Stereotactic Radiosurgery for Stage I Non-Small Cell Lung Cancer

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WellStar Kennestone Hospital
North Georgia Radiation Therapy
Marietta, GA
Early Stage NSCLC Management

**Surgical Techniques**
- Lobectomy –vs.- Limited Resection
- Open Thoracotomy –vs.- VATS

**Radiation Techniques**
- Fractionated EBRT –vs.- IMRT –vs.- IGRT
- Stereotactic Body Radiation Therapy (SBRT)

**Other** (RFA, Chemotherapy)
# Non Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>5yr Survival</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Ia - 80-85% Ib - 70%</td>
<td>Surgery only</td>
</tr>
<tr>
<td>II</td>
<td>II - 40-50%</td>
<td>Surgery (+/- XRT, Chemo)</td>
</tr>
<tr>
<td>III</td>
<td>IIIa - 10-20% (Chemo/XRT=30+% with response) IIIb - 10%</td>
<td>Pre-op Chemo/XRT 60% resectable 40% 2yr OS Chemo/XRT</td>
</tr>
<tr>
<td>IV</td>
<td>0-5%</td>
<td>Chemo/XRT</td>
</tr>
</tbody>
</table>
Early Stage NSCLC Management

Five year Survival Rates: 70-85%
### T1 and T2 NSCLC Survival After Resection

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>pT1N0</th>
<th>pT2N0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini et al</td>
<td>598</td>
<td>83%</td>
<td>65%</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>461</td>
<td>80%</td>
<td>62%</td>
</tr>
<tr>
<td>Mountain et al.</td>
<td>725</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>MDACC Experience</td>
<td>560</td>
<td>76%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Nesbitt et al., Ann Thor Surg, 1995
MDACC Thoracic Surgical Database
<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>LF %</th>
<th>LRF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini et al.</td>
<td>598</td>
<td>5.4%</td>
<td>7.6%</td>
</tr>
<tr>
<td>LCSG Trial (pT1N0)</td>
<td>125</td>
<td>-----</td>
<td>6.4%</td>
</tr>
<tr>
<td>MDACC</td>
<td>560</td>
<td>3.6%</td>
<td>10.1%</td>
</tr>
</tbody>
</table>
**Lobectomy -vs- Limited Resection**

**LCSG Randomized Trial, pT1N0: Long-Term Outcome**

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Lobectomy (n=125)</th>
<th>Limited Res (n=122)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional</td>
<td>8 (6%)</td>
<td>21 (17%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Distant</td>
<td>15 (12%)</td>
<td>17 (14%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death (Cancer)</td>
<td>21 (14%)</td>
<td>30 (24%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Death (Overall)</td>
<td>38 (30%)</td>
<td>48 (40%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Ginsberg et al., Ann Thor Surg, 1995
Early Stage NSCLC Management in Surgical HIGH RISK Patient

- Surgery is not benign

- Often pulmonary function extremely limited (as well as overall limited patient status)

- With surgery when FeV1 < 50% of predicted
  - Morbidity 30-40%
  - Mortality 3-8% with lobectomy & age > 80
  - Mortality 2-4% with lobectomy & age > 70

May prompt surgeons to do lesser resections, but....

Local Recurrence for wedge resections: 17-23%

Early Stage Medically Inoperable NSCLC Management

- XRT
- SBRT
- RFA

- CyberKnife®
- Novalis-TX®/Trilogy™ Truebeam/ Synergy®
- Tomotherapy®
- Conventional Linac with some form of respiratory compensation
Early Stage NSCLC Management

Five Year Survival Rates: 15-30%

Dose escalation improves LC & OS

Radiation pneumonitis (grade 3+) and lung fibrosis
<table>
<thead>
<tr>
<th>Total Dose</th>
<th>Reference</th>
<th>BED</th>
<th>LC%</th>
</tr>
</thead>
<tbody>
<tr>
<td>60G,30Fx</td>
<td>RTOG</td>
<td>72</td>
<td>15%</td>
</tr>
<tr>
<td>70G,35Fx</td>
<td>RTOG</td>
<td>84</td>
<td>24%</td>
</tr>
</tbody>
</table>
RADIOSURGERY FOR EARLY STAGE NON SMALL CELL LUNG CANCER
Early Stage Lung Cancer Components of Radiosurgical Treatment

- Extremely high doses of daily radiation
- Treatment course completed less than one week
- High precision localization
- Use of multiple beam angles
Early Stage Lung Cancer Radiosurgical Treatment

This approach delivers a higher biological effective dose (BED) to the target while minimizing the normal tissue toxicities in the attempt to improve local control and survival and minimize complications.
Local Control for Primary NSCLC by Dose Fractionation Schemes

<table>
<thead>
<tr>
<th>Total Dose</th>
<th>Reference</th>
<th>BED</th>
<th>LC%</th>
</tr>
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<tr>
<td>60G,30Fx</td>
<td>RTOG</td>
<td>72</td>
<td>15%</td>
</tr>
<tr>
<td>70G,35Fx</td>
<td>RTOG</td>
<td>84</td>
<td>24%</td>
</tr>
<tr>
<td>45G,3Fx</td>
<td>Blomgren</td>
<td>113</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>48G,3Fx</td>
<td>Blomgren</td>
<td>125</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>60G,3Fx</td>
<td>Timmerman</td>
<td>180</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>69G,3Fx</td>
<td>Emami</td>
<td>228</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>
Lung Cancer
Early Stage NSCLC
Radiosurgery Experience

- Georgetown University
- 93 patients
- 60 Gy / 3 fractions (BED = 180)
- 33 month median follow-up
- 90% local control
- No symptomatic pneumonitis
Lung Cancer
Early Stage NSCLC
Radiosurgery Experience

- Stanford University
- 52 patients
- 50 Gy / 4 fractions to 60 Gy / 3 fractions
- Median follow-up 12 months
- 92% local control
- No symptomatic pneumonitis
<table>
<thead>
<tr>
<th>Total cases</th>
<th>300 in 14 institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39-92 (median 76) years</td>
</tr>
<tr>
<td>Performance status</td>
<td>PS0:114, PS1:127, PS2-3: 59</td>
</tr>
<tr>
<td>Histology</td>
<td>ACA:138, SCC:129</td>
</tr>
<tr>
<td></td>
<td>other histology:33</td>
</tr>
<tr>
<td>Stage</td>
<td>stage IA:193, stage IB:107</td>
</tr>
<tr>
<td>Tumor Dose</td>
<td>10-12.5 Gy x 4 (TD=48 Gy mean)</td>
</tr>
<tr>
<td>Medical Operability</td>
<td>Inoperable:190, operable:110</td>
</tr>
<tr>
<td>Median Follow-up</td>
<td>32 months</td>
</tr>
</tbody>
</table>

Onishi et al.
Summary of Japanese SBRT studies for NSCLC

Overall survival of operable NSCLC patients irradiated with BED of >100 Gy according to T stage

Comparison of 5-year overall survival between surgery and SBRT

<table>
<thead>
<tr>
<th></th>
<th>Mountain *</th>
<th>JCOG*</th>
<th>JNCCH*</th>
<th>SBRT**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>67%</td>
<td>80%</td>
<td>74%</td>
<td>77%</td>
</tr>
<tr>
<td>Stage IB</td>
<td>57%</td>
<td>63%</td>
<td>53%</td>
<td>68%</td>
</tr>
</tbody>
</table>

* Surgery  ** Stereotactic Body Radiation Therapy
Japanese Clinical Oncology Group
SBRT Results for Stage I NSCLC

<table>
<thead>
<tr>
<th>Severe Adverse Events</th>
<th>Mortality</th>
<th>Morbidity (Grade 3-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 1%</td>
<td>3%</td>
</tr>
</tbody>
</table>
## Comparative Results of Surgical & SBRT Studies for Early Stage NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rx</th>
<th>5y OS%</th>
<th>5y LF%</th>
<th>M &amp; M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surgery</td>
<td>53-83</td>
<td>4-17</td>
<td>30-40/2-8</td>
</tr>
<tr>
<td>I*</td>
<td>RT</td>
<td>15-24</td>
<td>76-85</td>
<td>5-37/1-9</td>
</tr>
<tr>
<td>I*</td>
<td>SBRT</td>
<td>40-77</td>
<td>10-25</td>
<td>3-46/1-3</td>
</tr>
</tbody>
</table>

*medically inoperable
USING CYBERKNIFE RADIOSURGERY FOR MEDICALLY UNRESECTABLE STAGE I NON-SMALL CELL LUNG CANCER

WELLSTAR KENNESTONE HOSPITAL NORTH GEORGIA RADIATION THERAPY MARIETTA, GA
How does the CyberKnife work?

- A computer program evaluates the unique shape and tumor location to determine exactly how each of 1800 or more beams (nodes) of radiation will target the tumor.
- An x-ray source of the robotic arm delivers concentrated beams (nodes) of radiation to the tumor from multiple positions and angles without directly treating normal tissue.
1800 DIFFERENT BEAM ARRANGEMENTS
LUNG RADIOSURGERY

- CyberKnife is not the only method available for Radiosurgery
- My other experiences with body radiosurgery:
  - Elekta Synergy
  - Brain Lab / Trilogy
  - Truebeam
  - Tomotherapy

WHY I FEEL MOST COMFORTABLE WITH CYBERKNIFE
CyberKnife

Only system with real-time lung guidance – Synchrony System
Radiosurgery Field Size

Un-controlled Motion

Controlled Motion
USING CYBERKNIIFE RADIOSURGERY FOR MEDICALLY UNRESECTABLE STAGE I NON-SMALL CELL LUNG CANCER

WELLSTAR KENNESTONE HOSPITAL NORTH GEORGIA RADIATION THERAPY MARIETTA, GA
The treatment of choice for stage I non-small cell lung cancer (NSCLC) is surgery. However, many have medical contraindications to surgery. At our institution, the role of the thoracic surgeon is critical in the management of all stage I NSCLC patients, with most patients undergoing surgery and those medically unresectable underwent CyberKnife radiosurgery.
Since October 2006, 169 patients with NSCLC, stage I were treated with CyberKnife Stereotactic Radiosurgery. Treatment consisted of 60 Gy in 3 to 50 Gy in 4 fractions, depending on peripheral versus central location of the tumor.
PERIPHERAL LESION: 6000 cGy in 3 FRACTIONS
CENTRAL LESION: 5000 cGy in 4 FRACTIONS
METHODS

- Fiducial markers (1-5) placed by Interventional Radiology service
CyberKnife
Fiducial Placement

- Small gold markers placed into or near the tumor.
- Used by the computer to track the target lesion.
- Ideally place 3-5 markers 2 cm apart from each other.
- In difficult cases a single fiducial may be adequate.
Fiducial Placement Lung

- Placing fiducials into the lung poses risks:
  - Pneumothorax.
  - Bleeding, hemoptysis.
  - Migration.
CT Fiducial Placement

- 19 gauge biopsy needle.
- Place fiducial through the needle and push into tumor.
- Limit passes across the pleura.
Bronchoscopic Fiducial Placement

- Video flexible bronchoscopy
- Anesthesia
- Transbronchial needle aspiration #19/21 is loaded with the gold fiducial
- Super Dimension - Electromagnetic Guidance Bronchoscopy
- Fluoroscopy used to view deployment
Loading of Fiducial into TBNA Needle
Xsight Lung

- Lung tumor tracking without fiducials
- Ideal target:
  - >1 cm
  - Peripheral
RESULTS

- Minimum 2 year follow-up
- Local control accessed via serial PET/CT
- Pulmonary Function Testing done prior to each treatment and serially post Cyberknife radiosurgery
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>2 YR LOCAL CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL</td>
<td>84%</td>
</tr>
<tr>
<td>1 CM OR LESS</td>
<td>93%</td>
</tr>
<tr>
<td>1.1 – 2.0 CM</td>
<td>89%</td>
</tr>
<tr>
<td>2.1 – 3 CM</td>
<td>82%</td>
</tr>
<tr>
<td>3.1 – 4 CM</td>
<td>75%</td>
</tr>
<tr>
<td>4.1–6 CM</td>
<td>67%</td>
</tr>
<tr>
<td>CATEGORY</td>
<td>RATE</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>OVERALL PNEUMOTHORAX</td>
<td>27%</td>
</tr>
<tr>
<td>CHEST TUBE PLACEMENT</td>
<td>16%</td>
</tr>
<tr>
<td>PNEUMOTHORAX AFTER YEAR ONE OF PROGRAM</td>
<td>12%</td>
</tr>
<tr>
<td>OVERALL SYMPTOMATIC PNEUMONITIS</td>
<td>2.7%</td>
</tr>
<tr>
<td>PNEUMONITIS - TUMOR GREATER 3 CM</td>
<td>8.4%</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Excellent 2 yr local control
- Higher control with smaller tumors
- Acceptable complication profile
- Pneumothorax rate decreases with experience
- Increased symptomatic pneumonitis with larger tumors
NSCLC Left Upper Lung

DEMOGRAPHICS & HISTOLOGY

- 65 YO Female
- Histology: Poorly differentiated non-small cell lung carcinoma with focal squamous features PET/CT staged as T1 N0 M0 stage grouping I

CLINICAL HISTORY:

- Previous Treatment: None
- Patient unable to have surgery (FEV1=0.82)
NSCLC Left Upper Lung

TREATMENT PLANNING:

- Axial, sagittal and coronal planning images showing the tumor, lung parenchyma and isodose curves

TREATMENT DETAILS:

- Rx Dose & Isodose: 60 Gy in 3 fractions
- Tumor volume = 13.85 cc
- Number of Beams: 154
RESULTS:

- CR on CT 15 weeks post-CK mistaken for resection by Radiologist
- A follow-up PET/CT scan at 10, 20 & 33 months post-CK are negative at the site of the primary tumor and showed no evidence of disease.

Images:

Pre-treatment

15 weeks post-CK
FUTURE
THOUGHTS
## Comparative Results of Surgical & SBRT Studies for Early Stage NSCLC

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<td>5-37/1-9</td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td>SBRT</td>
<td>68-77</td>
<td>10-15</td>
<td>3-5/&lt;1</td>
</tr>
</tbody>
</table>

*medically inoperable
Surgery vs. Cyberknife SBRT

Time to compare directly with surgical resection

Randomize

cT1-2N0M0 NSCLC → CyberKnife SBRT → Resection
CyberKnife StereoTActic Radiosurgery vs. Surgery for Stage I NSCLC:

STARS Randomized Clinical Trial
STARS Study Overview

- **PI:** MD Anderson Cancer Center
  - Jack Roth, MD (Thoracic surgeon)
    - PI; MD Anderson
  - John J Kresl, MD, PhD (Rad Oncologist)
    - Co-PI; ROCA
  - Ritsuko Komaki, MD (Rad Oncologist)
    - Co-PI; MD Anderson
  - Joe Chang, MD, PhD (Rad Oncologist)
    - Co-PI; MD Anderson

- **Sponsor:** Accuray Incorporated

- **International study**
  - U.S.
  - Europe
  - Asia
STARS Study Population

- Histologically confirmed NSCLC
  - Stage IA (T1N0M0)
  - Stage IB (T2N0Mo,<4cm)
STARS Inclusion Criteria

1. Histological confirmation of non-small cell cancer will be required by either biopsy or cytology.
2. Stages IA and IB ($\leq$ 4 cm)
3. A PET/CT scan is required.
4. The patients must be considered a reasonable candidate for surgery
   1. Baseline FEV1 $\geq$ 40% predicted, post-operative predicted FEV1 $\geq$ 30% predicted, diffusion capacity $\geq$ 40% predicted
5. Patients must be $\geq$ 18 years of age.
6. The patient’s Zubrod performance status must be Zubrod 0-2.
STARS Study Objectives

• Primary Endpoint
  • To compare overall survival at 3, 4 and 5 years post treatment in operable early stage lung cancer patients

• Secondary Endpoints
  • To compare disease specific survival at 3, 4 and 5 years post treatment
  • To compare progression free survival at 3, 4 and 5 years post treatment
  • To compare grade 3 and above acute & chronic toxicities
STARS Surgical Arm

• Both open thoracotomy & video assisted thoracotomy (VATS) are acceptable procedures. Surgery may consist of any of the following:
  1) Lobectomy, 2) Sleeve resection, 3) Bilobectomy, 4) Pneumonectomy

• All accessible hilar (level 10) lymph nodes must be dissected from the specimen by the surgeon & submitted to the pathologist. A complete mediastinal lymph node sampling performed for each patient: right-sided lesions (4R, 7, & 9), left-sided lesions (5, 6, 7, & 9).

• Post-operative adjuvant chemotherapy will not be permitted
STARS CyberKnife® SBRT Arm

- **Fiducial Placement**
  - 1 - 5 fiducials will be required to be placed unless the Xsight Lung fiducial-less technology is available at the clinical site
  - All methods of fiducial placement will be allowed

- **Dosing & Margins**
  - Peripheral lesions
    - 60Gy delivered to the 80% isodose line (GTV + 5mm)
  - Central lesions
    - 50Gy delivered to the 80% isodose line (GTV + 5mm)

- **Post-operative adjuvant chemotherapy will not be permitted**
CyberKnife

Lung Cancer STARS Trial

Peripheral Tumors
20 Gy x 3

Central Tumors
12.5 Gy x 4

Defines zone of the proximal bronchial tree
SUMMARY

- Radiosurgery is an excellent treatment approach for medically inoperable early stage NSCLC
- For medically operable patients, randomized studies are underway to compare surgery vs. radiosurgery