Learning the craft of SBRT - The Cleveland Clinic lung cancer program experience

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CONFLICTS OF INTEREST

- NONE
OBJECTIVES

- Stereotactic Body Radiotherapy for Early Stage Lung Cancer- The Cleveland Clinic Experience
  - 1. Review the management of early stage lung cancer and the implications for Radiotherapy
  - 2. Review the principles and practice of stereotactic body radiotherapy (SBRT) as the apply to managing early stage lung cancer.
  - 3. Review the clinical experience to date in the development of a Lung SBRT program as demonstrated by the results from the Cleveland Clinic
CANADA as viewed from Cleveland!
In the beginning...
Up until 2003, CCF Radiation Oncology was beta-test site for Cyberknife
On the I-90 from Boston MA to Cleveland OH, 2003
In 2003, CCF Radiation Oncology opted to change to a Novalis-based system to develop stereotactic RT
Come quickly Watson! I've invented late-night lab nourishment. Three meals isn't enough, so I've created the FOURTH meal.
SBRT for Early Lung Cancer: The Cleveland Clinic program

- Program initiated in 6/04
- ~900 medically inoperable early stage NSCLC pts treated to date
  - Some oligometastatic cases (~50)
  - 20 stage I SCLC cases (!)
A little background first…

"Mind if I smoke?"

"Care if I die?"

(California Anti-Smoking Ad)
Epidemiology of Lung Cancer

Leading cause of cancer-related deaths worldwide
Most common malignancy worldwide
over 1 million cases now being diagnosed yearly

- **USA Cancer Statistics 2011**
  - Estimated new cases: 226,160
    - 14% of all new cancer diagnoses
  - Estimated Deaths: 160,340
- **#1 Cancer Killer of Men and Women**

INTRODUCTION

- Definition of Early Stage Non-Small Cell Lung Cancer (NSCLC)
  - Confined to lung, about 15-20% of total cases **[30-40,000 cases annually]**
  - By TNM staging: IA or IB
  - Thus, No LOCOREGIONAL lymph nodes

- Standard of care
  - Surgery: 5-year survival 50-70%
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 Good is “Gold”? 

Surgery is a very good but non-perfect treatment

- **NB:** path stage I 5-yr OS is “ONLY” 60-70%
  - Local failures, death from cancer (even controlling for pathological staging)
- Toxicity, pain and suffering
- Expense - hospitalization, recovery, lost work/income, etc.
- **Surgery not appropriate for many!**
INTRODUCTION

Many early stage pts [30-50%] potentially resectable but MAY have reasons for being medically inoperable

- Co-morbidities preventing surgical resection include
  - COPD
  - Cardio-vascular Disease
  - Poor performance status

- 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
EARLY STAGE LUNG CANCER

- Management of the medically inoperable early lung cancer pt
  - O.S. with primary conventional daily fractionated RT historically poor
  - BUT O.S. with RT confounded by
    - Patient co-morbidities (competing death causes)
    - RT interacting with co-morbidities
      - e.g. COPD exacerbation
3-5 Year Survival in Early Stage Lung Cancer

<table>
<thead>
<tr>
<th>Rx Modality</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>alive</td>
<td></td>
</tr>
<tr>
<td>Stage I Surgery</td>
<td>60-80%</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>

*clinically staged and mostly medically inoperable
RT generally 60 Gy delivered in 6 weeks
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
- Post-RT scan of 4/7/10
The efficacy and safety of RT reflect the interplay between:

- total \textit{dose} delivered to the malignant tumor
- the rate of dose delivery (daily \textit{fractionation})
- the \textit{volume} (and type) of tumor-bearing organ irradiated.
- The intrinsic \textit{tolerance} of the tissue irradiated
INTRODUCTION

- Novel Technology Solutions now available to “replace” surgery need in medically inoperable patient

- Stereotactic body radiotherapy (SBRT)
  - a/k/a “Extracranial Radiosurgery”, “Body Radiosurgery”, Stereotactic Ablative Radiotherapy (SABR)
Spread out the Entrance Dose/focus on the target!!
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

- 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.

Evolution of Stereotaxis


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

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.
## SBRT vs. Conventional Radiotherapy

<table>
<thead>
<tr>
<th>SBRT</th>
<th>Conventional Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many beams/arcfs</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>
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
INTRODUCTION

- **What is Lung SBRT? Technical**
  - Typically few-fraction (1 to 5) RT using **large** individual fraction doses
  - *High dose conformality*, i.e., “tight around target”
  - Rapid dose fall-off from target to surrounding normal tissue.
Many ways to skin a cat...
Use of “Image Guidance” -

Technology for frequent 2D and 3D imaging, during RT, to verify/direct radiation therapy checked against the “standard”:

Imaging coordinates set by images set at simulation and used for planning
Treatment Verification

Re-align to eliminate error between and during treatment
Compact Dose Deposition
INTRODUCTION

SBRT and Early Lung Cancer: CLINICAL EXPERIENCE

- Numerous series document safety of SBRT in early lung cancer
- Also report excellent local control.

SBRT and Early Lung Cancer: CLINICAL EXPERIENCE

Treatment Toxicities

- Reported rates generally low
  - > grade 3 pneumonitis, hypoxia: < 5%
- Related to tumor location
SBRT and Early Lung Cancer—Local control lung

Numerous studies report excellent local control. In all series, tumor recurrence is late (median about 18 months).

<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>84% (3 years)</td>
<td>43 Gy</td>
</tr>
</tbody>
</table>
SBRT and Early Lung Cancer

- **Treatment Toxicities**
  - **Reported rates generally low**
    - ≥ grade 3 pneumonitis, hypoxia: < 5%
  - **Related to tumor location**
    - RTOG SBRT eligibility
      - 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 at U Indiana
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%
  (Onishi et al)

FIGURE 6. Overall survival rate according to stage in medically operable patients irradiated with biologic effective dose ≥ 100 gray.
MEDICAL PHYSICS!

TEAMWORK
Sometimes Drinking on a Tuesday night is a good idea
SBRT for Early Lung Cancer: The Cleveland Clinic program

PATIENT SELECTION
Defined as early stage AND medically inoperable following; OR oligometastatic disease
- Review by the Thoracic Multidisciplinary Lung Team
  - Surgeon
  - Pulmonologist
  - Radiation Oncologist
  - Medical Oncologist
  - Imaging
  - (Cardiothoracic service/Cardiology)
SBRT for Early Lung Cancer: The Cleveland Clinic program

- Staging (complete) to include
  - **Access to PET**
    - Staging
    - Nodes
    - Is it cancer?
      - +/- Mediastinoscopy
        - EBUS TECHNOLOGY
      - +/- Biopsy of the Primary tumor-morbidity of procedure of importance
Guidelines for selecting for treatment

- Biopsy if feasible
- In non-biopsied
  - Get 2\textsuperscript{nd} opinion
  - CT growth on more than one image
  - PET-high uptake or serial uptake
  - Review by Pulmonology, Radiology, Nuclear medicine
- (EBUS for any borderline LNs by CT but especially by PET)
SBRT for Early Lung Cancer: The Cleveland Clinic program

- RT- 1\textsuperscript{st} Choice of initial 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**
      - T size 0.8-5.0 cm
      - Staged by CXR, CT chest, no PET, no mediastinoscopy
      - Results: 3 yr o.s. 86% for the 29 medically inoperable patients
SBRT for Early Lung Cancer: The Cleveland Clinic program

- RT- Choice of second treatment model
  - Participation in RTOG 0236 Trial

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

- SBRT dose: 60 Gy/3 fx over 8-14 days
- Closed Oct/2006
  - CCF #3 accruer in US
SBRT for Early Lung Cancer: The Cleveland Clinic program

- RT- Choice of second treatment model
  - Participation in RTOG 0236 Trial
  - Comprehensive normal tissue dose constraints
  - RTOG SBRT eligibility
    - 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 at U Indiana
SBRT for Early Lung Cancer: The Cleveland Clinic program

- RT- Choice of second treatment model
  - Participation in RTOG 0236 Trial
    - THE “FORBIDDEN ZONE” per Timmerman
SBRT for Early Lung Cancer: The Cleveland Clinic program
SBRT for Early Lung Cancer: The Cleveland Clinic program

- **Treatment Unit**
  - Novalis BrainLab System
    - 6MV Linac
    - Special characteristics
      - "Automated image-guided radiation therapy system, utilizes high-resolution X-rays to pinpoint internal tumor sites seconds before treatment, robotically corrects patient set-up errors and tracks any patient movement throughout the treatment, all within a standard treatment time slot"
SBRT for Early Lung Cancer: The Cleveland Clinic program

- SBRT on NOVALIS
  - By restriction (immobilization)
  - By tumor motion studies
  - By creating reference frame to provide real-time verification of patient positioning and set-up
SBRT for Early Lung Cancer: The Cleveland Clinic program

- Patients immobilized in a Novalis body cushion
  - compression by weighted abdominal belt was used to limit respiratory excursion.
SBRT for Early Lung Cancer: *The Cleveland Clinic program*

- Abdominal compression/breathing restriction
EXACTRAC® PATIENT POSITIONING SYSTEM

- At the time of simulation infrared sensitive markers are placed on the patient skin.

- The patient is scanned with markers

- The Marker are shown in the CT images for patient localization in the process of Treatment Planning
TREATMENT PLANNING
SBRT for Early Lung Cancer: The Cleveland Clinic program

- CT simulation images acquired at rest, at full inhalation, and at full exhalation were fused to generate an internal gross tumor volume (ITV) that reflected residual motion after external compression.

- **CT Sim:** Assessment of target motion
  - free breathing
  - full inhale
  - full exhale
SBRT for Early Lung Cancer: The Cleveland Clinic program

- SBRT on Novalis
  - Using an IMRT approach to cover the planning target volume (PTV=ITV + 3-5 mm margin).
SBRT for Early Lung Cancer: The Cleveland Clinic program

- IMRT dose delivery: centrally weighted beamlet “painting”
- Typically 7 non-opposing, non-coplanar beams
- IMRT beam calculations included heterogeneity corrections.
SBRT for Early Lung Cancer: The Cleveland Clinic program

- SBRT on NOVALIS
  - Planning per RTOG 0236
  - Non-coplanar arc techniques
  - Dose-volume constraints/fixed margins on GTV (1cm S/I; 0.5 cm M/L) per protocol
TREATMENT PLANNING
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

- SBRT administration
  - “In-House” standard
    - Central tumors: 50 Gy in 5 sequential fractions of 10 Gy [Monday through Friday]
    - Peripheral tumors: 60 Gy in 3 fractions [over 8-14 days, min 40 hrs/max 7 days between fractions]
      - Selected cases
        - 48 Gy in 4 fractions
        - 60 Gy in 8 fractions
        - 50 Gy in 10 fractions
        - 30 Gy in one fraction
SBRT for Early Lung Cancer: The Cleveland Clinic program

- Follow-up schedule for control and assessment of toxicity
  - 6 weeks, then Q3m for 2 yrs
    - CT chest + contrast Q 3months
    - PFTs/DLCO Q 6months
Developing Lung SBRT: An approach to Research

- **Collaborative Group Support**
  - RTOG 0236-phase I/II of 60 Gy/3 fx
    - CCF 3rd highest accruer
  - RTOG 0813-phase I/II- set MTD of SBRT for early-stage, centrally located NSCLC
    - Ongoing, CCF accrual YTD 6 pts
  - RTOG 0915-randomized phase II, peripheral tumors, 34 Gy/1 fraction vs. 48 Gy/4 fractions, primary end point of toxicity
    - CCF 3rd highest accruer
  - Roswell Park phase III study of 30 Gy/1 fx vs. 60 Gy/3 fx
    - 15 pts accrued YTD
Developing Lung SBRT: An approach to Research

- **1. Establish IRB approved prospective data registry of all SBRT patients**

- **2. Demonstrate efficacy**
3. **Establish acute safety**


4. **What about long-term safety?**


5. Advancing the discipline


- Videtic GM, Reddy C, Sorenson L. Prospective Study of Fatigue and Quality of Life after Stereotactic Body Radiotherapy for Medically Inoperable Early-Stage Lung Cancer. 52nd Annual meeting of ASTRO, October 31-November 4, 2010; San Diego, CA.
5. Advancing the discipline


- Woody NM, Stephans KL, Videtic GMM, Djemil T, Xia P. *Defining Target Volume for Lung Stereotactic Body Radiotherapy (SBRT): Fixed or Motion-derived Margins?* IJROB. Provisionally accepted.
Developing Lung SBRT: An approach to Research

6. Setting standards

Developing Lung SBRT: An approach to Research

- CCF technical innovations in SBRT
  - Development of implantation tool for SBRT fiducial insertion using “super”-dimension bronchoscope system
Local Recurrence Free Survival

Recurrence Free Survival (%)

Months since Treatment

\(p=0.54\)
Overall Survival

Overall Survival (%) vs Months since Treatment

- 3x20
- 5x10

Key Points:
- 90.5%
- 76.9%
- 76.9%
- 93.9%
- 83.1%
- 75.9%
- 55.5%

p = 0.68
Distant Metastasis Free Survival

Metastases Free Survival (%)

Months since Treatment

96.6% 70.5% 70.5%
97.7% 78.2% 67.5%

p=0.54
Stereotactic body radiation therapy for inoperable early stage lung cancer.

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

<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>

Figure. Patient Course After Initiation of Stereotactic Body Radiation Therapy

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

- Single fraction dosing for peripheral tumors?
- Ideal dose for central tumors
- Enhanced staging (EBUS?)
- Slightly more operable patients
- Treatment of larger tumors
- Adjuvant chemo?
- Boost for stage III disease, or recurrence
- Very limited use for select oligometastatic patients.
"It doesn't cure anything, but the side effects are out of this world."
Conclusions

- SBRT powerful tool for treating early lung cancer safely and effectively in medically inoperable pts
- Cancer control rates impressive, likely comparable to surgery
- Distant control: an area for innovation and investigation, given the nature of the patient population
Conclusions

- Morbidity of treatment strikingly minimal **in the acute phase**
- LATE TO VERY LATE TOXICITY:
  - Clearly highlights necessity of long term follow-up (years)
  - Will be critical to define for operable patients
Conclusions

- Current technique for treating pts at CCF with tumor motion control and coverage by SBRT of potential tumor volume safe, tolerable, feasible, rapid
- Further enhancements in delivery technique being explored
- Studies in medically operable pts warranted!
THANK YOU!

THE CANADIAN HIGH-FIVE

Because in Canada, stitches are free