

# Application of Hypofractionation in the Lung



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# Evolution of Radiation Delivery

- Brachy to ortho to cobalt to linac, 1-D to 2-D to 3-D to IMRT
- All used to deliver low dose rate treatment (40 rad per hour or 2 Gy per day)
- Why?
  - We think it is has biological advantages (4 R's)
  - We are good at it
  - We have long term outcome data that we can quote
  - Our clinics are set up specifically to deliver it
  - We get reimbursed for it

# Indications for Conventional Radiotherapy

- Adjuvant treatment: treating for suspected occult microscopic tumor
  - Involves treating large volumes of “normal” tissue
- Primary treatment: treating gross deposits of tumor
  - Often done in conjunction with an adjuvant treatment
  - So, involves treating large volumes of “normal” tissue

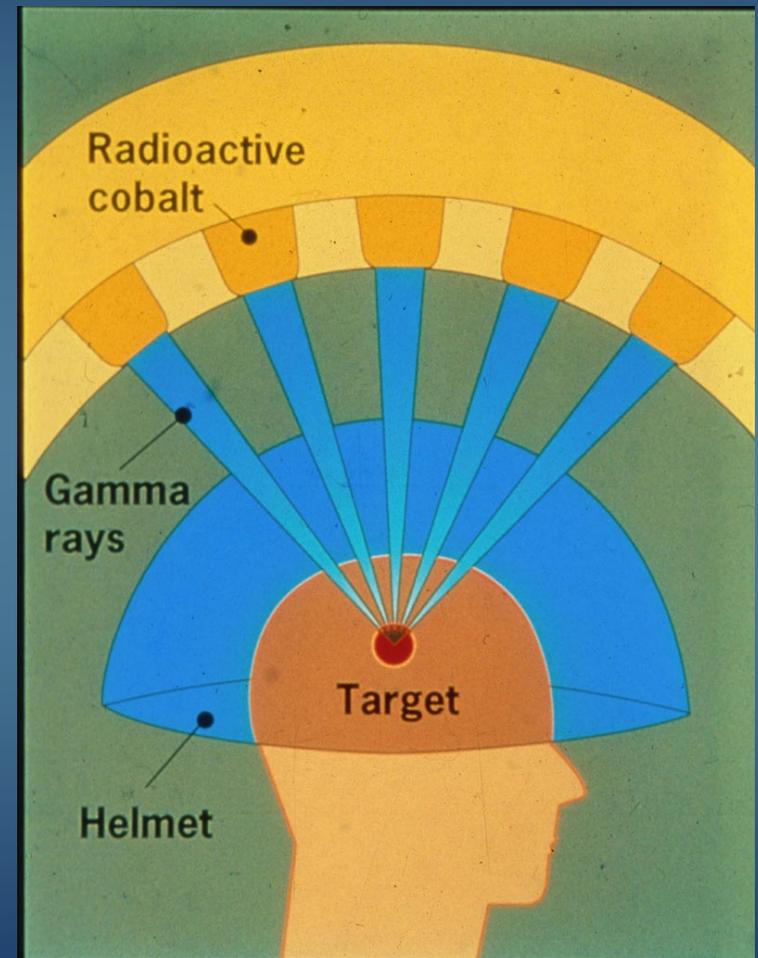
# My Observations about Conventional Radiotherapy

- By its nature and historical use, it treats considerably more normal tissue than tumor to a high dose (50+ Gy)
- Works well as regional adjuvant therapy (e.g., breast, rectum, sarcoma)
- However, conventional radiotherapy is pathetically ineffective for gross disease, especially for common carcinogen-induced carcinomas (ask your patients)

# How do radiation oncologists bear this?

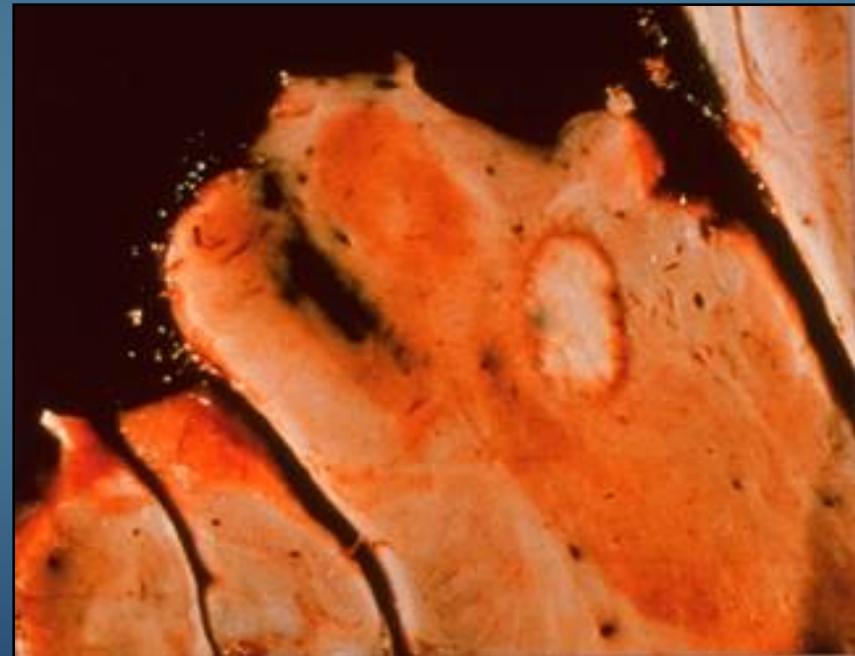
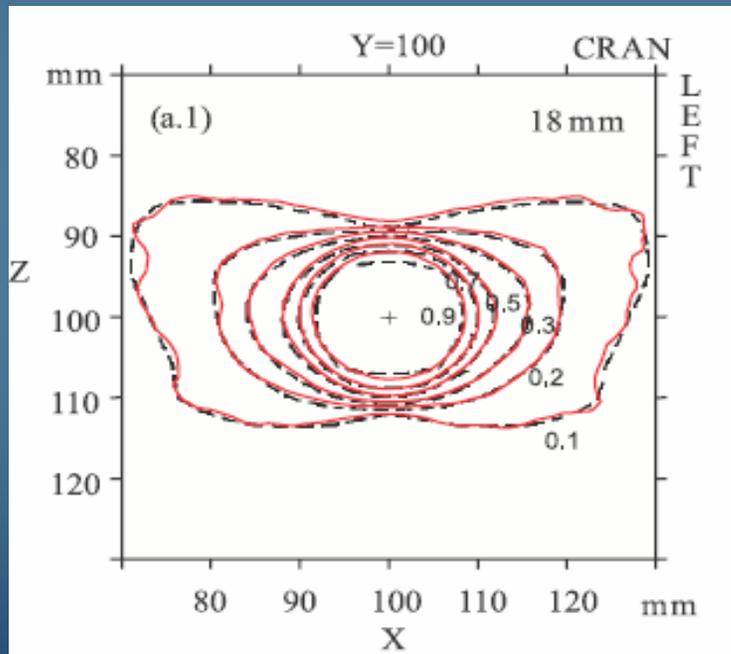
- They focus on the better tolerance of radiotherapy compared to surgery (we can treat frail patients)
- They fiercely maintain the “first do no harm” dictum (reasonable considering the therapy doesn’t work)
- BUT, they don’t consider tumor recurrence to be a toxicity or their fault (the patient failed radiotherapy, not radiotherapy failed the patient)

# Spreading out Entrance Dose



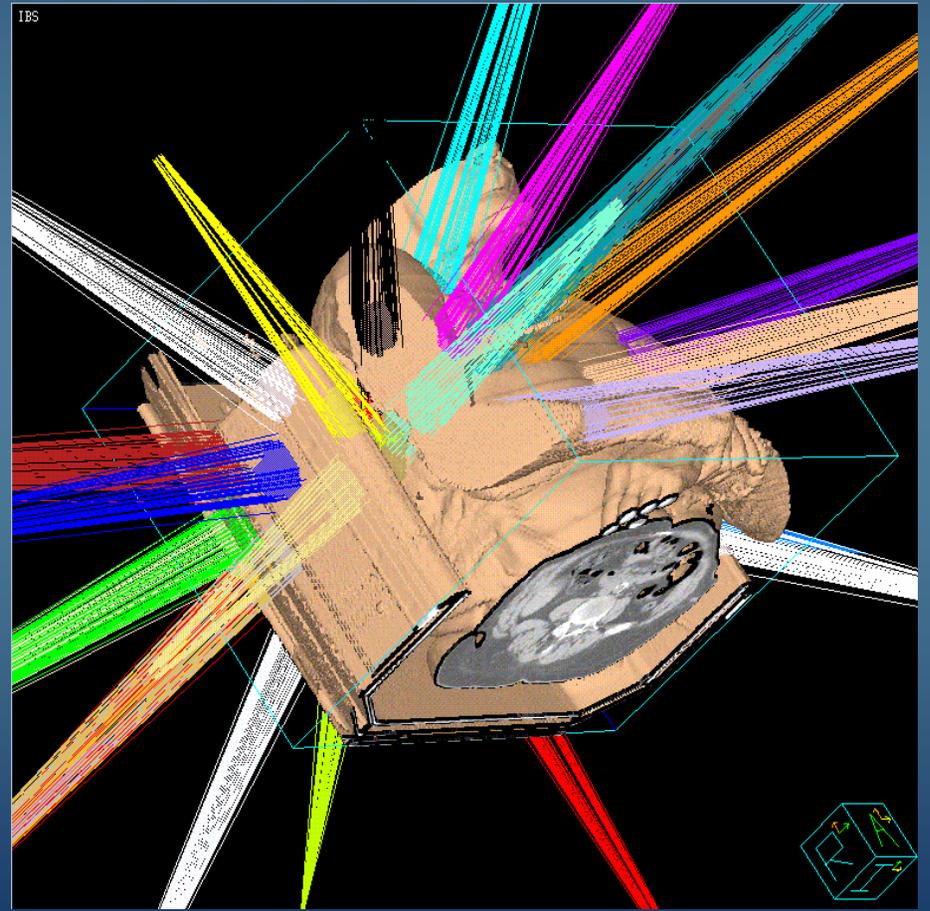
# Lesion Produced by the Gamma Knife

- Dose per fraction  $> 8-10$  Gy



**Steep dose gradients**

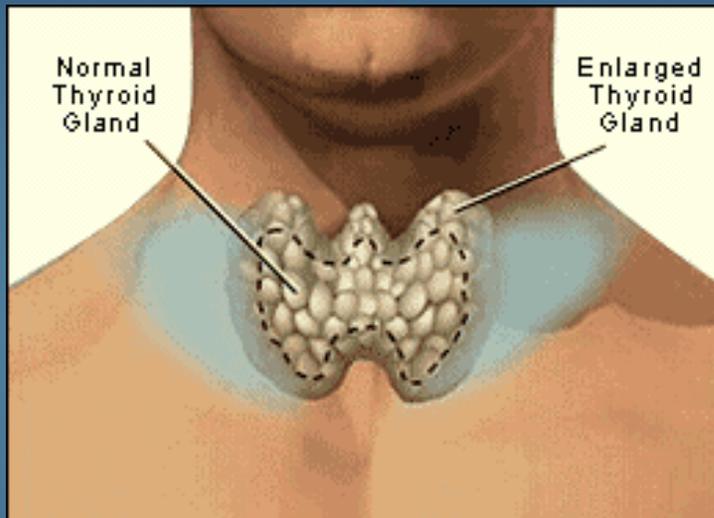
# Imitation is Flattering



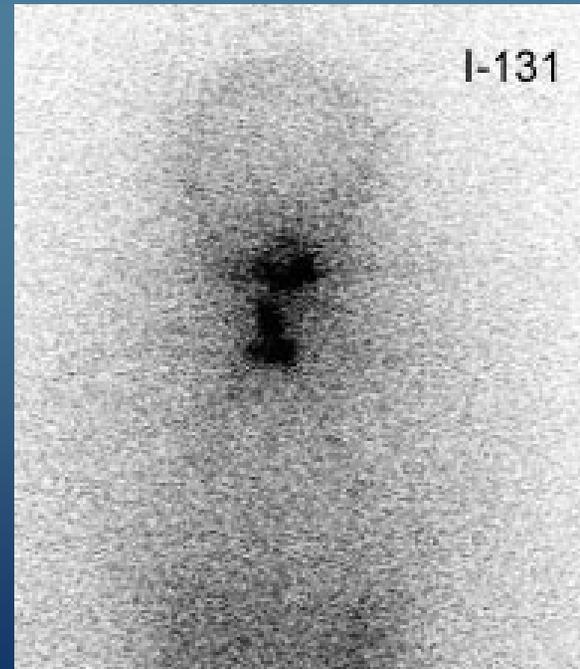
# Why is radiosurgery so successful?

- Advanced technology to avoid entrance damage and normal tissue exposure
- Advanced imaging to insure accurate targeting
- Very large dose per treatment to ablate the target

# Iodine Scavenging by Thyroid Tissue



→ IV administration of Radioactive Iodine 131 (beta emitter)



- Well differentiated thyroid cancer frequently metastatic
- Prior to 1942 often lethal
- I-131 first and still most successful targeted therapy

# Why Ablate?

- *Cancer vs. Conventional Cancer Therapy:* Cancer usually wins
- *Cancer vs. Ablative Therapy:* Therapy usually wins

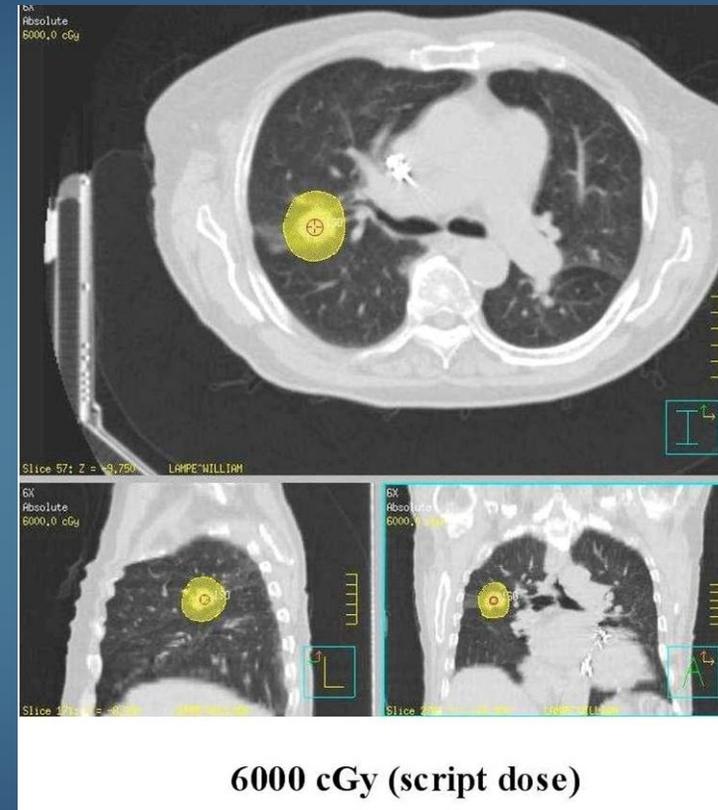
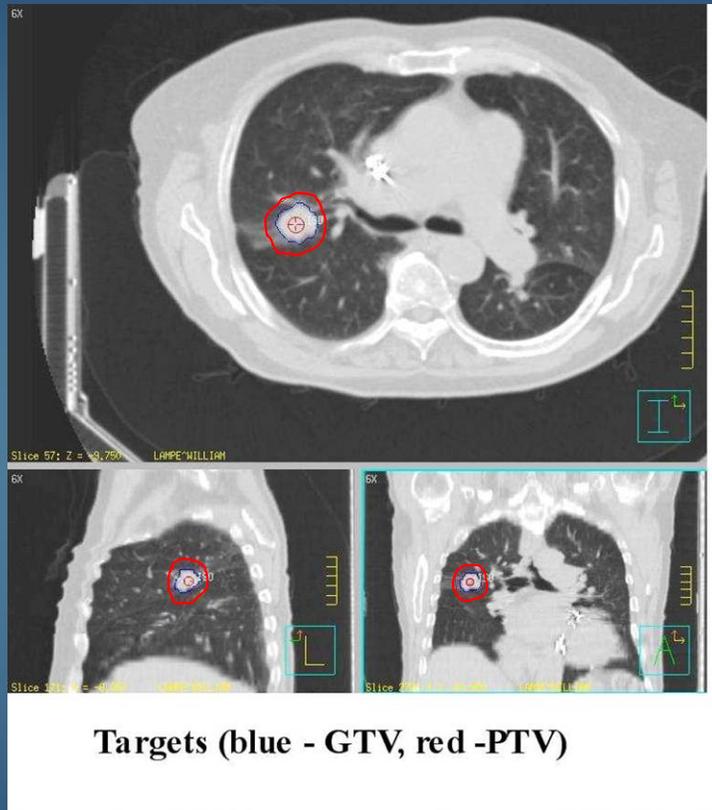
# Fractionation Options

- Conventionally fractionated radiotherapy
  - small daily doses
  - go to very high cumulative doses
  - strategy for IMRT implementation
- Hypofractionated radiotherapy
  - larger daily doses (3-6 Gy)
  - used for palliation
- Ablative radiotherapy
  - very high daily doses (8-20 Gy)
  - overwhelm tumor repair
  - causes “late” effects that may be intolerable

# Ablative Treatments Must Avoid Volume

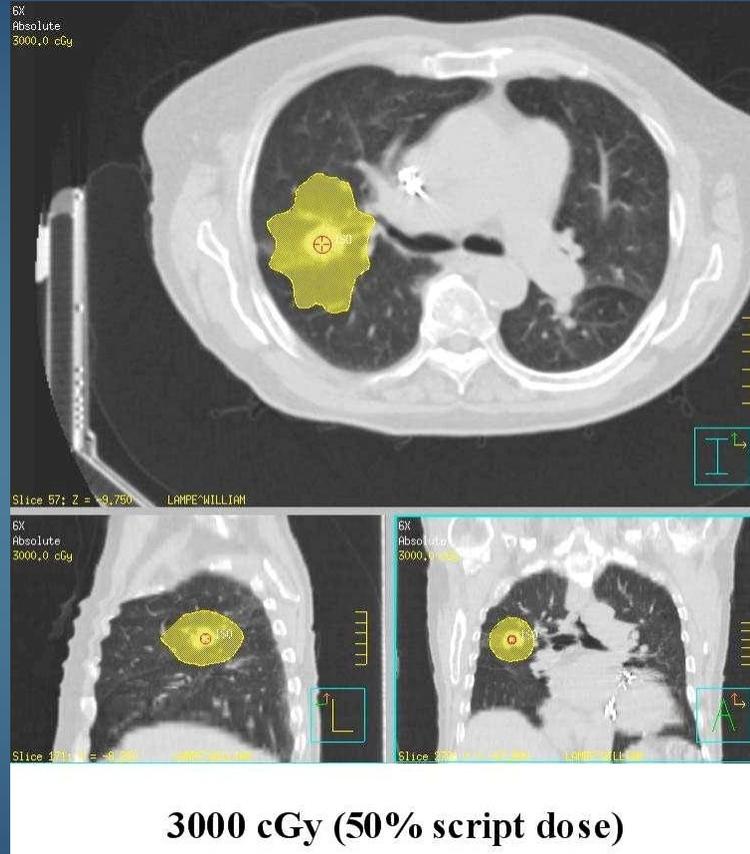
- Requirements for ablative hypofractionation:
  - Abandon prophylactic treatment
  - Account for organ motion
  - Achieve sharper dose fall-off gradients to normal tissue (mimic radiosurgery)
- These requirements need advanced technology

# Conformal high dose



- This constitutes the tumor control (place it well)
- Being conformal is easy – especially with many beams or arcs

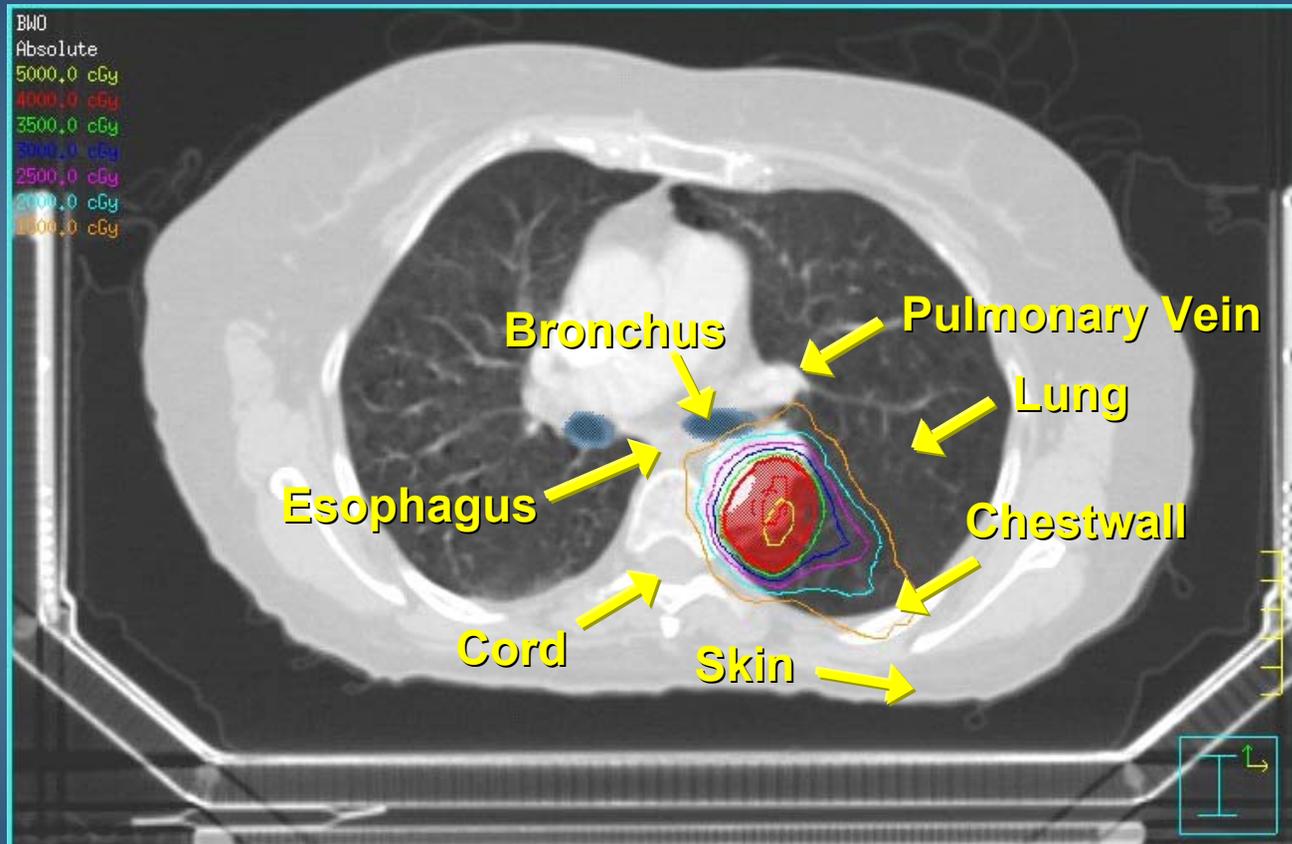
# Compact intermediate dose



**This is the hardest part of the SBRT process and distinguishes a good plan from a poor plan!**

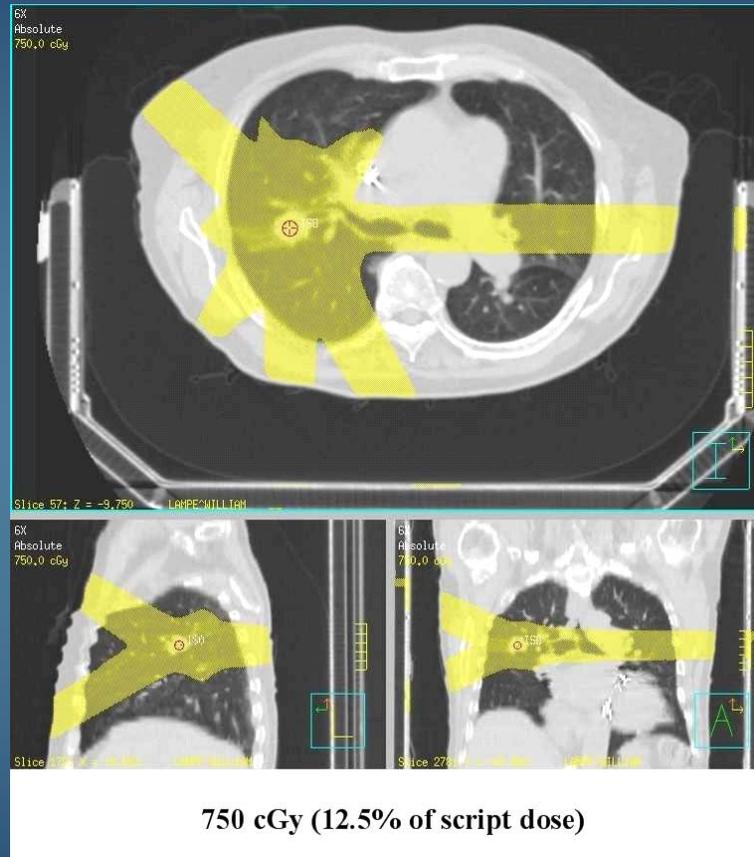
- This accounts for toxicity. All of this dose is in normal tissues
- Infinite possibilities – some much more toxic than others

# Respect Normal Tissue Constraints



- Scant data for 5 or fewer fractions
- Particularly more difficult for serial tissues compared to parallel

# Very large low dose volume



- SBRT (and radiosurgery) Assumption: A little dose to a lot of normal tissue is better than a lot of dose to a little normal tissue

# 3-5 Year Outcome in Early Stage Lung Cancer

	<u>Rx Modality</u>	<u>% alive</u>
• Stage I	Surgery	60-80%
• Stage I*	Radiotherapy (RT)	15-45%

	<u>Rx Modality</u>	<u>% LC</u>
• Stage I	Surgery	60-80%
• Stage I	Radiotherapy (RT)	15-45%

\*clinically staged and mostly medically inoperable

RT generally 60-66 Gy delivered in 6-7 weeks

# Typical Patient Scenario with Conventional Radiotherapy

- T2,N0,M0 lung cancer in a 65 year old smoker with poor PFTs and heart disease - not a surgical candidate
- Nice person, wants to live
- We get to know and like the patient during 6-7 week course of radiation
- Most likely tumor recurs, metastasizes, causes morbidity and ultimate death within 3 years.

# Clinical Model: Medically Inoperable Stage I Lung Cancer using SBRT

- Indiana University (IU) phase I toxicity study:  
Doses as high as 22 Gy X 3 fractions tolerable (47 patients)<sup>1</sup>
- IU phase II efficacy study:  
Doses of 20-22 Gy X 3 fractions yields extremely high levels of local control (70 patients)<sup>2</sup>

<sup>1</sup> Timmerman, et. al., Chest, 2003

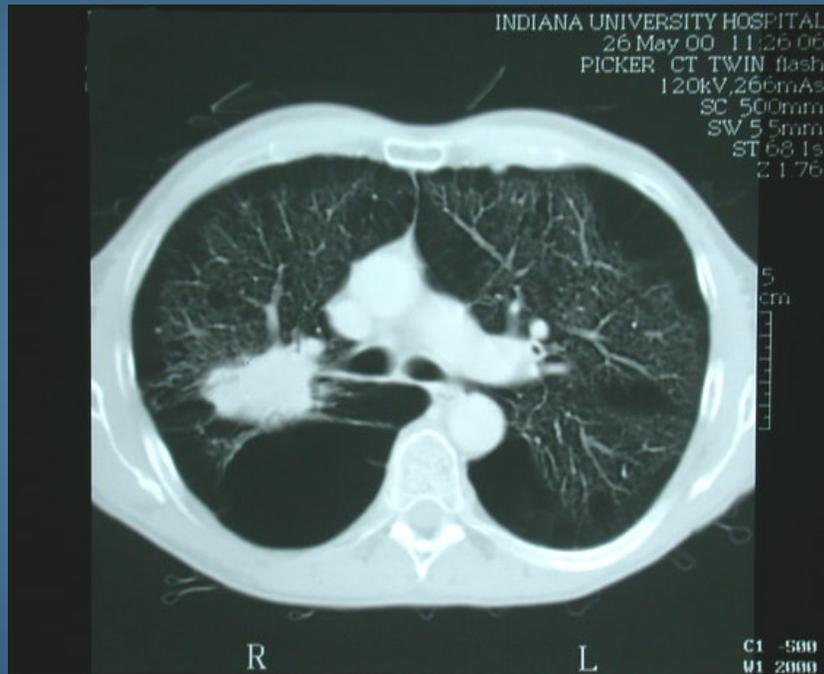
<sup>2</sup> Timmerman, et. al., JCO, 2006

# Phase I Dose Escalation Study

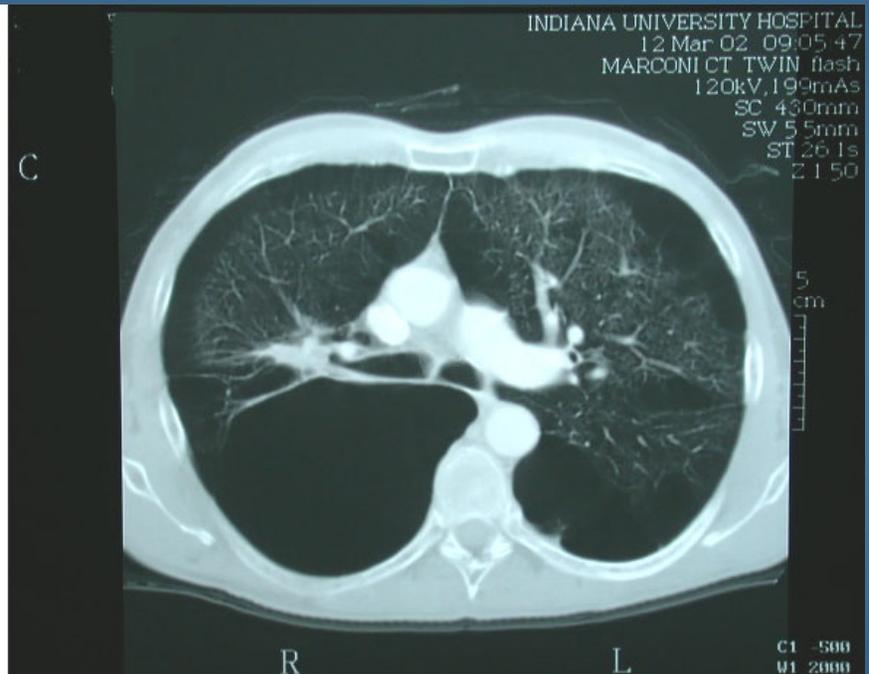
## Chest 124:1946-55, 2003

- 47 patient Phase I study using 3 fractions
- Starting dose 24 Gy total (8 Gy/fx)
- 3 separate dose escalation groups:
  - T1 tumors: 60 Gy total (20 Gy/fx) without DLT
  - Small T2 tumors: 66 Gy total (22 Gy/fx) without DLT
  - Big T2 tumors (5-7 cm): 2/5 patients with DLT at 72 Gy total (24 Gy per fraction)

# T2 Tumor, 36 Gy

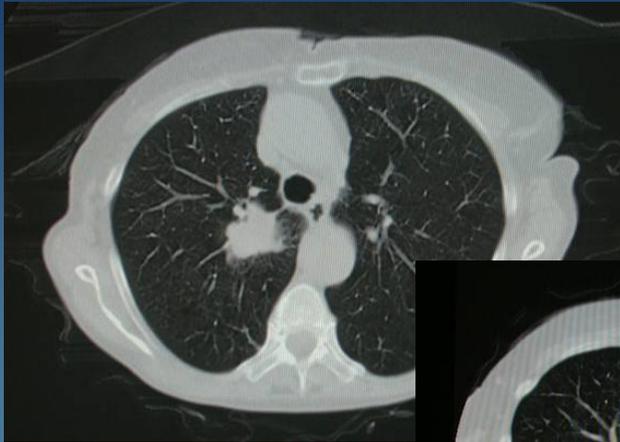


**Pre-Treatment**



**22 mo. Post-Treatment**

# T2 Tumor, 72 Gy



Pre-Rx



3 mo.



9 mo.



18 mo.

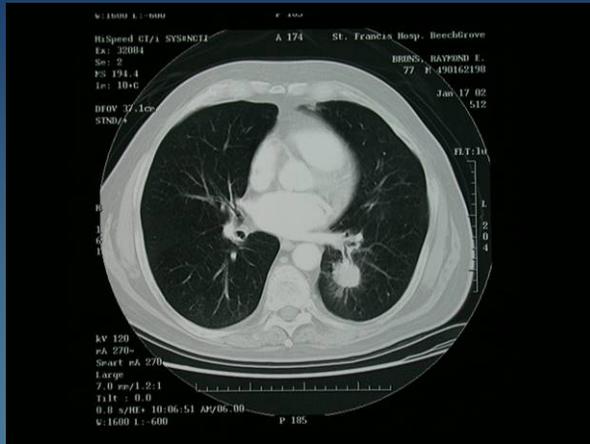
# T2 Tumor, 72 Gy



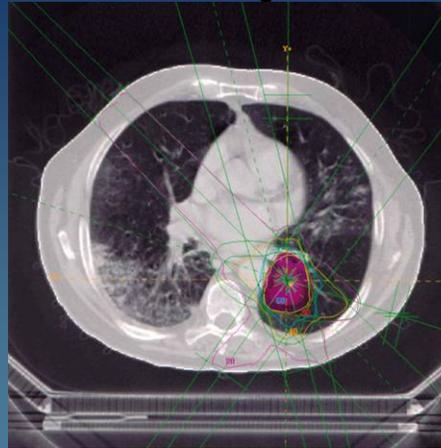
Pre-Rx

18 mo.

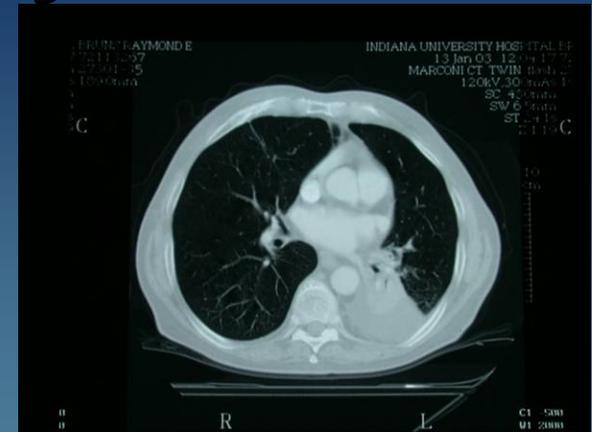
# T1 tumor, 60 Gy



Pre-treatment



Treatment planning



One year post treatment



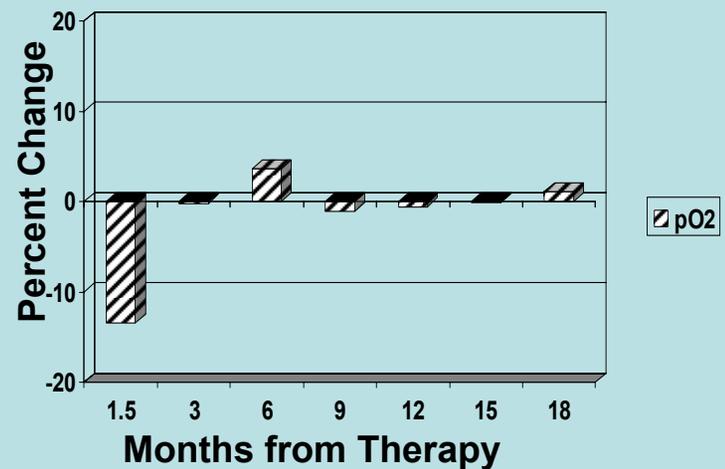
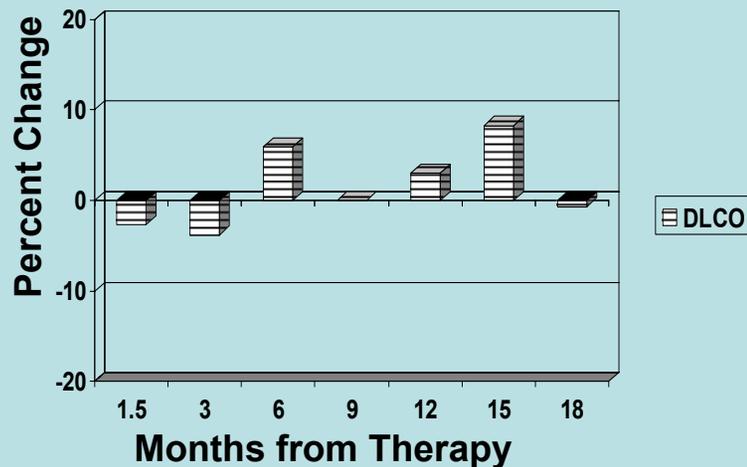
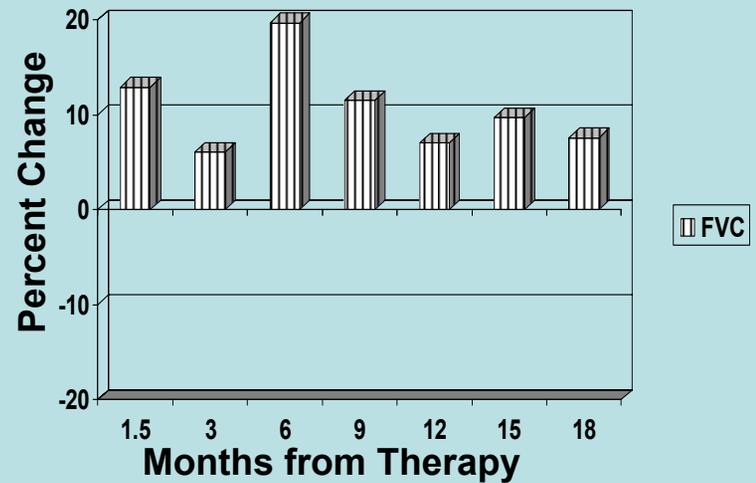
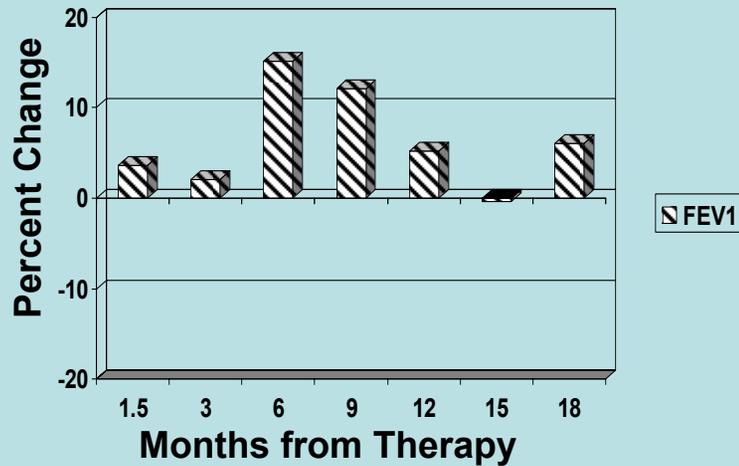
Post treatment bronchoscopy

Wedge-like collapse  
of segmental bronchus

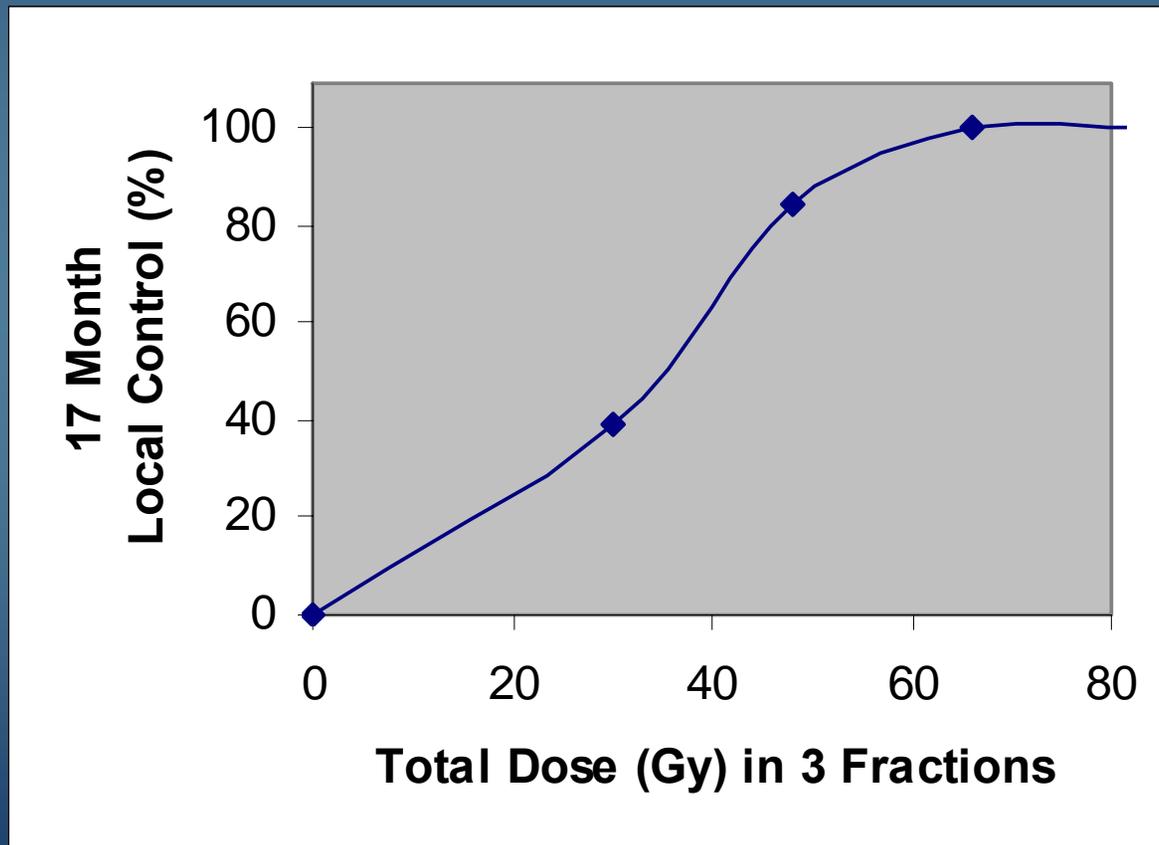
No evidence of tumor  
recurrence on PET

No tumor cells on bronchial  
biopsy or brushings

# Pulmonary Function Tests



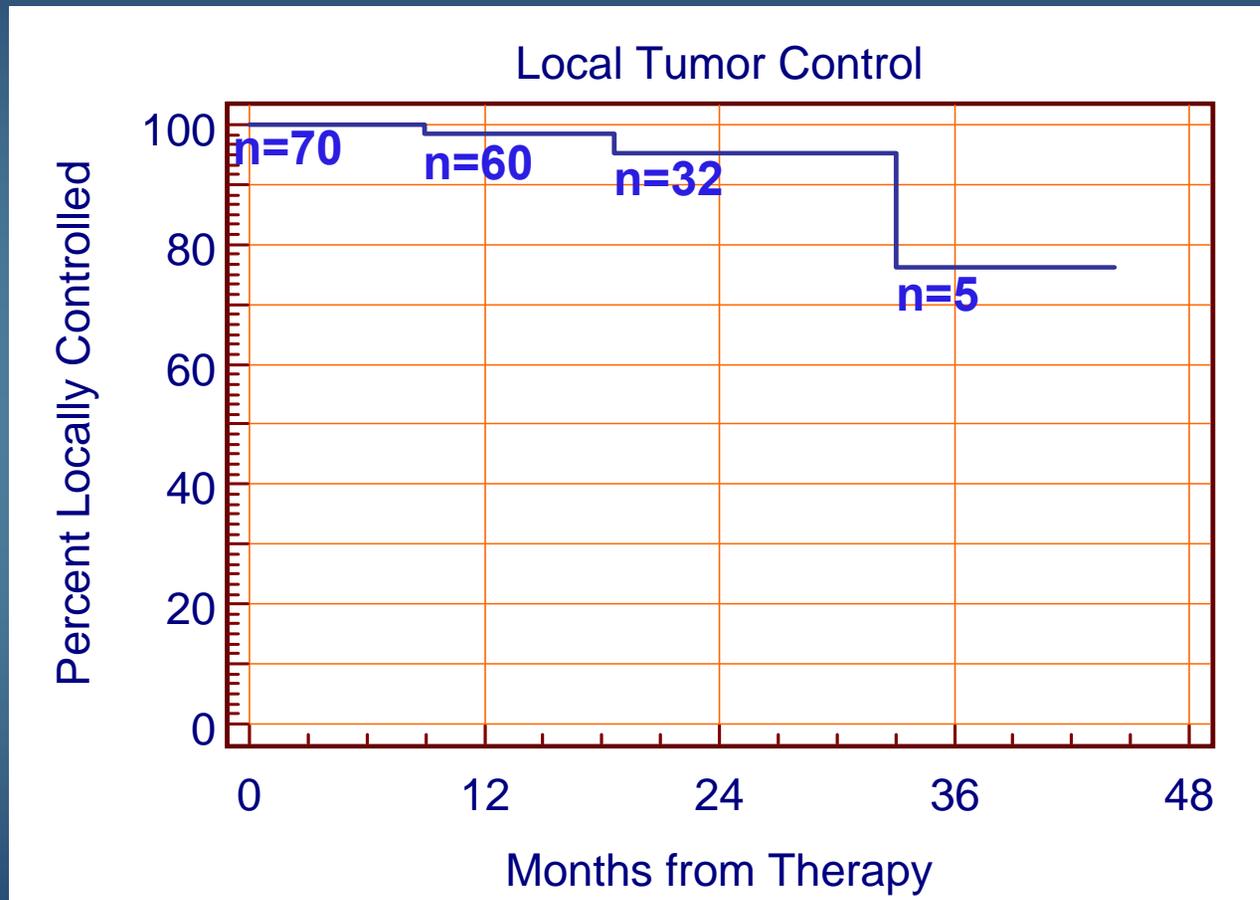
# Phase I Dose Response for Local Control



# Indiana Phase II Study

- NIH R-21 grant funded prospective study
- Phase I dose: T1 = 20 Gy X 3 fractions = 60 Gy  
T2 = 22 Gy X 3 fractions = 66 Gy
- Control and toxicity monitored by independent Data Safety Monitoring Committee
- 70 patients (35 T1, 35T2)

# IU Phase II Local Control



## Preliminary Results

- Median follow-up = 18 months
- One year local control = 98%
- Two year local control = 95%

# T1 Patient, 60 Gy



Pre-Rx



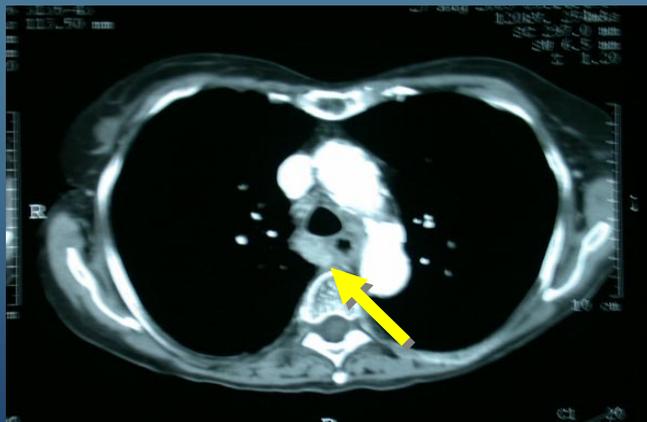
3 mo.



9 mo.



15 mo.

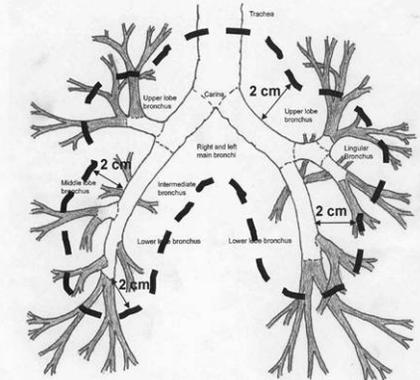
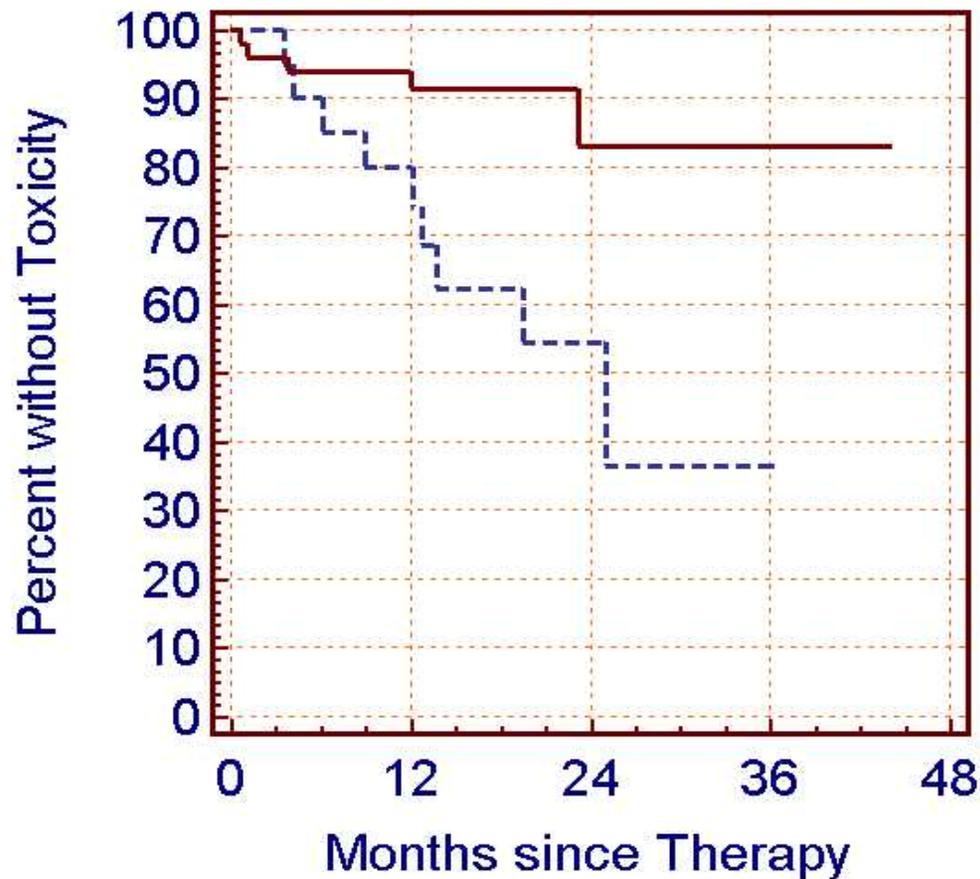


15 mo.

- Ongoing heavy smoking
- Local recurrence at 15 mo.
- Fatal hemoptysis at 19 months post-Rx
- Death scored related to Rx

# Grade 3-5 Toxicity: Location

Grade 3-5 Toxicity Free Survival  
Zone of the Proximal Bronchial Tree Status

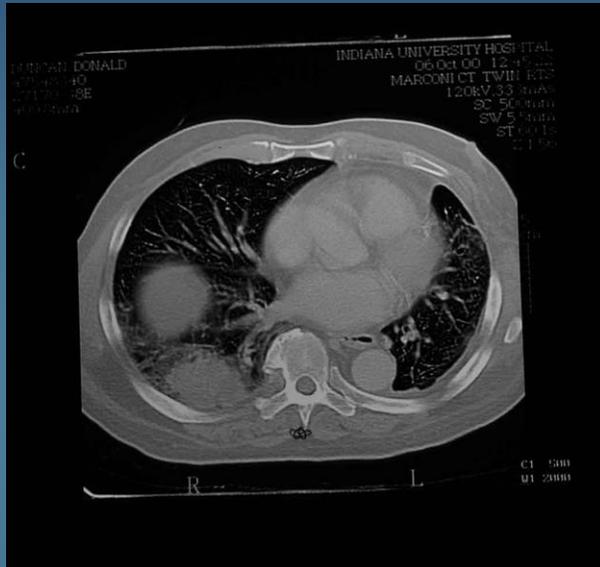


--- Defines zone of the proximal bronchial tree

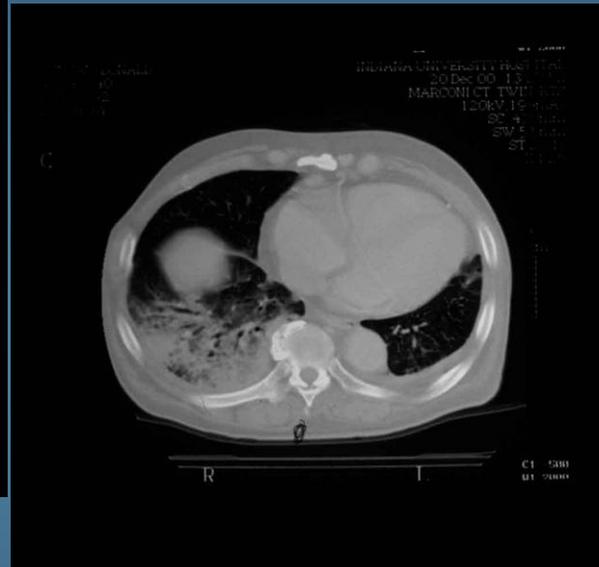
location  
----- inside  
———— outside

$p = 0.003$

# T2 tumor, 42 Gy



**Pre-Treatment**



**6 wks. Post-Treatment  
(radiation pneumonitis)**



**10 wks. Post-Treatment**

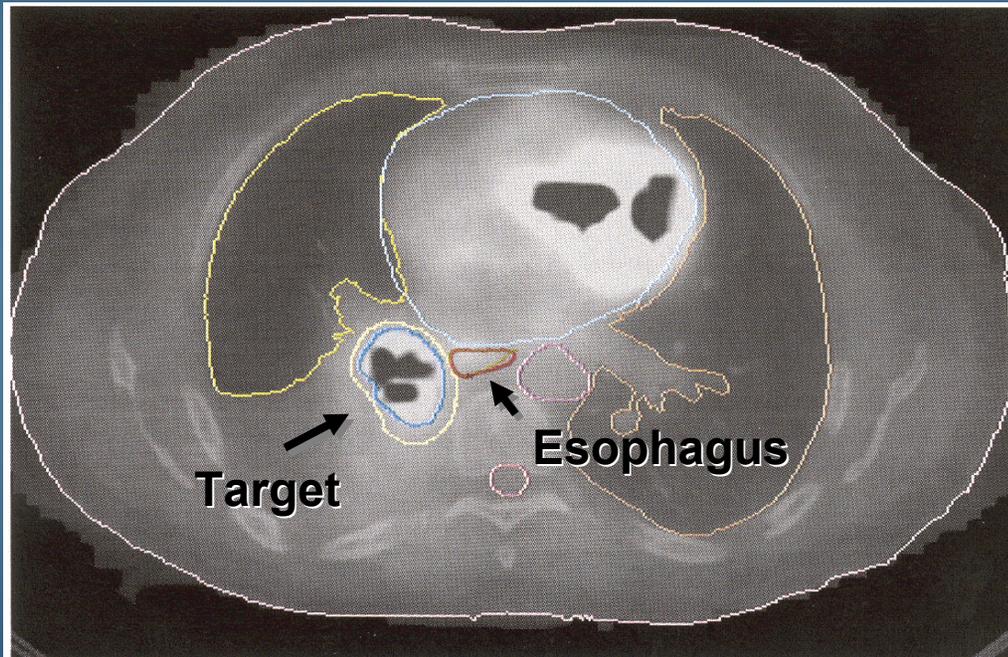
**Grade 3 Radiation Pneumonitis**

# Skin/Chest Wall Toxicity

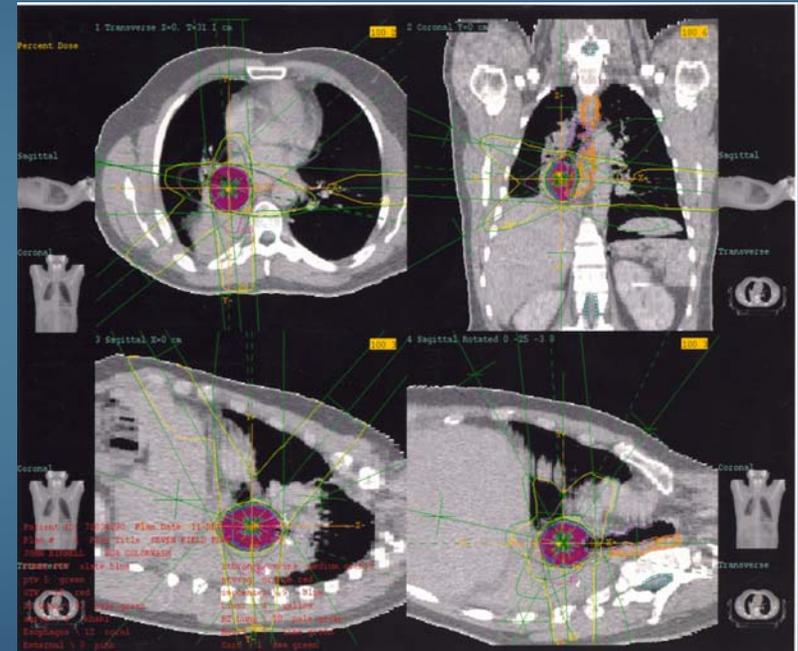


**Solution: Spread out entrance dose (more beams)**

# Malignant Obstruction – Recurrent NSCLC

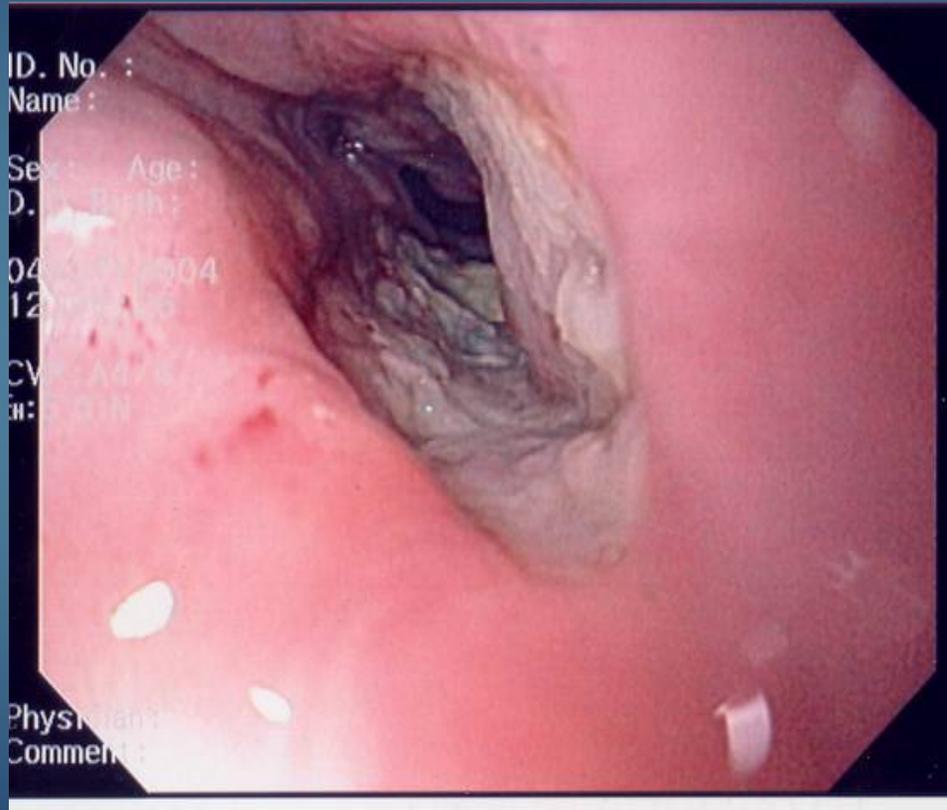


CT-PET Fusion



SBRT treatment

# Malignant Obstruction – Recurrent NSCLC



4 Months Post-Rx Upper Endoscopy – Severe Esophagus Damage

# RTOG 0236 Dose Constraints

Maximum PTV Dimension (cm)	Ratio of Prescription Isodose Volume to the PTV		Ratio of 50% Prescription Isodose Volume to the PTV, R <sub>50%</sub>		Maximum Dose 2 cm from PTV in any Direction, D <sub>2cm</sub> (Gy)		Percent of Lung receiving 20 Gy total or more, V <sub>20</sub> (%)		PTV Volume (cc)
	Deviation		Deviation		Deviation		Deviation		
	none	minor	none	minor	none	minor	none	minor	
2.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	1.8
2.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	3.8
3.0	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	7.4
3.5	<1.2	1.2-1.4	<3.9	3.9-4.1	<28.1	28.1-30.1	<10	10-15	13.2
4.0	<1.2	1.2-1.4	<3.8	3.8-4.0	<30.4	30.4-32.4	<10	10-15	21.9
4.5	<1.2	1.2-1.4	<3.7	3.7-3.9	<32.7	32.7-34.7	<10	10-15	33.8
5.0	<1.2	1.2-1.4	<3.6	3.6-3.8	<35.1	35.1-37.1	<10	10-15	49.6
5.5	<1.2	1.2-1.4	<3.5	3.5-3.7	<37.4	37.4-41.7	<10	10-15	69.9
6.0	<1.2	1.2-1.4	<3.3	3.3-3.5	<39.7	39.7-41.7	<10	10-15	95.1
6.5	<1.2	1.2-1.4	<3.1	3.1-3.3	<42.0	42.0-44.0	<10	10-15	125.8
7.0	<1.2	1.2-1.4	<2.9	2.9-3.1	<44.3	44.3-46.3	<10	10-15	162.6

# Tolerances

- Based on some experience, some derivation, and considerable speculation for 3 fraction treatments – not validated with long term data
- Total dose limits over 3 fractions:

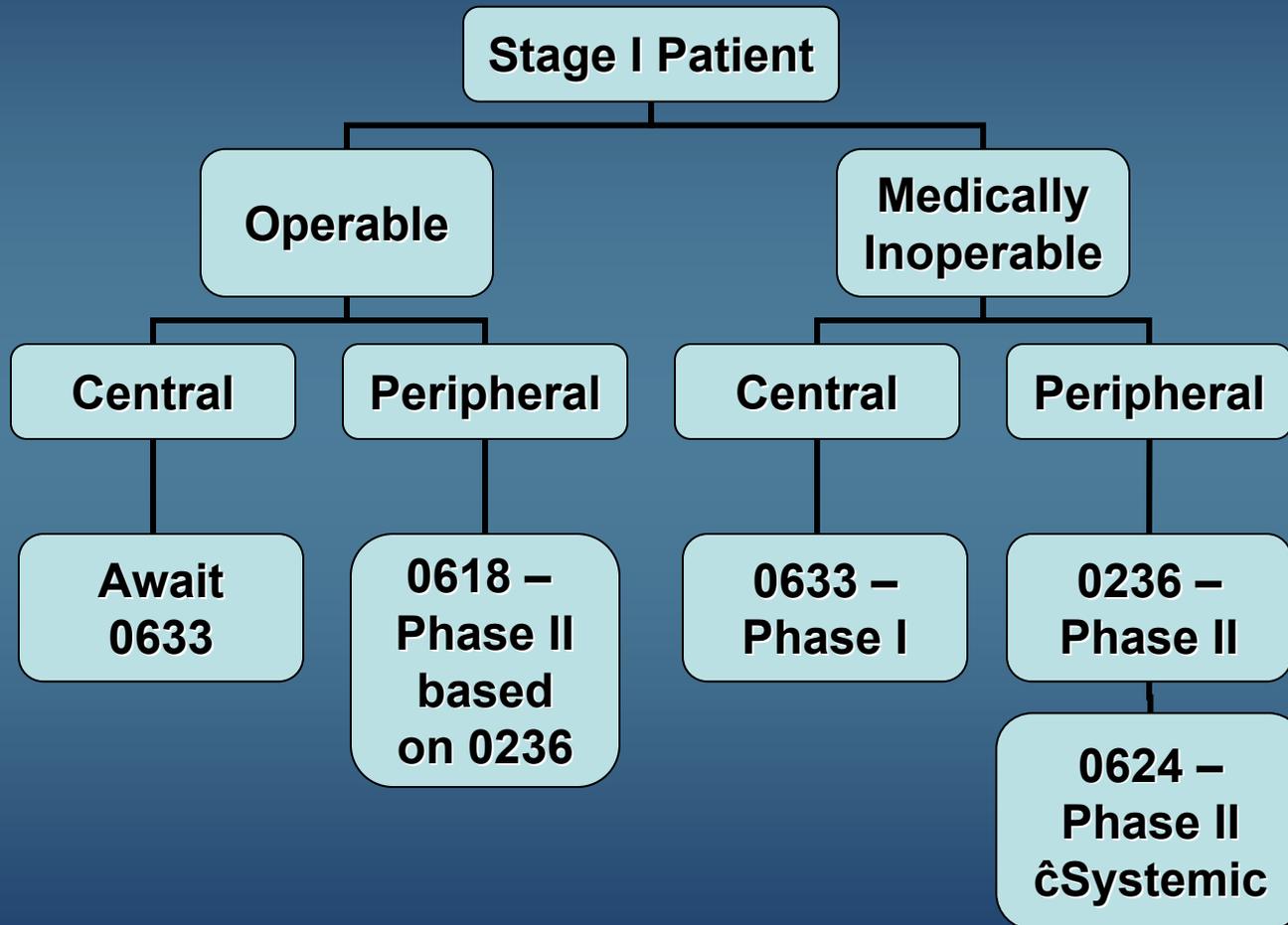
Spinal cord	any point	18 Gy
Esophagus	any point	27 Gy
Trachea/Bronchus	any point	30 Gy
Heart/Great Vessels	any point	30 Gy
Brachial plexus	any point	24 Gy
Skin	any point	18-24* Gy

\*15 Gy if in a skin fold

# RTOG 0236 Status

- RTOG 0236 Phase II: SBRT using 54 Gy in 3 fractions for patients with early stage medically inoperable lung cancer
- Excluded patients with central tumors
- Closed October 2006 after enrolling 56 patients
- Median f/u 9 months, one patient with local failure (toxicity analysis at ASTRO annual meeting)

# RTOG Stage I Lung Cancer



# RTOG-0618: Stereotactic Body Radiation Therapy (SBRT) in Operable Early Stage Non-small Cell Lung Cancer

PI: Robert Timmerman, M.D.

Surgery Co-PI: Harvey Pass, M.D.

Med Onc Co-PI: Marty Edelman, M.D.

Pathology Co-PI: William Geddie, M.D.

Comorbidity Co-PI: Beth Gore, M.D.

Physics Co-PI: Jim Galvin, Ph.D.

# Should Surgery be Challenged?

- Surgery is not a perfect treatment
- Local failures, death from cancer (even controlling for pathological staging)
- Toxicity, pain and suffering
- Expense
  - hospitalization, recovery, lost work/income, etc.

02/19/2006

# Legitimate Alternative to Lobectomy for Stage I NSCLC

- Requirements:
  - Local control **90%** or more at 5 years (actuarial)
  - Survival **60-80%** at 5 years (actuarial)
  - Grade III or higher toxicity **<15-20%**
  - Ideally less invasive than thoracotomy
  - Ideally more convenient
  - Ideally less costly
  - **All proven by prospective testing**

# RTOG 0618

- Build on experience, guidelines, and QA program from RTOG 0236 using 18 Gy X 3 fractions (54 Gy) given in about one week
- Primary objective = 2 year local control, secondary objectives survival and toxicity
- Target local control = 90% (similar to lobectomy) justifying treatment dose

# Local Control Lung

Author	Treatment	Local Control
<i>North America/Europe</i>		
Timmerman, 2006	20-22 Gy X 3	95% (2+ years)
Bauman, 2006	15 Gy X 3	80% (3 years)
Fritz, 2006	30 Gy X 1	80% (3 years)
Nyman, 2006	15 Gy X 3	80% (crude)
Zimmerman, 2005	12.5 Gy X 3	87% (3 years)
Timmerman, 2003	18-24 Gy X 3	90% (2 years)
<i>Asia</i>		
Xia, 2006	5 Gy X 10	95% (3 years)
Hara, 2006	30-34 Gy X 1	80% (3 years)
Onimaru, 2003	6 Gy X 8	70% (3 years)
Nagata, 2005	12 Gy X 4	94% (3 years)
Onimaru, 2003	7.5 Gy X 8	100% (3 years)

# What's the Right Dose?

- Many institutional experiences (some called phase II) using a variety of prescriptions doses
- Most often, dose was chosen by institutional leader(s) using educated guessing or conversions
- Only two classic phase I dose finding studies published (Indiana and Cleveland)
- Editorial: Retrospective pooling of multiple institution data using different dose prescriptions is NOT a legitimate dose finding study

# Classic Methodology for Prospectively Determining Optimal Therapy Dose for Lethal Cancers

- Want to find a balanced between benefit and harm from the new therapy
- Start with phase I dose escalation toxicity study – ONLY variable effecting outcome is dose
- Escalate until exceeding predetermined level of severe toxicity (usually 15-20%)
- Determine highest (maximum) tolerable dose (MTD)

# Further Testing

- Phase II study:
  - Use the MTD from the phase I study (cancer is a tough competitor)
  - Treat more patients at this dose than in the phase I study (e.g., 50 patients rather than 10)
  - Confirm toxicity with larger sample (<15-20% severe)
  - Look for glimmer of benefit (inconclusive)
- Phase III study:
  - Randomized – controls for selection bias (not true for phase II)
  - Compares the most potent form of the new therapy vs. standard

# Why Use the MTD in a Phase III Trial?

- Assume cancer recurrence is potentially deadly
- You usually get only one chance at a phase III trial:
  - Phase III trials are very expensive (around \$6000 per patient)
  - Phase III trials are big (usually over 100 patients)
  - Phase III trials take a long time (therapies change)
  - Colleagues consider treatment a black box (perturbations don't matter)
- Example of moving the wrong form of a therapy to phase III:
  - Radiation vs. surgery for inguinal lymph node therapy in vulvar CA

# Further Testing II

- Assume new therapy wins in the phase III trial
- Now do refinement studies (phase II or III)
  - Change schedule (e.g., number of fractions)
  - Change dose (de-escalate)
  - Change technique (e.g., shrink margins)
  - Add combination therapy
  - etc.

# Question?

- Since the only formal prospective phase I study completed for lung cancer using SBRT was the Indiana University trial (MTD = 54-60 Gy in 3 fractions),

Why doesn't everyone use this dose for further study rather than the multitude of dose prescriptions seen in institutional published reports?

# Answer(s)

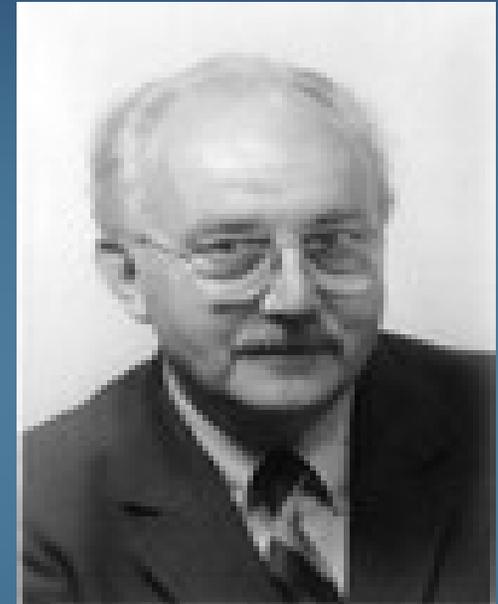
- Several trials were already ongoing and reporting good preliminary results (e.g., from Germany and Japan) prior to completing and publishing the Indiana trial
- 54-60 Gy in 3 fractions sounds kind of frightening
- Editorial: The starting dose for the Indiana trial was 24 Gy in 3 fractions, the whimpiest dose ever used in a SBRT trial!

# Typical Slide Shown at Meetings

Prescription Dose	BED-10 (Gy) Early (tumor)	BED-3 (Gy) Late
12 Gy X 4 = 48 Gy	106 (100%)	240 (100%)
15 Gy X 3 = 45 Gy	113 (107%)	270 (113%)
30 Gy X 1 = 30 Gy	120 (113%)	330 (138%)
12 Gy X 5 = 60 Gy	132 (125%)	300 (125%)
20 Gy X 3 = 60 Gy	180 (170%)	460 (192%)
2 Gy X 30 = 60 Gy	72	100

# Models in Radiation Oncology

- Models are NOT real!
  - “All models are wrong. Some models are useful”. - George Box
- Results from models do NOT trump measured data.
- If there is a discrepancy between the model and data, believe the data.



# The Actual Data

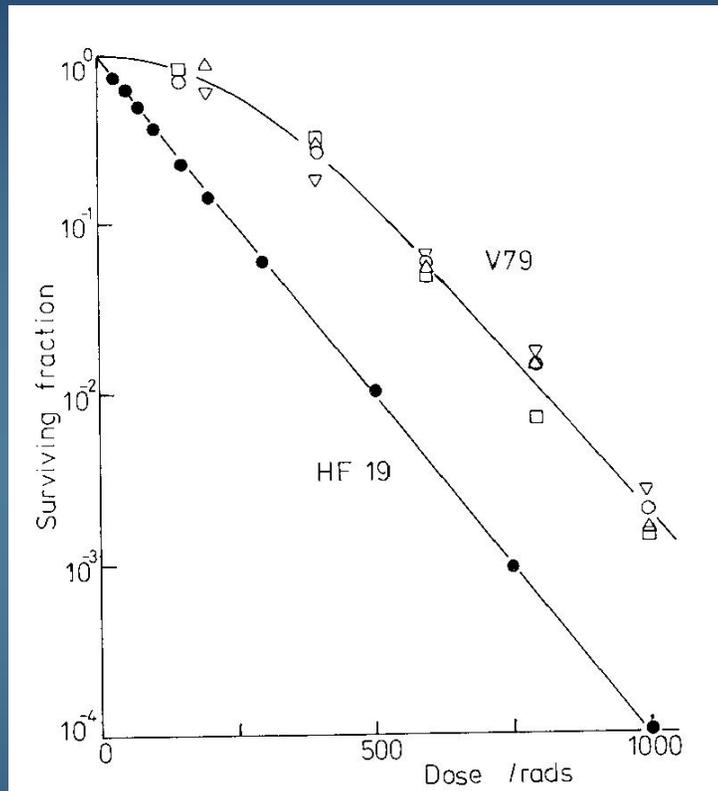


FIGURE 1. Survival curves for V79 Chinese hamster cells (open symbols) and HF 19 human diploid fibroblasts (closed circles) after irradiation with 250 kVp X-rays. Lines drawn by eye from the data of Cox et al.<sup>6</sup> and McNally and de Ronde.<sup>7</sup>

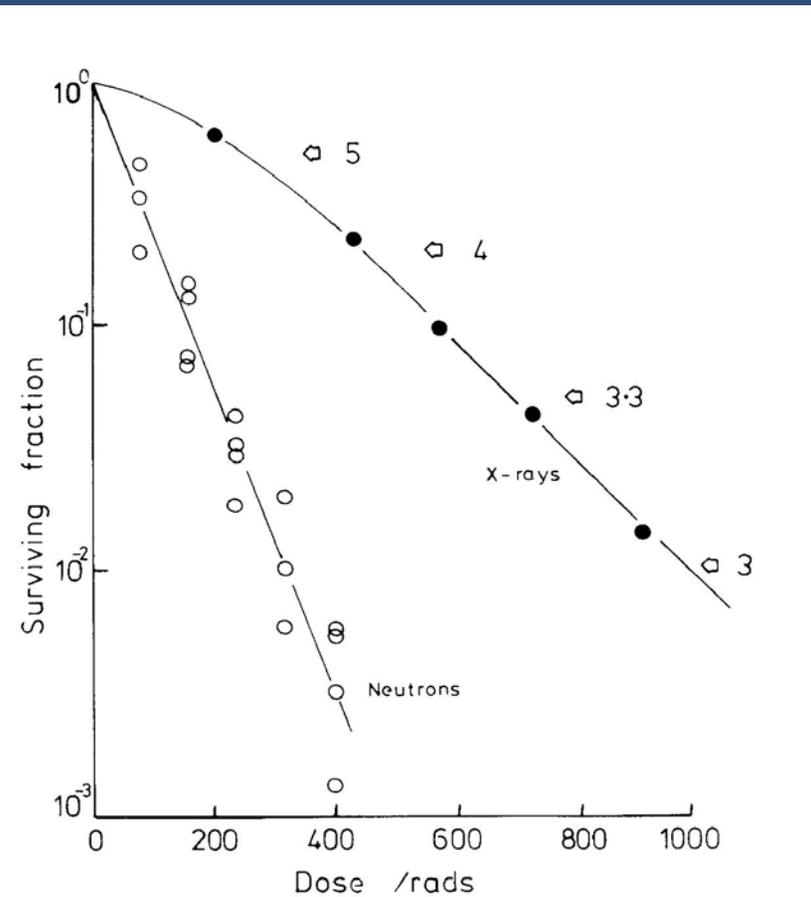
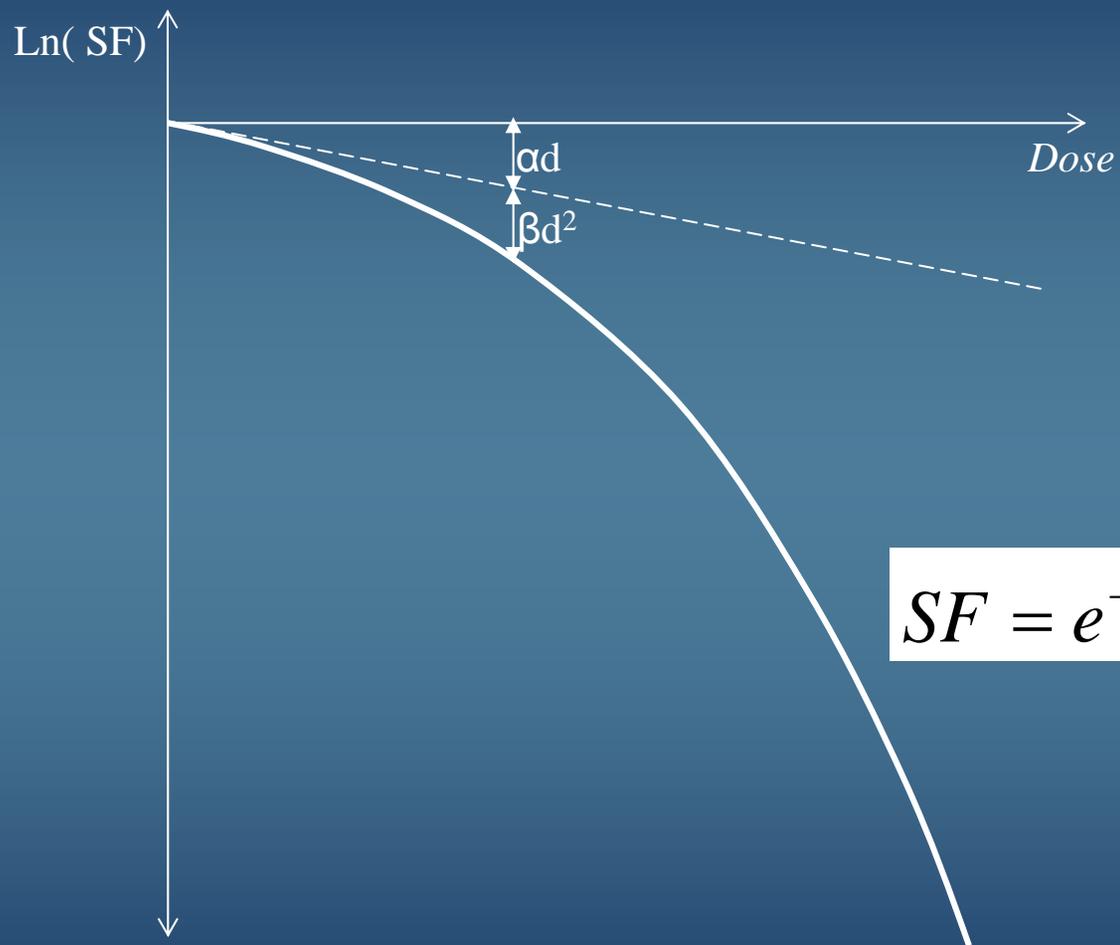


FIGURE 8. Survival curves for Ehrlich ascites cells irradiated with 250 kVp X-rays or cyclotron neutrons. The lines have been drawn by eye and the numbers to the right of the X-ray survival curve represent the RBE measured at the level of the arrows.

# Linear Quadratic Model

- Originally called the “theory of dual radiation action” by Kellerer and Rossi in describing high vs. low LET radiation (1972)
- Truncated power series (two terms) - Fits the shoulder very well
- Cell kill contributions from linear and quadratic terms
- DNA double strand breaks incorporated as mechanism of cell inactivation

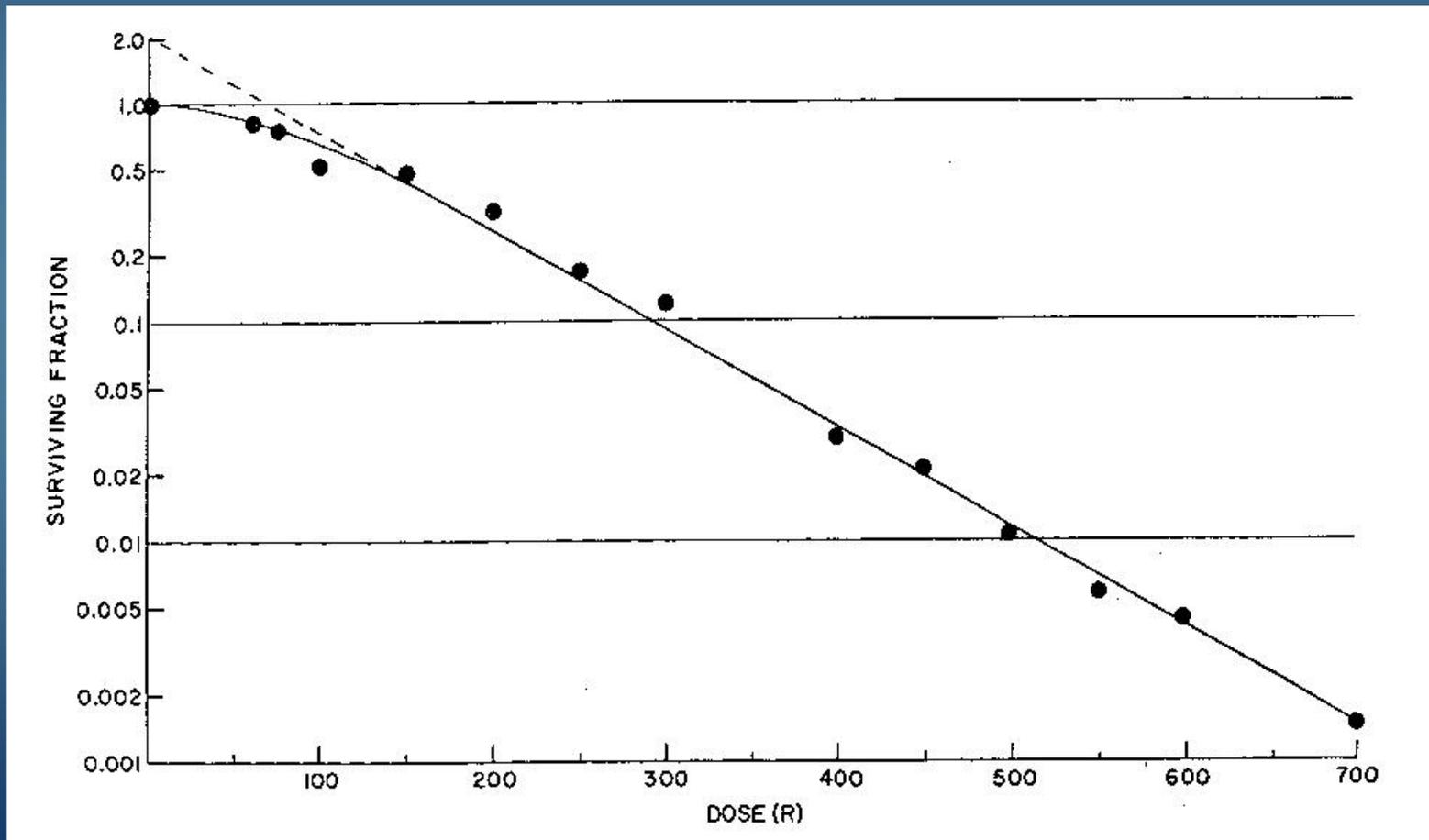
# LQ Model



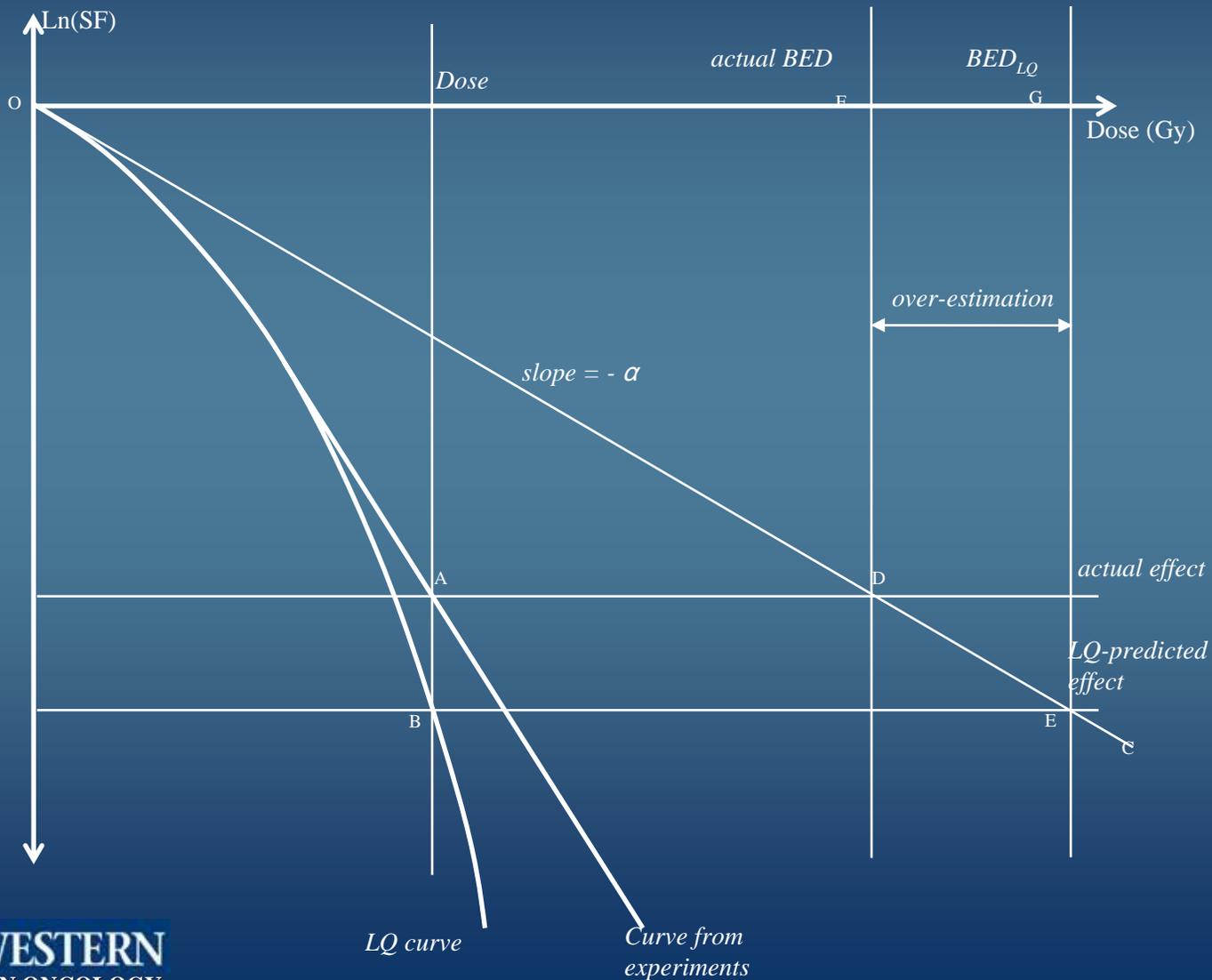
$$SF = e^{-(\alpha \cdot D + \beta \cdot D^2)}$$

# Survival Curve from Experiments

- The first known mammalian cell survival curve



# Over-Prediction by LQ and BED

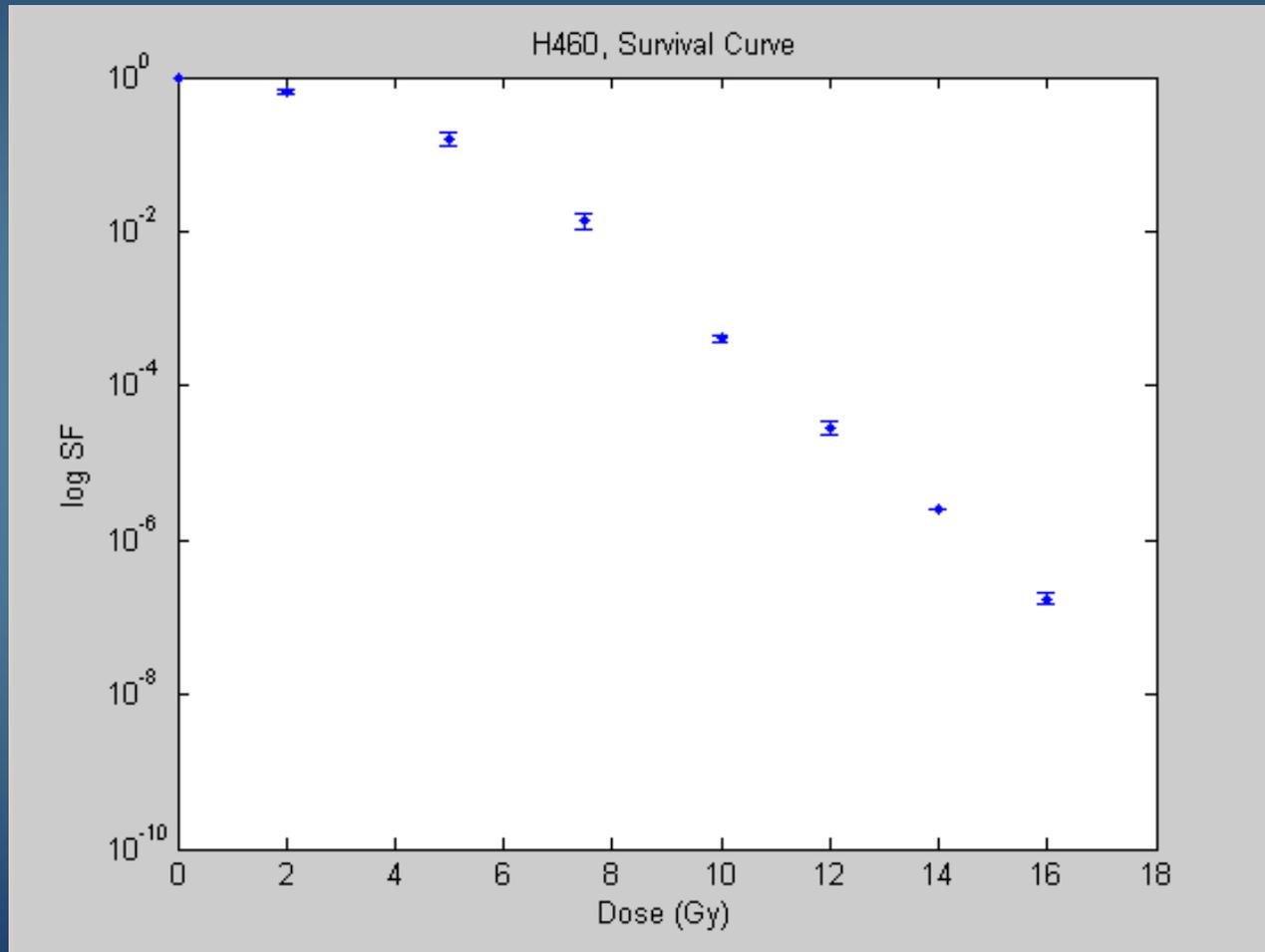


# Models for SBRT

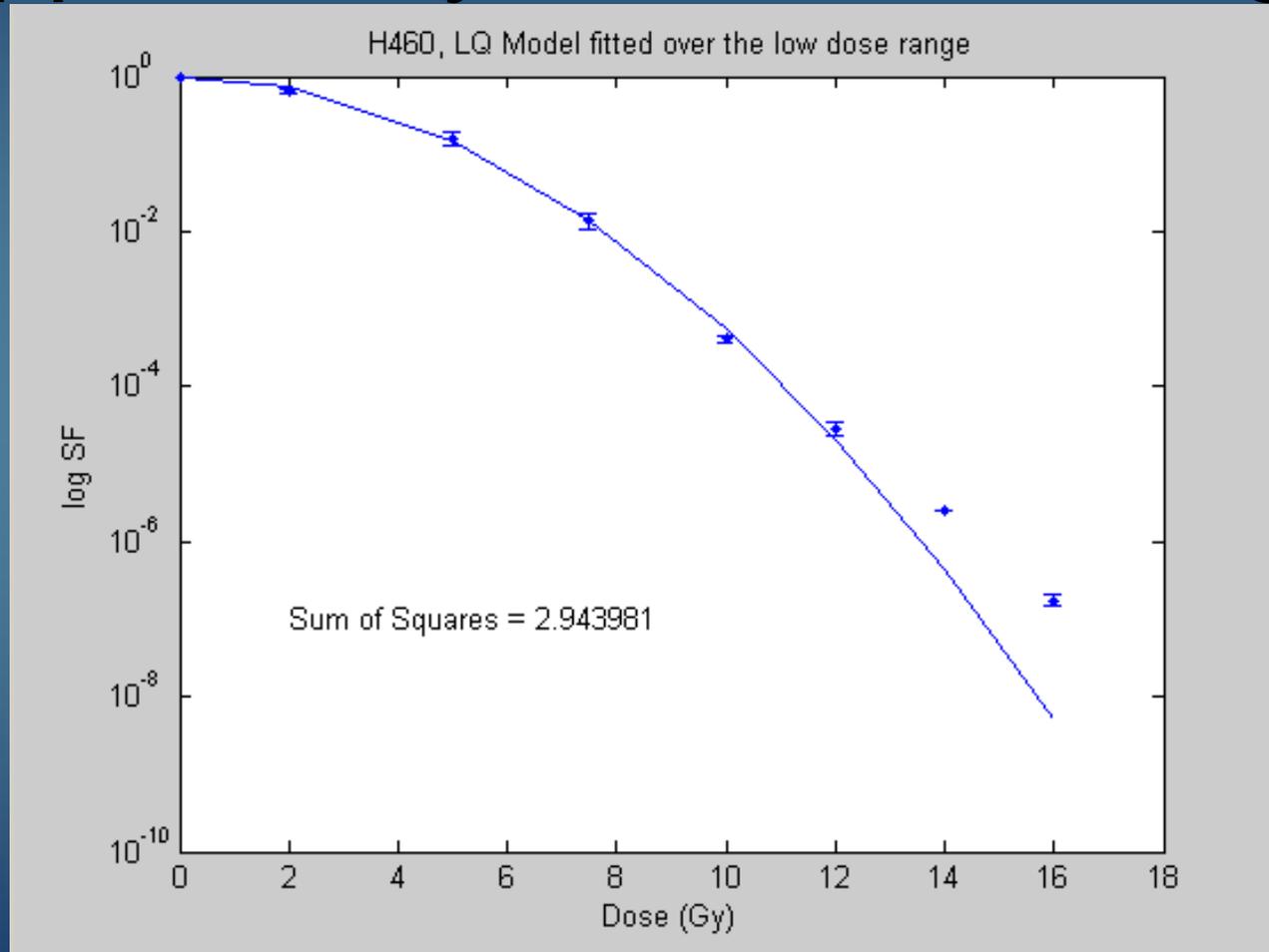
- Guerrero-Li Modified LQ model and Curtis Lethal-Potentially-Lethal Model
  - Mathematically sound
  - Too complicated for everyday clinical use.
  - Modification factors not well characterized.
- Using extremely large  $\alpha/\beta$  ratio ( $\sim 20$  Gy)
  - Valid?
  - The curve straightens, but the low-dose fit suffers.

Guerrero, Phys Med Biol, 2004, 49:4825  
Curtis, Radiat Res, 1986, 106:252  
Fowler, Personal Communications

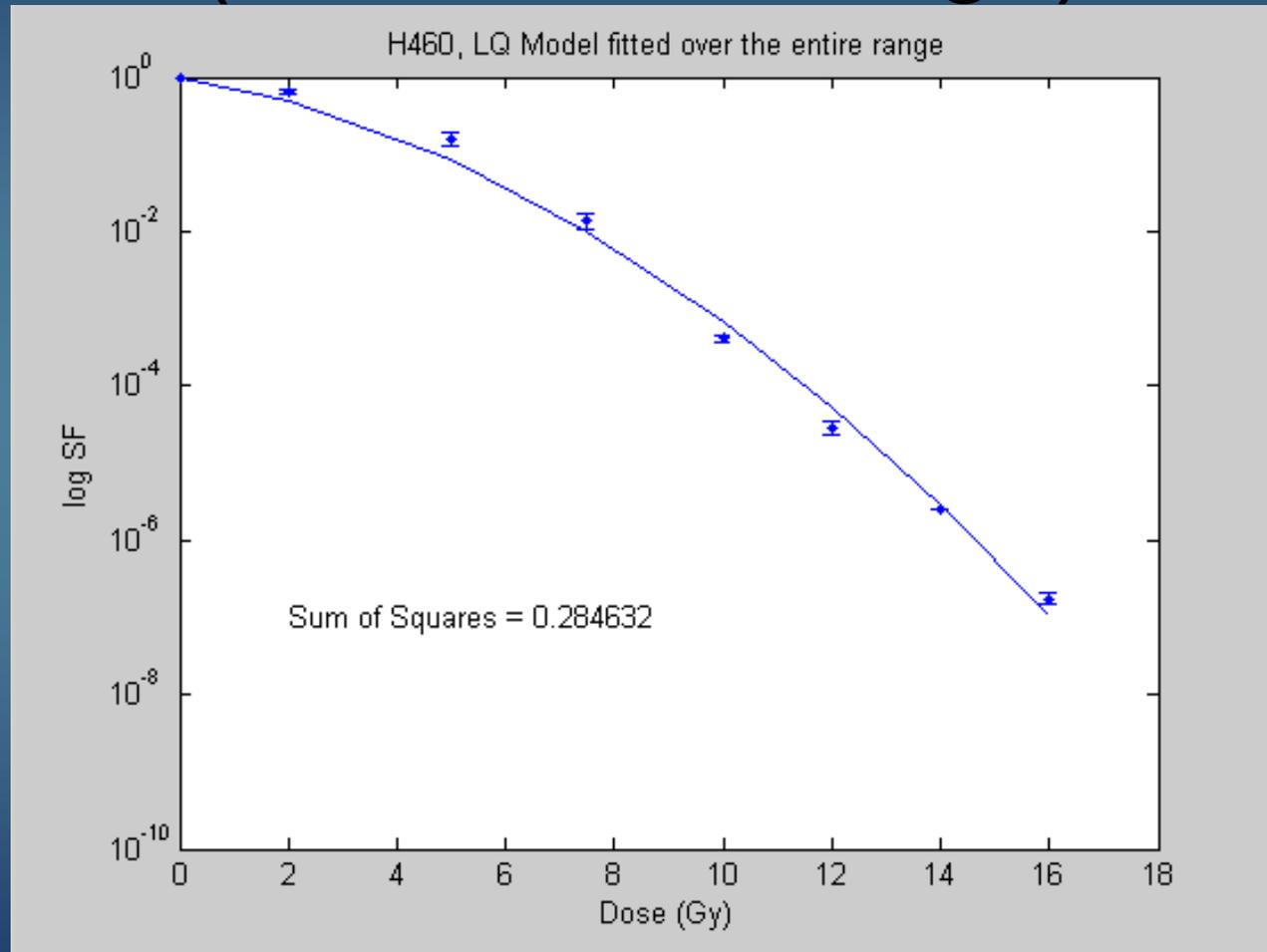
# H460 Survival Curve



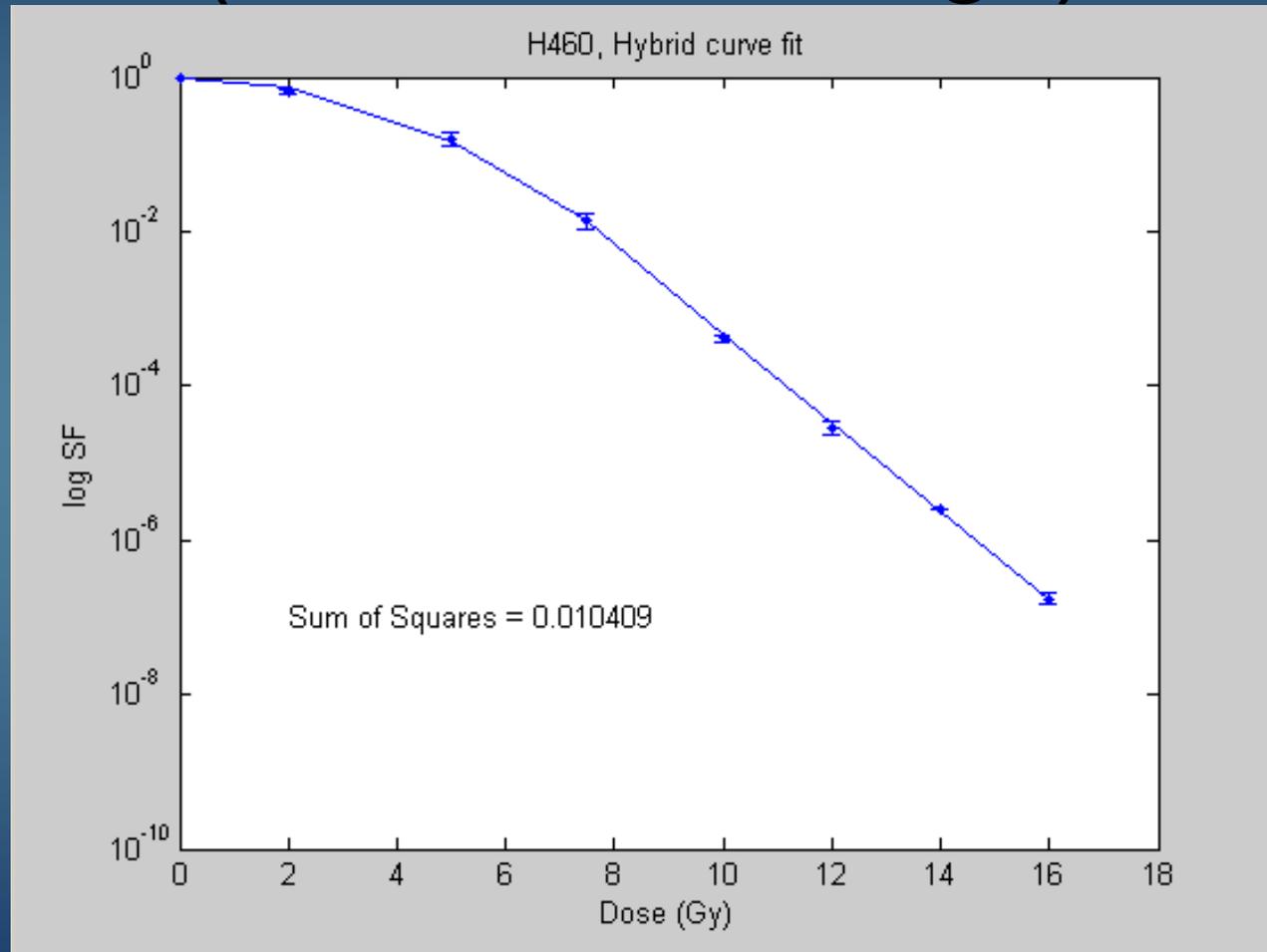
# H460 Fitted with LQ (applied only to low dose range)



# H460 Fitted with LQ (entire dose range)

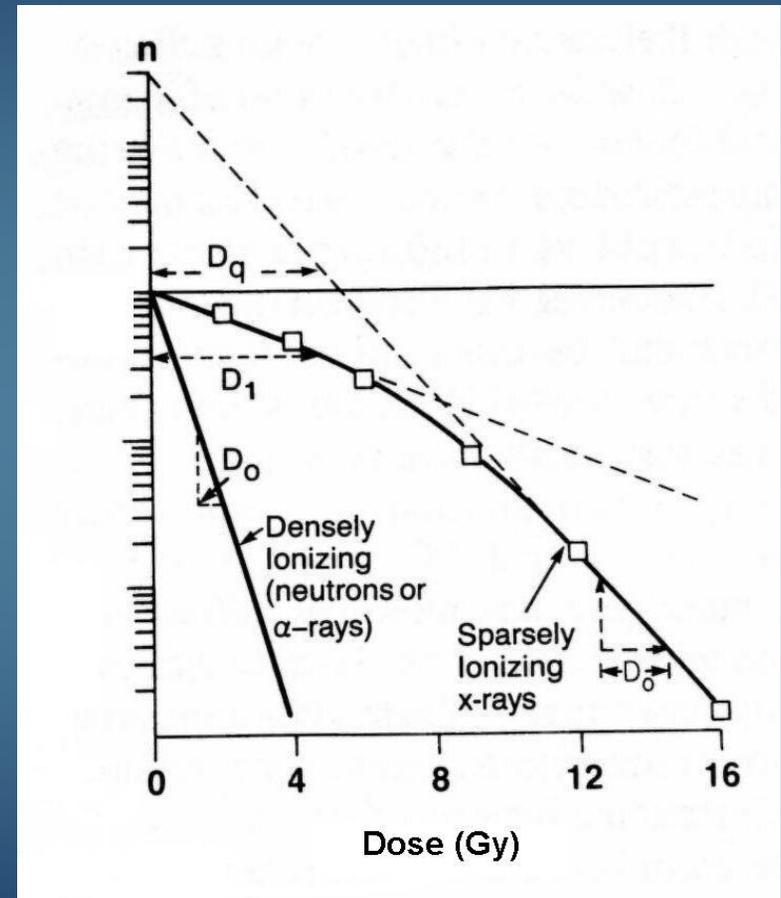


# H460 Hybrid Curve Fit (entire dose range)



# The Multi-target models

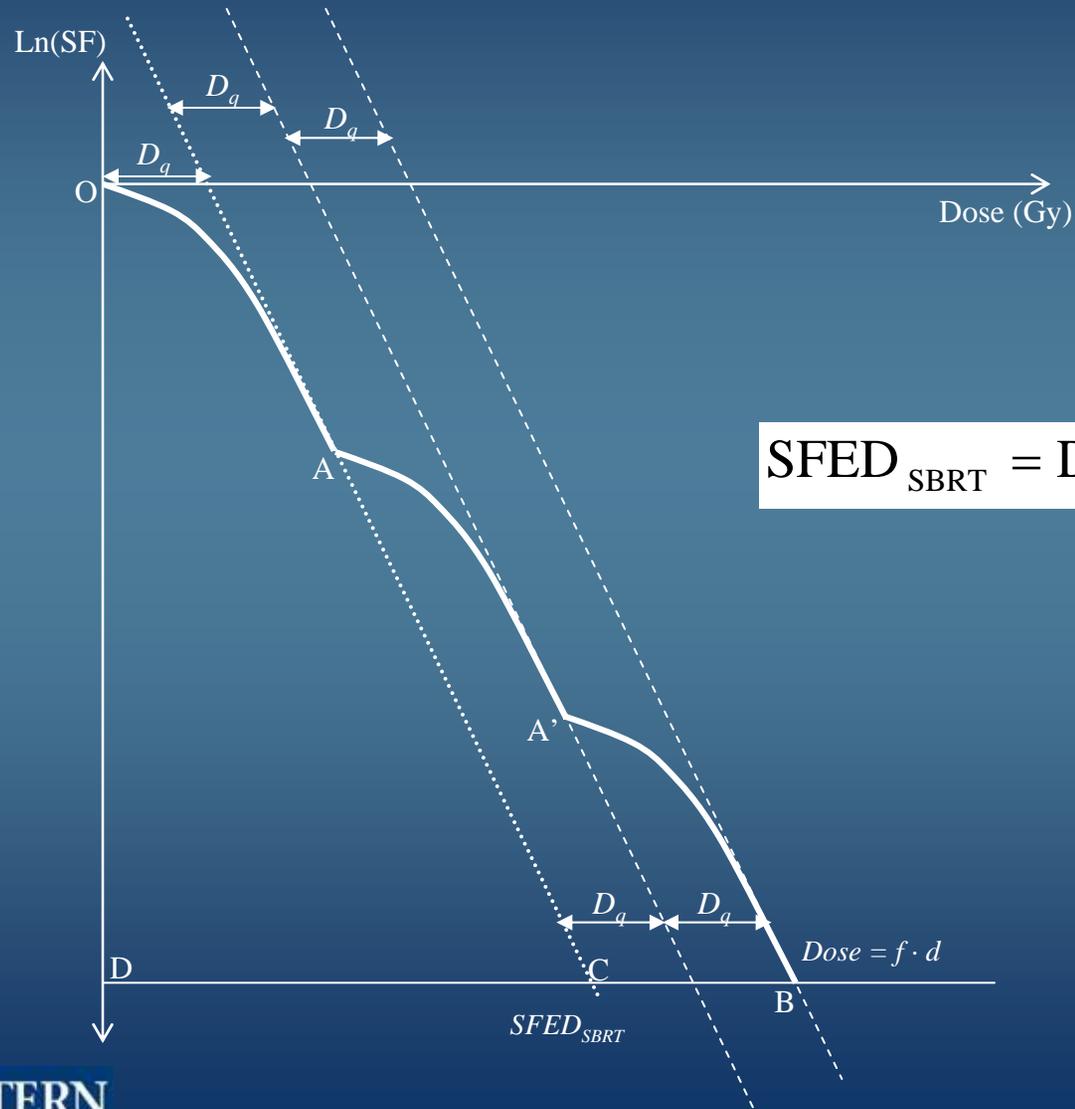
- Originally proposed by Puck and Markus (1956)
- Each cell contains a defined number of critical sites (targets) each of which are essential for survival
- Terminal portion is exponential (linear on log scale) consistent with data



# Single Fraction Equivalent Dose

- Definition: “The dose of radiation, if delivered in a single fraction, that would achieve the same effect as the dose-fractionation scheme in question.”
- Can be used just like how BED is being used for CFRT.
  - To compare potency and toxicity.
  - To design rational dose escalation scheme
- More intuitive than BED.

# SFED for SBRT



$$SFED_{SBRT} = D - (f - 1) \cdot D_q$$

# Updated Comparisons

Prescription Dose	BED-10 (Gy) Early (tumor)	SFED-2 (Gy)
12 Gy X 4 = 48 Gy	106 (100%)	42 (100%)
15 Gy X 3 = 45 Gy	113 (107%)	41 (98%)
30 Gy X 1 = 30 Gy	120 (113%)	30 (71%)
12 Gy X 5 = 60 Gy	132 (125%)	52 (124%)
20 Gy X 3 = 60 Gy	180 (170%)	56 (133%)

# SBRT + Erlotinib for 2<sup>nd</sup> Line Therapy in NSCLC (PI, Kavanagh)

- NSCLC failed 1<sup>st</sup> line chemotherapy
- $\leq 6$  discrete lesions (any site except brain)
- Week 1 Erlotinib, Week 2-4 SBRT+Erlotinib, Week 5+ Erlotinib until progression
- Endpoint = progression free survival
- Test of Norton-Simon hypothesis

# Extreme or Ablative Hypofractionation

- One option to increase dose potency (others include sensitizers, etc) and control tumors
- Obviously will cause late effects (desirable in tumor, not in normal tissues)
- Must follow patients carefully for long periods
- More SBRT prospective trials than any other radiotherapy related innovation in history of field (doesn't mean it's not used inappropriately)

# Obvious SBRT Shortcomings

- SBRT enabled by technological innovation. BUT, won't be enough to allow broad implementation
- We don't understand mechanisms of action
  - Vascular injury?
  - Mucosal injury?
  - Supporting stromal injury?
- Can this injury be modulated?
- Frontier of basic/translational science research

# Conclusions

- Technology facilitates, but does not always allow, ablative dose SBRT
- SBRT requires different strategy formulation (e.g., abandon adjuvant Rx)
- Medically inoperable early stage lung cancer has been an important clinical model to test SBRT
- Toxicity is late and mostly related to serial organs
- Put LQ to BED
- Investigation is continuing in multiple organ models
- SBRT may realistically challenge surgery

# Happy Trials!

