Treatment of Early Stage Lung Cancer-
The stereotactic era

34th Annual Leland R. Cowan Cancer Symposium
LDS Hospital, Salt Lake City, Utah
Saturday, January 30, 2016

Gregory M. M. Videtic, MD, CM, FRCPC
Department of Radiation Oncology
Taussig Cancer Institute
The Cleveland Clinic
Conflicts of interest

• None
CANADA.. as viewed from Cleveland!
Objectives

• 1. To review the principles and practice of radiotherapy in the management of early stage lung cancer

• 2. To review the principles and practice of stereotactic body radiotherapy (SBRT) as they apply to early stage lung cancer

• 3. To review the results of SBRT in lung cancer as they apply to local control, overall survival and toxicity, and quality of life

• 4. To understand research trends in the development of lung SBRT
Best to have a little background first…

“Mind if I smoke?”

“Care if I die?”

(California Anti-Smoking Ad)
Introduction: The Scope of the Problem

Estimated Deaths

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>89,510</td>
<td>70,880</td>
</tr>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>27,050</td>
<td>40,460</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>26,000</td>
<td>26,180</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Pancreas</td>
</tr>
<tr>
<td>16,840</td>
<td>16,530</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Ovary</td>
</tr>
<tr>
<td>12,320</td>
<td>15,280</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Leukemia</td>
</tr>
<tr>
<td>11,280</td>
<td>9,470</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>10,900</td>
<td>9,060</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>9,630</td>
<td>7,400</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td>9,600</td>
<td>5,590</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>8,080</td>
<td>5,500</td>
</tr>
<tr>
<td>All Sites</td>
<td>All Sites</td>
</tr>
<tr>
<td>289,550</td>
<td>270,100</td>
</tr>
</tbody>
</table>

- 213,380 patients are diagnosed yearly with lung cancer in the US with approximately 160,390 deaths
Introduction: The Scope of the Problem

EARLY STAGE LUNG CANCER “by the book”

• “Surgical resection remains the gold standard for treatment of patients with stage I and II NSCLC…”


  5-year Overall Survival for stage I NSCLC
  
  clinical stage IA-61%
  
  pathologic stage IA-67%
  
  clinical stage IB-38%
  
  pathologic stage IB-57%
EARLY STAGE
Node Negative Lung Cancer

Gold Standard Rx = Surgery

- Time honored position
- Patient selection
  - proper staging (pathologic node negative)
  - adequate pulmonary reserve
  - absent or controlled medical problems
- Effective treatment
  - impressive local control (65-90%)
  - overall survival 60-80% at 5 years
How **Gold** is Gold?

- Surgery is a very good but non-perfect treatment

- **NB:** path stage I 5-yr OS is “ONLY” 67%
  - Local failures but distant failures driving death from cancer (even controlling for pathological staging)

- Toxicity, pain and suffering, QOL

- Expense, hospitalization, recovery, lost work/income, etc.

- Surgery not appropriate for many!
EARLY STAGE LUNG CANCER

• Significant proportion [15-40%, i.e., 30-80,000 pts] of NSCLC patients presents however with impaired cardiopulmonary reserve
  — Increased risk of peri-operative complications
  — Long-term disability with standard anatomic resections
  — These patients are deemed medically inoperable
INTRODUCTION

• Doing “nothing” is not good in med inop pts
  • McGarry et al. (Chest 2002): Lung cancer cause of death in 53% of 75 stage I medically inoperable pts treated with observation alone
HOORAY FOR CHAINSAWS :3
Limited Resection- ??

- 1973-Jensik et al. suggest lesser resection might be an adequate operation for early stage disease in a compromised pt.

- Wedge resections promoted for pts with limited pulmonary function- parenchymal sparing
  - Theoretical advantages of lesser resections
    - Preservation of pulmonary function
    - Decreased perioperative mortality and morbidity
    - Ability of the patient to undergo further resection in the future if a second primary cancer should develop.

Theoretical disadvantages
- Poorer local control
- How much normal tissue should be resected as an adequate margin
- Impact on survival
The left lower lobe wedge resection is almost completed.
Randomized Trial of Lobectomy Versus Limited Resection for T1 N0 Non-Small Cell Lung Cancer


- Lung Cancer Study Group
  - “A prospective, multiinstitutional randomized trial …comparing limited resection with lobectomy for patients with peripheral T1 N0 non-small cell lung cancer documented at operation. Analysis included locoregional and distant recurrence rates, 5-year survival rates, perioperative morbidity and mortality, and late pulmonary function assessment.”
Randomized Trial of Lobectomy Versus Limited Resection for T1 N0 Non-Small Cell Lung Cancer.

• Methods
  – Large wedge resections accepted
  – At least 2 cm of normal lung tissue was required to be resected beyond the tumor
  – After completion of resection, surgeon had to confirm clinically that tumor completely resected
  – Lymph node stations had to be sampled

• Results
  – 32.8% of cases had wedge resections
  – 276 patients randomized, with 247 patients eligible for analysis
Lung Cancer Study Group
Ginsberg, et al.

Fig 1. Time to death (from any cause) by treatment for 247 eligible patients.

Fig 2. Time to recurrence (excluding second primaries) by treatment for 247 eligible patients.
Lung Cancer Study Group
Ginsberg, et al.

- 5 year local-regional recurrence
  Limited = 30%
  Lobectomy = 10%

- Site of recurrence
  mostly suture line for limited

---

Table 3. Recurrence and Death Rates for the 247 Eligible Patients on LCSG 821

<table>
<thead>
<tr>
<th>Event</th>
<th>Limited Resection</th>
<th>Lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Rate (per person/y)</td>
</tr>
<tr>
<td>Recurrence (excluding second primary)</td>
<td>38</td>
<td>0.101</td>
</tr>
<tr>
<td>Recurrence (including second primary)</td>
<td>42</td>
<td>0.112</td>
</tr>
<tr>
<td>Locoregional recurrenced</td>
<td>21</td>
<td>0.060</td>
</tr>
<tr>
<td>Nonlocal recurrenced</td>
<td>17</td>
<td>0.048</td>
</tr>
<tr>
<td>Death (with cancer)</td>
<td>30</td>
<td>0.073</td>
</tr>
<tr>
<td>Death (all causes)</td>
<td>48</td>
<td>0.117</td>
</tr>
</tbody>
</table>

*a Note locoregional recurrence rates and death rates are significantly increased after limited resection. b One-sided (refer to text); c two-sided (refer to text); d for definition of recurrences, refer to text. NS = not significant.*
Early stage lung cancer “101”

• Pts with clinical stage I NSCLC can be considered falling into three treatment groups:
  – good-risk patients, usually treated with lobectomy
  – high-risk patients, usually treated with sublobar (segmental or wedge) resection
  – medically inoperable patients, traditionally treated with external beam radiation therapy.
Stage I NSCLC: Spectrum of Health

- Medically Operable
- “High risk” Operable
- Medically Inoperable

Lobectomy

SBRT
Doing right by our patients with Early Stage Lung Cancer: What to do?
Doing right by our patients: Surgery, “Radiosurgery” and Early stage Lung cancer

- **PATIENT SELECTION**
  
  Define: stage AND medically operability AND patient preference BY:
  
  - Review by the Thoracic Multidisciplinary Lung Team
    - Thoracic Surgeon
    - Pulmonologist
    - Radiation Oncologist
    - Medical Oncologist
    - (Cardiothoracic service/Cardiology)
    - Radiology
  - Staging (complete) to include
    - **PET**
    - +/- Mediastinoscopy
    - +/- Biopsy- morbidity of procedure of importance
Doing right by our patients: Surgery, “Radiosurgery” and Early stage Lung cancer

• Innovation in each discipline!
Innovation Focus-
Stereotactic Body Radiotherapy (SBRT) in the Management of Non-Small Cell Lung Cancer

• The emerging “standard” for the medically inoperable patient
Radiation Therapy (RT) & Early Stage Lung Cancer
Examples of isodose coverage for a patient with peripheral stage I lung carcinoma comparing a simple parallel-opposed beam arrangement versus a conformal four-field technique.

FIGURE 44.11. Examples of isodose coverage for a patient with a peripheral stage I lung carcinoma comparing a simple parallel-opposed beam arrangement versus a conformal four-field technique.
# 5 Year Survival in Early Stage Lung Cancer: S vs. RT results

<table>
<thead>
<tr>
<th>Rx Modality</th>
<th>% alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I Surgery</td>
<td>60-80%</td>
</tr>
<tr>
<td>Stage I* RT</td>
<td>15-45%</td>
</tr>
<tr>
<td>Stage II Surgery</td>
<td>30-50%</td>
</tr>
<tr>
<td>Stage II* RT</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

*clinically staged and mostly medically inoperable

RT generally 60 Gy delivered in 6 weeks
5-year Local Control (LC) in Lung Cancer: S vs. RT results

<table>
<thead>
<tr>
<th>Rx Modality</th>
<th>% LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I Surgery</td>
<td>65-90%</td>
</tr>
<tr>
<td>Stage I Radiotherapy (RT)</td>
<td>15-45%</td>
</tr>
<tr>
<td>Stage II Surgery</td>
<td>30-50%</td>
</tr>
<tr>
<td>Stage II RT</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

- Obvious deficiency of conventional radiation is failure to attain local control
“OLD-SCHOOL” RADIOTHERAPY ALONE CAN CURE LUNG CANCER!

- SELECTION—e.g. stage I laryngeal cancer
- LUCK?—tumor biology as predictor

“The real reason we use conventionally fractionated RT is in fact because of the normal tissues, not the tumor.” *Bob Timmerman, 2007*
87 yo WF, T2 lesion RUL, bx=adenoCA, PET SUV=16.92 at lesion, medically inoperable

EBRT 70 Gy/35fx: per plan to the 97% isodose line using 10 MV photons via LAO/POST/RPO field set ups.

• Pre-RT CT 4/28/04
  4/7/10

Post-RT scan of
Local Progression-Free Survival Is a Function of Dose

~ 84 Gy would be needed for ~ 50% local progression-free survival in 30 months.
RT “facts” for lung cancer

• The efficacy and safety of RT reflect the interplay between
  – total dose delivered to the malignant tumor
  – the rate of dose delivery (daily fractionation)
  – the volume (and type) of tumor-bearing organ irradiated.
  – The intrinsic tolerance of the tissue irradiated
GOAL:
Compact Dose Deposition/Minimal Tissue injury
Spread out the Entrance Dose/
Focus on the target
Evolution of Stereotaxis

- Safe delivery of very high doses of radiation to the brain was pioneered in the 1950s by the famed neurosurgeon, Lars Leksell, at the Karolinska Hospital in Sweden.

- Leksell determined that to achieve SRS, a very large number of narrow radiation beams would have to come from several directions and using a rigid three-dimensional reference frame, focus on the target while sparing the adjacent normal tissues, providing safety and high accuracy.
The theoretical basis for lung SBRT

- Extra-cranial SBRT- Modeled after brain radiosurgery principles
  - Multiple convergent beams
  - Rigid patient immobilization
  - Precise localization via stereotactic coordinate system (“STEREOTACTIC”)
  - Single fraction treatment
  - Size-restriction for target
Evolution of Stereotaxis


Fig. 1. Schematic view of the stereotactic body frame and the position of the patient in the frame.
Evolution of Stereotaxis


A stereotactic body frame with a fixation device has been developed for stereotactic radiation therapy of extracranial targets, a precision localization and positioning system in analogy with the stereotactic head frames used for intracranial targets. Results of the first 42 treated tumors in 31 patients are presented. Most of the patients had solitary tumors in liver, lung or retroperitoneal space. Clinical target volumes ranged from 2 to 622 cm$^3$ (mean 78 cm$^3$) and minimum doses to the planning target volumes (PTV) of 7.7–30 Gy/fraction (mean 14.2 Gy) were given on 1–4 occasions to a total minimum dose to the PTVs of 7.7–45 Gy (mean 30.2 Gy) to the periphery of the PTV and total mean doses to the PTVs of 8–66 Gy (mean 41 Gy). The central part of the tumor was usually given about 50% higher dose compared to that of the periphery of the PTV by a planned inhomogeneous dose distribution. Some of the patients received stereotactic radiation therapy concomitantly to more than one target, in others new metastases were also treated which appeared during the follow-up period. We observed a local rate of no progressive disease of 80% during a follow-up period of 1.5–38 months. Fifty percent of the tumors decreased in size or disappeared.
Evolution of Stereotaxis

- **Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience.**
  
  Uematsu et al.

  - 66 lung tumors in 45 patients treated using a stereotactic system, and high dose RT schedules [30–75 Gy in 5–15 fractions over 1–3 weeks]. Local progression was observed only in two of the 66 tumors (3%).

*Cancer* 1998;82:1062–70.
XRT Fractionation Options

- Conventionally fractionated radiotherapy
  - small daily doses
  - go to very high cumulative doses
  - tolerable for most normal tissues

- Hypofractionated radiotherapy
  - larger daily doses (3-8 Gy)
  - used mostly for palliation

- Ablative radiotherapy (Stereotactic)
  - very high daily doses (8-20 Gy)
  - overwhelm tumor repair
  - causes “late” effects that may be intolerable
So…What is SBRT?

- **TUMOR REQUIREMENTS**
  - Limited to small volume / discrete targets
  - No prophylactic coverage of potential micrometastases (e.g. mediastinum not treated in lung cancer)
So…What is SBRT?

- **TUMOR REQUIREMENTS**
  - Appropriate for tissues with “parallel functional units”
  - e.g. lung, kidney
  - Small volumes of normal tissue receive high dose RT without clinical impact due to functional reserve of untreated organ
Ablative Treatments (Stereotactic) Must Exclude Normal Tissue

• 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
INTRODUCTION

• What is Lung SBRT? Technical
  – Multiple convergent beams of RT aimed at target
  – Requires rigid patient immobilization

  **MUST account OR compensate for organ motion**
  – Precise localization of target via stereotactic coordinate system
  – Size-restriction for target
Use “Image Guidance”-Technology for frequent 2D and 3D imaging, during RT, to verify/direct radiation therapy checked against the “standard” : the imaging coordinates set by the images set at simulation and used for planning.
Treatment Verification

- Re-align to eliminate error between and during treatment
• What is Lung SBRT? Technical

Typically few-fraction (1 to 5) RT using very large individual fraction doses

High dose conformality, i.e., “tight around target”

Rapid dose fall-off from target to surrounding normal tissue.
# SBRT vs. Conventional Radiotherapy

<table>
<thead>
<tr>
<th>SBRT</th>
<th>Conventional Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many beams/arcs</td>
<td>2-4 beams</td>
</tr>
<tr>
<td>Small beam apertures</td>
<td>“Swaths” of radiation</td>
</tr>
<tr>
<td>Daily image guidance</td>
<td>Weekly image guidance</td>
</tr>
<tr>
<td>Strict motion control</td>
<td>No motion control</td>
</tr>
<tr>
<td>Large “ablative” daily dose</td>
<td>Small “forgiving” daily dose</td>
</tr>
<tr>
<td>1-5 treatments (1-2 weeks)</td>
<td>30-45 treatments (6-9 weeks)</td>
</tr>
</tbody>
</table>
SBRT and Early Lung Cancer

Entering into the world of SBRT CLINICAL EXPERIENCE

Numerous series document efficacy and safety of SBRT in early lung cancer

Recent review of rationale, techniques, applications and optimization of SBRT for various extracranial sites (Song et al. Oncology, 2004)

- Includes lung cancer (primary/metastatic)
SBRT and Early Lung Cancer—Local control lung—Numerous studies report excellent local control.

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Local Control</th>
<th>Single Fraction Equivalent Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America/Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timmerman, 2006</td>
<td>20-22 Gy X 3</td>
<td>95% (2+ years)</td>
<td>56 – 62 Gy</td>
</tr>
<tr>
<td>Bauman, 2006</td>
<td>15 Gy X 3</td>
<td>80% (3 years)</td>
<td>41 Gy</td>
</tr>
<tr>
<td>Fritz, 2006</td>
<td>30 Gy X 1</td>
<td>80% (3 years)</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Nyman, 2006</td>
<td>15 Gy X 3</td>
<td>80% (crude)</td>
<td>41 Gy</td>
</tr>
<tr>
<td>Zimmerman, 2005</td>
<td>12.5 Gy X 3</td>
<td>87% (3 years)</td>
<td>43.5 Gy</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xia, 2006</td>
<td>5 Gy X 10</td>
<td>95% (3 years)</td>
<td>32 Gy</td>
</tr>
<tr>
<td>Hara, 2006</td>
<td>30-34 Gy X 1</td>
<td>80% (3 years)</td>
<td>30 – 34 Gy</td>
</tr>
<tr>
<td>Nagata, 2005</td>
<td>12 Gy X 4</td>
<td>94% (3 years)</td>
<td>42 Gy</td>
</tr>
</tbody>
</table>

•In all series, tumor recurrence is late (median about 18 months)
SBRT is better than conventional XRT!

**Local Control**

- **Historic comparisons**
  - EBRT 60-66 Gy / 30-33 fx, ~50% (Qiao, Lung Cancer 2003)
  - Beaumont experience (Lanni, Am J Clin Oncol 2011)
  - SBRT (48-60 Gy in 4-5 fx, n=45) vs. EBRT (70 Gy/35 fx, n=41)
  - 3y LC, **88% vs. 66%** (p=0.10)

- **Meta-analysis** (Grutters, Radiother Oncol 2010)
  - SBRT (n=895) vs. EBRT (n=1326)
  - 2y OS, **70% vs. 53%** (p=<0.001)
  - 2y DFS, **83.4% vs. 67.4%** (p=0.006)
SBRT and Early Lung Cancer

Treatment Toxicities

- Reported rates generally remarkably low
  - ≥ grade 3 pneumonitis, hypoxia: < 5%
- Related to tumor location
- Chest wall
  - IU data “central” vs. “peripheral”
    - Tumors must be at “2 cm or beyond the zone of the proximal bronchial tree”
    - Restriction due to high bronchial injury rates
  - Based on work of Timmerman et al.
SBRT for Early Lung Cancer: *The Cleveland Clinic program*

- Program opened 6/04
- CCF SBRT - 1st Choice for treatment model
  - Uematsu et al. IJROBP 2001; 51:666-670
    - 5 yr. reported experience with Stage I NSCLC
    - 50 patients (medically inoperable / refused surgery)
    - **Dose 50-60 Gy / 5-10# / 1-2 wks**
2004.10.26 - Pre-treat

74 yo AAF
RULobectomy 1992
R pneumonectomy 1998
LUL lesion 2004
SBRT 50 Gy/5fx
Compl’n 11/19/2004

2009.03.09 - 4.5 yrs post-SBRT
SBRT for Early Lung Cancer: *The Cleveland Clinic program*

- Radiographic response of a patient with a T2bN0 stage IIA 6.5-cm tumor treated with 60 Gy in 8 fractions. Representative images are from pretreatment PET/CT (A).
- Treatment plan with ITV (red) (B).
- Complete response at 5.9 years post treatment (C).
ADVANCING THE UNDERSTANDING OF LUNG SBRT
RTOG 0236

• First North American cooperative group trial using SBRT
  – Phase II study based on the previously published phase I study from Indiana Univ.
  – **Peripheral** NSCLC, <5cm, N0
  – 60 Gy in 3 fractions spaced over 8-14d

• Prior to activation, the RTOG and partners (ATC, RPC) developed extensive accreditation and compliance criteria for this new therapy
Stereotactic body radiation therapy for inoperable early stage lung cancer.

Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Beziak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H. Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. robert.timmerman@utsouthwestern.edu

Table 3. Pretreatment Characteristics of Patients Enrolled In Radiation Therapy Oncology Group 0236 (N = 55)\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>72 (48-89)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (4)</td>
</tr>
<tr>
<td>White</td>
<td>51 (93)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (38)</td>
</tr>
<tr>
<td>Female</td>
<td>34 (62)</td>
</tr>
<tr>
<td>Zubrod performance status score(^b)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (22)</td>
</tr>
<tr>
<td>1</td>
<td>35 (64)</td>
</tr>
<tr>
<td>2</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IA (T1 tumor)</td>
<td>44 (80)</td>
</tr>
<tr>
<td>IB (T2 tumor)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Large cell undifferentiated</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Non–small cell lung carcinoma not otherwise specified</td>
<td>16 (29)</td>
</tr>
</tbody>
</table>

The vertical bars indicate censored observations. The failure rate was 47% for overall survival and 54% for disease-free survival.
RTOG 0236

  - 55 pts were evaluable
  - median follow-up of 34.4 months (range, 4.8-49.9 months).
  - 44 patients with T1 tumors and 11 patients with T2 tumors

- **3-year primary tumor control rate was 97.6% !!!!!!!**
- **3-year rate of disseminated failure was 22.1%**
- **Disease-free survival and overall survival at 3 years were 48.3% and 55.8%, respectively.**
  - Median SURVIVAL was 48.1 months

- Grade 3 AEs were reported in 7 pts (12.7%); grade 4 in 2 pts (3.6%). No grade 5.
  - rib fractures and dermatitis have been observed especially for chest wall tumors
Notes of Caution (Central Tumors)

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

J Clin Oncol 24:4833-4839. © 2006 by American Society of Clinical Oncology

- 6 possibly treatment related deaths:
  - 4 bacterial pneumonia
  - 1 pericardial effusion
  - 1 hemoptysis*

* (ascribed to carinal recurrence)
Completed Clinical Trials in Lung SBRT (North America)

- RTOG 0813-phase I/II- set MTD of SBRT for early-stage, centrally located NSCLC (preliminary results presented at ASTRO 2015)
- RTOG 0915-randomized phase II, peripheral tumors, 34 Gy/1 fraction vs. 48 Gy/4 fractions, primary end point of toxicity (results published 2015)
- RTOG 0618- phase II, high risk operable patients, SBRT and surgical salvage, demonstrate that sustained (> 2 years) high local control is achievable in this population. (publication pending)
CONCLUSIONS
For medically inoperable early NSCLC:

• SBRT provides excellent local control, minimal pulmonary and other morbidities and is well suited to the vulnerable
  —It is superior to conventional RT

• Further prospective trials will refine SBRT practice

• NB: Ablative dose per fraction treatments have only been prospectively tested in MEDICALLY INOPERABLE patients
THE FOLLOWING PREVIEW HAS NOT BEEN APPROVED FOR
ALL AUDIENCES
BY THE MOTION PICTURE ASSOCIATION PEOPLE
SBRT and Early Lung Cancer

- Interesting SBRT data from Japan in operable pts who declined surgery

- 5 year survivals for stage IA and IB comparable to surgery
  - Stage IA=77%
  - Stage IB=68%

RISKS
We all take them.
Some are unnecessary.
SBRT vs. surgery for clinical stage I NSCLC

• Problem #1...
  – Treatment groups are inherently different!

Vs.
SBRT vs. surgery for clinical stage I NSCLC

- Problem #2...
  - Definition of “medically operable”?

  - FEV₁
  - FVC
  - Smoking
  - Diabetes
  - DLCO
  - Performance Status
  - Cardiac Co-morbidity
  - Predicted Postoperative Pulmonary Reserve

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The High-risk EARLY STAGE Pt.: Who’s who?

- Medical/surgical definition- e.g. RTOG 0915

3.1.5 The patient’s resectable NSCLC must be considered medically inoperable by an experienced thoracic cancer clinician (a thoracic surgeon, medical oncologist, radiation oncologist, or pulmonologist) or a standard lobectomy and mediastinal lymph node dissection/sampling procedure. The patient may have underlying physiological medical problems that would prohibit a surgery due to a low probability of tolerating general anesthesia, the operation, the postoperative recovery period, or the removal of adjacent functioning lung. These types of patients with severe underlying health problems are deemed “medically inoperable.” Standard justification for deeming a patient medically inoperable based on pulmonary function for surgical resection of NSCLC may include any of the following:
  - Baseline FEV1 < 40% predicted;
  - Postoperative FEV1 < 30% predicted;
  - Severely reduced diffusion capacity;
  - Baseline hypoxemia and/or hypercapnia;
  - Exercise oxygen consumption < 50% predicted;
  - Severe pulmonary hypertension;
  - Diabetes mellitus with severe end organ damage;
  - Severe cerebral, cardiac, or peripheral vascular disease;
  - Severe chronic heart disease.

If the patient has resectable disease but declines surgery after consulting with a thoracic surgeon, he/she will be considered eligible.
The High-risk EARLY STAGE Pt.: Who’s who?

• Patient definition
  – “Get it all”
  – “Don’t hurt me!”
  – “Patients with lung cancer can be treated by either surgical extirpation or radiation. The former may offer increased five-year survival and prolonged life expectancies as compared to the latter, but subjects patients to the immediate risk of thoracotomy. We interviewed patients with "operable" lung cancer and found that they were quite averse to taking risks involving the possibility of immediate death. When these data about patients' attitudes were combined with data about survival after both radiation therapy and operation, it appeared that radiotherapy would be the preferred therapeutic plan for several of these patients.”
Comparisons of SBRT and Surgery

• **Lowest** level evidence
  – Raw comparisons of surgery and SBRT (i.e., my paper vs. your paper)
  – Easily confounded by imbalances in patient, tumor, and treatment factors.
  – As it turns out, also confounded by practices for coding failures.

  – *The individual data itself is great, but comparisons are for now, nearly worthless, (it’s a start).*
Caveats for comparisons of SBRT and Surgery

• **Overall**
  – What medical “risk” patient population?
  – Tumor stage / size?
  – Type of staging?

• **Surgery**
  – Lobar? Sublobar? Both?
  – Open vs. VATS?
  – Skill set practioner/institution?

• **SBRT** . . . *rapidly learning* . . . *heterogeneity of data* . . .
  – Dose / fractionation?
    – BED = Biologically Effective Dose
    – $< 100 \text{ Gy}_{10}$ results in **worse** LC and OS!
  – Dose / location relative to organs at risk?
    – Central tumors, Chest wall, Lung
The High-risk pt: Choose your weapons?

• Clinical def’ns
  – Local failure
  – Staging
  – QOL/Pulmonary
  – Mortality/morbidity
  – Technical skills
  – Survival
Stereotactic Radiation for Stage I NSCLC

- Lung SBRT has a track record of efficacy in inoperable pts., now reaching the intermediate term, in more robust/operable patients.
  - Japanese data with 10 year survivors
  - Long term IU and VUmc data
  - Multi-institutional RTOG 0236 data
  - Many single institution series
  - Japanese, VUmc data for operable patients
  - Need larger, cooperative databases
    - Intermodality data, better matching
Comparisons of SBRT and Surgery

Uematsu, IJROBP 2001

– 50 pts w/T1 (n=24) or T2 (n=26) N0 NSCLC tx’d w/SBRT from 10/94-06/99.
– 29 pts were medically operable but refused surgery
– Mix of SBRT doses, prior radiation, etc.

All 50

3y LC  94%
CSS  88%
OS   66%

29 medically operable

3y OS  86%
Comparisons of SBRT and Surgery

*Onishi, IJROBP 2010*

- 87 pts w/medically operable T1 (n=65) or T2 (n=22) N0 NSCLC tx’d w/SBRT to BED > 100Gy from 1995-2004 at 14 Japanese institutions.

**Local control**

5y LC 86.7% (All)

**Overall survival**

- 5y OS (All) 69.5%
- CSS 76.1%
Comparisons of SBRT and Surgery

• **Lagerwaard et al.**
  

• 177 pts w/medically operable, T1 (n=60%) or T2 (n=40%) N0 NSCLC tx’d w/SBRT from 2003-2010 in the Netherlands.
  
  – SBRT delivered using “risk adapted” scheme (60 Gy in 3, 5, or 8 fx)
  
  – Median age 76
  
  – Median F/U 32 mo
  
  – 3y LC 93%
  
  – 3y OS 84.7%, median OS 61.5 mo
SBRT vs. surgery for clinical stage I NSCLC

Medically inoperable / High risk operable - Grills, JCO 2010

— Median potential F/U 30 mo

Table 2. Wedge Resection Versus Lung SBRT: 30-Month Outcomes Comparison

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>% of Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>RR</td>
</tr>
<tr>
<td>All patients, n = 124</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>SBRT, n = 55</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Wedge resection, n = 69</td>
<td>0.07*</td>
<td>0.34</td>
</tr>
<tr>
<td>Exclude pT4, synchronous primary, no biopsy, n = 110</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>SBRT, n = 52</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Wedge resection, n = 58</td>
<td>0.05</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Patterns of Failure after Stereotactic Body Radiation Therapy or Lobar Resection for Clinical Stage I Non–Small-Cell Lung Cancer

Cliff G. Robinson, MD,* Todd A. DeWees, PhD,* Issam M. El Naqa, PhD,† Kimberly M. Creach, MD,* Jeffrey R. Olsen, MD,* Traves D. Crabtree, MD,* Bryan F. Meyers, MD,* Varun Puri, MD,* Jennifer M. Bell, BSN,* Parag J. Parikh, MD,* and Jeffrey D. Bradley, MD*

J Thorac Oncol 2013; 8:192-201
FIGURE 2. Kaplan-Meier curves for local control, primary tumor control, regional control, distant control, overall survival, and cancer-specific survival between the entire cohort of patients treated with iodine resion or SBRT. SBRT, stereotactic body radiation therapy.
Markov Modeling Comparisons (Puri et al., JTCVS 2011, and Louie et al., IJROBP 2010)

- Attempt to model a comparison of SBRT and surgery using available data
  - Demonstrate Surgery to be cost effective…
  - … However, outcome highly sensitive to surgical mortality rate
- When surgical mortality exceeds 4% model favors SBRT (Louie)

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>High risk (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative Mortality</td>
<td>2.7%</td>
<td>7%</td>
</tr>
<tr>
<td>Any comp</td>
<td>38%</td>
<td>43.8%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>22.7%</td>
<td>21%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>19.9%</td>
<td>27%</td>
</tr>
</tbody>
</table>
Quality of Life Comparisons: SBRT


van der Voort van Zyp, *IJROBP* 2010 (Netherlands)
Quality of Life and Survival in the 2 Years After Surgery for Non–Small-Cell Lung Cancer. JCO 2008; 26:233-214

Patients with clinical stage I or II NSCLC (n = 173) completed HRQOL questionnaires before surgery, at discharge, 1 month after surgery, and then every 4 months for 2 years.

Surgery had a substantial impact on HRQOL, and although many disease-free survivors experienced recovery, some lived with long-term HRQOL impairment.
Quality of Life Comparisons: Surgery (only pts w/o recurrence)

Kenny et al., JCO 2008

Overall QOL

Physical Functioning

Emotional Functioning

Pain

Fatigue

Dyspnea
Potential Advantages of Surgical Resection

- Confirmation of Cancer Diagnosis
- Pathological Staging
- Nodal Dissection
- Information for Adjuvant Therapy
- Clear Measures of Outcome to Allow Salvage
Lack of biopsy in some SBRT series

- Wash U data also suggests no difference by radiographic vs pathological diagnosis
  — Robinson, IJROBP 2012

Two separate Netherlands reports suggest same (Laagerward et al, ASTRO 2011), and worse (Palma JCO 2010) outcome in non-biopsied patients.
Comparisons of SBRT and Surgery – *Toxicity*?

**SBRT**
- Skin toxicity?
- Fatigue?
- Chest wall toxicity?
- Pneumonitis?
- Brachial plexopathy?
- Bleeding?
- Fistula?

**Surgery**
- Death?
- Post-op pain?
- Infection?
- Atrial fibrillation?
- Extended hospital stay?
- Decreased pulmonary function?
- Post-thoracotomy pain?

*Source: Cleveland Clinic*
Comparisons of SBRT and Surgery

- **Highest** level evidence
  - Randomized trials
    - None completed
  - 2 trials of SBRT vs. lobectomy for medically operable pts
    - ROSEL
      - Terminated early
    - STARS
      - OVER!
    - Question asked too early...???
  - 1 trial SBRT vs. sublobar resection for “high risk” operable pts
    - Only 10 pts of planned 420 enrolled

—ACOSOG Z4099/RTOG 1021
COULD NOT ACCRUE
ACOSOG Z4099/RTOG 1021
Phase III Trial for High-risk patients
Opened June 2011

Histological confirmation
NSCLC and confirmation
N2/N3 negative lymph nodes

Registration and Randomization

ARM 1:
Sublobar Resection ± Brachytherapy (SR)

ARM 2:
Stereotactic Body Radiation Therapy (SBRT) 18 Gy X 3 = 54 Gy

Endpoint: 3 year OS
Accrual = 420 patients

Closed
Controversy not far behind…

  - Pooled results from the poorly accruing phase 3 trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL)
  - 58 patients were enrolled and randomly assigned (31 to SABR and 27 to surgery).
  - Estimated overall survival at 3 years was 95% in the SABR group compared with 79% in the surgery group

*Figure 2: Overall survival (A) and recurrence-free survival (B)*

One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR = stereotactic ablative radiotherapy. HR = hazard ratio.
In the works...

VALOR: Recruitment Sites

Joint Lung Cancer Trialist’s Coalition
JoLT-Ca

A Randomized Phase III Study of Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

The STABLE-MATES Trial
Conclusions: Surgery versus SBRT

• Surgery is the gold standard for operable patients

• For inoperable or marginally operable patients with Stage I lung cancer, SBRT offers excellent local control and similar survival to surgical approaches

• SBRT results will be similar, regardless of delivery device. Differences are method of imaging, +/- fiducials, treatment time, etc.

• Randomized trials have failed to accrue for various reasons; patients and surgeons
Summary

• Organ sparing treatment is unlikely to give a better oncological outcome than resection…
  — Pathological staging
  — More information for adjuvant decisions
  — Clear measures of outcome, allowing early salvage if needed

…BUT, it can get very, very close (under the right circumstances).

• SBRT in this setting has several potential advantages:
  — Outpatient
  — Incision free, anesthesia free
  — Generally spares more lung tissue
  — Different, but likely milder complication profile
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Conclusions

- Multidisciplinary management the Gold-standard Rx approach
- Stage I: Extent of surgery and surgical expertise matters
  - Good pulmonary function: Lobectomy is standard of care
- **SBRT is a competitive and less morbid option** than limited resection for an Elderly, Borderline operable who can only tolerate limited lung resection (particularly wedge) or in medically inoperable cases
- At present SBRT not a rival to Surgery….it gives chance of cure for more localized lung cancers who were otherwise ignored
- But **BEWARE about FUTURE**…
- **SBRT going to be a challenge to Surgery in fit operable patients**
- Randomized trails are needed…**But will the Patients allow us to do this????**
Do The Right Thing
A Spike Lee Joint

It's the hottest day of the summer. You can do nothing, you can do something, or you can...
Thank You!
Merci!