Stereotactic Body Radiotherapy (SBRT) or Stereotactic Ablative radiotherapy (SABR) in Non-Small Cell Lung Cancer

The Indiana University Experience

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Disclosures

NONE
Stereotactic Body Radiotherapy (SBRT)
Stereotactic Ablative Radiotherapy (SABR)

- **Stereotactic body radiation therapy (SBRT)** has been used to describe the complex process of high-dose precision treatment of an extracranial malignancy using a single dose or a small number of fractions.

- **Stereotactic ablative radiotherapy (SABR)** has been gaining traction, since the term ablative may more accurately describe the radiobiological and pathological consequences of high dose-per-fraction treatment on cell division and tissue function.
Utilizing Technology for SBRT - SABR

- Stereotactic targeting
- IMRT
- 4-D motion assessment
- Motion control
- Image guidance

ALL FACILITATING STEREOTACTIC ABLATIVE RADIOTHERAPY
Stereotactic Ablative Radiation Therapy

Outpatient

20-60 Minutes Per Treatment

No Sedation or Anesthesia (painless)

1-5 Treatments qod

Entire course of Rx in 1-2 weeks

Immediate Return To Activities
The proximity of lung tumors to critical thoracic structures requires that the high doses used in SBRT be delivered accurately and precisely to minimize normal tissue exposure to radiation.

Consistent, reproducible, and comfortable patient immobilization is essential for ensuring treatment accuracy.

- Elekta Body Frame
- Body Pro-Lok System
Lung tumors often move relative to other thoracic structures during the respiratory cycle. This motion can vary significantly depending upon the location of the tumor and patient characteristics.

Target volumes are determined using mechanisms to predict and quantify tumor motion such as 4D-CT and fluoroscopy.

Several methods exist to reduce or compensate for tumor motion:
- Abdominal compression places a pressure device on the abdomen to reduce motion related to the diaphragm.
- Deep inspiration and breath holding attempts to arrest the tumor in a reproducible position within the respiratory cycle.
- Respiratory gating combines these approaches to trigger delivery of radiation during a specific segment of the respiratory cycle.
- Tumor tracking systems actually move the radiation beam to follow the motion of the tumor.
Dealing With Tumor Motion

- Fluoroscopy or 4-D CTs (or MRIs) are available to assess extent of motion with “snapshots”
- Motion control techniques include regulated breath hold, gating, chasing (tracking), and chest wall breathing
Improvements in CT, 4D-CT, MRI, PET/CT allow increased accuracy in target delineation, while sparing excessive normal tissue irradiation

- When tumor is hard to differentiate from normal tissue, such as tumors adjacent to the chest wall or associated with atelectasis or consolidation, PET/CT can help delineate targets more precisely

Planning priorities

- Respect the spinal cord constraint
- Similar priority for the brachial plexus
- Cover the tumor conformally
- Create “compactness” of dose
- Respect other normal tissue constraints
Principles of SBRT: Spread out Entry Damage

Multiple beams (typically 10 to 12) or large angle arc rotations

Non-opposing beams
  Avoid overlap of dose at points of entrance and exit
  Further spread out the entrance and exit dose within normal tissues
Principles of SBRT: Punishing Target Dose

- Conformity of the shape of the isosurface defined by the prescribed dose to the outer surface of the PTV
- Rapid falloff of the dose outside the PTV to normal surrounding tissues, isotropically in all directions
- Non-uniform dose distribution within the PTV

This dose defines tumor control (place it well)
Principles of SBRT: Steep gradients to normal tissues

- This intermediate dose
  - Can kill microscopic tumor tentacles
  - BUT, accounts for toxicity

3000 cGy (50% script dose)
Principles of SBRT: Large low dose volume

- SBRT (and SRS) 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)
Traditional DVH Interpretation

Volume that gets *at least* 15 Gy

<table>
<thead>
<tr>
<th>ROI Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Line Type</strong></td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>PTV</td>
</tr>
</tbody>
</table>
Critical Volume Interpretation

Volume that is *spared* 15 Gy

**ROI Statistics**

<table>
<thead>
<tr>
<th>ROI</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>% Outside Grid</th>
<th>% &gt; Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>3.9</td>
<td>7263.3</td>
<td>469.6</td>
<td>842.6</td>
<td>0.00 %</td>
<td>0.00 %</td>
</tr>
<tr>
<td>PTV</td>
<td>4077.2</td>
<td>7705.4</td>
<td>7060.8</td>
<td>523.6</td>
<td>0.00 %</td>
<td>0.00 %</td>
</tr>
</tbody>
</table>
Image Guided Radiotherapy (IGRT)

- Sophisticated image guidance, typically with computed tomography (CT), is incorporated into the treatment unit and allows validation of patient positioning prior to each treatment. IGRT minimizes the uncertainty associated with external reference points and allows accurate tumor localization in near real time.
- Because lung tumors are very distinct on CT scan, pretreatment reference volumes can be linked to the image and appropriate adjustments can be reliably made on the day of treatment.
What is the benefit of Image Guidance?

- It’s not to just see if things are setup well; rather, allows you to shrink margins without missing

- This is the CTV to PTV margin
  - CTV + motion = ITV
  - ITV + setup error = PTV
  - Setup error = inter- and intra-fraction components

- Image guidance can reduce set-up errors dramatically
IGRT – CBCT

- Initial acquisition
IGRT - CBCT

- Final adjustment
SBRT at Indiana University

- 2000  Opened Phase I, medically inoperable St INSCLC
- 2002  Finished Phase I NSCLC
- 2003  Opened Phase I/II study in liver metastases
- 2004  Opened Phase I/II trial in HCC
- 2004  Finished Phase I study in liver metastases
- 2005  Completed Phase II – NSCLC
- 2005  Completed Phase I Liver metastasis
- 2007  Completed Phase II Liver metastasis
- 2007  Completed Phase I primary HCC
- 2008  Open Phase II primary HCC
- 2013  Open Phase Ib, SBRT+Sorafenib in HCC-CPA
# 3-5 Year Outcome in Early Stage NSCLC

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Surgery</th>
<th>60-80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I*</td>
<td>Conventional XRT</td>
<td>15-45%</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Stage I</th>
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</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Conventional XRT</td>
<td>15-45%</td>
</tr>
</tbody>
</table>

*clinically staged and mostly medically inoperable (some refused surgery)
High Dose: Conventional Radiation vs. Image Guided Hypofractionated Radiotherapy

Targets (blue - GTV, red - PTV)
6000 cGy (script dose)

3000 cGy (50% script dose)
Early Stage NSCLC Risk Groups

- Refer to risks from surgery
- 3 Groups:
  - Average Risk
    - Generally can tolerate removal of an entire lobe
  - High Risk
    - Can tolerate partial removal of a lobe
  - Medically Inoperable
    - Cannot tolerate surgery for lung cancer
- Patients who refuse surgery can be in any group
Legitimate Alternative to Lobectomy for Stage I NSCLC

- Requirements:
  - Local control ≥90% 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
## SBRT - Treatment Results: Lung

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Histologies</th>
<th># T’d Targets</th>
<th>Dose/fx</th>
<th>CTV vol (median cc)</th>
<th>Median FU (m)</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren 1998</td>
<td>Primaries and Mets</td>
<td>17</td>
<td>3x10 Gy to 2x15Gy (65% Iso)</td>
<td>3-198 (15)</td>
<td>8</td>
<td>94%</td>
</tr>
<tr>
<td>Uematsu 1998</td>
<td>Primaries and Mets</td>
<td>66</td>
<td>5-15 fx’s (30-76Gy)</td>
<td>0.5-55</td>
<td>11</td>
<td>97%</td>
</tr>
<tr>
<td>Onimaru 2003</td>
<td>Primaries and Mets</td>
<td>57</td>
<td>48-60Gy in 8 fxs (80% iso)</td>
<td>0.6-6 cm</td>
<td>18</td>
<td>100% 60 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70% 48 Gy</td>
</tr>
<tr>
<td>AUTHOR</td>
<td>Histologies</td>
<td># T’d Targets</td>
<td>Dose/fx</td>
<td>CTV-PTV vol (median cc)</td>
<td>Median FU (m)</td>
<td>Local Control</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------</td>
<td>---------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Hof 2003</td>
<td>Primaries</td>
<td>10</td>
<td>1x26Gy (80% Iso)</td>
<td>5-19 cc</td>
<td>15</td>
<td>80%</td>
</tr>
<tr>
<td>Wulf 2005</td>
<td>Primaries and Mets</td>
<td>92</td>
<td>3x10 Gy, 3x12-12.5 Gy (100% Iso) 1x26Gy (80% iso)</td>
<td>2-256 cc</td>
<td>14</td>
<td>2y –LC 3x10, 71% 3x12.5, 92% 1x26, 100%</td>
</tr>
<tr>
<td>Nagata 2005</td>
<td>Primaries</td>
<td>45 32 St IA 13 St IB</td>
<td>4x12 Gy (isocenter)</td>
<td>13 cc</td>
<td>30</td>
<td>100% DFS 2 &amp; 5y 71% OS 2 &amp; 5 y 72%</td>
</tr>
<tr>
<td>Baumann 2009</td>
<td>Primaries</td>
<td>57 40 St I 17 St IIA</td>
<td>3x15Gy (67% isodose)</td>
<td>20-162 cc</td>
<td>35</td>
<td>3y-LC, 92% OS 3y= 60% DFS 3y= 88%</td>
</tr>
<tr>
<td>Senthini, 2012</td>
<td>Primaries</td>
<td>676 379, T1 297,T2</td>
<td>T1, 3x18-20Gy T2, 5x11-12Gy</td>
<td>28.9 cc</td>
<td>33</td>
<td>2-y LC, 95.1% 2-y OS, 60%</td>
</tr>
</tbody>
</table>
# SBRT - Toxicity: Lung

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Histologies</th>
<th># T’d Targets</th>
<th>Acute Pneumonitis</th>
<th>Late Severe &gt;grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomgren, 1998</td>
<td>Primaries and Mets</td>
<td>17</td>
<td>“Some” developed pneumonitis, fibrosis</td>
<td>6%</td>
</tr>
<tr>
<td>Uematsu, 1998</td>
<td>Primaries and Mets</td>
<td>66</td>
<td>Grade 1</td>
<td>0%</td>
</tr>
<tr>
<td>Onimaru, 2003</td>
<td>Primaries and Mets</td>
<td>57</td>
<td>Grade 2, 4%</td>
<td>2%</td>
</tr>
<tr>
<td>Hof, 2003</td>
<td>Primaries</td>
<td>10</td>
<td>Grade 1-2, “some”</td>
<td>0%</td>
</tr>
<tr>
<td>Wulf, 2005</td>
<td>Primaries and Mets</td>
<td>92</td>
<td>Grade 2</td>
<td>0%</td>
</tr>
<tr>
<td>Nagata, 2005</td>
<td>Primary</td>
<td>45</td>
<td>Grade 2, 2 pts</td>
<td>0%</td>
</tr>
<tr>
<td>Baumann, 2009</td>
<td>Primary</td>
<td>57</td>
<td>Overall grade 3= 28%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Results of a Phase I study with SBRT in medically inoperable Stage I NSCLC patients. Indiana University Experience

Robert Timmerman, M.D. et al

*Chest, 2003; 124: 1946-1955
IJROBP, 2005; 63: 1010-1015*
Eligibility

- Biopsy-proven T1-T2 (≤ 7cm), No, Mo by clinical staging
- PET/CT: No evidence of regional or metastasis
- Pre-defined criteria constituting medical contraindication to lobectomy (e.g., <40% predicted PFT parameters)

<table>
<thead>
<tr>
<th>Tumor anywhere in lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous chest RT</td>
</tr>
<tr>
<td>No plans for systemic therapy</td>
</tr>
<tr>
<td>KPS 60-100</td>
</tr>
<tr>
<td>No lower limits of pulmonary function</td>
</tr>
</tbody>
</table>
Objectives

- **Phase I:**
  - To determine the MTD of SBRT in the treatment of clinically unresectable patients with
    - Stage I [T1-T2 (< 7 cm), No, Mo] NSCLC

- **Phase II:**
  - To determine the rates of PR and CR
  - To determine DFS and OS in treated patients, in order to define if the therapy is promising enough for further clinical investigation
Dose escalation in cohorts of 3 patients, starting at 800 cGy/fx, 3 fx, with 200 cGy/fx increments in dose/fx at each dose escalation step, until dose-limiting toxicity (grade 3 cardio-pulmonary or esophageal or any grade 4) was reached

- @ 1400 cGy/fx, two separate dose escalations based on tumor size (≤ 3cm vs > 3cm)

Planning:
- Prescription dose to the isodose encompassing ≥ 95% of PTV [generally the 80% isodose line]
  - ≥ 99% of PTV covered by 90% prescription dose
  - Hot spots allowed only within the PTV
Results

- Trial began accrual in February 2000
- 47 patients Phase I study
- Median follow-up – 24 m
  - T1 27.4 m +/- 12.5 m
  - T2 19.1 m +/- 11.3 m
- Mean GTV
  - T1 8.51 +/- 6.32 cc
  - T2 50.5 +/- 36.71 cc

- Finished 7 dose escalations
  - 60 Gy total (20 Gy/fx) for T1 without reaching MTD
  - 66 Gy total (22 Gy/fx) for small T2 (< 5 cm) without reaching MTD
  - Big T2 tumors (5-7 cm): 2/5 patients with DLT at 72 Gy total (24 Gy/fx)
    - MTD defined at 66 Gy (3 fx, 22 Gy/fx)
Symptomatic (not radiographic) pneumonitis occurred less frequently than anticipated

- Lung / Heart Toxicity
  - T1: One patient (1600 cGy) transient grade 3 hypoxemia
  - T2: Two patients (1400 cGy & 2400 cGy) grade 3 pneumonitis and one patient (2400 cGy) grade 4 pericardial toxicity [window]

Patients treated at higher doses nearly all experienced collapsed lung near and beyond the target obscuring response assessment

- Other Toxicity
  - 1 patient had Grade III dermatitis (2000 cGy plus Mexico beach sun exposure); 2 Grade I dermatitis
Tumor and Normal Tissue response after high-dose SBRT

Bronchial injury with downstream effects
Indiana University Phase I Trial

Pre-Treatment

22 mo. Post-Treatment

12 Gy X 3 = 36 Gy
T2 tumor, 42 Gy (14 Gy/fx)

Pre-Treatment

6 wks. Post-Treatment (radiation pneumonitis)

10 wks. Post-Treatment

Grade 3 Radiation Pneumonitis – Additional patients treated without further toxicity
T1 tumor, 60 Gy (20 Gy/fx)

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
A. Stage I non-small cell lung carcinoma treated to 54 Gy in 3 fractions prescribed to 80% isodose line (cyan line) and 50% isodose line is shown in red
B. CT chest 5 months after SBRT showed mixed ground-glass opacity and consolidation
C. CT chest 8 months after SBRT showed progression to modified conventional pattern
Phase I/II Local Control vs. Script Dose

Dose-response curve for LC after SBRT

Group 1: 24-36 Gy
Group 2: 42-54 Gy
Group 3: 60-72 Gy

P = 0.01 (log rank)
Dose Response

4-year Local Control vs. Total Dose in 3 Fractions

Optimal Therapeutic Window Below MTD

Courtesy of Dr. R. Timmerman, 2013
70 patients enrolled Jan. 2002 – Sept. 2004
  - T1: 35 pts; T2: 35 pts

Phase I dose:
  - T1= 20 Gy x 3 fractions = 60 Gy
  - T2= 22 Gy x 3 fractions = 66 G

23/70 on home O₂
  - Mean FEV₁ 1.13 (40% predicted)
  - Mean DLCO 11.2 (42% predicted)
  - Mean GTV 16.7 cc, range 1.2-211.8 cc
IU Phase II - Survival

- Median FU 17.5 months
- 28 patients have died:
  - 17 from co-morbidities,
  - 5 from lung cancer,
  - 6 from treatment-related toxicity at median 12 months post Tx
- Median survival **32.6 m**

![Kaplan-Meier plot of overall survival (OS).](image)
IU Phase II - Local Control

- Response rates @ 3 m
  - CR+PR, 60%,
  - SD, 40%
- After 3 m, 17 pts had radiographical abnormalities in the treated area or its vicinity, prompting a PET scan or biopsy
- 10 pts recurred
  - Local alone = 3 pts, @ 9, 16, and 33 m, from Tx
  - Local + Distant = 0 pts
  - Distant = 7 pts

Fig 1. Kaplan-Meier plot of time from treatment until local failure (percent with local control).
IU Phase II - Toxicity

- 58 / 70 pts had Grade 1-2 toxicity (mostly fatigue and pneumonitis) at median 1.5 m post Tx and resolving by 3-4 m post Tx
- 8 pts had grade 3-4 toxicity (pneumonia, decline in PFT, pleural effusion, apnea, and skin reaction) at median 7.6 months post Tx (1.1-25 m)
- 6 pt died as a result of SBRT toxicity (grade 5), 0.6-19.5 m post Tx
  - 4 pts died from bacterial pneumonia besides ATB
  - 1 pt from pericardial effusion (tumor adjacent to the mediastinum, suprahilar)
  - 1 pt with tumor recurrence at the carina developed massive hemoptysis and death at 19.5 m after SBRT. This patient was scored as having died as a result of a treatment complication rather than progressive cancer
- Total 14 patients with grade 3-5 toxicity (20%) confirming phase I toxicity predictions
Central tumors had an 11-fold increased risk of severe toxic effects compared with patients with peripheral tumors [46% versus 17%].
Patients with peripheral tumor locations had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with perihilar/central tumors.

Patients with perihilar/central tumors have an 11-fold increased risk of experiencing severe toxicity compared with more peripheral locations.

Four of the six deaths as a result of toxicity observed in the study were in patients with perihilar/central tumors.

In the analysis of patients experiencing high-grade (grade 3 to 5) toxicity, both univariate and multivariate analysis showed that tumor location (hilar/pericentral v peripheral) was a strong predictor of toxicity ($P \leq 0.004$).
Local Control in Early Stage NSCLC

<table>
<thead>
<tr>
<th>Author/Ref.</th>
<th>Treatment</th>
<th>Local Control</th>
<th>Single Fraction Equivalent Dose (Gy)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America/Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timmerman et al. (2006)37</td>
<td>20–22 Gy × 3</td>
<td>95% (2 + yr)</td>
<td>56–62</td>
</tr>
<tr>
<td>Bauman et al. (2006)42</td>
<td>15 Gy × 3</td>
<td>80% (3 yr)</td>
<td>41</td>
</tr>
<tr>
<td>Fritz et al. (2006)43</td>
<td>30 Gy × 1</td>
<td>80% (3 yr)</td>
<td>30</td>
</tr>
<tr>
<td>Nyman et al. (2006)44</td>
<td>15 Gy × 3</td>
<td>80% (crude)</td>
<td>41</td>
</tr>
<tr>
<td>Zimmerman et al. (2005)45</td>
<td>12.5 Gy × 3</td>
<td>87% (3 yr)</td>
<td>43.5</td>
</tr>
<tr>
<td>Timmerman et al. (2003)35; McGarry et al. (2005)36</td>
<td>18–24 Gy × 3</td>
<td>90% (2 yr)</td>
<td>50–68</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xia et al. (2006)46</td>
<td>5 Gy × 10</td>
<td>95% (3 yr)</td>
<td>32</td>
</tr>
<tr>
<td>Hara et al. (2006)47 2006</td>
<td>30–34 Gy × 1</td>
<td>80% (3 yr)</td>
<td>30–34</td>
</tr>
<tr>
<td>Nagata et al. (2005)41</td>
<td>12 Gy × 4</td>
<td>94% (3 yr)</td>
<td>42</td>
</tr>
</tbody>
</table>

IU experience

60 Gy in 3 fxs, **SFED of > 50Gy**, associated with the highest rates of local control
Phase II - Conclusions

- Preliminary local control is very good with this SBRT regimen
- Toxicity occurs at an acceptable rate despite the population’s co-morbidities
- Both local failure and grade 3-5 toxicity occur “late” demanding adequate follow-up
- Tumors in the “zone of the proximal bronchial tree” should not be treated with this SBRT regimen
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 (6Gy/fx)
- **Esophagus** any point 27 Gy (9Gy/fx)
- **Trachea/Bronchus** any point 30 Gy (10Gy/fx)
- **Heart/Great Vessels** any point 30 Gy (10Gy/fx)
- **Brachial plexus** any point 24 Gy (8Gy/fx)
- **Skin** any point 18-24* Gy
- **Chest Wall** any point 45 Gy (V30 < 10ml)

*15 Gy if in a skin fold
Brachial plexopathy from SBRT in early stage NSCLC

Forker J et al; Radiother & Oncol, 2009

- 276 T1–T2 No, or peripheral T3 No lesions in 253 patients
- 37 lesions in 36 pts were apical lesions
  - Median dose: 57 Gy (30–72)
- 7/37 apical lesions: grade 2–4 plexopathy
  - 4 pts, grade 2
  - 2 pts, grade 3
  - 1 pt, grade 4
- 2-year Kaplan–Meier risk of brachial plexopathy for maximum brachial plexus dose >26 Gy was 46% vs 8% for doses ≤26 Gy (p = 0.04 for likelihood ratio test).

**Conclusions**: Brachial plexus maximum dose should be kept <26 Gy in 3 or 4 fractions when using SBRT.
Chest wall toxicity after SBRT for malignant lesions of the Lung and Liver.


- 347 lesions treated in 311 pts
  - 280 lung lesions, 67 liver lesions
  - 203 chest wall lesions
- Median FU, 19 months
- Median TD, 54Gy (median D/fx, 18Gy)
- Median time to CW toxicity, 9 m
- Crude incidence of CW toxicity of any grade 14% (47 of 347), with 36 episodes of CW pain and 18 rib fractures
  - Most of the toxicity was grade 1-2, with only 3 pts with CW lesions experiencing grade 3-4. No grade 5 toxicity
- CW Volume receiving 15-40 Gy, was highly predictive of grade III-IV toxicity

<table>
<thead>
<tr>
<th>Location</th>
<th>CW pain</th>
<th>Rib fracture</th>
<th>Either one</th>
</tr>
</thead>
<tbody>
<tr>
<td>CW lesions</td>
<td>16%</td>
<td>8%</td>
<td>21%</td>
</tr>
<tr>
<td>Non-CW lesions</td>
<td>3%</td>
<td>1%</td>
<td>4%</td>
</tr>
</tbody>
</table>

P value

0.0015    <0.0001    <0.0001
Chest wall toxicity after SBRT for malignant lesions of the Lung and Liver.


We predict a 10% risk of CW toxicity when 15 cc of CW receives 30 Gy or 5 cc receives 40 Gy.
We predict a 30% risk of toxicity when 40 cc of CW receives 30 Gy or 15 cc receives 40 Gy.

In order to minimize any grade CW pain and/or rib fracture when treating lesions in close proximity to the CW, max dose to the CW and/or ribs should be < 50 Gy and < 5 cc of CW should receive ≥ 40 Gy.
For a clinically relevant 30% risk of any grade CW toxicity, the EC50 model would limit the volume of CW receiving 15 Gy, 20 Gy, 30 Gy, and 40 Gy to less than 240 cc, 130 cc, 40 cc, and 15 cc, respectively.

Fig. 3. Dose–volume relationship for a 30% risk of chest wall toxicity of any severity.
A DOSE–VOLUME ANALYSIS OF RADIATION PNEUMONITIS IN NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH STEREOTACTIC BODY RADIATION THERAPY


251 PATIENTS NODE-NEGATIVE ST I–IIIB NSCLC TREATED WITH SBRT @ IU – 60 GY IN 3 FRACTIONS

• RISK OF RP AND V5, V10, V20, AND MLD

• RESULTS:
  • Median follow-up, 17 months.

• RP NOTED IN 42 PTS
  • Total lung DVHs were available for 143 patients.
  • G2–4 RP was noted in 4.3% of patients with MLD ≤ 4 Gy compared with 17.6% of patients with MLD >4 Gy (p = 0.02), and in 4.3% of patients with V20 ≤4% compared with 16.4% of patients with V20 >4% (p = 0.03).

• CONCLUSION:
  • Overall rate of G2–4 RP was 9.4%.
  • Symptomatic RP correlated with MLD and V20

<table>
<thead>
<tr>
<th></th>
<th>Median MLD</th>
<th>V5</th>
<th>V10</th>
<th>V20</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-1</td>
<td>4Gy</td>
<td>20%</td>
<td>12%</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Grade 2-4</td>
<td>5Gy</td>
<td>24%</td>
<td>16%</td>
<td>6.6%</td>
<td>9.4%</td>
</tr>
<tr>
<td>P value</td>
<td>0.14</td>
<td>0.70</td>
<td>0.08</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4 Gy</td>
<td>20%</td>
<td>12%</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>
First North American cooperative group trial using SBRT in medically inoperable stage I NSCLC
- PTV: 20 Gy x 3 = 18 Gy x 3 (with heterogeneity corrected.)

Target population: peripheral stage I NSCLC patients
- Medically inoperable
- Tumor < 5 cm
- Peripheral location in chest

Prior to activation, the RTOG and partners (ATC, RPC) developed extensive accreditation and compliance criteria for this new therapy

Phase II study based on the phase I-II study from IU
# QA Plan and Accreditation

<table>
<thead>
<tr>
<th>QA Plan</th>
<th>Prior to enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No history of providing QA for SABR trials</td>
<td></td>
</tr>
<tr>
<td>• RTOG partnered with Advanced Technology Consortium and Radiological Physics Center to develop:</td>
<td></td>
</tr>
<tr>
<td>o accreditation procedures</td>
<td></td>
</tr>
<tr>
<td>o compliance criteria</td>
<td></td>
</tr>
<tr>
<td>o comprehensive QA plan</td>
<td></td>
</tr>
<tr>
<td>• Intended to facilitate uniform treatment across centers</td>
<td></td>
</tr>
<tr>
<td>• Irradiate a stage I cancer phantom</td>
<td></td>
</tr>
<tr>
<td>o Target coverage</td>
<td></td>
</tr>
<tr>
<td>o Dose gradients</td>
<td></td>
</tr>
<tr>
<td>• Provide strategy and documentation of ability to control motion:</td>
<td></td>
</tr>
<tr>
<td>o Initial motion assessment</td>
<td></td>
</tr>
<tr>
<td>o Mechanism for control if motion &gt;5-10 mm</td>
<td></td>
</tr>
<tr>
<td>• Provide documentation of accuracy to deliver treatment:</td>
<td></td>
</tr>
<tr>
<td>o Validation of accuracy</td>
<td></td>
</tr>
</tbody>
</table>
Eligibility

- Non-small cell lung cancer - bx proven
- T1, T2 (≤ 5 cm) and T3 (chest wall only, ≤ 5 cm), No, Mo
  - Based on non-invasive clinical staging (PET/CT)
- Strictly defined medical problems preclude surgery [PFT, exercise testing...]
  - Generally, frail patients
- Only allowed peripheral tumors outside of “zone of proximal bronchial tree”
Endpoints

- Primary endpoint 2-year Primary local control (by PET)
- Secondary endpoints disease free survival, overall survival, patterns of failure, and toxicity
- All planning data sent to ATC electronically for QA and to ultimately use as a volumetric control/toxicity database
RTOG 0236 Characteristics

- Opened May 2004 and closed October 2006
- 59 patients enrolled (55 evaluable)
- 62% female, median age 72 years
- Zubrod performance 0 (12 patients), 1 (35), 2 (8)
- 44 patients with T1 tumors, 11 with T2 tumors
- Median follow-up = 34.4 months (range 4.8-50 m)
Reduced pulmonary function and cardiovascular disease were the most common reasons for medical inoperability.


<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Severe cerebral, cardiac, or peripheral vascular disease</td>
<td>24 (43.6%)</td>
</tr>
<tr>
<td>9. Severe chronic cardiac disease</td>
<td>22 (40.0%)</td>
</tr>
<tr>
<td>Total with more than one reason</td>
<td>38 (69.1%)</td>
</tr>
<tr>
<td>1. Baseline FEV1 &lt; 40% Predicted</td>
<td>19 (34.6%)</td>
</tr>
<tr>
<td>2. Predicted post-op FEV1 &lt; 30% of predicted</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td>3. Severely reduced diffusion capacity</td>
<td>22 (40.0%)</td>
</tr>
<tr>
<td>4. Baseline hypoxemia and/or hypercapnia</td>
<td>10 (18.5%)</td>
</tr>
<tr>
<td>5. Exercise oxygen consumption &lt; 50% of predicted</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>6. Severe pulmonary hypertension</td>
<td>6 (10.9%)</td>
</tr>
<tr>
<td>7. Diabetes mellitus with severe end organ damage</td>
<td>3 (5.5%)</td>
</tr>
</tbody>
</table>
## Results

### Response Rate
- Twenty-eight patients (51%) had a complete response at a median of 6.5 months (range, 1.6-42.6 months) from completion of SBRT.
- Partial response was recorded in 21 patients (38%).
- The overall response rate (CR+PR) was 89% (95% CI, 81%-97%).

### Local Failures
- Local recurrence: Primary tumor failure and/or failure within the involved lobe of the lung
  - 1 pt had primary tumor failure
    - 3-year Kaplan Meier Primary Tumor Control = 98%
  - 3 pts had failure within the involved lobe
    - 3-year Kaplan Meier Local Control = 90.7%
Patterns of Failure

- **Local**: 4 failures (7.2%)
  - 1 primary tumor, 3 involved lobe

- **Regional**: 2 failures (3.6%)
  - 1 hilar, 1 mediastinal

- **Distant**: 11 failures (20%)
  - 3-year rates of distant recurrence were 5.9% for squamous histology and 30.7% for non-squamous histology.
Local Control

3-year Kaplan Meier
Primary Tumor Control = 98%

3-year Kaplan Meier
Local Control = 90.7%

Patients at Risk: 55

Fail: 1
Total: 55

Months after Start of SBRT:

- 0 6 12 18 24 30 36

Local Control (%):

- 0 25 50 75 100
Disease Free Survival

3-year DFS = 48% (95% CI: 34-61%)
Median DFS = 34.4 m (95% CI: 25 m - not reached)
T1, 36 m; T2, 31 m
Dead/Fail: 30
Total: 55
MST: 34.4
(95% CI): (25, not reached)
Results

- Twenty-six patients (46.3%) died during the period of observation after treatment
  - Ten patients (18% of entire study population; 95% CI, 8%-23%) died of lung cancer.
  - Two patients died of non–protocol-related medical interventions
  - 5 of comorbid problems, specifically stroke, myocardial infarction, aggravation of emphysema, and second malignancy.
  - Nine patients died of unknown causes.
Overall Survival

3-year OS = 56% (95% CI: 42-68%)

MST = 48.1 months (95% CI: 29.6 m - not reached)
T1, not reached; T2, 34 m

Dead: 26
Total: 55

MST: 48.1
(95% CI): (29.6, not reached)
Severe Toxicity

- No grade 5 toxicities (treatment deaths)
- Two (4%) grade 4 protocol specified toxicity (decline in PFTs to <25% predicted & hypocalcemia)
- Seven (13%) grade 3 protocol specified toxicities
- Three of 55 patients (5%) had “unexpected” grade 3 rib and skin toxicity associated with chest wall tumors
## RTOG 0236 - Comments

<table>
<thead>
<tr>
<th>Encouraging findings</th>
<th>Role for improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Local and regional tumor control was very high</td>
<td>• Central tumors not allowed</td>
</tr>
<tr>
<td>◦ Essential step in affording cancer cure</td>
<td>• While no grade 5 toxicity, still some grade 3-4</td>
</tr>
<tr>
<td>• No toxic deaths</td>
<td>• Begging for an effective adjuvant therapy</td>
</tr>
<tr>
<td>◦ Excluded patients with central tumors</td>
<td>• Limited scope (only medically inoperable)</td>
</tr>
<tr>
<td>• QA infrastructure was effective</td>
<td>• Phase II study is NOT high level evidence</td>
</tr>
<tr>
<td>◦ good compliance (and control/toxicity)</td>
<td></td>
</tr>
</tbody>
</table>
RTOG 0813 (Bezjak, PI)

- Phase I/II for central tumors in medically inoperable patients
- Uses 5 fraction regimen
- Allows IMRT only if motion is <5 mm
- Started at 10 Gy x 5, Currently at 12 Gy x 5
RTOG 0915 (Videtic/Chang/Singh PIs)

- Randomized phase II comparing two alternate and less aggressive prescription dose (12 Gy x 4 vs. 34 Gy x 1)
- Medically inoperable, peripheral tumors
- Endpoint is toxicity (less toxic will win)
- Ultimately, winner will face 18 Gy x 3 (RTOG standard) in phase III trial with OS endpoint
Regarding elderly (>75) patients with early lung cancer:
- Included treated and untreated patients
- SABR increased utilization of RT in early stage lung cancer in elderly by 16% with corresponding decrease in untreated group and improved survival (period 2005-2007)
- No change in utilization of surgery or conventional radiation
- Survival increased significantly attributable specifically to SABR
SBRT vs surgical resection for Stage I NSCLC. A non-Randomized study

- 462 pts underwent surgery
- 76 SBRT
- Surgical patients were younger (P<.001), lower comorbidity scores (P<.001), and better pulmonary function
- In an unmatched comparison, overall 5-year OS and LC were better with surgery
- 57 high-risk surgical patients were matched to 57 patients undergoing stereotactic body radiation therapy.
- In the matched comparison there was no difference in 3-year LC or OS
First North American cooperative group trial using SABR in **operable** patients
- Pilot trial of 33 patients

Planned to use surgery as early salvage for local or regional failures

Completed enrollment 2010
- To date, control rates are very good

Effectively, the RTOG “lead in” into treating **high risk operable** patients
# Surgery vs SABR

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sublobar</strong></td>
<td><strong>Sublobar</strong></td>
</tr>
<tr>
<td>- Better tolerated than lobectomy</td>
<td></td>
</tr>
<tr>
<td>- lymph node information</td>
<td></td>
</tr>
<tr>
<td>- Long term results for cancer control</td>
<td></td>
</tr>
<tr>
<td><strong>SABR</strong></td>
<td></td>
</tr>
<tr>
<td>- Non-invasive, no recovery, convenient</td>
<td></td>
</tr>
<tr>
<td>- High primary tumor control in inoperable</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SABR</strong></td>
</tr>
<tr>
<td></td>
<td>- Invasiveness – need to recover</td>
</tr>
<tr>
<td></td>
<td>- Poorer tumor control than lobectomy (especially with wedge)</td>
</tr>
<tr>
<td></td>
<td><strong>SABR</strong></td>
</tr>
<tr>
<td></td>
<td>- No histological lymph node assessment</td>
</tr>
<tr>
<td></td>
<td>- Fibrosis confounding f/u</td>
</tr>
<tr>
<td></td>
<td>- No comparative survival data</td>
</tr>
</tbody>
</table>
Patients randomized to SBRT will receive 18Gy in three fractions, for a total dose of 54Gy. Brachytherapy is allowed with Surgery. All registered patients will be followed for study endpoints, regardless of the status of their treatment. That includes patients receiving adjuvant therapy for any reason.
Expanded Eligibility

- Based on feedback from sites, a protocol amendment was accepted to expand eligibility
- Tumors may be up to 4 cm in diameter
- While biopsy is encouraged, enrollment may proceed without tissue IF 2 of the following:
  - Smoking history
  - Documented growth
  - Absence benign calcification
  - Hypermetabolic by PET
  - Evidence of spiculation by CT
Conclusions

- SBRT for lung cancer is effective and tolerable
  - Prospectively studied
  - Encouraging and reproducible results
  - Admittedly imperfect therapy with both failure and harm

- SBRT is an established standard therapy for medically inoperable patients

- SBRT is being compared to less invasive/less radical surgery in high risk operable patients
  - Momentum extremely strong for SBRT, but ideally studies will be done
Gracias!