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

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

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

750 cGy (12.5% of script dose)
# 3-5 Year Outcome in Early Stage Lung Cancer

<table>
<thead>
<tr>
<th>Rx Modality</th>
<th>% alive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>60-80%</td>
</tr>
<tr>
<td>Radiotherapy (RT)</td>
<td>15-45%</td>
</tr>
</tbody>
</table>

*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)\(^1\)

- IU phase II efficacy study:
  Doses of 20-22 Gy X 3 fractions yields extremely high levels of local control (70 patients)\(^2\)

\(^1\) Timmerman, et. al., Chest, 2003
\(^2\) Timmerman, et. al., JCO, 2006
Phase I Dose Escalation Study

- 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

Wedge-like collapse of segmental bronchus

No evidence of tumor recurrence on PET

No tumor cells on bronchial biopsy or brushings

Post treatment bronchoscopy
Pulmonary Function Tests

- FEV1
- FVC
- DLCO
- pO2

Percent Change vs. Months from Therapy
Phase I Dose Response for Local Control

![Graph showing the relationship between total dose (Gy) in 3 fractions and local control rate over 17 months. The x-axis represents total dose (Gy) in 3 fractions ranging from 0 to 80, and the y-axis represents the local control rate (%) ranging from 0 to 100. The graph shows an increasing trend in local control with increasing dose.](image-url)
Indiana Phase II Study

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

Percent without Toxicity

0 10 20 30 40 50 60 70 80 90 100

0 12 24 36 48

Months since Therapy

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

<table>
<thead>
<tr>
<th>Maximum PTV Dimension (cm)</th>
<th>Ratio of Prescription Isodose Volume to the PTV</th>
<th>Ratio of 50% Prescription Isodose Volume to the PTV, ( R_{50%} )</th>
<th>Maximum Dose 2 cm from PTV in any Direction, ( D_{2cm} ) (Gy)</th>
<th>Percent of Lung receiving 20 Gy total or more, ( V_{20} ) (%)</th>
<th>PTV Volume (cc)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Deviation</td>
<td>Deviation</td>
<td>Deviation</td>
<td>Deviation</td>
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</tr>
<tr>
<td>2.0</td>
<td>none &lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.9 3.9-4.1</td>
<td>&lt;28.1 28.1-30.1</td>
<td>&lt;10 10-15 1.8</td>
</tr>
<tr>
<td>2.5</td>
<td>none &lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.9 3.9-4.1</td>
<td>&lt;28.1 28.1-30.1</td>
<td>&lt;10 10-15 3.8</td>
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<td>1.2-1.4</td>
<td>&lt;3.9 3.9-4.1</td>
<td>&lt;28.1 28.1-30.1</td>
<td>&lt;10 10-15 7.4</td>
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<tr>
<td>3.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.9 3.9-4.1</td>
<td>&lt;28.1 28.1-30.1</td>
<td>&lt;10 10-15 13.2</td>
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<tr>
<td>4.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.8 3.8-4.0</td>
<td>&lt;30.4 30.4-32.4</td>
<td>&lt;10 10-15 21.9</td>
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<tr>
<td>4.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.7 3.7-3.9</td>
<td>&lt;32.7 32.7-34.7</td>
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<td>1.2-1.4</td>
<td>&lt;3.6 3.6-3.8</td>
<td>&lt;35.1 35.1-37.1</td>
<td>&lt;10 10-15 49.6</td>
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<tr>
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<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.5 3.5-3.7</td>
<td>&lt;37.4 37.4-41.7</td>
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<tr>
<td>6.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.3 3.3-3.5</td>
<td>&lt;39.7 39.7-41.7</td>
<td>&lt;10 10-15 95.1</td>
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<tr>
<td>6.5</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;3.1 3.1-3.3</td>
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<tr>
<td>7.0</td>
<td>&lt;1.2</td>
<td>1.2-1.4</td>
<td>&lt;2.9 2.9-3.1</td>
<td>&lt;44.3 44.3-46.3</td>
<td>&lt;10 10-15 162.6</td>
</tr>
</tbody>
</table>
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

Stage I Patient

Operable
- Central
  - Await 0633
- Peripheral
  - 0618 – Phase II based on 0236

Medically Inoperable
- Central
  - 0633 – Phase I
- Peripheral
  - 0236 – Phase II
  - 0624 – Phase II cSystemic
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.
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

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

*In all series, tumor recurrence is late (median about 18 months)*
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!
<table>
<thead>
<tr>
<th>Prescription Dose</th>
<th>BED-10 (Gy)</th>
<th></th>
<th>BED-3 (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early (tumor)</td>
<td>Late</td>
<td></td>
</tr>
<tr>
<td>12 Gy X 4 = 48 Gy</td>
<td>106 (100%)</td>
<td>240 (100%)</td>
<td></td>
</tr>
<tr>
<td>15 Gy X 3 = 45 Gy</td>
<td>113 (107%)</td>
<td>270 (113%)</td>
<td></td>
</tr>
<tr>
<td>30 Gy X 1 = 30 Gy</td>
<td>120 (113%)</td>
<td>330 (138%)</td>
<td></td>
</tr>
<tr>
<td>12 Gy X 5 = 60 Gy</td>
<td>132 (125%)</td>
<td>300 (125%)</td>
<td></td>
</tr>
<tr>
<td>20 Gy X 3 = 60 Gy</td>
<td>180 (170%)</td>
<td>460 (192%)</td>
<td></td>
</tr>
<tr>
<td>2 Gy X 30 = 60 Gy</td>
<td>72</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
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. and McNally and de Ronde.⁷

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

\[ SF = e^{-(\alpha D + \beta D^2)} \]
Survival Curve from Experiments

- The first known mammalian cell survival curve

Puck and Marcus, J Exp Med, 1956;103:653
Over-Prediction by LQ and BED

\[ \text{Ln(SF)} \]

Dose
actual BED
BED_{LQ}
Dose (Gy)

\[ \text{slope} = -\alpha \]

\[ \text{LQ curve} \]

\[ \text{Curve from experiments} \]

over-estimation
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 (~20 Gy)
  - Valid?
  - The curve straightens, but the low-dose fit suffers.

Fowler, Personal Communications
H460 Survival Curve

![H460, Survival Curve](image)
H460 Fitted with LQ
(applied only to low dose range)
H460 Fitted with LQ (entire dose range)

Sum of Squares = 0.284632
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

<table>
<thead>
<tr>
<th>Prescription Dose</th>
<th>BED-10 (Gy)</th>
<th>SFED-2 (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Gy X 4 = 48 Gy</td>
<td>106 (100%)</td>
<td>42 (100%)</td>
</tr>
<tr>
<td>15 Gy X 3 = 45 Gy</td>
<td>113 (107%)</td>
<td>41 (98%)</td>
</tr>
<tr>
<td>30 Gy X 1 = 30 Gy</td>
<td>120 (113%)</td>
<td>30 (71%)</td>
</tr>
<tr>
<td>12 Gy X 5 = 60 Gy</td>
<td>132 (125%)</td>
<td>52 (124%)</td>
</tr>
<tr>
<td>20 Gy X 3 = 60 Gy</td>
<td>180 (170%)</td>
<td>56 (133%)</td>
</tr>
</tbody>
</table>
SBRT + Erlotinib for 2nd Line Therapy in NSCLC (PI, Kavanagh)

- NSCLC failed 1st 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!