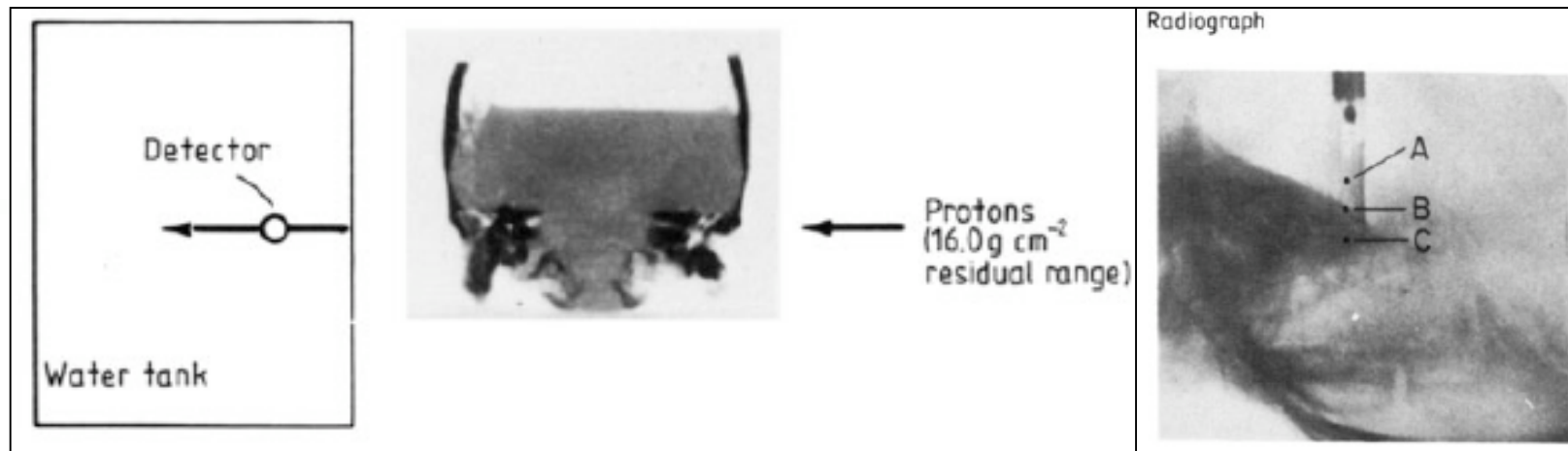
Protons Through Base of Skull: 90 to 20% fall of increases from 6 to 32 mm

Urie, et al,

Can Degradation Occur for Lung Treatments Also?

Is degradation a function of "texture"?

Average lung density ~= 0.2

Titt

Homogenous slab
ρ = 0.2 gm/cc

Voxels = (1 mm)³
Av ρ = 0.2 gm/cc

Voxels = (2 mm)³
Av ρ = 0.2 gm/cc

P

Dependence of Distal Edge Degradation on Texture

Voxels = (3 mm)³
Av ρ = 0.2 gm/cc

Voxels = (4 mm)³
= 0.2 gm/cc

Titt
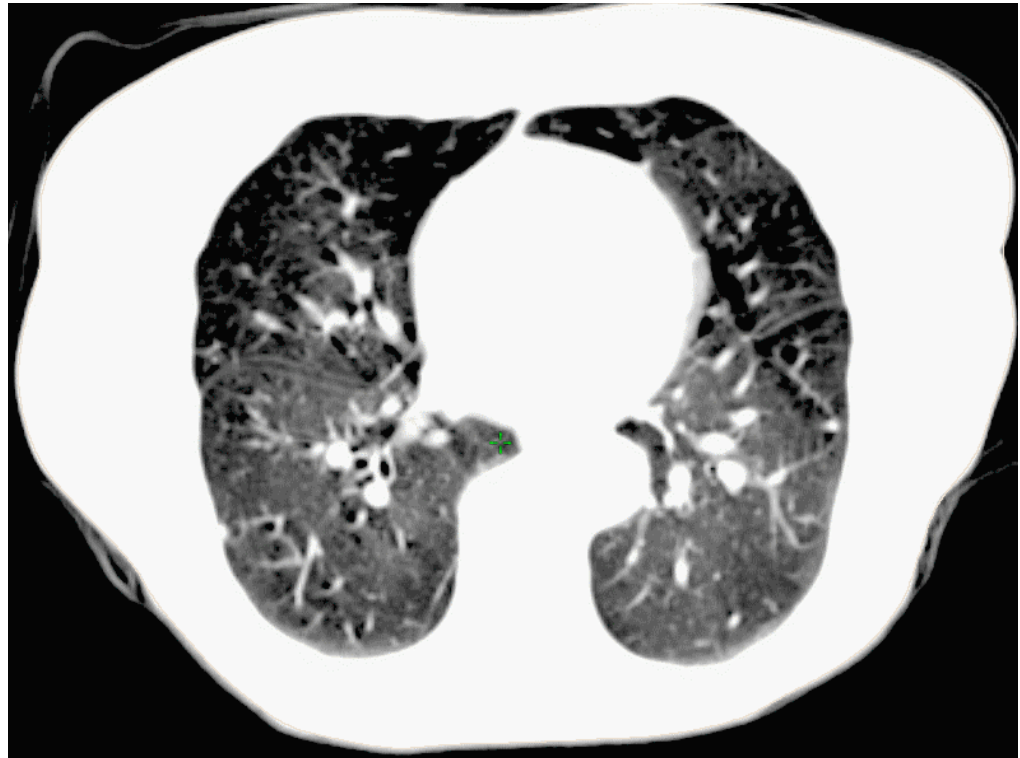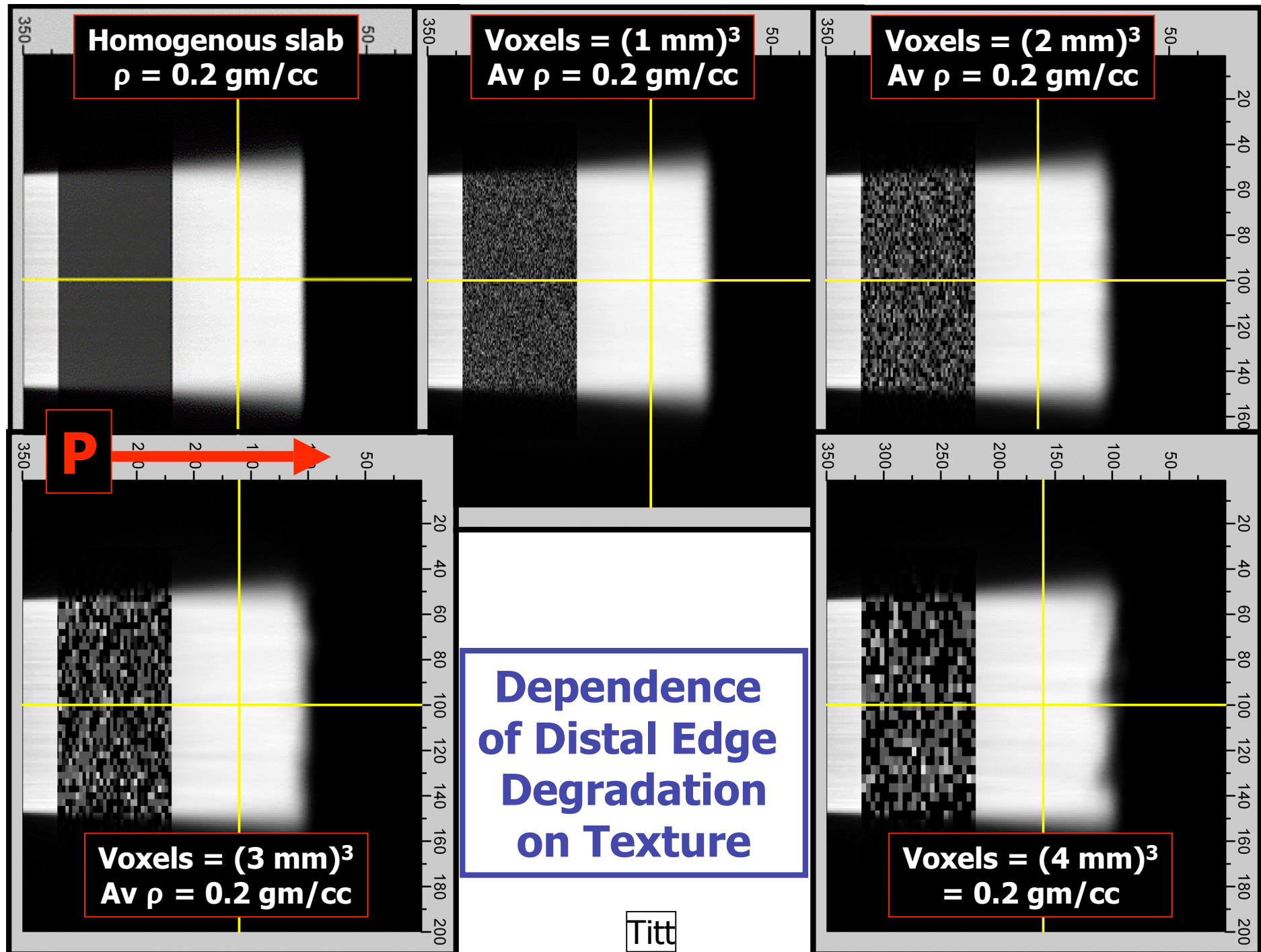
Distal Edge Degradation Through Lung Equivalent Material – Dependence on Texture

90% - 20% Distal Edge
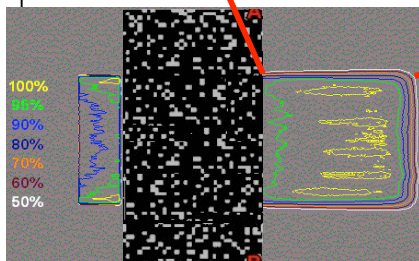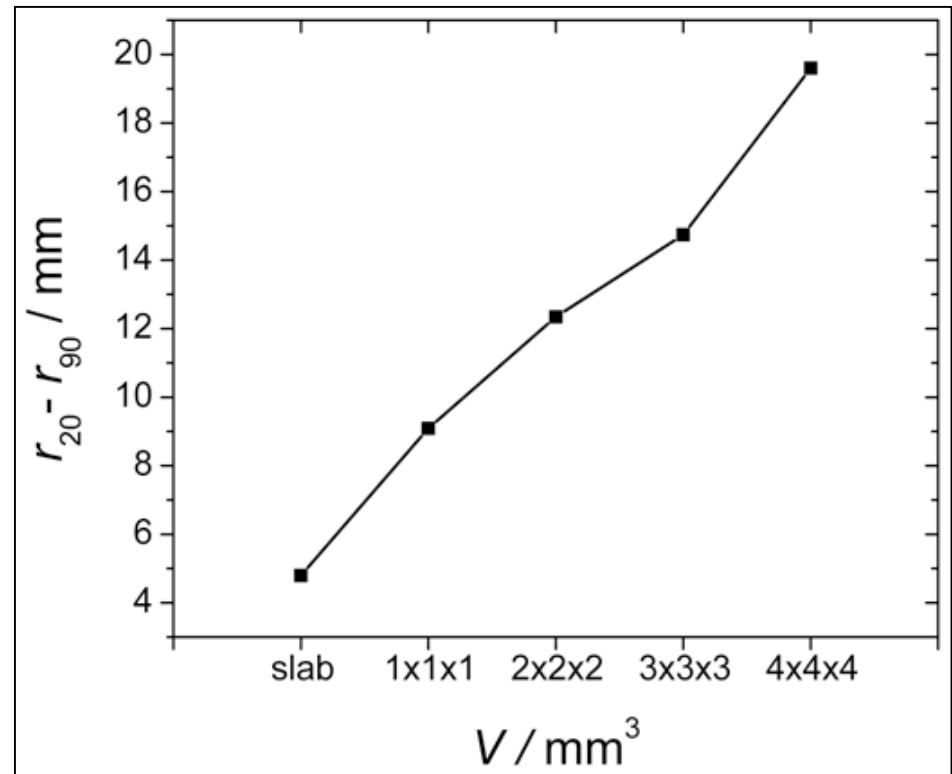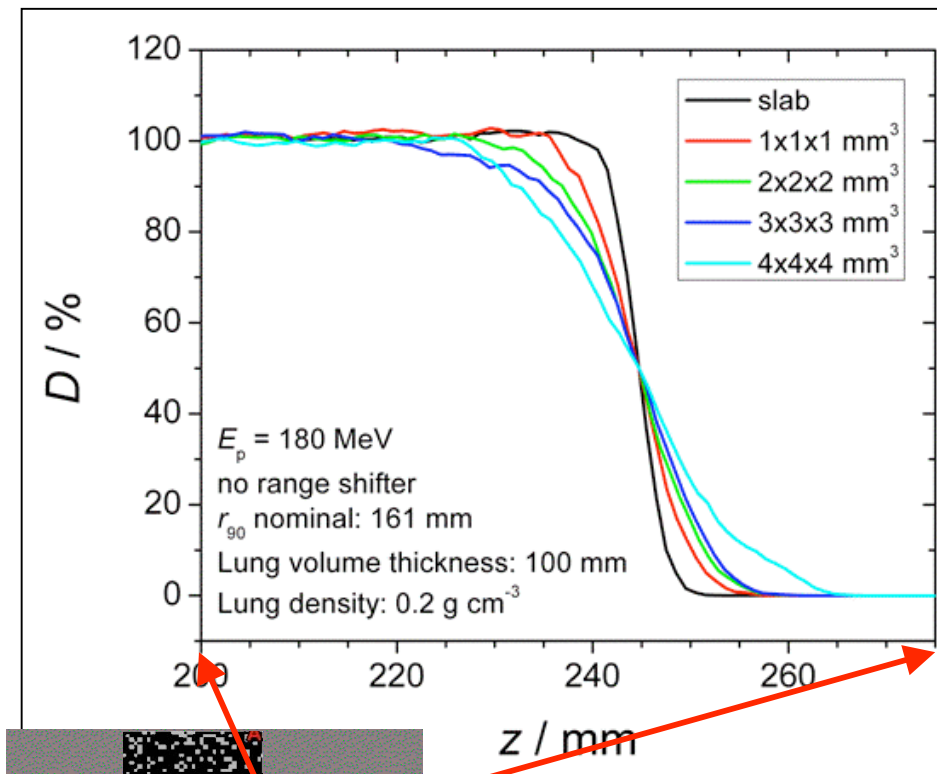
Repairing Distal Edge Degradation
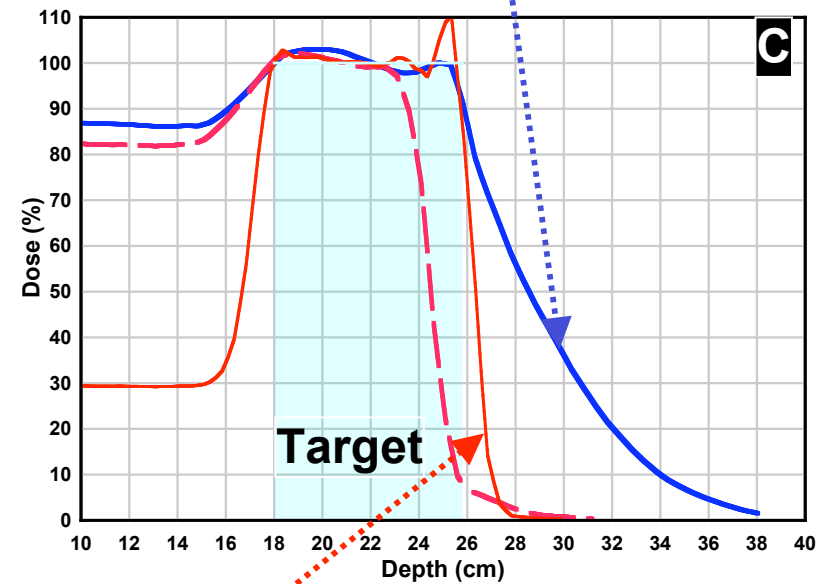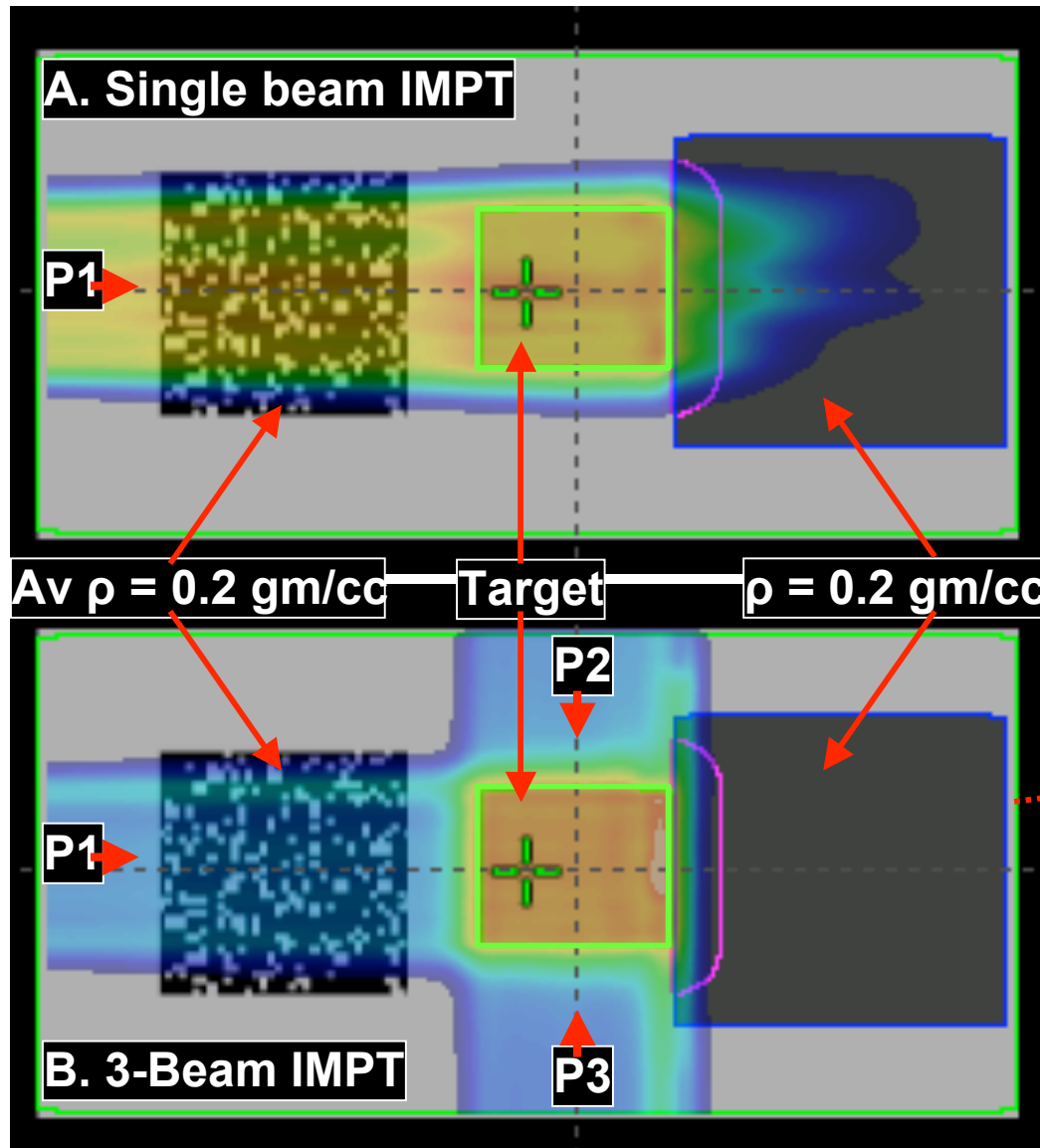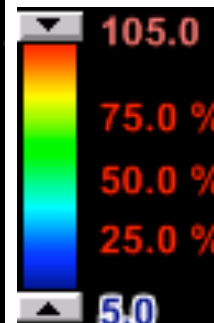
MC vs. Semi-Empirical Dose Computation Methods
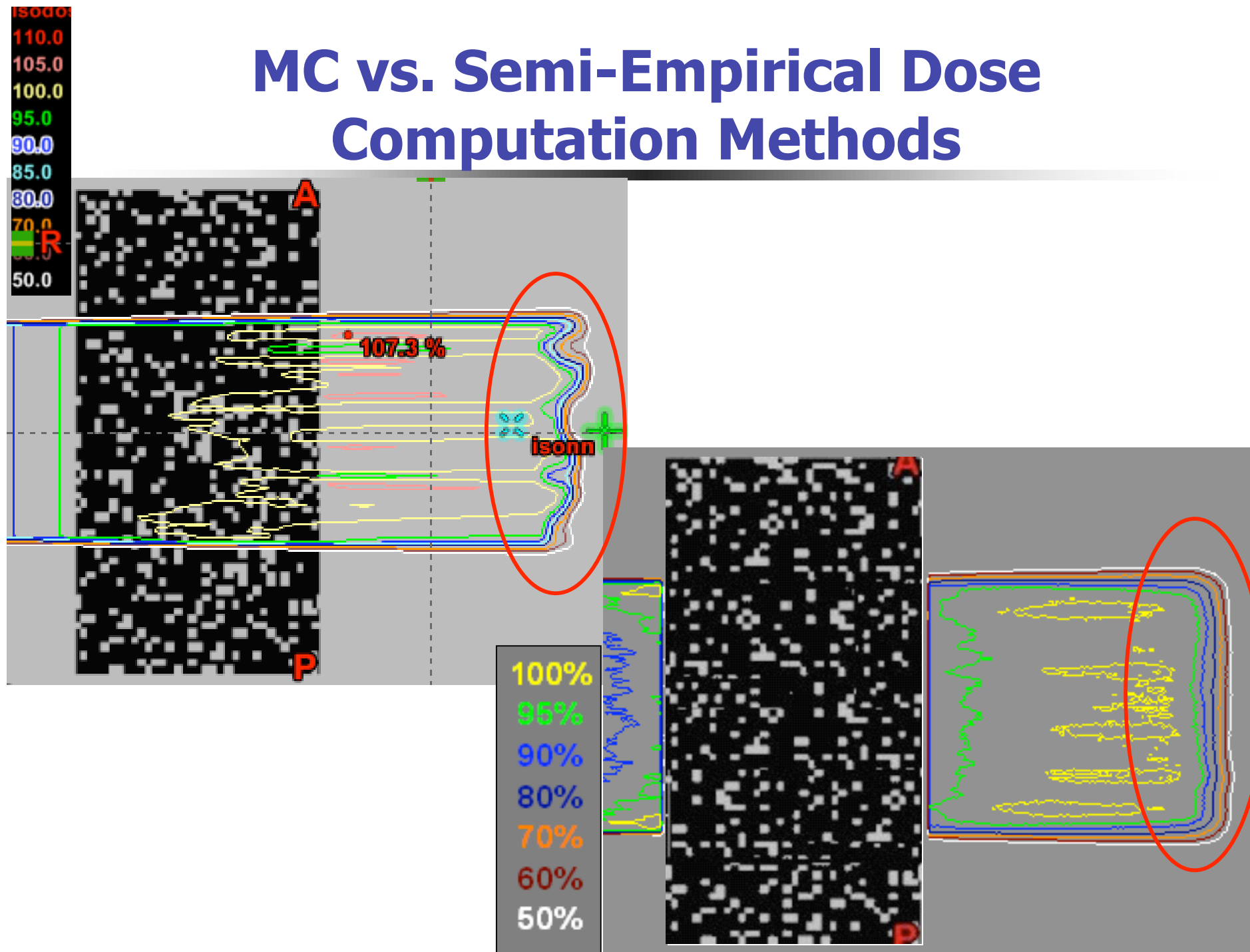
Sphenoid sinus; 13 fields (+ photons)

Monte Carlo **MC - XiO**

Total Dose

- **-8 Gy(RBE)**
- **-6 Gy(RBE)**
- **-4 Gy(RBE)**
- **-2 Gy(RBE)**
- **+2 Gy(RBE)**
- **+4 Gy(RBE)**
- **+6 Gy(RBE)**
- **+8 Gy(RBE)**

- **10 Gy(RBE)**
- **20 Gy(RBE)**
- **30 Gy(RBE)**
- **40 Gy(RBE)**
- **50 Gy(RBE)**
- **60 Gy(RBE)**
- **65 Gy(RBE)**
- **70 Gy(RBE)**
- **75 Gy(RBE)**

- **0.25**
- **0.5**
- **0.75**
- **1**
- **1.25**
- **1.5**

XiO **γ**
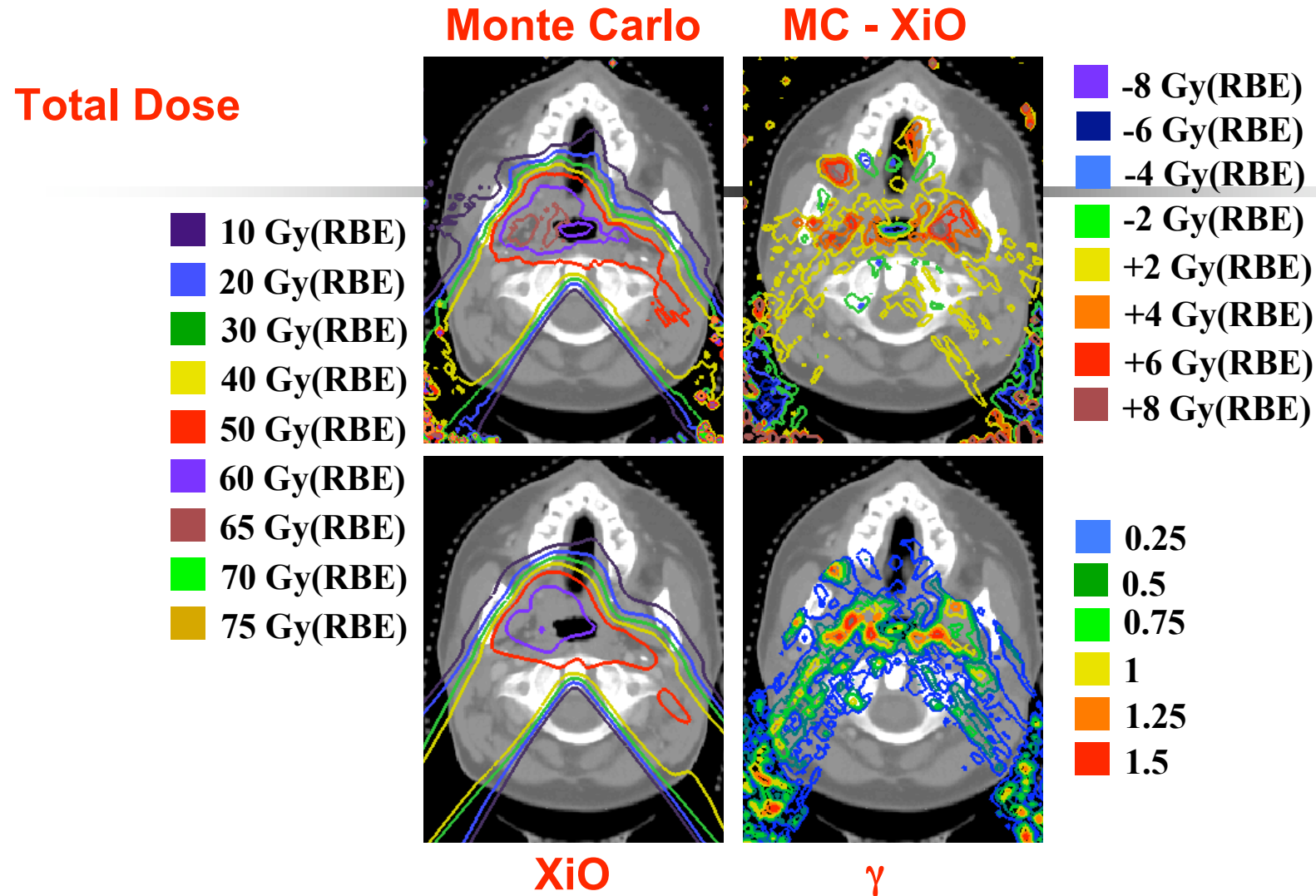
Doses normalized to CTV dose

H. Paganetti (MGH)

How can we achieve WYS ≅ WYG or achieve what is theoretically possible?

- **Image-guided interventions**
  - **Intra-fractional motion – Gating and breath-hold**
  - **Inter-fractional changes and set up uncertainties – Adaptive replanning**
- **Reduction on uncertainties in data (e.g. CT artifacts) used to compute dose distributions**
- **Monte Carlo methods to overcome the approximations in computational models**
- **Improved understanding and incorporation of biological factors in treatment planning**

Another Step: Robust Planning and Evaluating Robustness of Plans

- **Robust planning**
  - **Designing plans that are insensitive (or less sensitive) to uncertainties**
  - **MGH research (Bortfeld, et al)**
- **Evaluation of plan robustness**
  - **Goitein's original suggestion**
  - **Extensions by Lomax and by Zhang**

Proton Plan Evaluation in the Presence of Uncertainties – A Lung Example

- 100 plans with randomly selected positional & range uncertainties
- In the "coolest" plan, each voxel is assigned dose D_L
- In the "hottest" plan, each voxel is assigned dose D_H
- 10% probability that the voxel dose is outside D_L and D_H limit
- D_L and D_H specify the error bar for nominal voxel dose

Probability (Frequency)

Lowest 10% doses to voxel

Nominal Voxel dose

Highest 10% doses to voxel

Voxel Dose

D_L, Dose shown in the coolest plan

D_H, Dose shown in the hottest plan

Dong, Zhang MDACC

A. Nominal/Median

7864.7 cGy

D. Difference (Error Bars)

34516 cGy

B. 10% Coolest

7721.1 cGy

C. 10% Hottest

7869.9 cGy
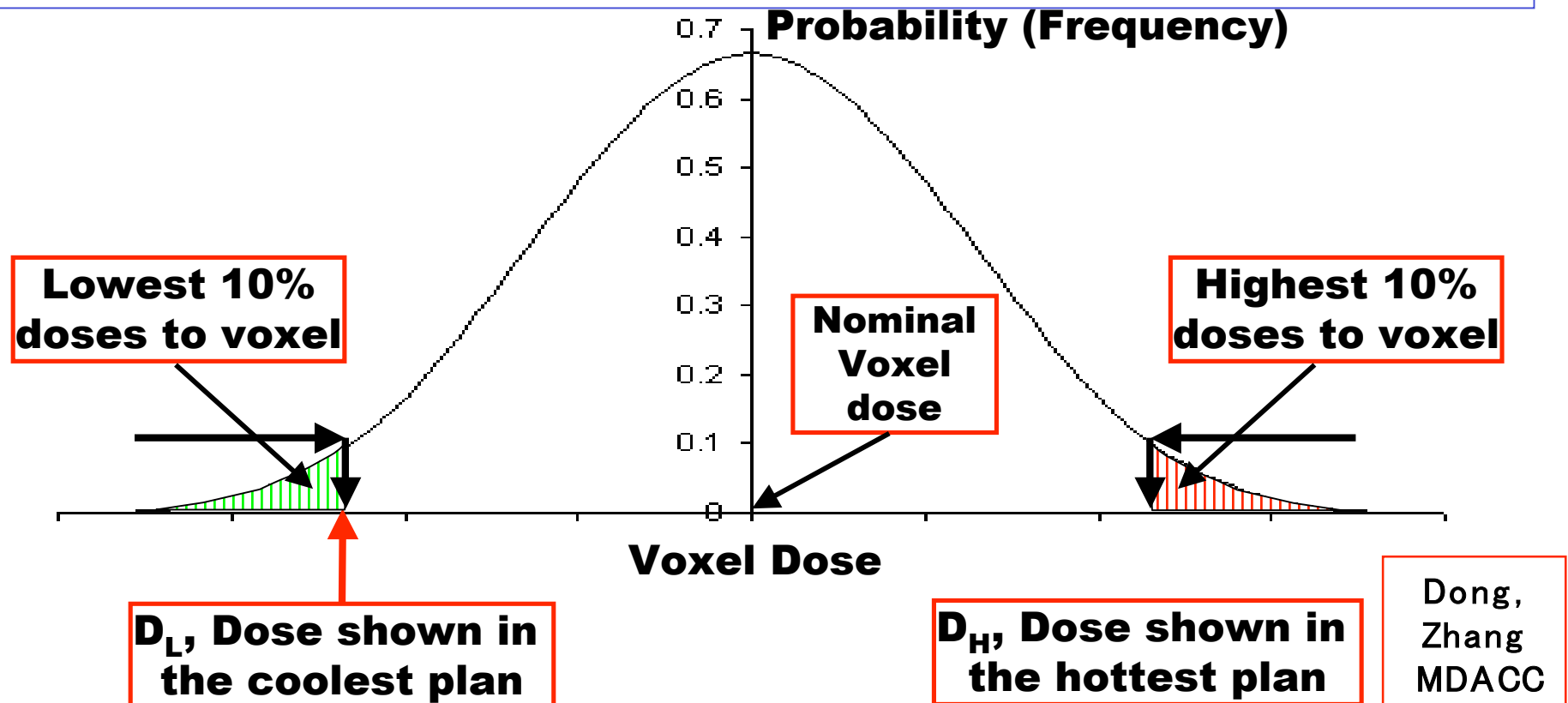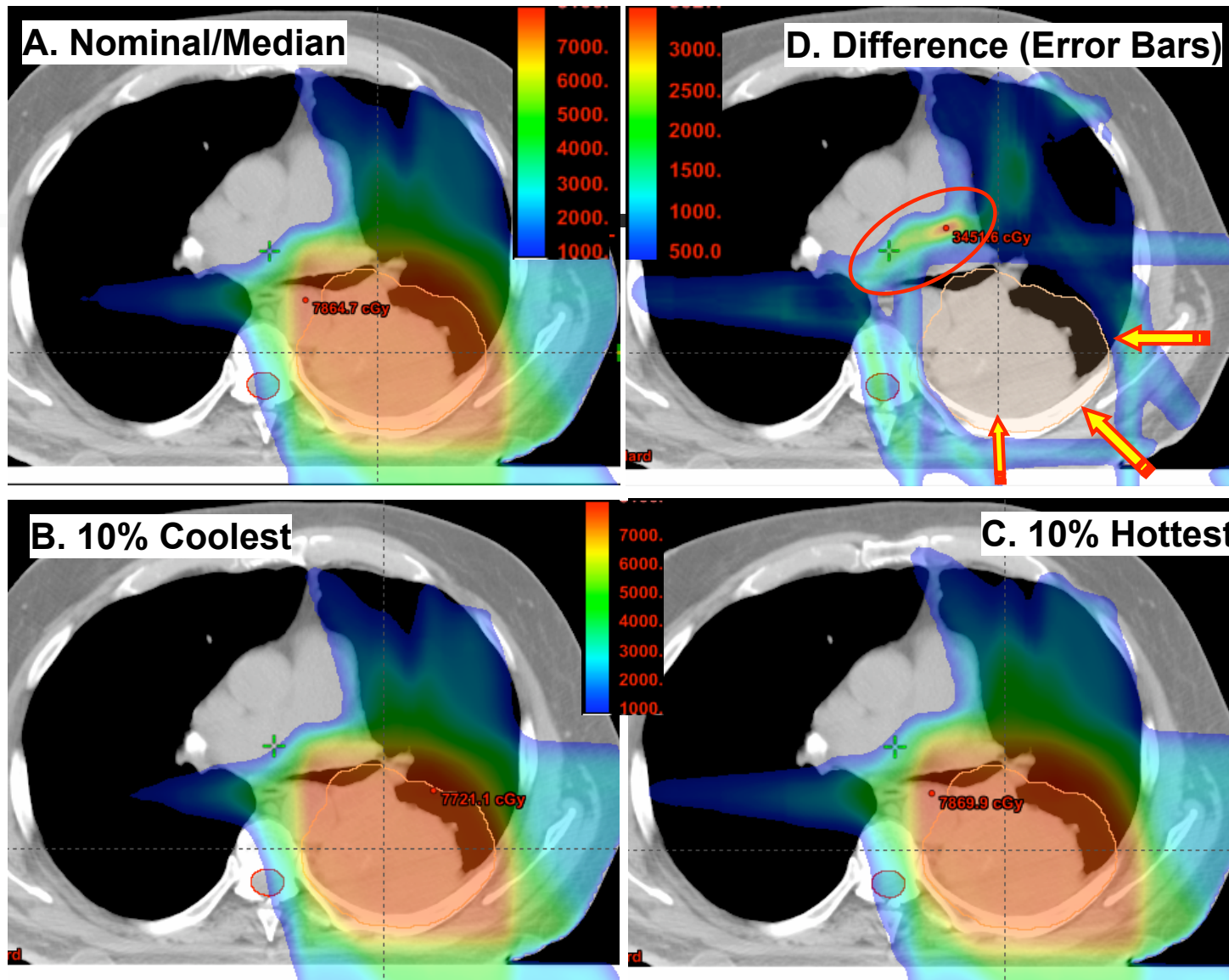
Dong, Zhang MDACC

Plan B has 10% probability that each voxel will receive the shown dose or lower
Plan C has 10% probability that each voxel will receive the shown dose or higher
Plan D is (hottest − coolest) and shows the range of doses each voxel may receive
It also indicates that target is covered adequately & greatest uncertainty is outside

How Do We Verify Plans are Worthy of Our Trust?

- **Verification in a phantom is necessary but not sufficient**
- **Other possibilities**
  - **In-vivo dosimetry**
  - **Treatment-time imaging + MC calculations**

Clinical Trials

- **The fact that protons are more vulnerable to uncertainties is not necessarily a case for equipoise**
  - It would be unfair to compare current states of the art of IMRT and proton therapy
- **Randomized trials must consider uncertainties and how they may affect each modality when comparing different arms**
  - Best estimates of dose distribution actually delivered should be made

MDACC Proton vs. Photon Randomized Trials

- **Stage II-IIIB NSCLC randomized trial:** The motivation for this trial is that a reduction in the rate of pneumonitis with equivalent tumor control may be realized using **protons compared to photons** in patients with stage II-IIIB NSCLC receiving concurrent chemotherapy and will be tested in a **Bayesian adaptive randomized trial**.

MDACC Proton vs. Photon Randomized Trials

- **Stage I/II (T1-3N0M0) NSCLC randomized (adaptively) trial:** **The goal of this trial is to determine if optimized image-guided proton therapy with standard fractionation and higher biologically equivalent dose (BED) compared with the highest dose regimen safely achieved with photon therapy can lead to improved local control and quality of life in centrally located stage IA NSCLC or stage IB and selected stage II (T3N0M0) NSCLC.**

Summary

- **Appearances can be deceiving (WYS ≠ WYG)**
- **Protons are more sensitive and vulnerable to uncertainties**
  - **Error bars are larger**
- **To exploit the full potential of protons, we need to**
  - **Improve understanding of physics, biology and clinical issues**
  - **Improve technology**
    - **Planning systems**
    - **Delivery systems**
  - **Reduce uncertainties (Achieve WYS ≅ WYG)**
  - **Conduct physics studies and clinical trials**

Summary

- **Protons are good**
- **Whether the current state of the art is good enough is questionable**
- **But can be much better**

Achieving WYS = WYG is an essential

And is equivalent to going from Faith-Based PT to Faithful PT

Acknowledgements

Thanks

Clinical Trials

- **Strategies to advance the state of the art need to be developed**
  - **They are likely to be different compared to photons (e.g., distal edge degradation problem, management of motion for IMPT vs. IMRT)**

- **This does not necessarily mean that we need to wait to conduct trial – only that we need to collect sufficient information (e.g., repeat imaging data) to evaluate the consequences of uncertainties**

- **We may not be able to the advantage of one modality vs. another; but may be able identify the reasons for the observations**

Clinical Trials

- **MDACC is proposing to conduct randomized trials for lung – using ADAPTIVE RANDOMIZATION**
  - **3DCRT vs. IMRT vs. Proton therapy of locally advanced NSCLC**
  - **IMRT at photon MTD vs. IMPT at proton MTD**

Protons Stop, But Exactly Where?
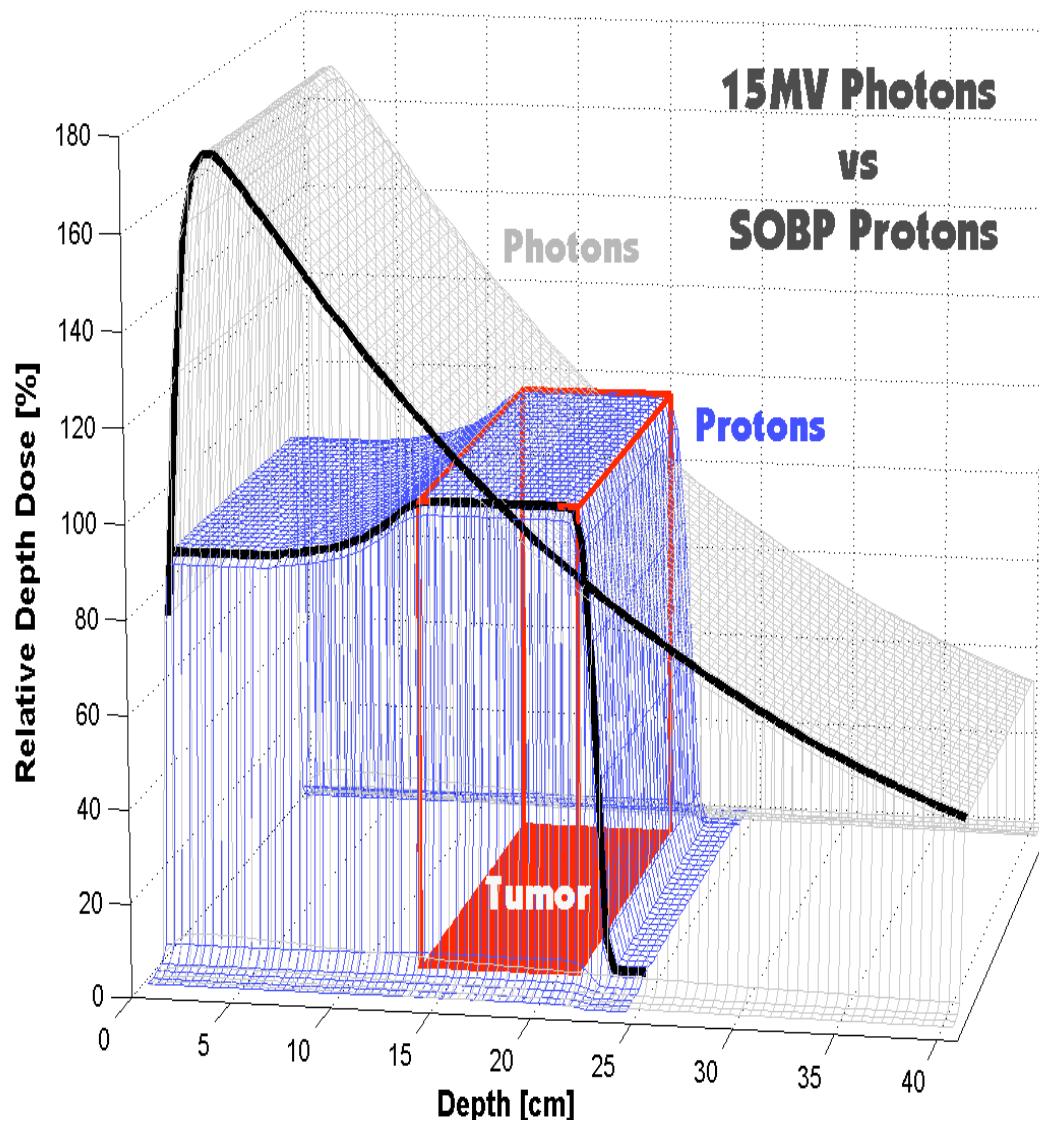
On a dime?

Is the distal fall-off as sharp?

And conducting trials, especially randomized trials of photons and protons is not easy

- **Several articles and editorials on the subject**
- **Some say it is not necessary to conduct randomized trials**
- **At least controlled**

Achieving WYSIWIG in Proton Therapy

- **What you see on a proton treatment may be significantly different from what the actually patient gets**

- **Probable causes**

  - **Intra-fractional motion**

  - **Inter-fractional changes and set up uncertainties**

  - **Uncertainties in data (e.g. CT artifacts) used to compute dose distributions**

  - **Approximations in computational models**

  - **Biological factors**

Achieving WYSIWIG in Proton Therapy

- **What are the consequences of WYS ≠ WYG?**
  - **Larger margins, certain directions avoided**
  - **Insufficient knowledge of dose actually delivered**
  - **Week correlation of response to dose distributions**
  - **May not fully exploit the potential of PT**

NSCLC Proton Therapy at MDACC
- Esophageal Reaction

Cox
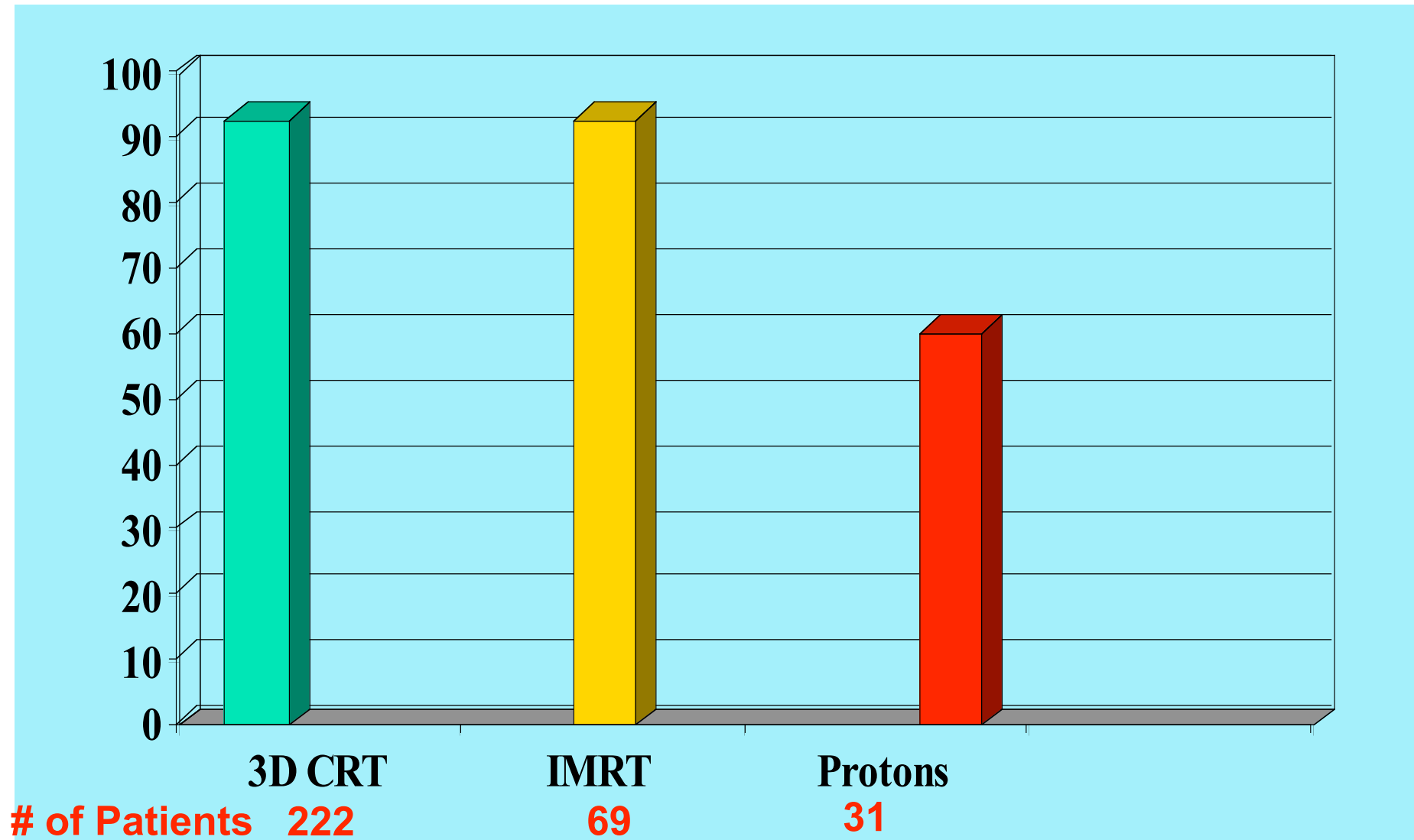
Proton Plan Robustness
Assigning Appropriate Error Bars

- **Considering that uncertainties affect protons and photons differently and are incorporated differently in plans**

- **How do we ensure target coverage and sparing of normal tissues, especially for reduced margins?**

- **How do we compare a proton plan with a photon plan?**

- **How do we add a proton plan to a photon plan?**