Citation Key

for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

Public Domain – Government: Works that are produced by the U.S. Government. (17 USC § 105)

Public Domain – Expired: Works that are no longer protected due to an expired copyright term.

Public Domain – Self Dedicated: Works that a copyright holder has dedicated to the public domain.

Creative Commons – Zero Waiver

Creative Commons – Attribution License

Creative Commons – Attribution Share Alike License

Creative Commons – Attribution Noncommercial License

Creative Commons – Attribution Noncommercial Share Alike License

GNU – Free Documentation License

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

Public Domain – Ineligible: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

Fair Use: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

Introduction to Radiation Oncology - Clinical

Ted Lawrence, MD, PhD

Department of Radiation Oncology

University of Michigan

Winter 2009

Who Cures Cancer?

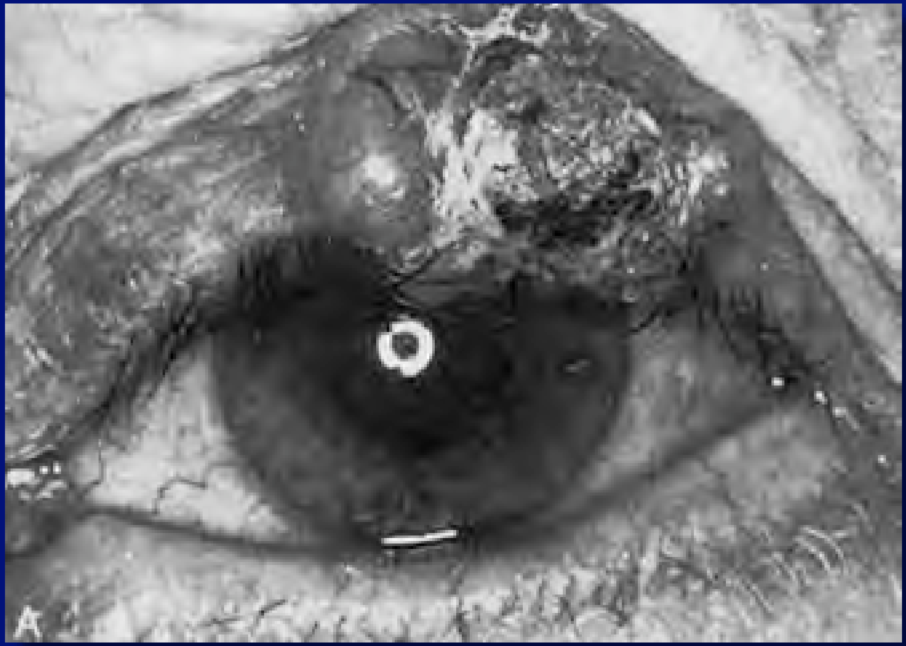
- Surgery - 150,000 patients per year
- Radiation - 85,000 patients per year
- Chemotherapy - 15,000 patients per year!

Vincent DeVita, NCI Grant Rounds, 1983

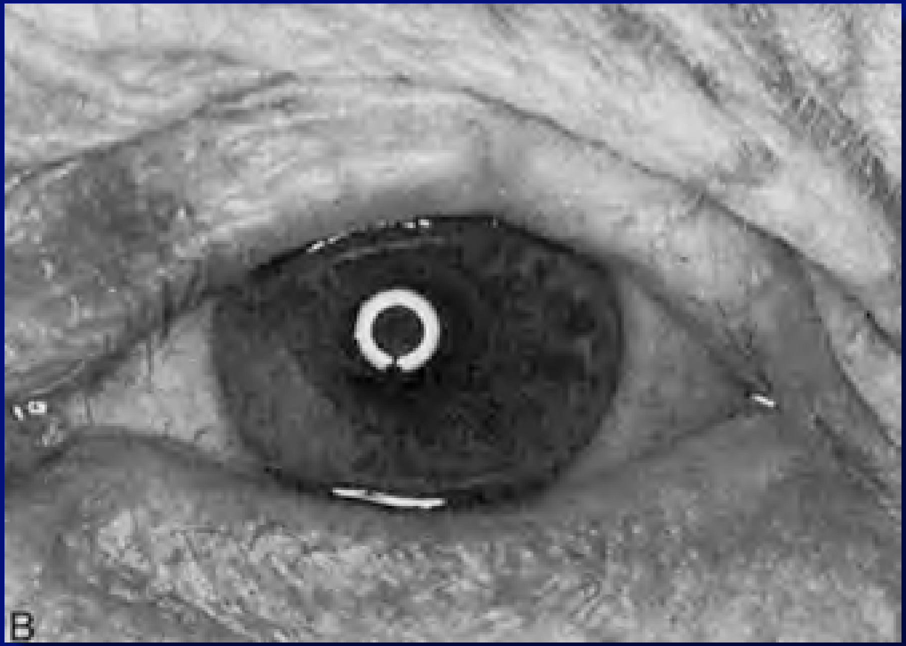
Standard radiation alone can cure

- Brain tumors (low grade)
- Head and neck cancers (early stage)
- Skin cancers (all)
  - Especially lip, eyelid, nose, and ear
- Lymphomas (all but advanced stage)
- Seminoma (all but advanced stage)
- Soft tissue sarcoma (any stage)
- Lung cancer (early stage)
- Cervix and endometrial cancer (early stage)

Treatment of Skin Cancer



PD-INEL Source Undetermined



PD-INEL Source Undetermined

And has an important role in palliation

- Brain metastases
- Lung metastases
  - Producing airway obstruction or superior vena cava syndrome
- Bone metastases
  - Producing spinal cord compression
- Esophageal obstruction
- Bile duct obstruction

Improving outcome: Individualizing Therapy

- **By improving our ability to hit the tumor and miss the normal tissue**

- **By customizing combinations of radiation with chemotherapy or molecularly targeted therapy**

- **By assessing tumor and normal tissue response during treatment and tailoring therapy to these responses**

Radiation therapy: *The process*

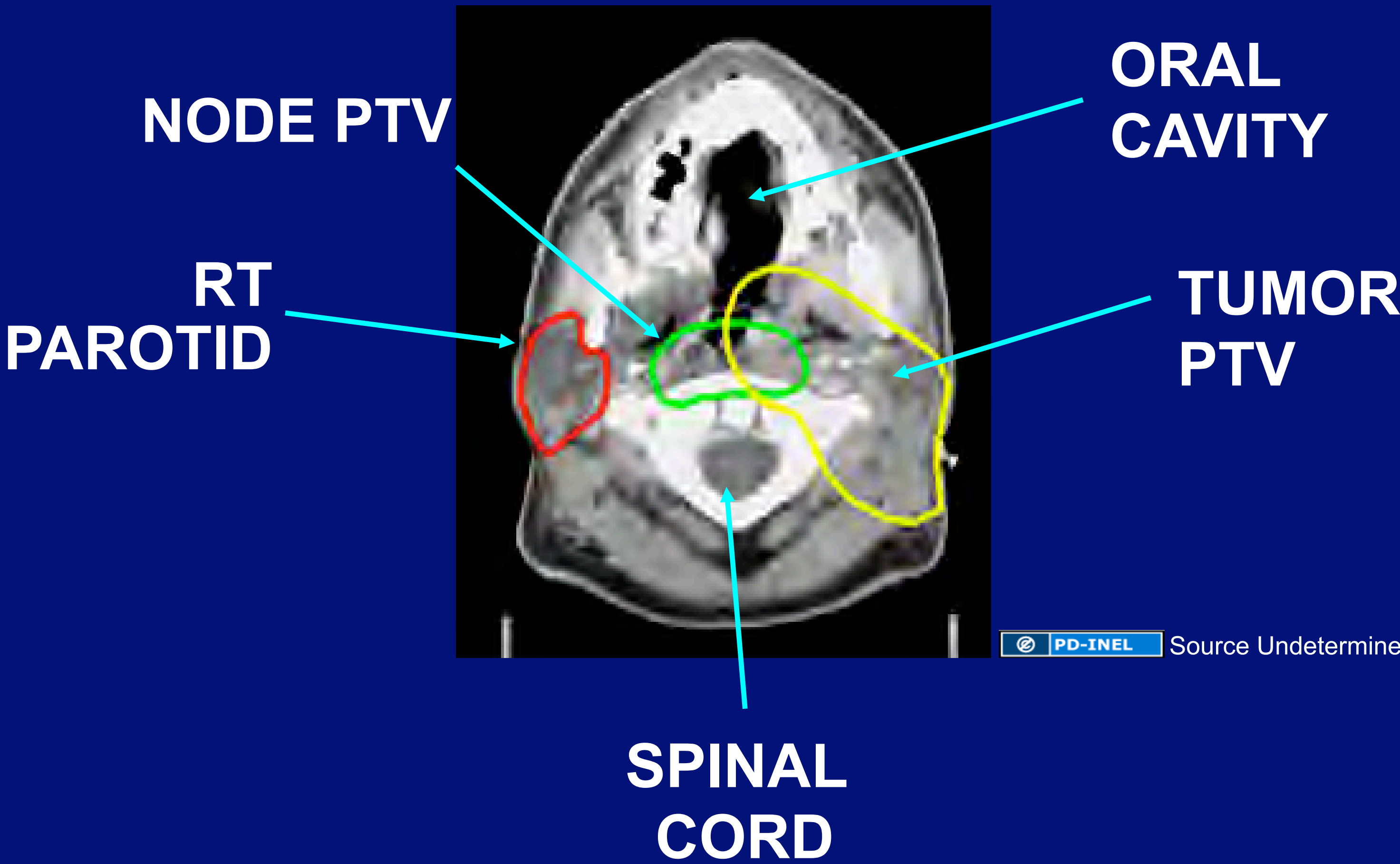
- **Treatment planning**
  - **Determine 3D orientation of tumors and normal tissues**
  - **Planning radiation**
    - Conformal treatment
    - Tools to quantify dose (dose-volume histograms)
- **Position patient and tumor**
  - **Localize patient on treatment machine**
  - **Account for organ motion**
- **Treatment delivery**

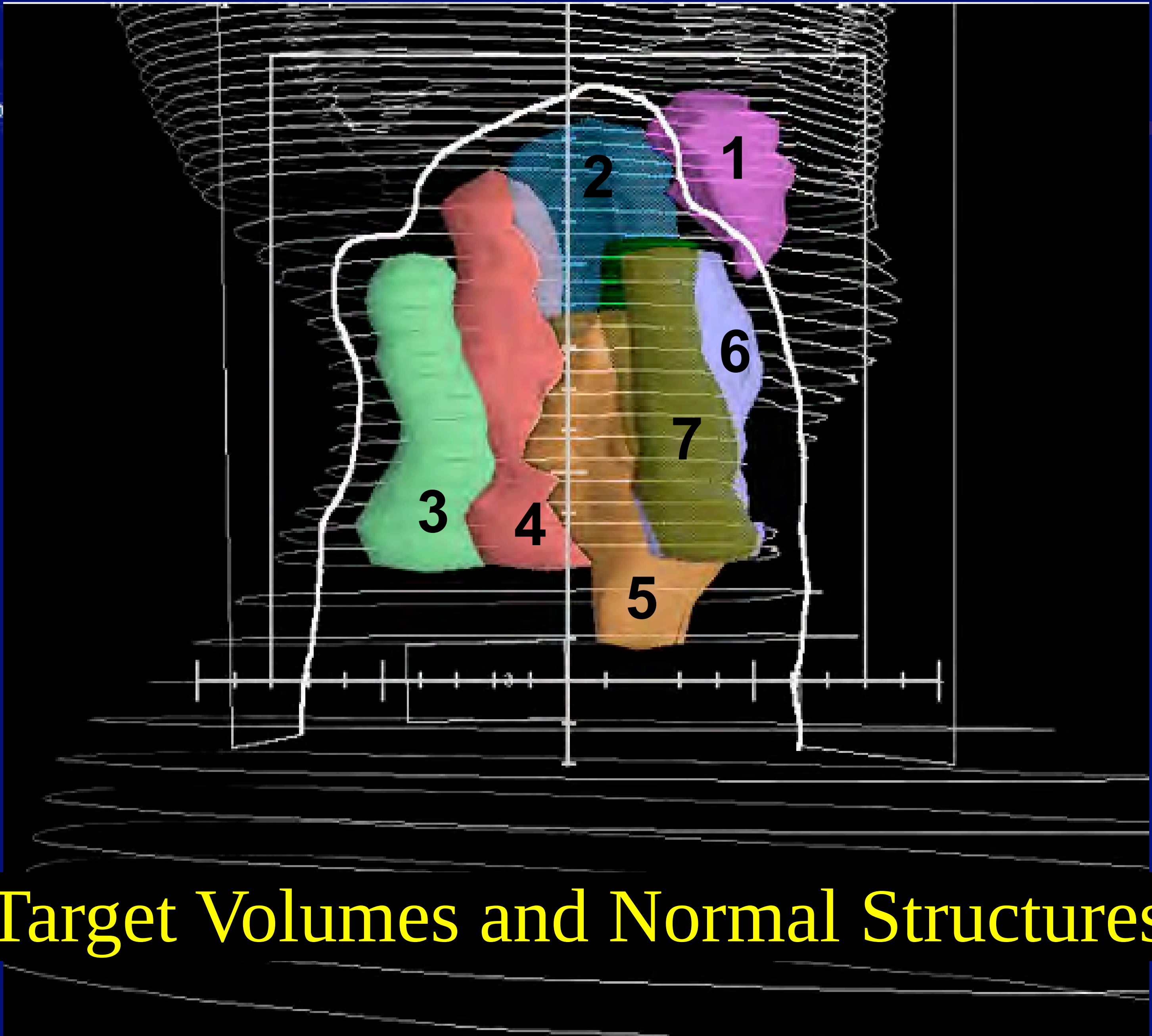
"Standard" Radiation Therapy

- Treatment based on population estimate of what might control a tumor
- Estimate the risk of normal tissue damage base on the most sensitive 5% of the population
- Treatment delivered to initially prescribed dose
  - Stop only for unacceptable acute toxicity
- Emphasis making isodose lines conform more tightly to the tumor

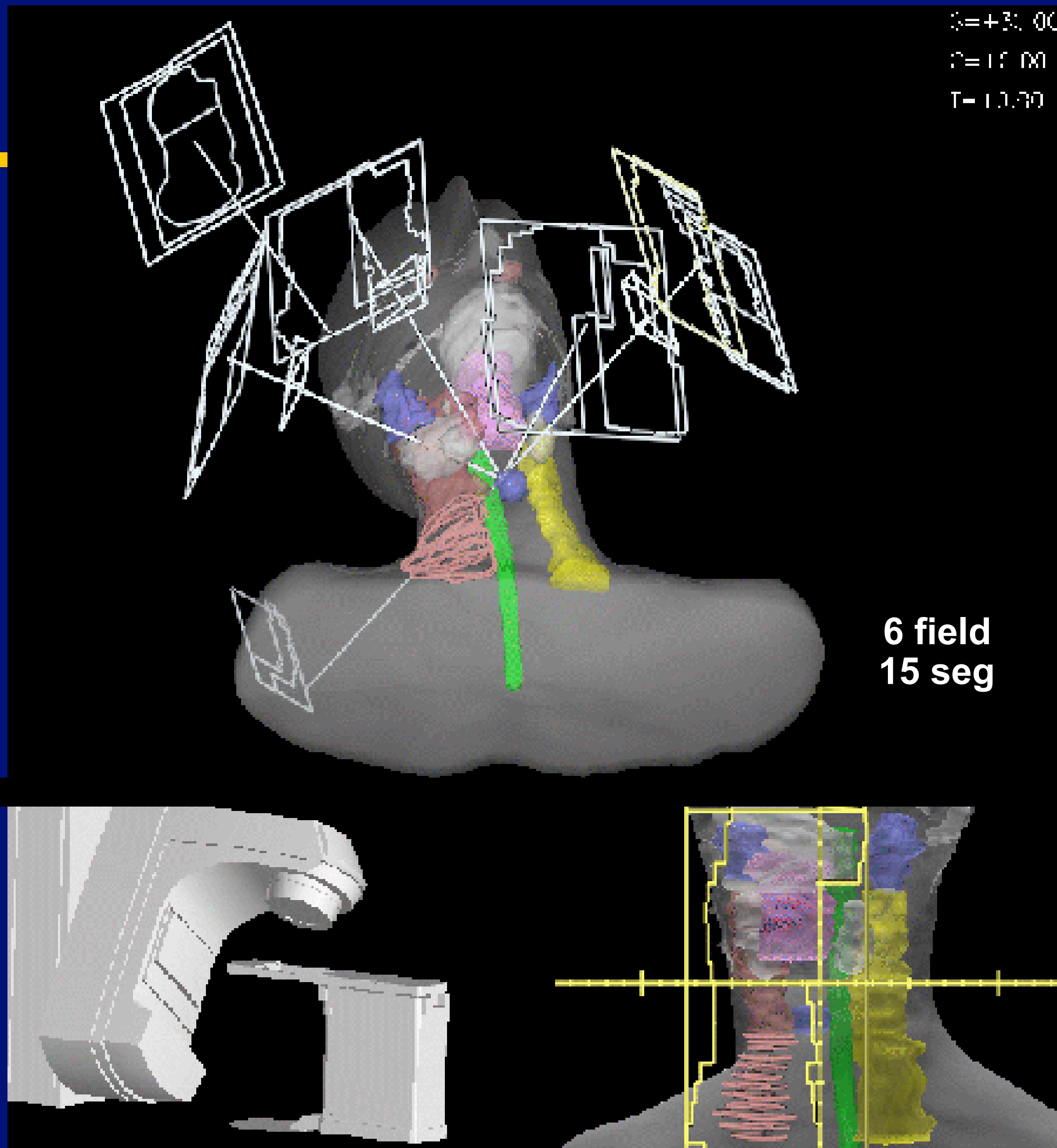
Partial Parotid Gland Sparing:

Conformal Techniques in Patients Undergoing Bilateral Neck Irradiation

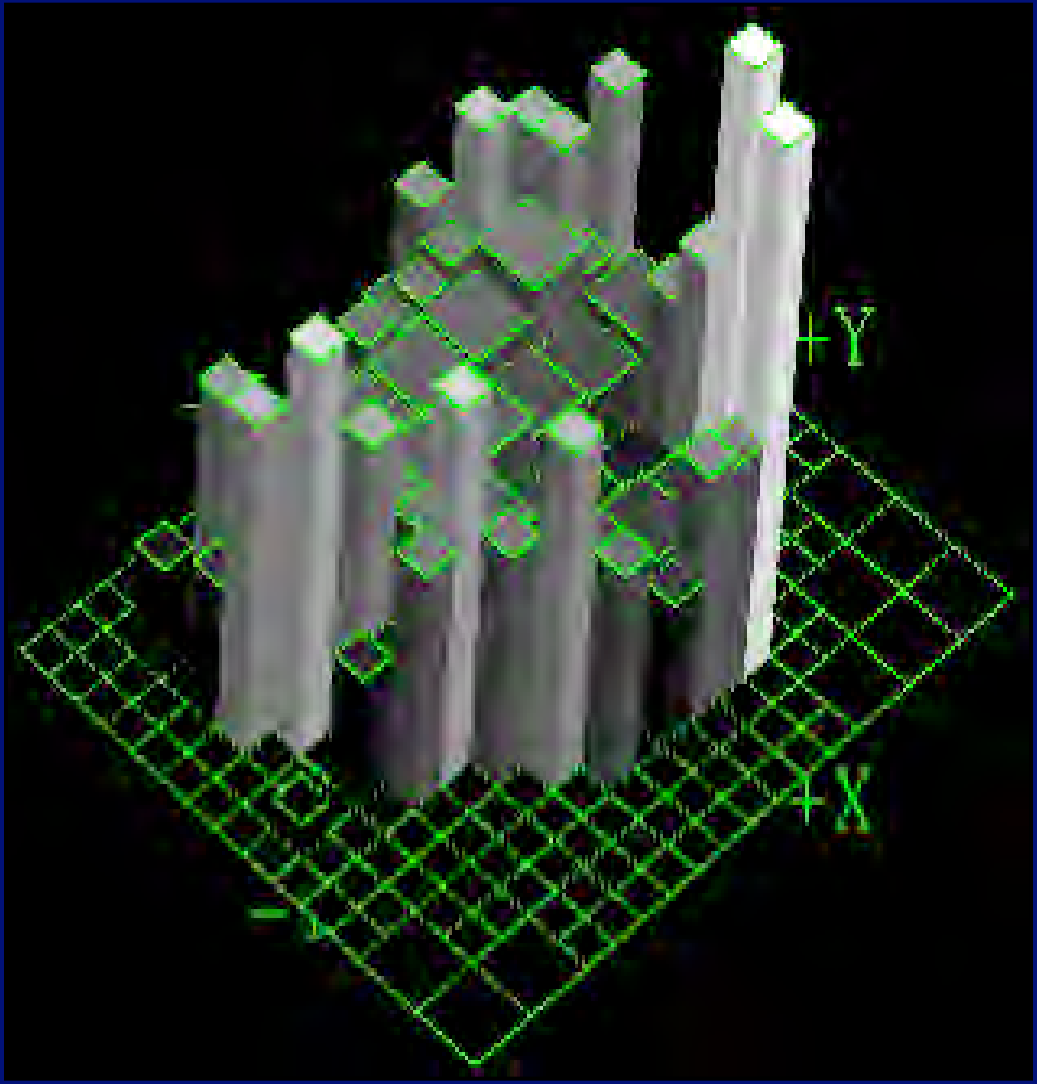


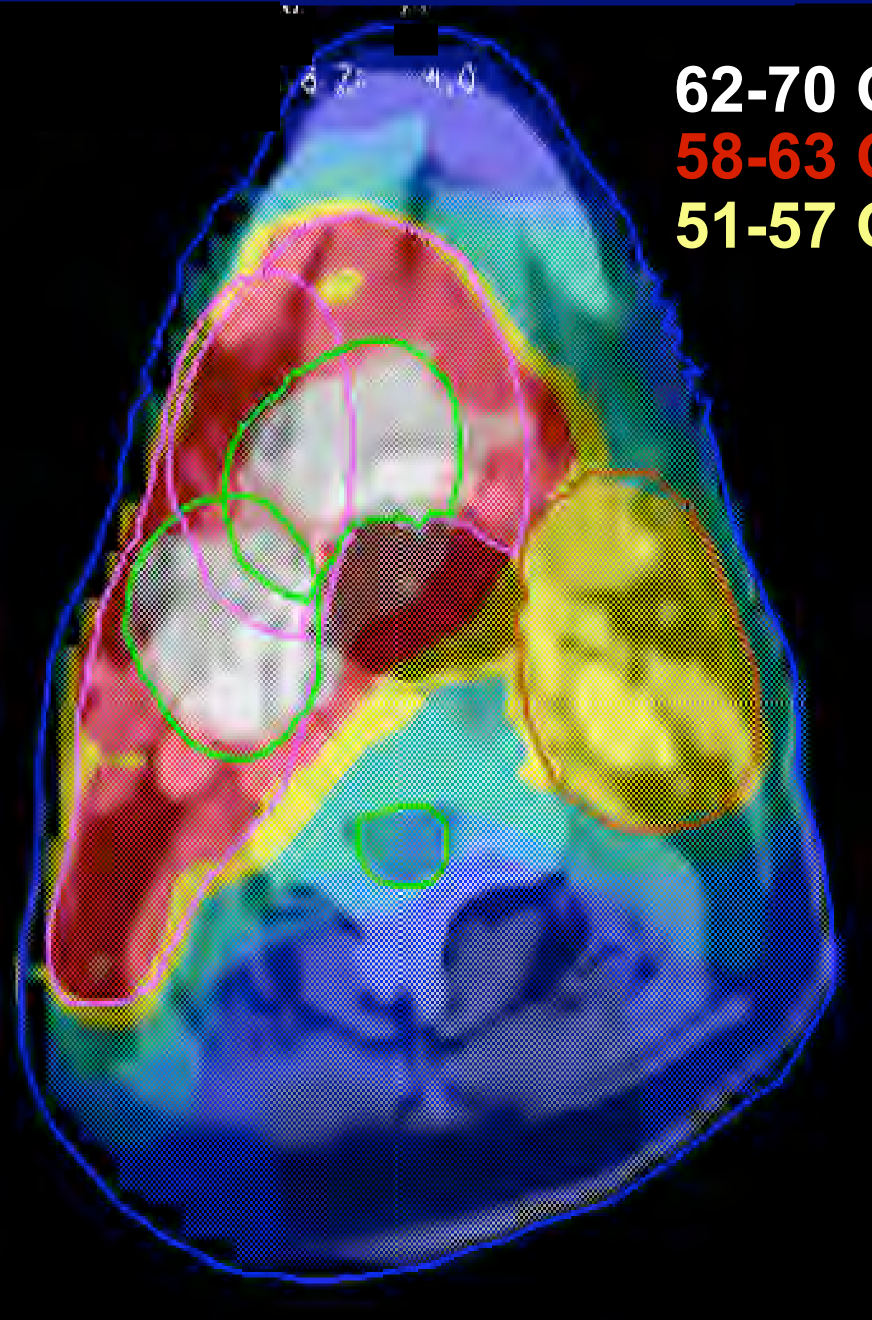


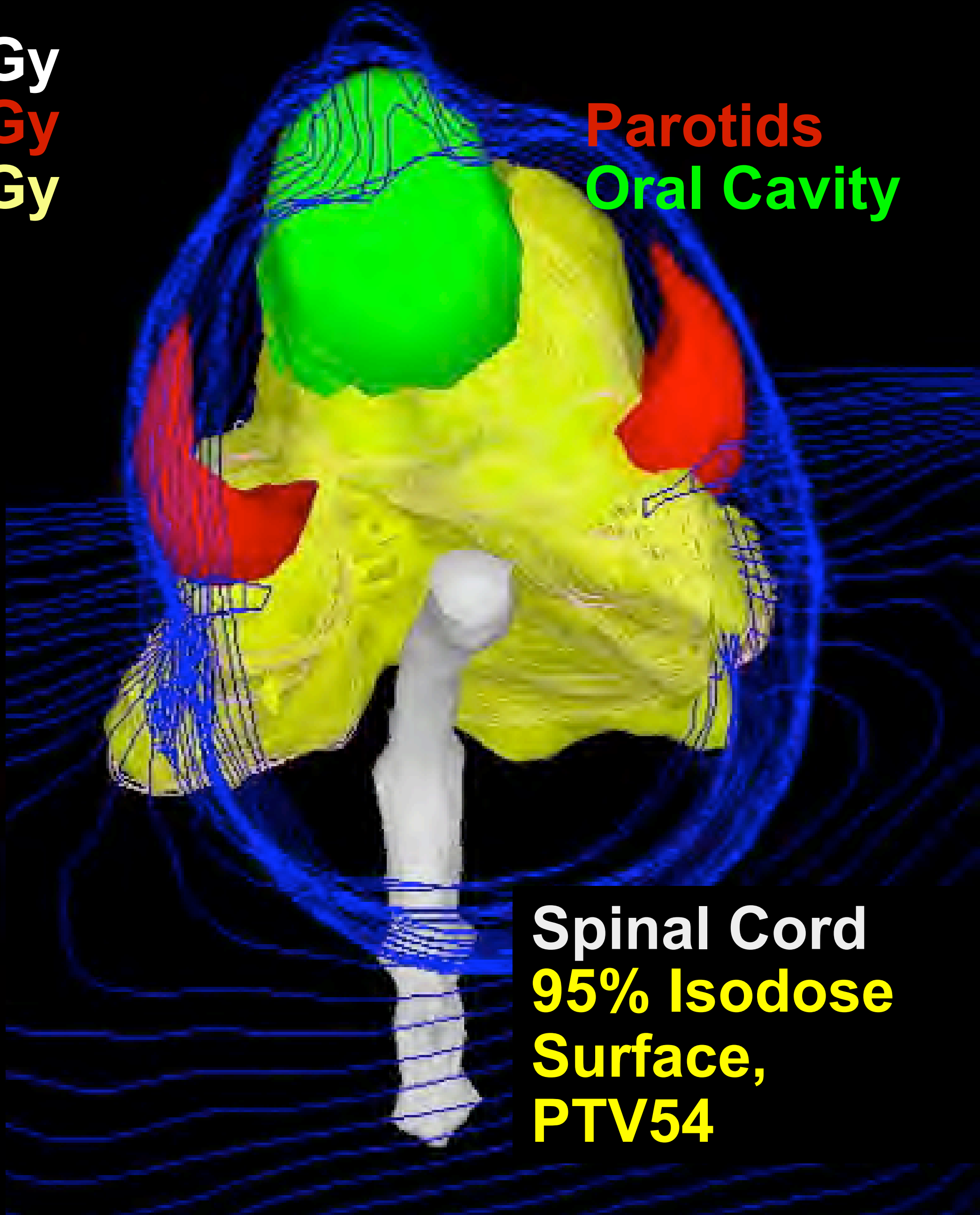
Target Volumes and Normal Structures


6 field
15 seg

Intensity Modulated Radiation Therapy (IMRT)




62-70 Gy
58-63 Gy
51-57 Gy

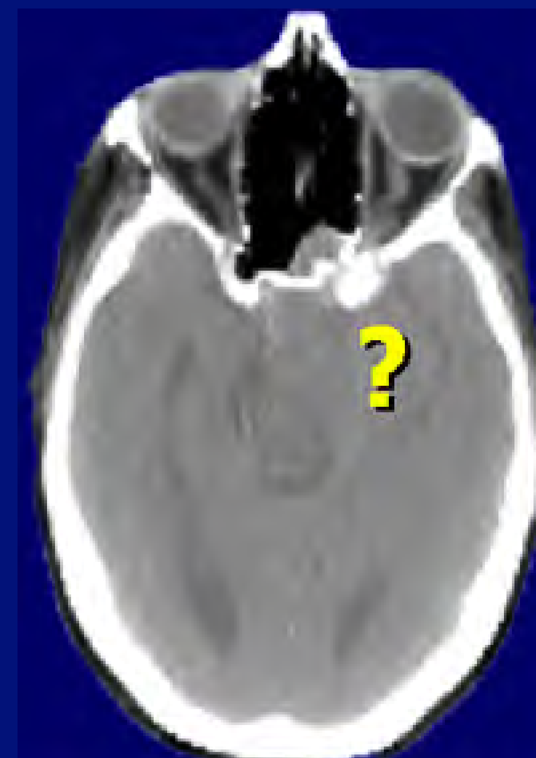

Parotids
Oral Cavity
Spinal Cord
95% Isodose Surface, PTV54

MR-CT Registration

Move info between MR and CT

regions

doses

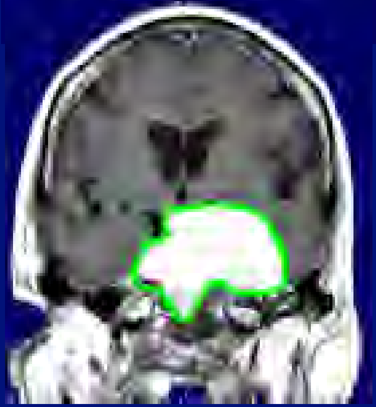


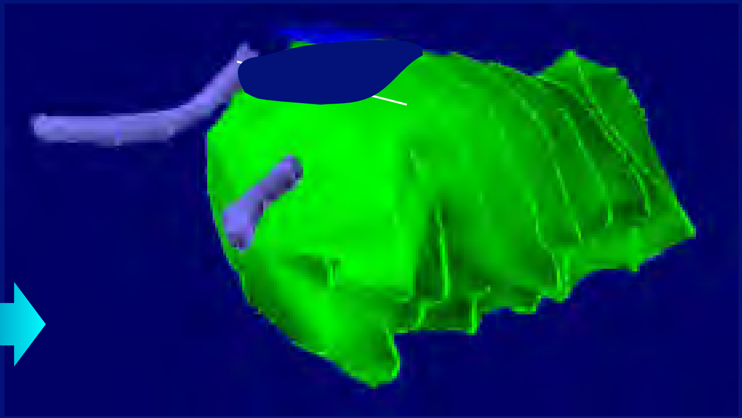
 Kessler, University of Michigan

Target Volume Definition

Define volumes on MR data

Axial "Target"

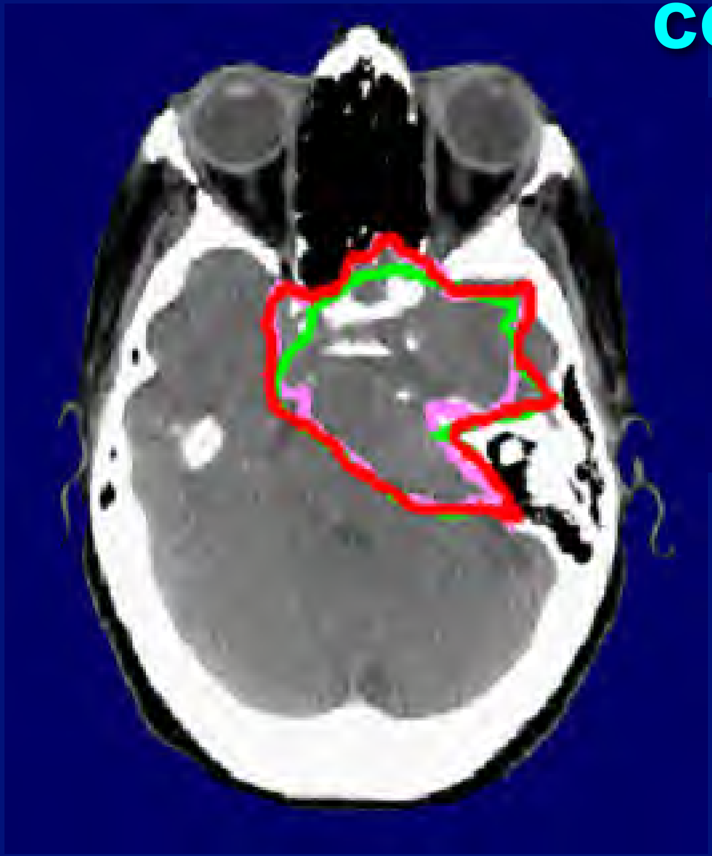




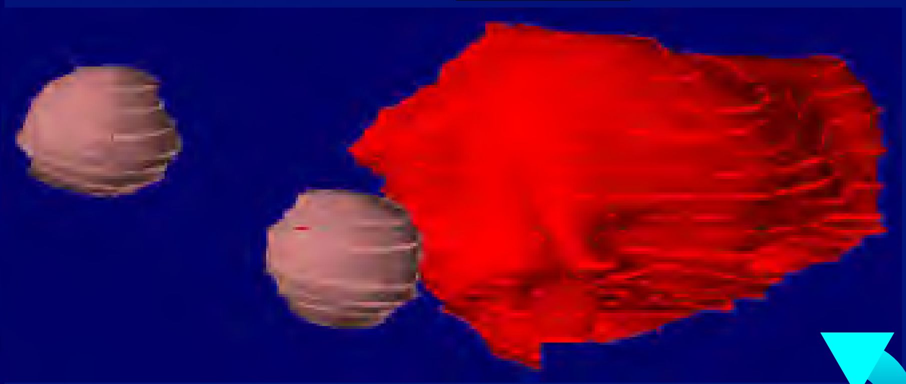
Coronal "Target" + Optic Structures

Target Volume Definition

Map to CT data and combine



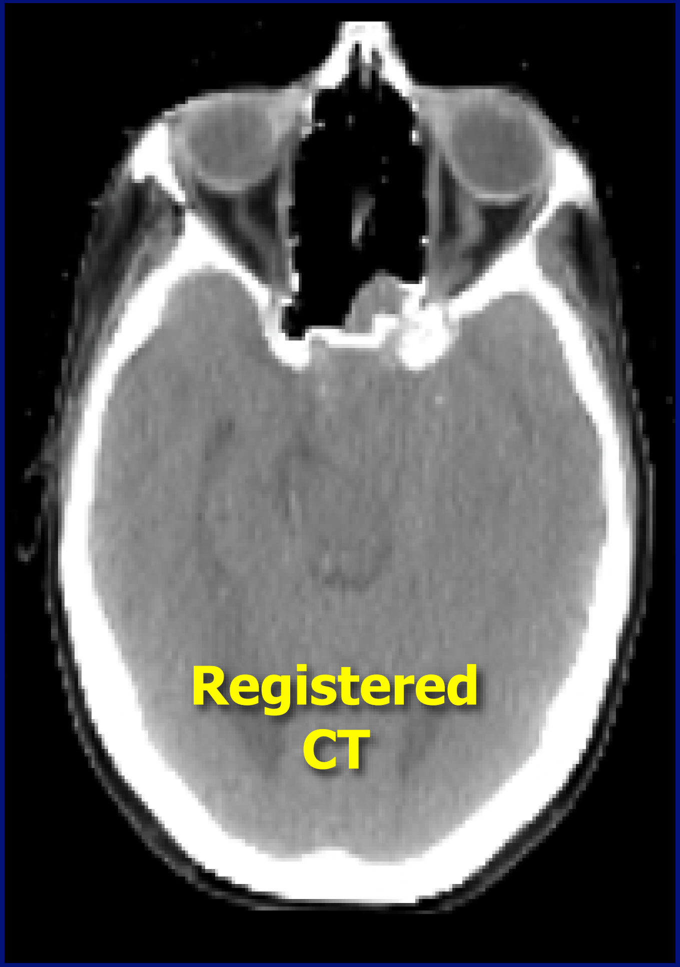
PD-INEL Source Undetermined

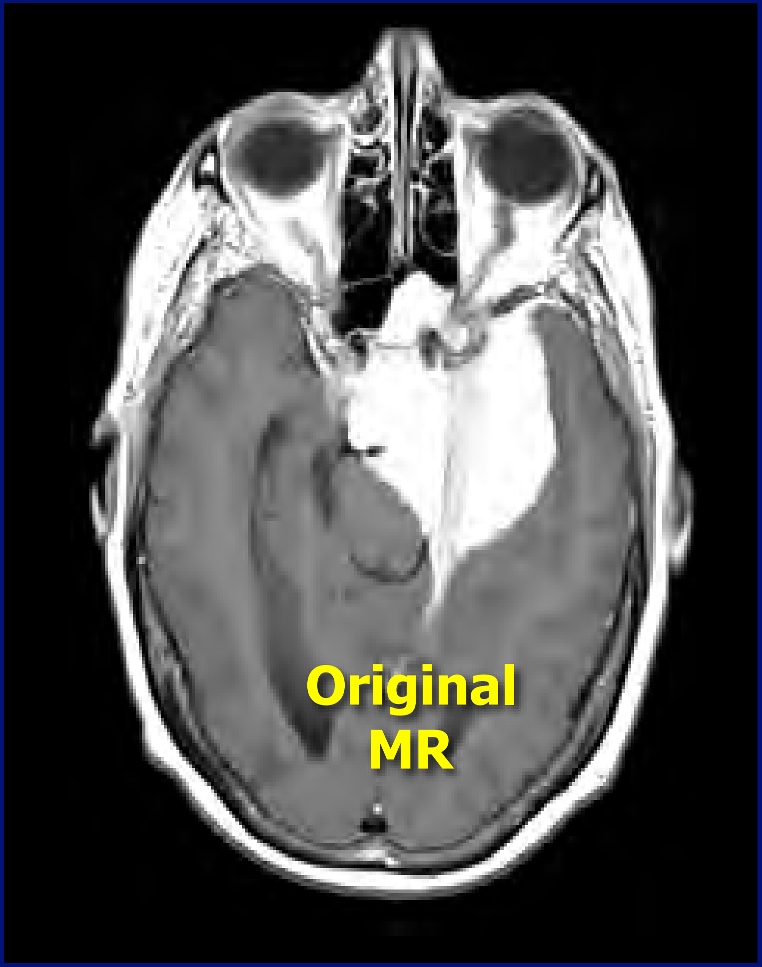


MR-derived
CT target volume !

PD-INEL *Kessler, University of Michigan*

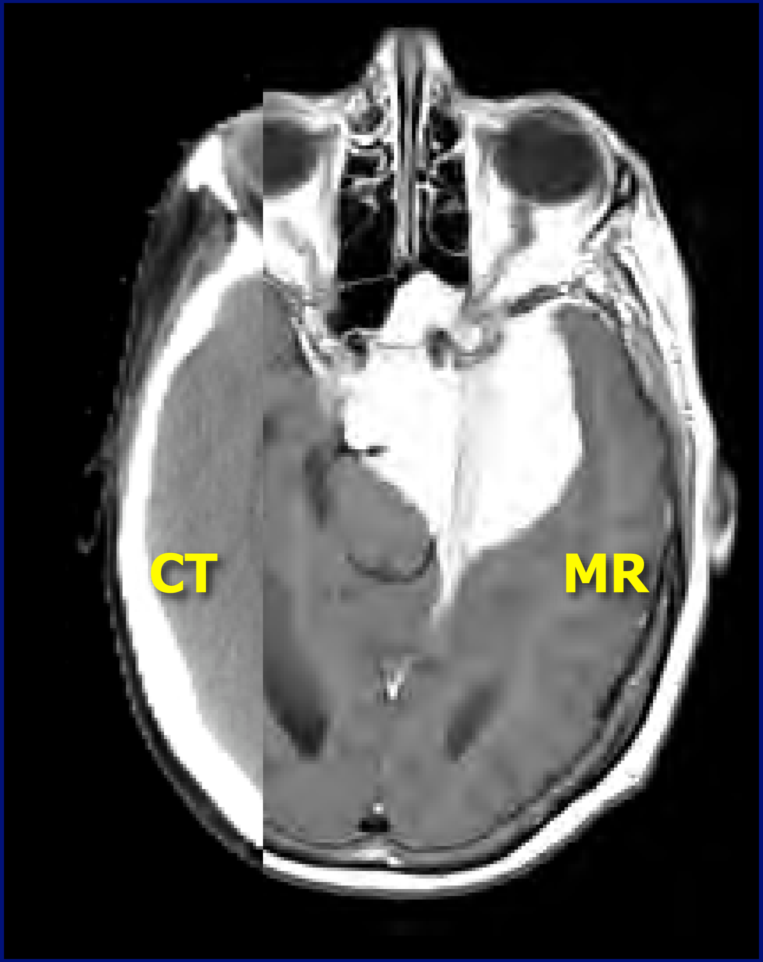
Brain Example



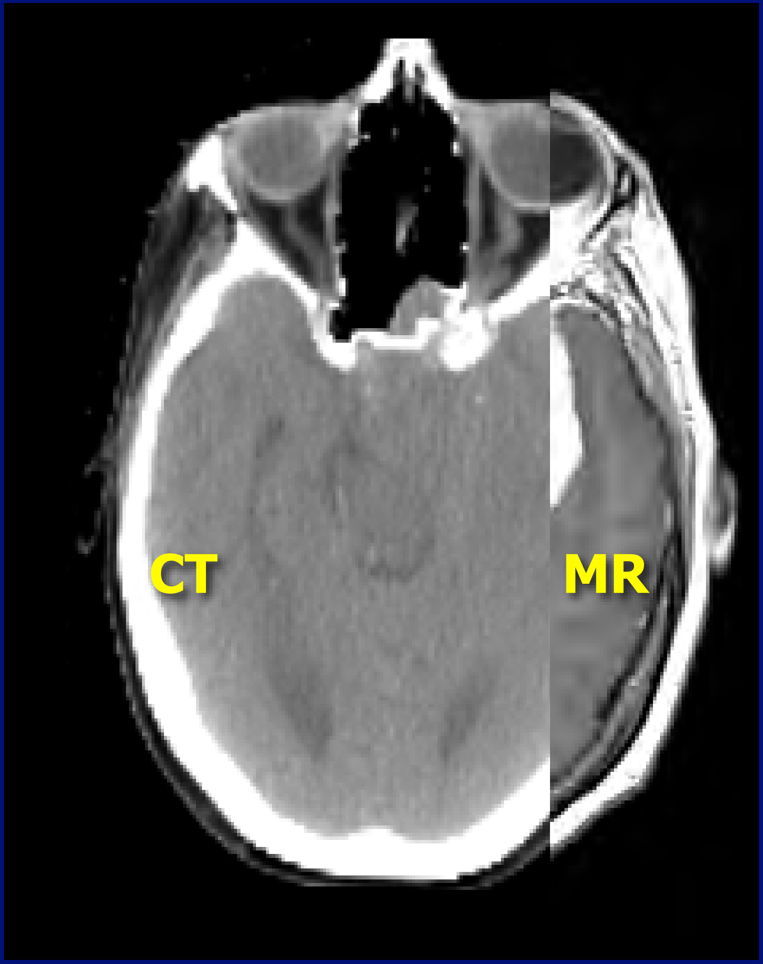


University of Michigan Medical School

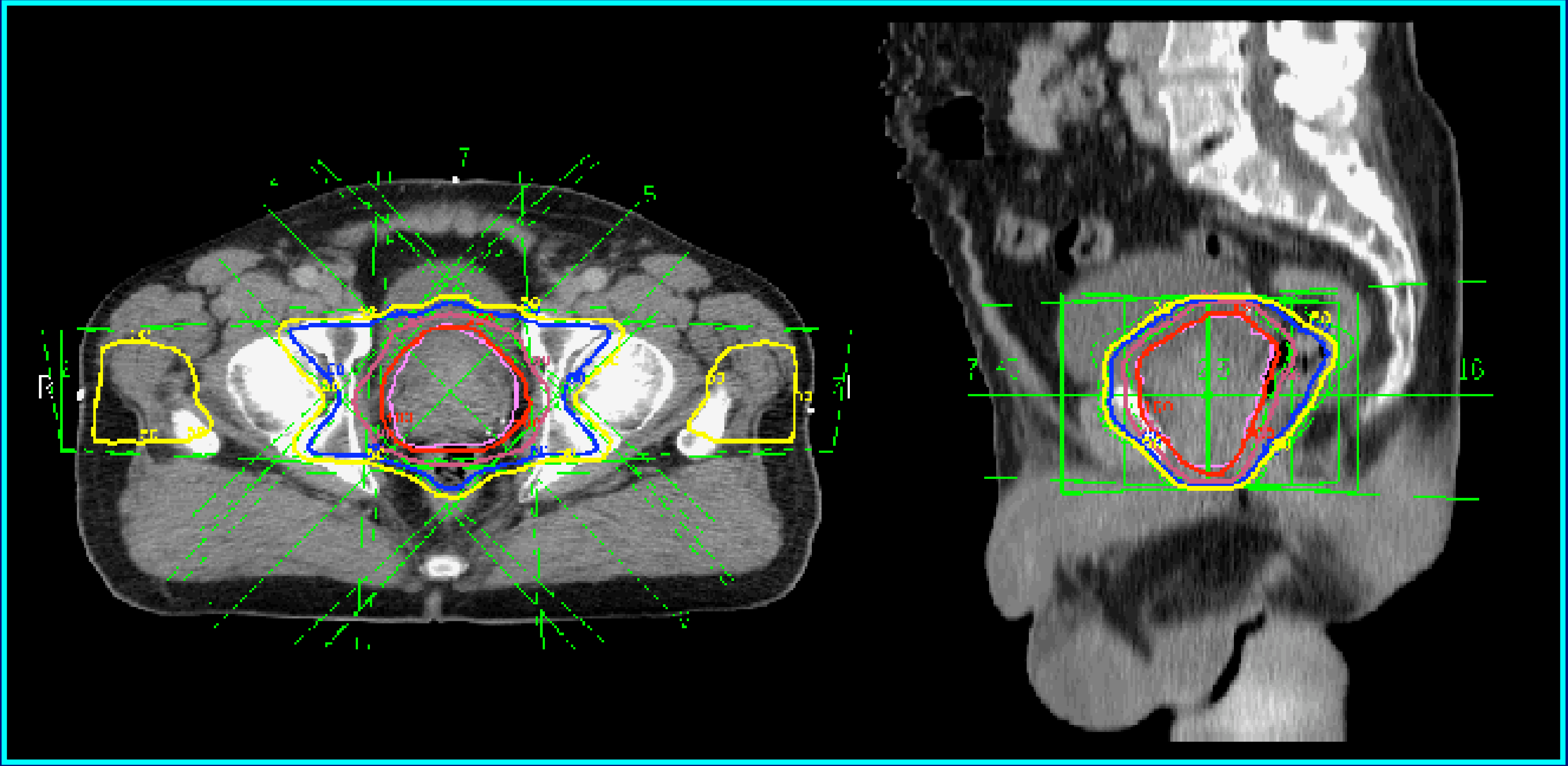
Brain Example



Brain Example

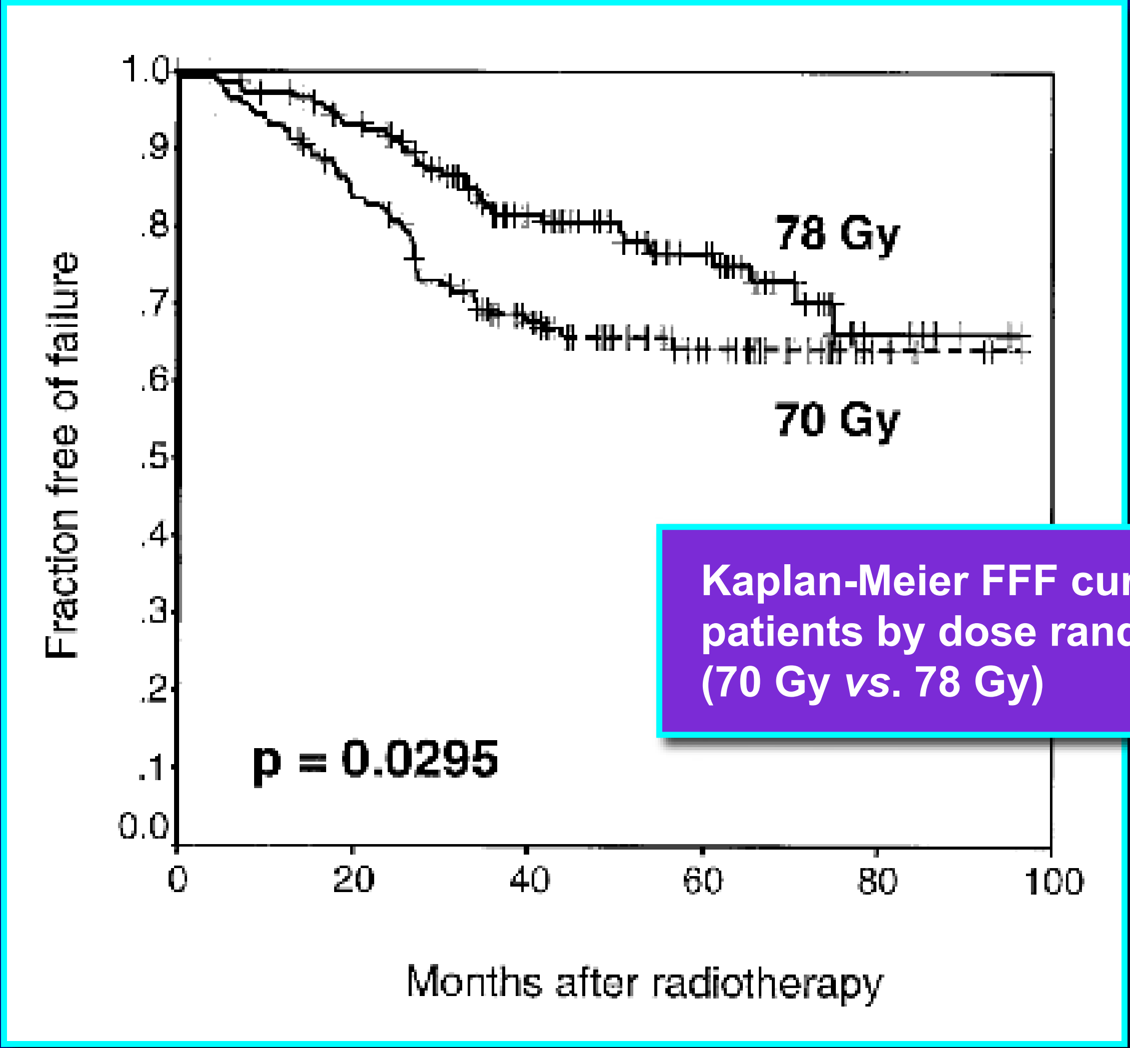


Six Field Prostate



 Ten Haken et al Int J Radiat Oncol Biol Phys 16:193, 1989

All Patients by Dose Randomization

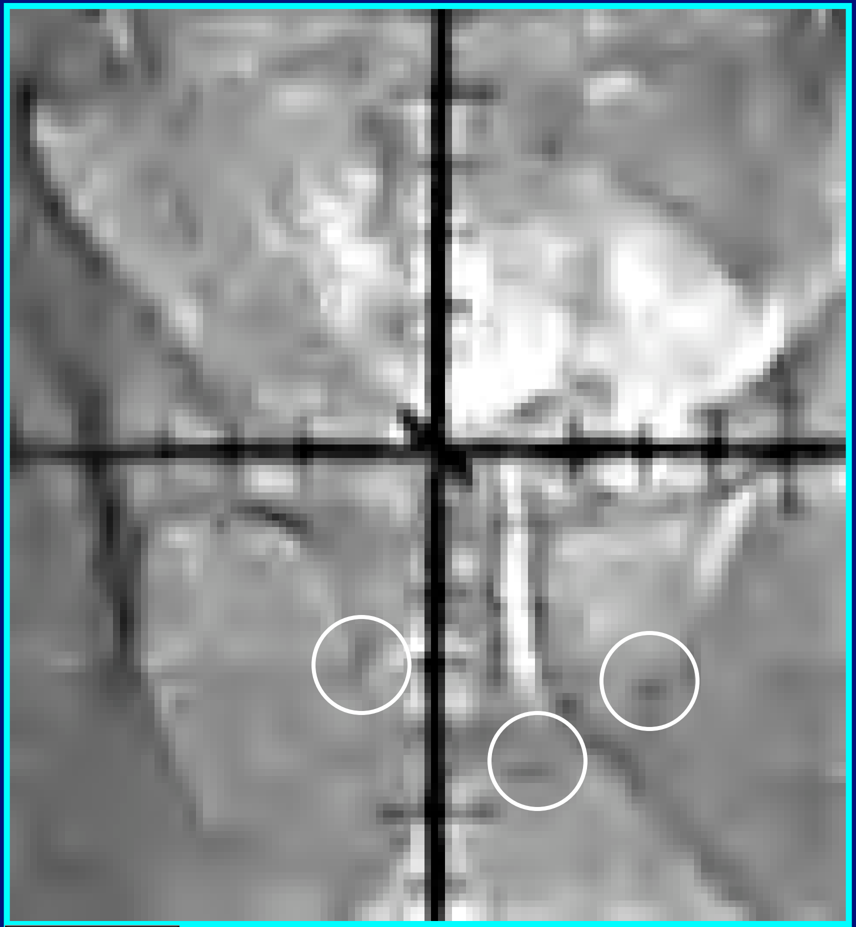


Kaplan-Meier FFF curves for all patients by dose randomization (70 Gy *vs.* 78 Gy)

PD-INEL Pollack, et. al., IJROBP, 53:5, 2002

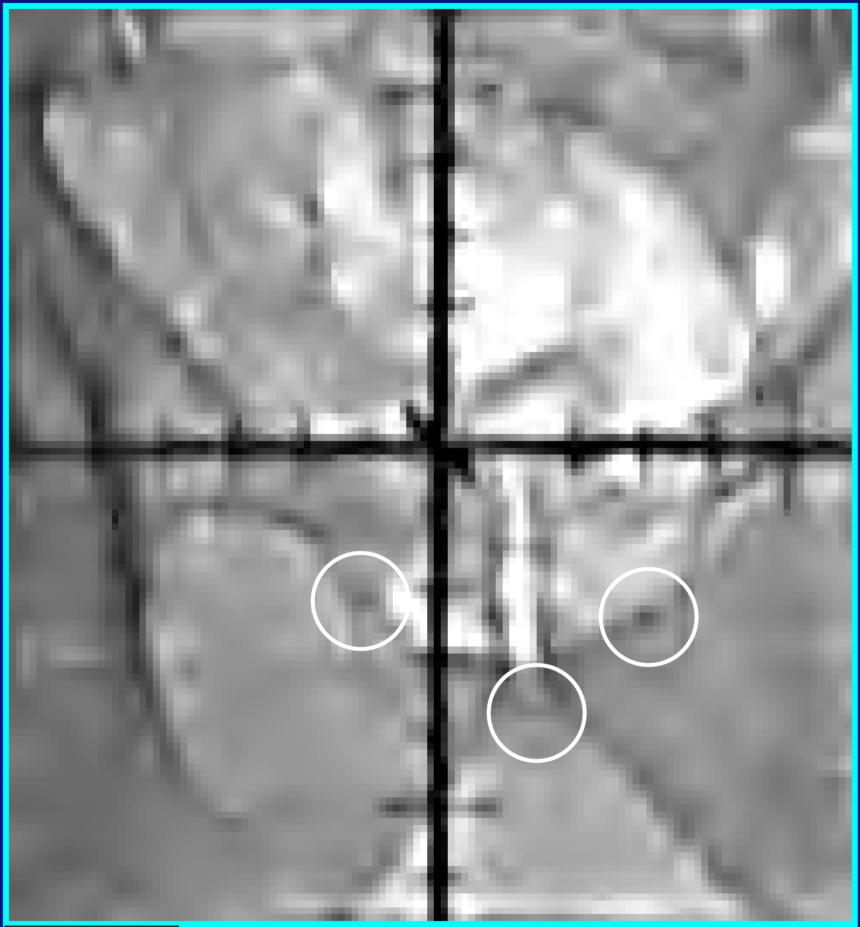
Prostate Motion

Inhale



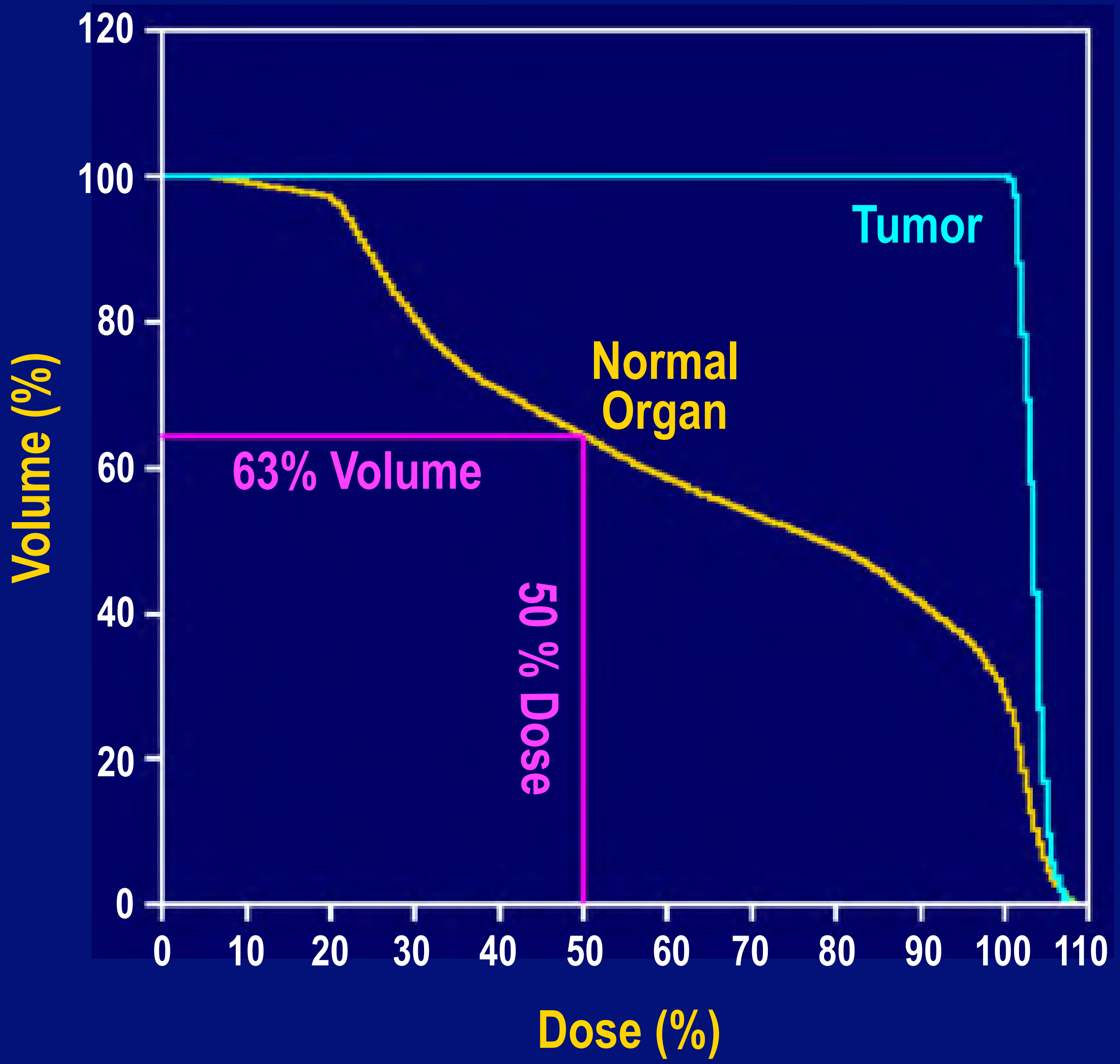
PD-INEL Source Undetermined

Exhale



PD-INEL Source Undetermined

Dose Volume Histogram (DVH)



Two hypotheses

- Unresectable intrahepatic cancer could be cured by radiation (± chemotherapy) if a high dose could be given
- A high dose could be safely given if we
  - Limited the dose to the normal liver
  - Understood how much of the liver could be irradiated safely
    - Requires knowing the relationship between the risk of complication and the DVH of the normal liver

Retrospective Analysis of RILD

- **Dose prescribed by volume of normal liver irradiated**
  - **Of 9 of 79 patients developed radiation-induced liver disease (RILD)**
- **Fit data to an NTCP model**
  - **Clinical guesses greatly overestimated the risk of partial liver radiation**
  - **Recalculated the parameters and fit the data to the model**

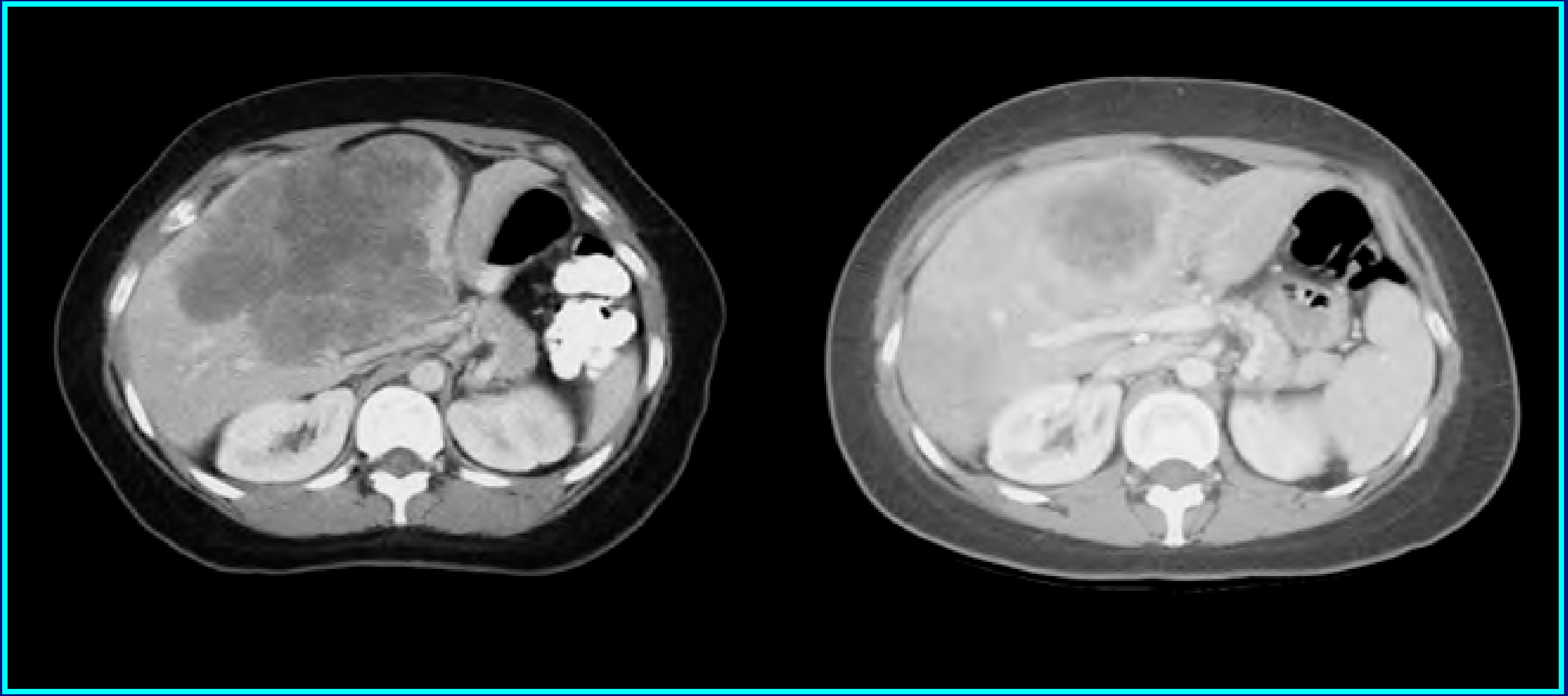
Lawrence TS, et al, Int J Radiat Oncol Biol Phys, 23:781, 1992

New Dose Escalation Trial

- Designed a prospective trial to test the model parameters
- We were able to deliver a median dose of 57 Gy
- The actual rate of complications (1/21 patients or 4.8%) was close to the calculated rate (9%)

McGinn CJ, et al, J Clin Oncol,16:2246, 1998

Radiographic Response

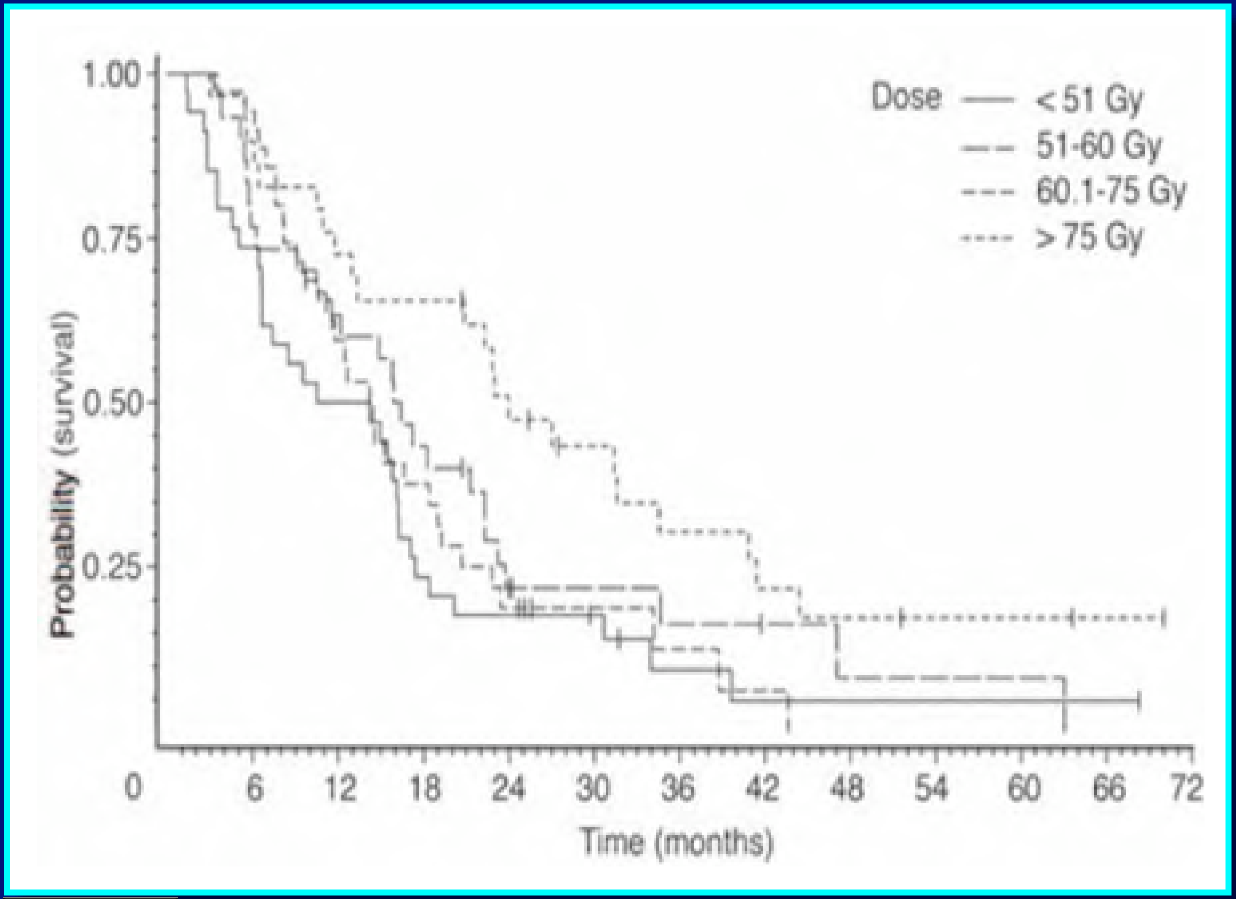


PD-INEL Source Undetermined

Pre-radiation

6 months post-radiation

Overall Survival of Patients by Dose Quartile



 Ben-Josef E., et.al, J Clin Oncol 23:8747, 2005

Improvements Over 2D Produced by Highly Conformal Therapy: *2007*

Organ	2D Max dose (Gy)	3D Max dose (Gy)	Benefit
Lung	60-70	102	1%/Gy 2 yr PFS
Prostate	68-70	78-86.4	1-2%/Gy increase in 5 year PFS
Liver	30	90	24 *vs* 6-10 mos OS for ≥70 Gy *vs* less
Head & Neck	70-76	70-76	↓ Xerostomia

PD-INEL T. Lawrence

Improving outcome: Individualizing Therapy

- **By improving our ability to hit the tumor and miss the normal tissue**
- **By customizing combinations of radiation with chemotherapy or molecularly targeted therapy**
- **By assessing tumor and normal tissue response during treatment and tailoring therapy to these responses**

Chemotherapy with Radiation is Superior to Radiation Alone

- High grade glioma
- Locally advanced head and neck cancer
- Stage III non-small cell lung cancer
- Esophageal cancer
- Pancreas cancer
- Cervix cancer
- Adjuvant therapy
  - Rectal cancer
  - Stomach cancer

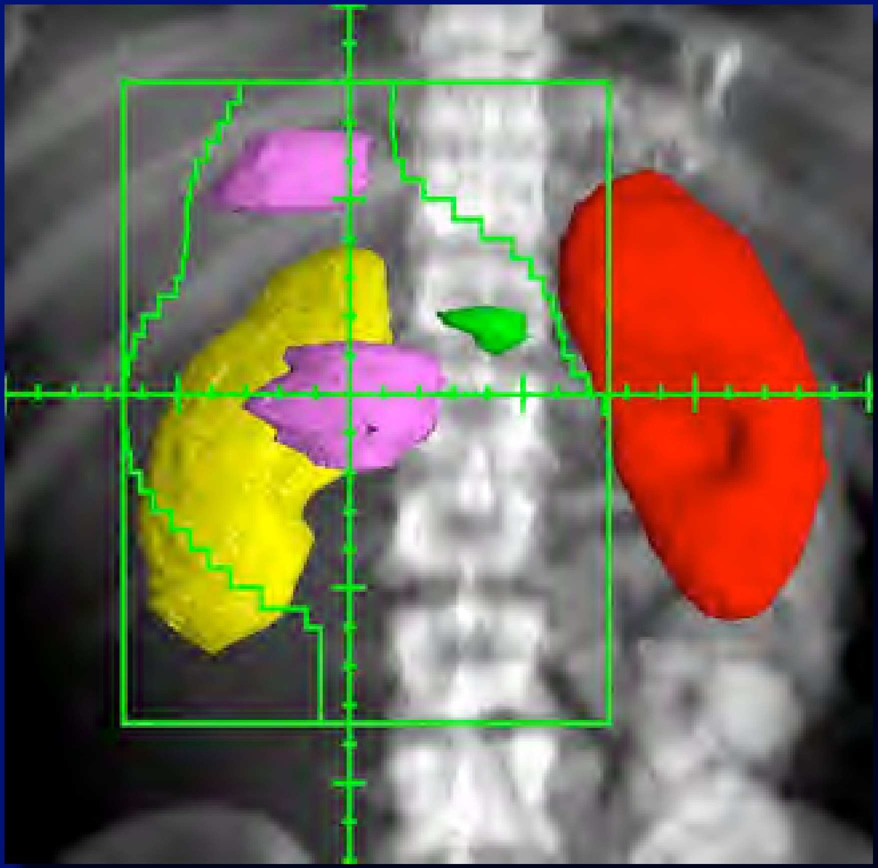
Chemotherapy with Radiation Permits Organ Conservation

- **Concurrent**
  - **Locally advanced laryngeal cancer**
    - Avoids laryngectomy
  - **Anal cancer**
    - Avoids colostomy
- **Sequential**
  - **Breast cancer**
  - **Extremity sarcoma (± chemotherapy)**

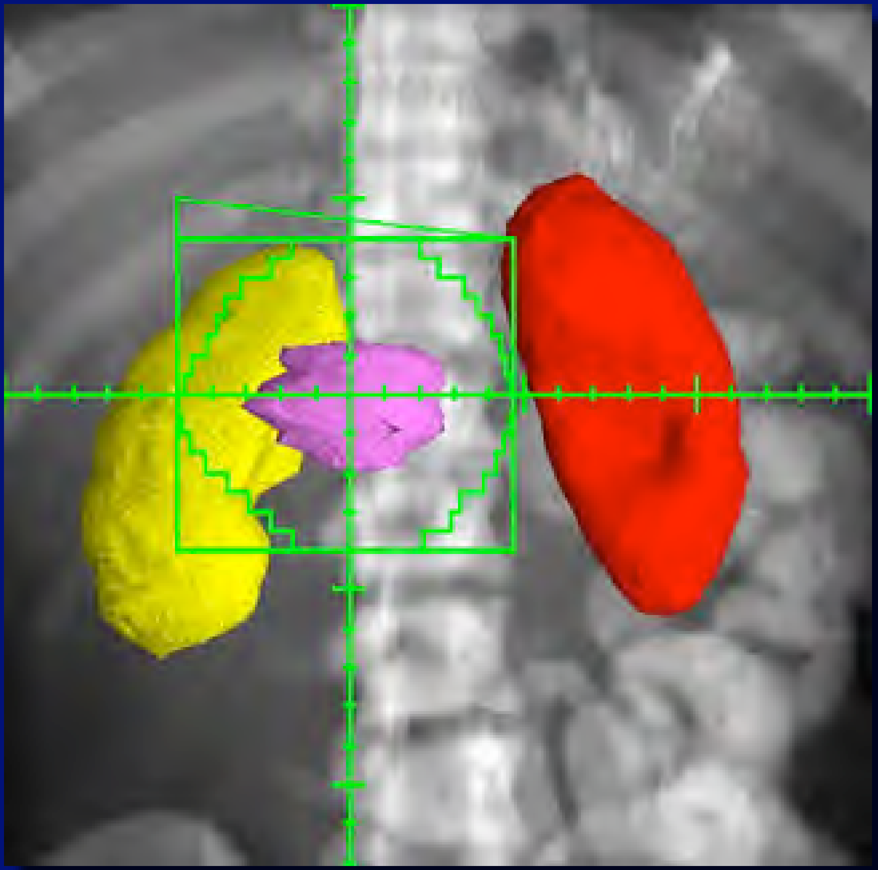
Unresectable Pancreas Cancer

- **Address both local and distant disease**
- **Full dose gemcitabine with concurrent dose escalating radiation**
  - **To do this safely, needed to decrease the irradiated volume**
  - **Radiation dose escalation trial**

Treatment Volumes with Concurrent Full Dose Gemcitabine



Prophylactic irradiation

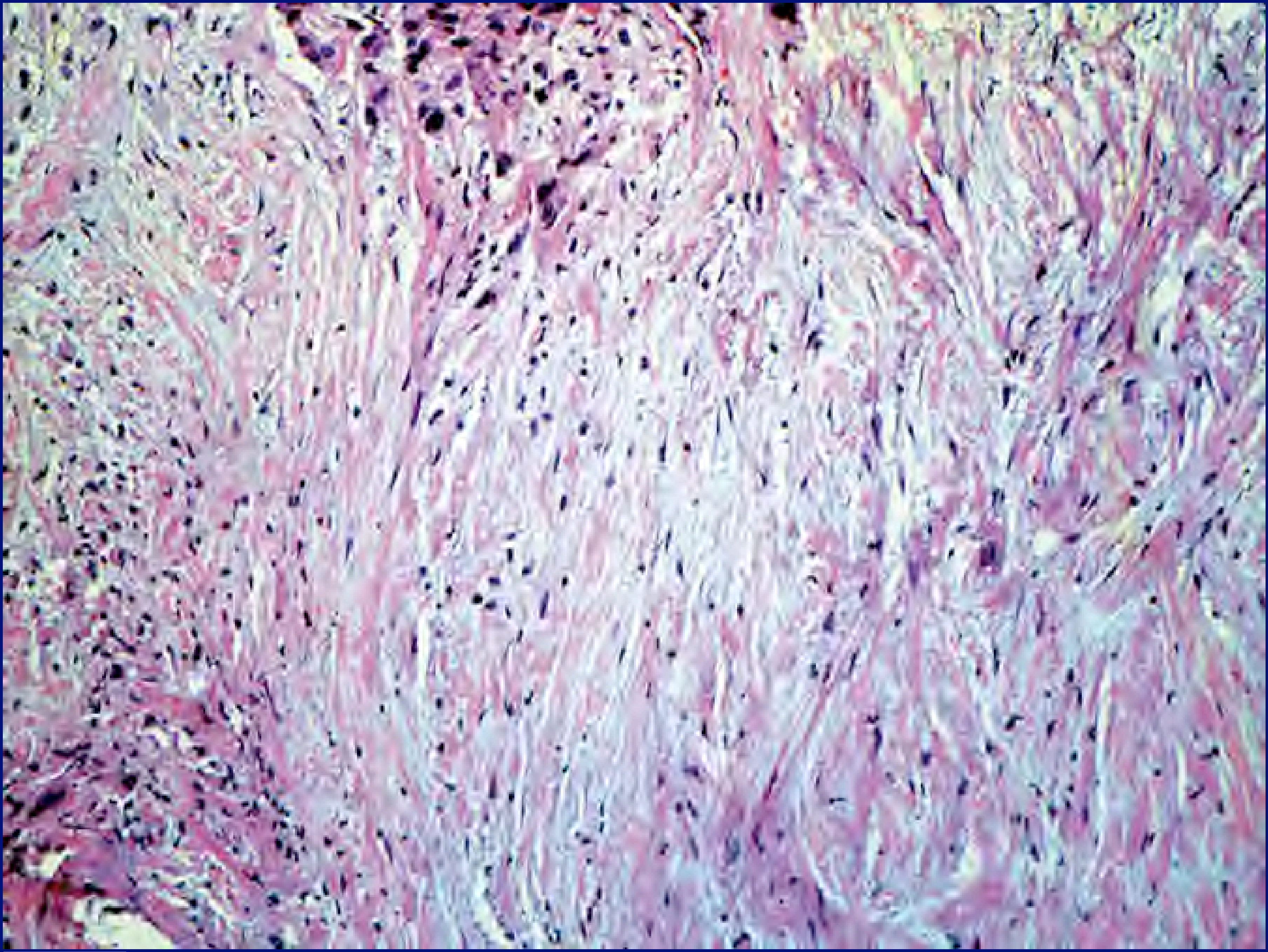


No prophylactic irradiation

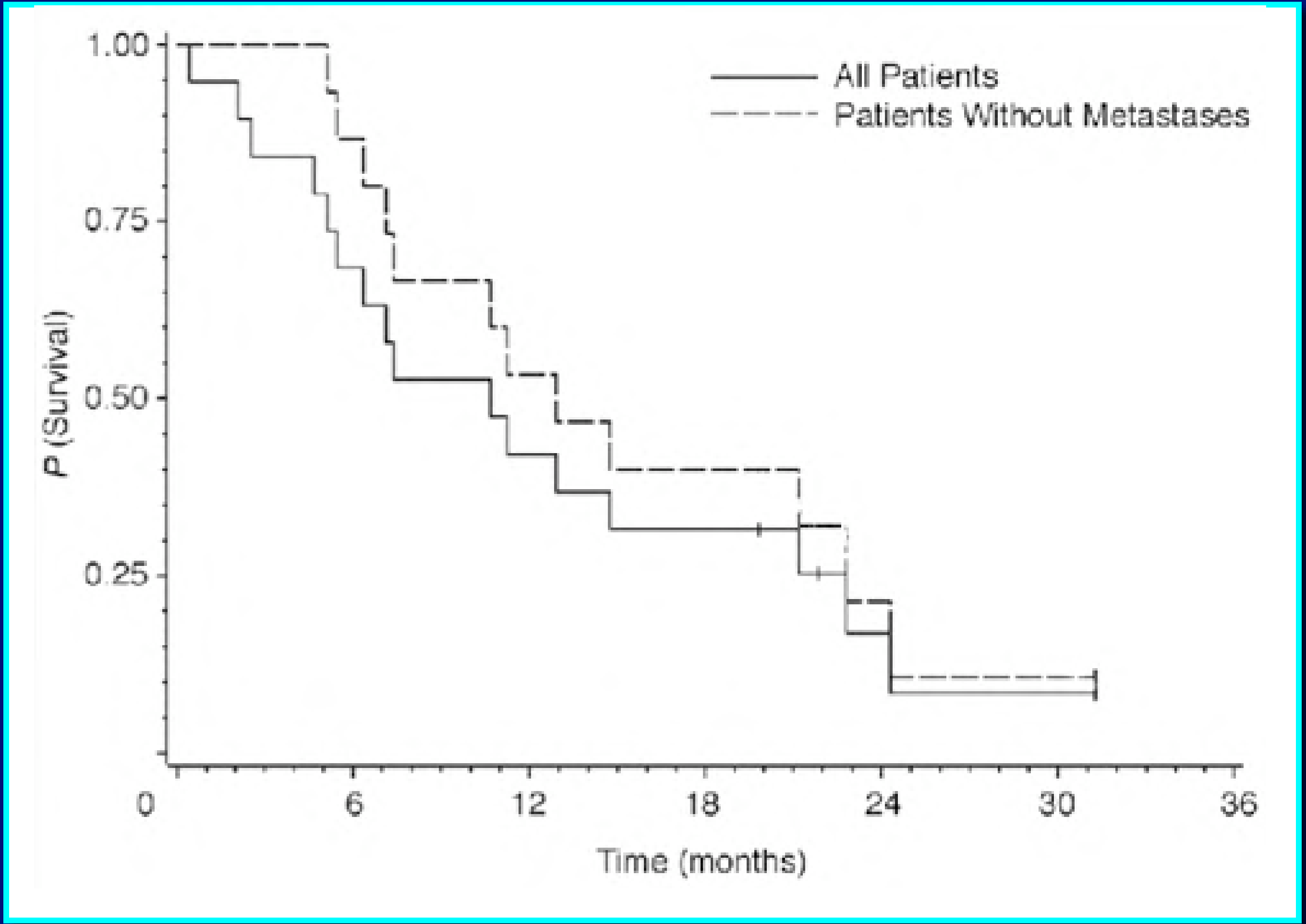
University of Michigan
Medical School

Response to Gem-RT

PD-INEL McGinn et al .J Clin. Oncol. 19: 4202, 2001

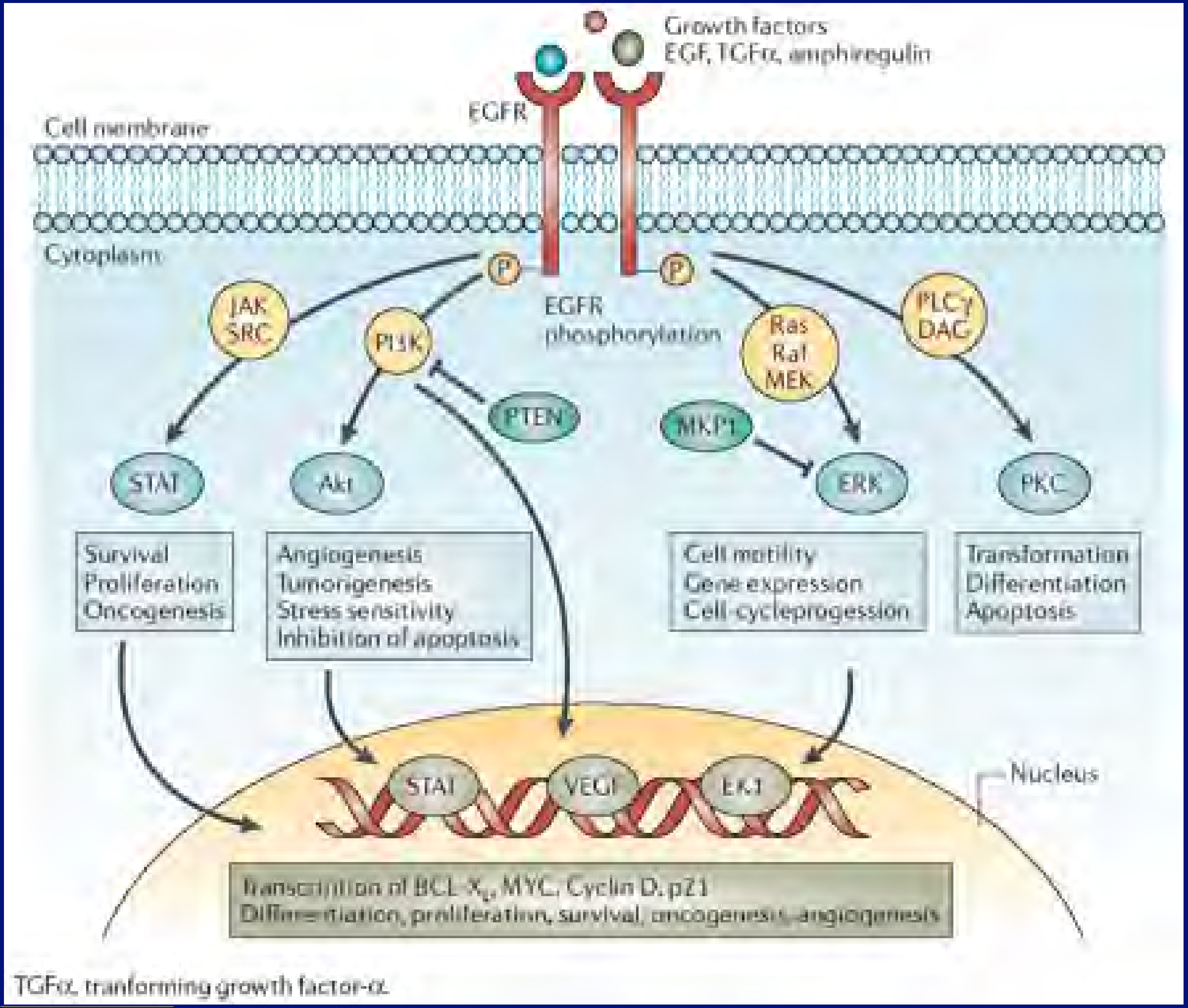


Gemcitabine + Cisplatin + Radiation



PD-INEL Muler et al J. Clin. Oncol 22:238, 2004

Growth Factor Receptors



PD-INEL Nyati MK et al Nature Reviews Cancer Nov 2006

Phase III Study Design

University of Michigan Medical School

Stratify by

- Karnofsky score: 90-100 vs. 60-80
- Regional Nodes: Negative vs. Positive
- Tumor stage: AJCC T1-3 vs. T4
- RT fractionation*: Concomitant boost vs. Once daily vs. Twice daily

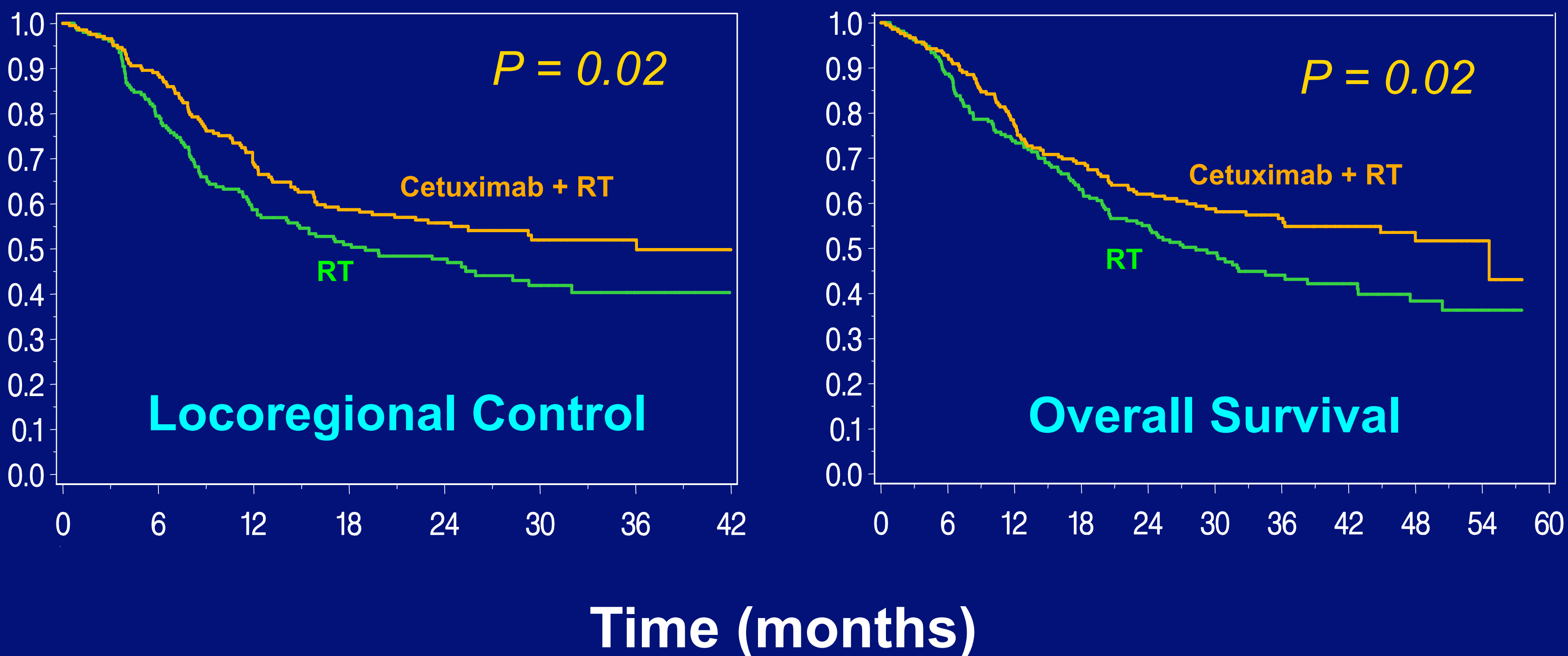
R A N D O M I Z E

Arm 1
Radiation therapy

Arm 2
Radiation therapy + Cetuximab, weekly**

* Investigators' choice

Cetuximab + RT *vs* RT Alone



T. Lawrence

Improving outcome: Individualizing Therapy

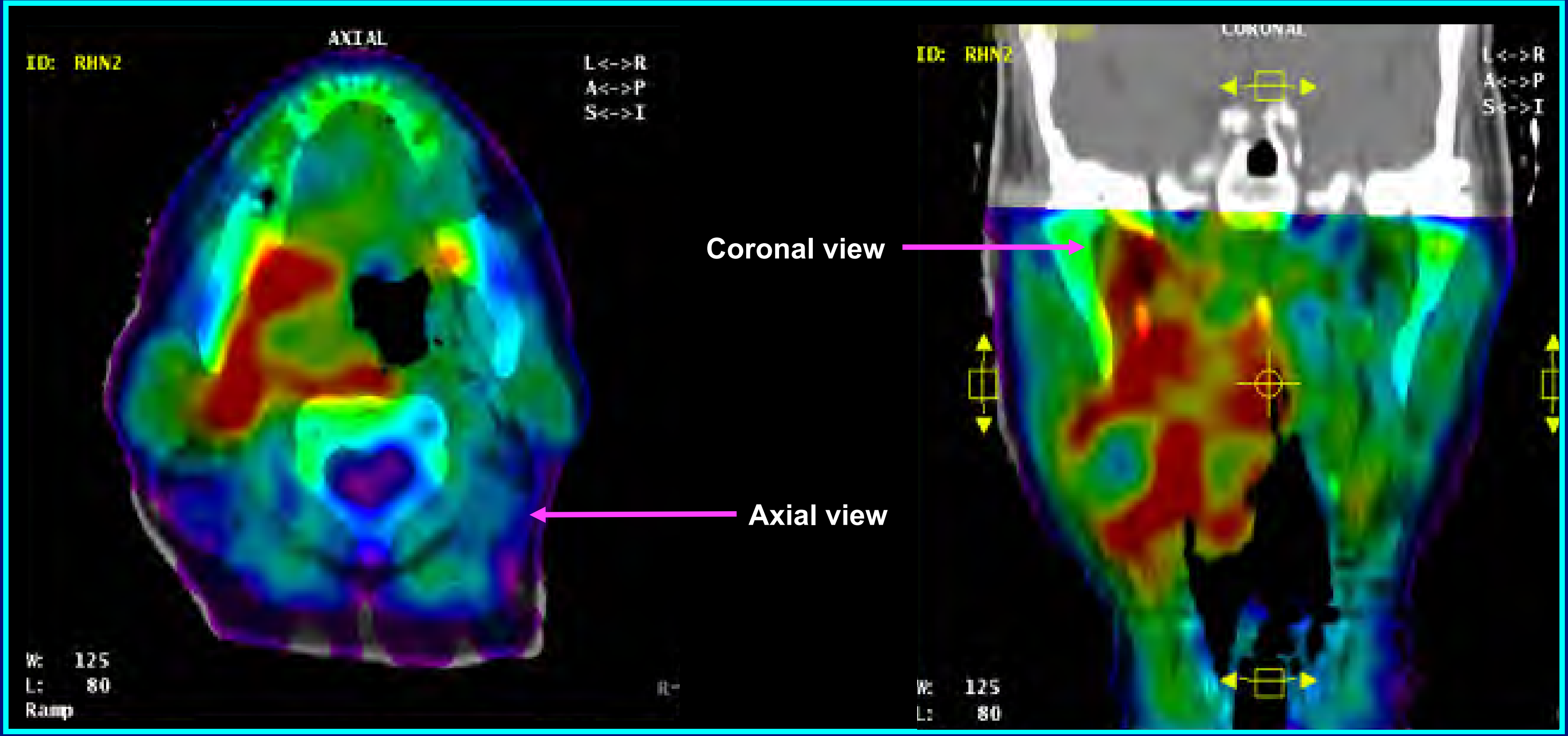
- By improving our ability to hit the tumor and miss the normal tissue
- By customizing combinations of radiation with chemotherapy or molecularly targeted therapy
- By assessing tumor and normal tissue response during treatment and tailoring therapy to these responses

Normal Tissues

- TGFβ1 is a marker for lung damage
- Prospective trial to select patients for dose escalation
  - Eligibility escalate dose above 73.6 Gy only if TGFβ1 level suggested they were not experiencing lung damage
- Only 2/14 patients treated at 80 Gy or above developed dose limiting toxicity (at 86.4 Gy)
- Further follow-up, grade 4 and 5 complications occurred, but only in patients who were NOT dose escalated (because of high TGFβ1)

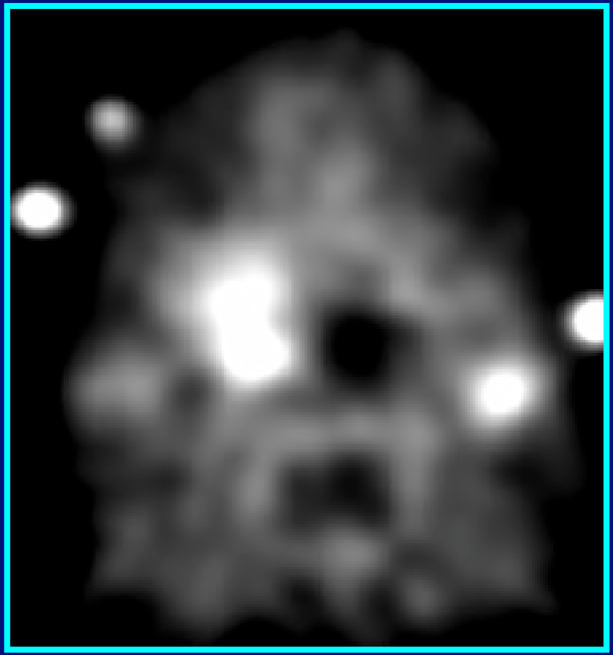
Anscher et al J. Clin Oncol 19:3758, 2001
Anscher et al Int. J. Radiat. Oncol. Biol. Phys. 56:988,2003

Cu-ATSM PET to Image Hypoxia

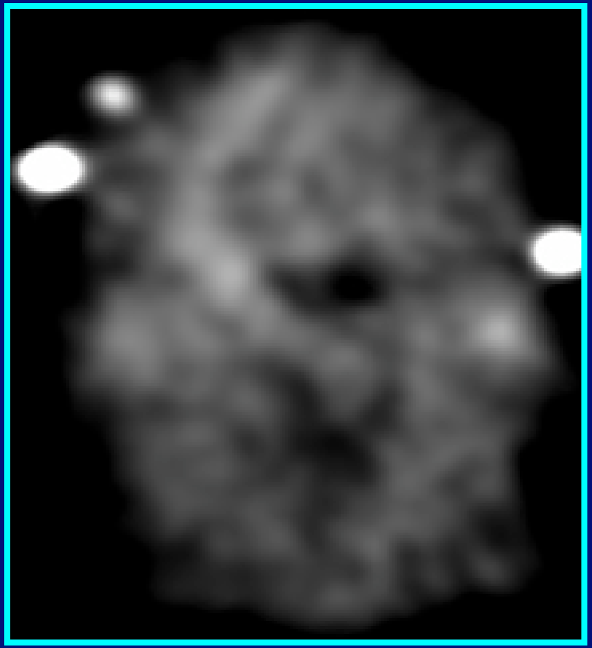


 Chao, IJROBP 2001; 49(4): 1171-1182

Change in Hypoxic GTV During RT



Before Radiation



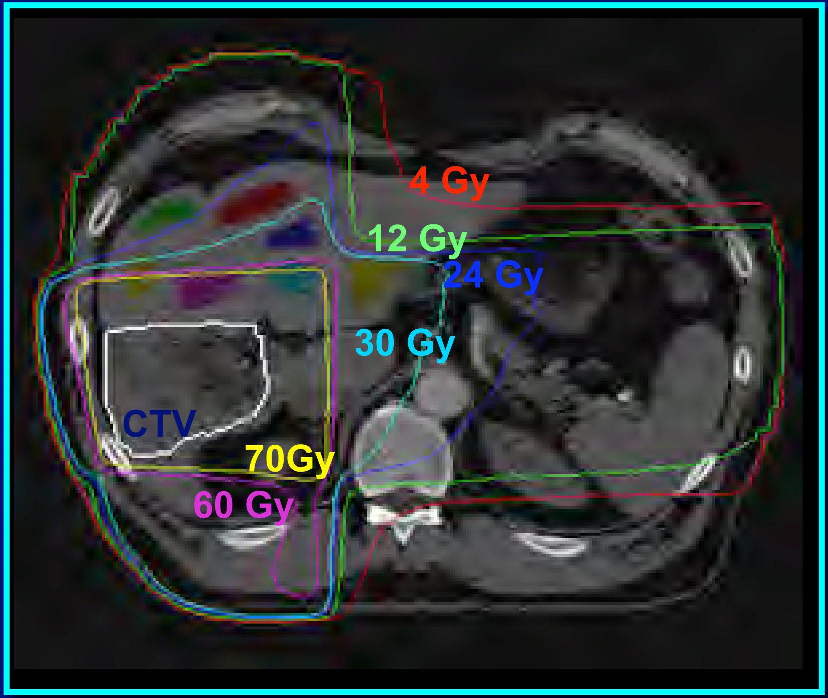
After 20 Gy

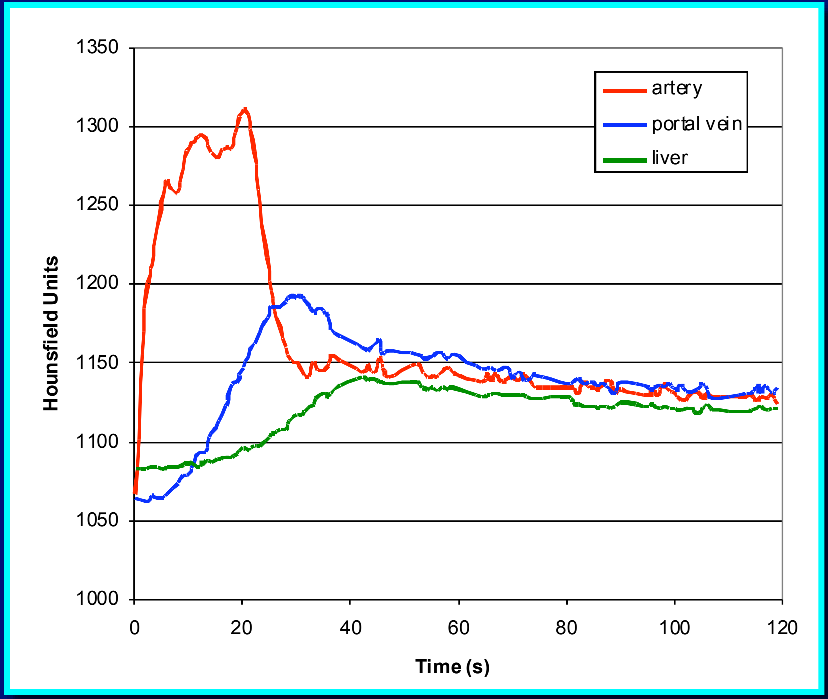
 Chao el al., IJROBP 54:72, 2002 (Both images)

DCE-CT to predict liver injury

- Radiation-induced liver disease (RILD) occurs 2 weeks to 3 months after treatment
  - Too late to adjust radiation dose
- RILD is caused by veno-occlusive disease
- Hypothesis: can decreased blood flow during a course of radiation be detected?
  - Dynamic contrast-enhanced CT

Time Courses of Contrast Uptake

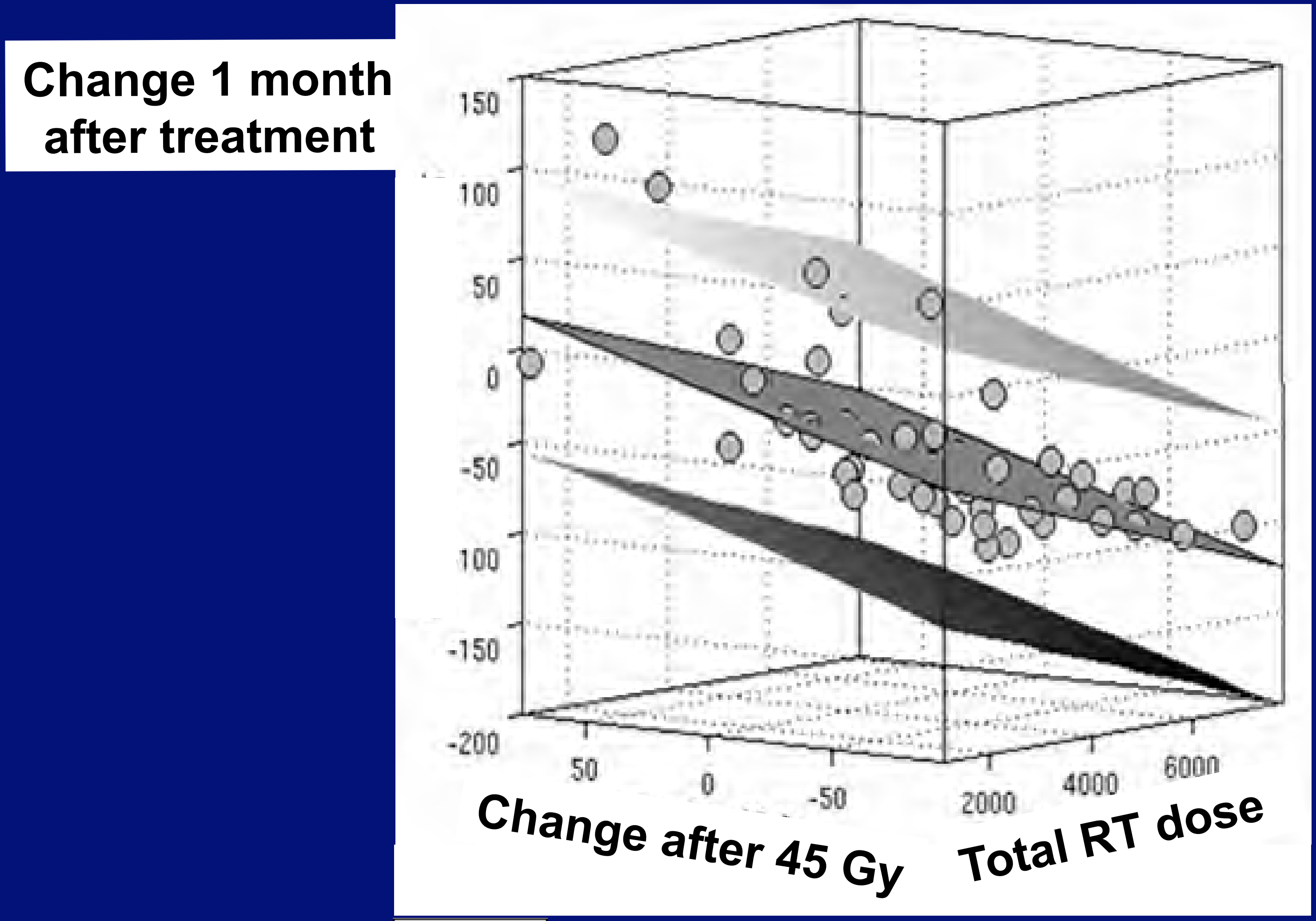




PD-INEL Cao Y et al , Medical Physics (accepted) 2006 (Both images)

University of Michigan Medical School

Predicting Changes in Portal Venous Perfusion

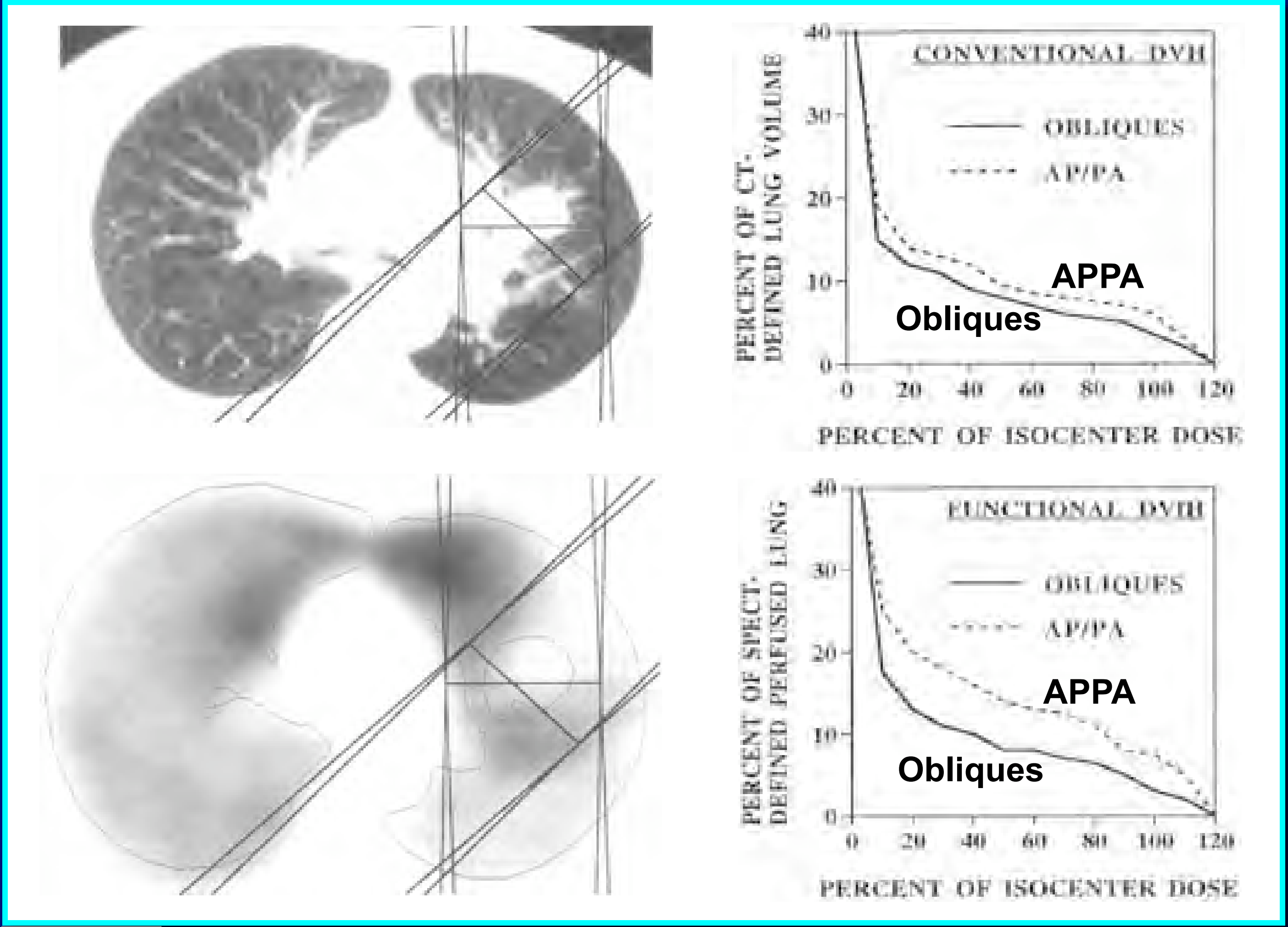


 Cao Y et al , Medical Physics (accepted) 2006

Functional lung DVH

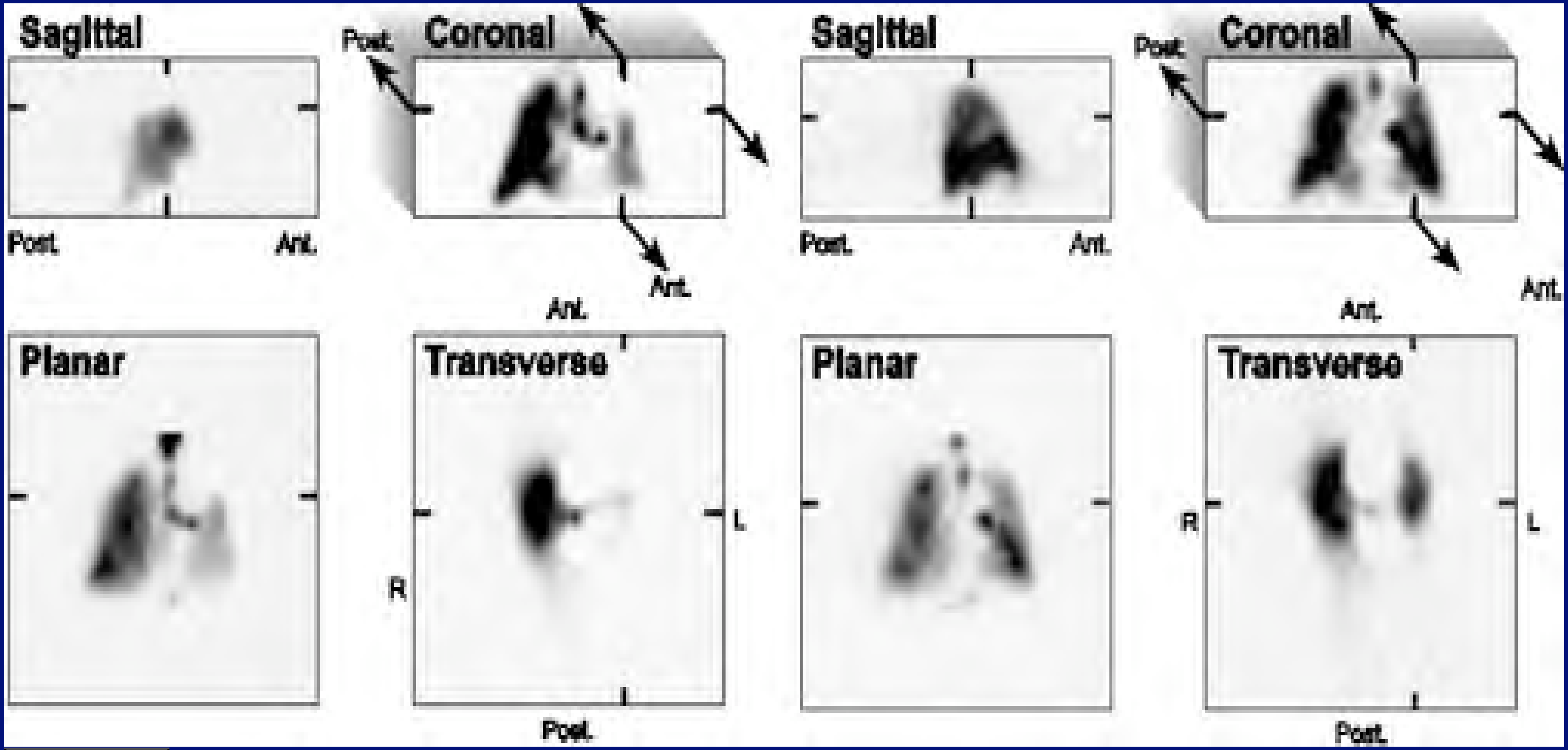
- Lung cancer typically occurs in patients with damaged lungs due to smoking
- In contrast to liver, in which volume can act as a surrogate for function, not all parts of the lung may be equal
- "Functional lung DVH" - take into account which parts of the lung work

Functional normal lung DVH



PD-INEL Marks LB et al Sem Oncol 13:333, 2003

Ventilation changes after 50 Gy

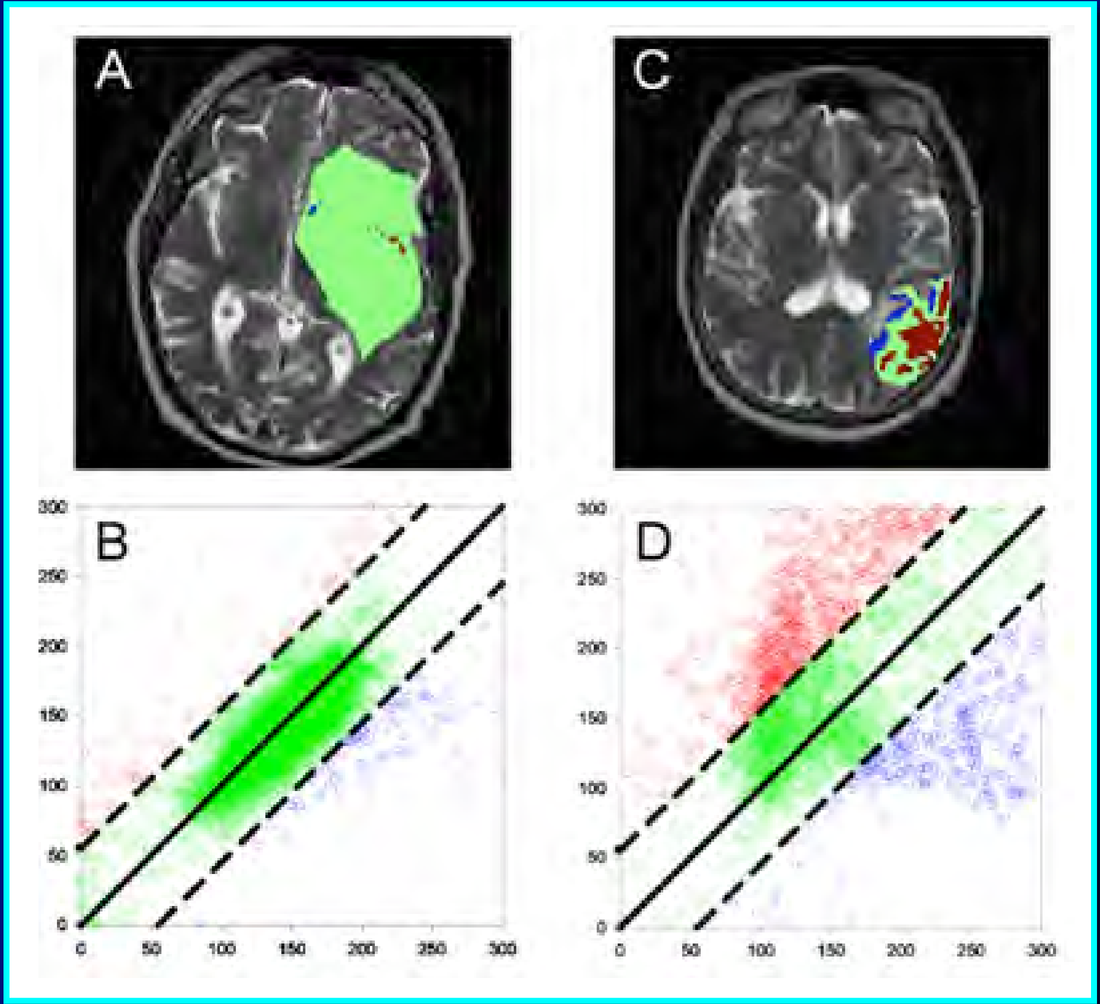


PD-INEL Kong F,unpublished, 2005

Diffusion MRI predicts brain tumor response

- **Diffusion MRI measures water mobility**
- **Hypothesis**
  - **In a responding tumor**
    - Mobility could increase when cells die
    - Mobility could decrease if cells shrink before dying
  - **In a non-responding tumor**
    - No change in mobility
- **Tumors were imaged pretreatment and again 3 weeks into treatment**
  - **How did the change in mobility correlate with response?**

Diffusion MRI predicts response

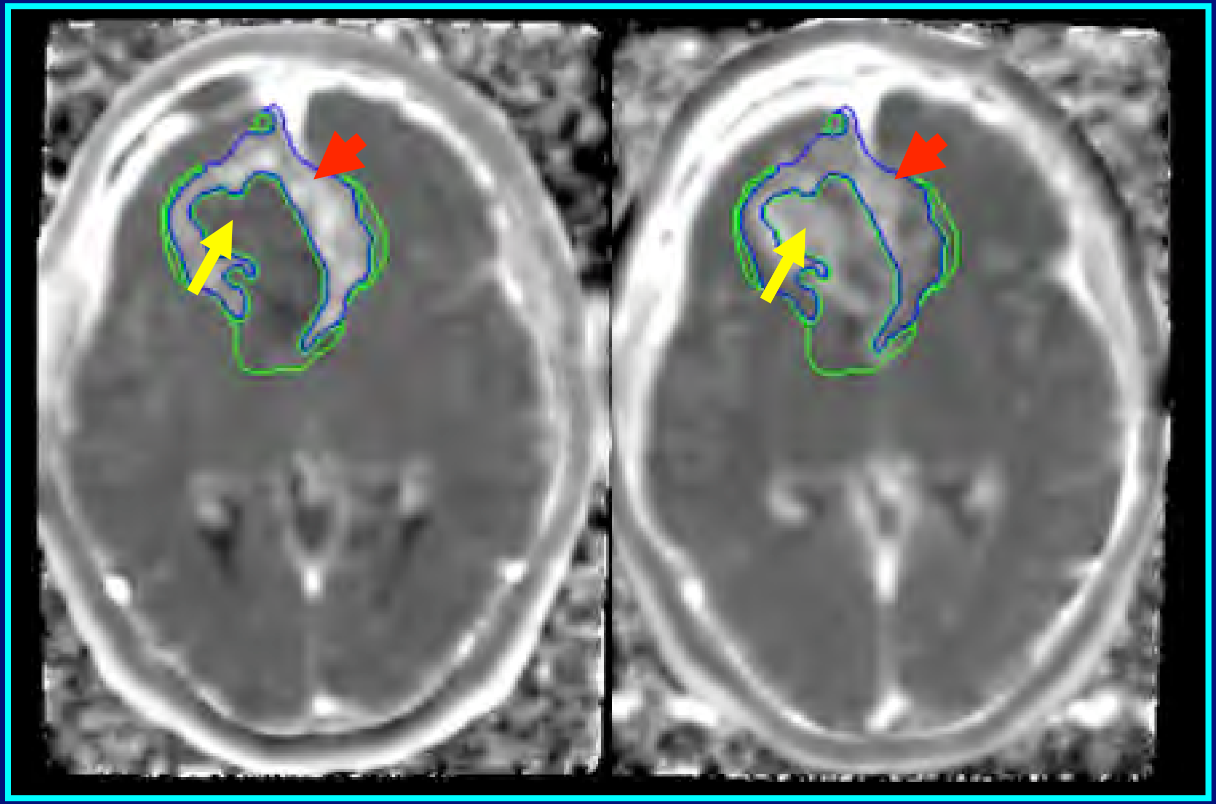


 Hamstra DA et al , Proc Nat Acad Sci USA 102: 16759, 2005

RT affects brain tumor blood flow

- **MRI can measure brain tumor blood flow**
- **Although high grade brain tumors show regions of increased blood flow, some parts have little flow**
- **Hypothesis**
  - **Radiation might increase blood flow to regions with poor initial flow**
  - **If this were true, radiation might increase delivery of systemic chemotherapy into a tumor**
    - Might partially explain why concurrent chemotherapy and radiation benefits patients with glioblastoma

Blood-Brain/Tumor Barrier Opening During RT



Pre RT

Week 3 during RT

Red: initially enhanced region; Yellow: initially non-enhanced tumor region

Cao, Y. et al J Clin Oncol 23: 4127, 2005

“Standard” Radiation Therapy

- Treatment based on population estimate of what might control a tumor
- Estimate the risk of normal tissue damage base on the most sensitive 5% of the population
- Treatment delivered to initially prescribed dose
  - Stop only for unacceptable acute toxicity
- Emphasis making isodose lines conform more tightly to the tumor

New Radiation Therapy

- Treatment based on molecular targeting of aberrant growth pathways
- Estimate the risk of normal tissue damage base on the individual patient using functional and metabolic imaging with adjustments during treatment
- Emphasis on
  - Multimodality research
  - Multimodality therapy
  - Continued technical advances, but in a broader context

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 4: Source Undetermined
Slide 9: Source Undetermined
Slide 10: Source Undetermined
Slide 11: Source Undetermined
Slide 12: Source Undetermined
Slide 13: Sources Undetermined
Slide 14: Kessler, University of Michigan
Slide 15: Kessler, University of Michigan
Slide 16: Kessler, University of Michigan
Slide 17: Kessler, University of Michigan
Slide 18: Kessler, University of Michigan
Slide 19: Kessler, University of Michigan
Slide 20: Ten Haken et al Int J Radiat Oncol Biol Phys 16:193, 1989
Slide 21: Pollack, et. al., IJROBP, 53:5, 2002
Slide 22: Sources Undetermined
Slide 23: Theodore Lawrence
Slide 27: Source Undetermined
Slide 28: Ben-Josef E., et.al, J Clin Oncol 23:8747, 2005
Slide 29: Theodore Lawrence
Slide 34: Sources Undetermined
Slide 35: McGinn et al .J Clin. Oncol. 19: 4202, 2001
Slide 36: Source Undetermined
Slide 37: Muler et al J. Clin. Oncol 22:238, 2004
Slide 38: Nyati MK et al Nature Reviews Cancer Nov 2006
Slide 40: Theodore Lawrence
Slide 43: Chao, IJROBP 2001; 49(4): 1171-1182
Slide 44: Chao el al., IJROBP 54:72, 2002 (Both images)
Slide 46: Cao Y et al , Medical Physics (accepted) 2006 (Both images)
Slide 47: Cao Y et al , Medical Physics (accepted) 2006
Slide 49: Marks LB et al Sem Oncol 13:333, 2003
Slide 50: Kong F,unpublished, 2005
Slide 52: Hamstra DA et al , Proc Nat Acad Sci USA 102: 16759, 2005
Slide 54: Cao, Y. et al J Clin Oncol 23: 4127, 2005