HEALING MANKIND ONE PATIENT AT A TIME
PREDICTING TUMOR CONTROL FROM LUNG SBRT/SABR: A CLINICIAN’S PERSPECTIVE

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RR UCLA MEDICAL CENTER JONSSON COMPREHENSIVE CANCER CENTER NATIONAL CANCER INSTITUTE DESIGNATED
OBJECTIVES

- Understand the increasing role for lung SBRT/SABR
- Understand the need to balance tumor control and toxicity in choosing dose
- Understand difficulties and controversies in comparing dose amongst regimen (3DCRT to SBRT/SABR)
- Understand goals of SBRT Thoracic TCP Working Group – Preliminary Findings
SCOPE OF THE PROBLEM
## LUNG CANCER

### Stage Distribution: IASLC Lung Cancer Data Base

**Clinically Staged Cases, N = 53,646**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>28%</td>
</tr>
<tr>
<td>II</td>
<td>27%</td>
</tr>
<tr>
<td>III</td>
<td>9%</td>
</tr>
<tr>
<td>IV</td>
<td>36%</td>
</tr>
</tbody>
</table>

### Estimated New Cases*

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>217,730</td>
<td>207,090</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,750</td>
<td>105,770</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>72,090</td>
<td>70,480</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>52,760</td>
<td>43,470</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>38,670</td>
<td>33,930</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,380</td>
<td>30,160</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>35,370</td>
<td>29,260</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,420</td>
<td>22,870</td>
</tr>
<tr>
<td>Leukemia</td>
<td>24,890</td>
<td>21,880</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,370</td>
<td>21,770</td>
</tr>
<tr>
<td>All Sites</td>
<td>789,620</td>
<td>739,940</td>
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</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>86,220</td>
<td>71,060</td>
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<tr>
<td>Lung &amp; bronchus</td>
<td>66,050</td>
<td>59,840</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>26,580</td>
<td>24,790</td>
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<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>16,030</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,720</td>
<td>13,850</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,660</td>
<td>9,500</td>
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<td>Esophagus</td>
<td>11,650</td>
<td>9,180</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,710</td>
<td>7,950</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>10,410</td>
<td>6,190</td>
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<tr>
<td>Urinary bladder</td>
<td>8,210</td>
<td>5,720</td>
</tr>
<tr>
<td>All Sites</td>
<td>299,200</td>
<td>270,290</td>
</tr>
</tbody>
</table>
LUNG CANCER BY AGE

Percent of New Cases by Age Group: Lung and Bronchus Cancer

SEER 18 2007-2011, All Races, Both Sexes

Lung and bronchus cancer is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

70

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Lung and Bronchus Cancer

SEER, 2007-2011
EARLY STAGE NSCLC TREATMENT OPTIONS

- Surgery
  - Lobectomy/pneumonectomy
  - Sublobar resection (segmentectomy, wedge)
- Radiation
  - SBRT
  - EBRT
- Observation

Medically operable
Borderline medically operable
Medically inoperable
Wouldn’t touch with a 10-foot pole

Courtesy of J. Bradley
Percy Lee, M.D.
COULD LUNG SBRT PLAY A BIGGER ROLE IN THE TREATMENT OF EARLY STAGE NSCLC IN THE NEAR FUTURE?
LUNG CANCER SCREENING: NLST

- **Purpose:** Could yearly CT screening reduce lung cancer mortality compared to CXR screening?

Aberle D, et al., NEJM 2011
Results:
- 53,454 patients
- High risk: 55-74 years old, 30 pk-year, if former smoker, quit within previous 15 years
- Rates of positive screen: 24% vs. 7% (CT vs. CXR)
- 247 vs. 309 deaths from lung cancer per 100,000 person-year from CT vs. CXR
- 20% relative reduction in lung cancer mortality from low-dose CT screening (6.7% absolute reduction) compared to CXR screening

Aberle D, et al., NEJM 2011
NLST FINDINGS

A. Lung Cancer

- Low-dose CT
- Chest radiography

Cumulative No. of Lung Cancers vs. Years since Randomization

B. Death from Lung Cancer

- Chest radiography
- Low-dose CT

Cumulative No. of Lung-Cancer Deaths vs. Years since Randomization
NLST CONCLUSIONS

- Yearly low-dose CT screening in high-risk population reduce lung cancer mortality compared to CXR screening
- Potentially, many of these patients are too frail for surgery: SBRT
- Possibly, more cancers are detected at earlier stage, obviating the need for surgery: SBRT
SBRT/SABR
The diagram illustrates the therapeutic ratio, showing the relationship between dose and the percentage of cure (benefit) and toxicity. The therapeutic ratio is defined as the benefit divided by the toxicity, aiming to maximize the benefit while minimizing toxicity. This concept is crucial in the field of medical oncology, particularly in the context of Stereotactic Body Radiotherapy (SBRT), which is used to deliver high doses of radiation to cancerous tumors while minimizing exposure to surrounding healthy tissues. The diagram highlights the goal of achieving a balance where the benefit of treatment is maximized with minimal toxicity, ensuring patient safety and effectiveness in cancer therapy.
RTOG 0236: Peripheral Tumor SBRT Dose

- First North American cooperative group trial of SBRT
- Phase II: 55 pts (44 Stage IA, 11 Stage IB), medically inoperable, peripheral tumors
- 54 Gy in 3 treatments
- Tumor control: 98%, Survival 72% at 3 years, median OS 48 months

36 month local control = 98% (CI: 84-100%)

RTOG 0236 – Peripheral Tumor SBRT Dose

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

Robert Timmerman; Rebecca Paulus; James Galvin; et al.
Central Tumor Toxicity with SBRT

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 Yianoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abidrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

Percy Lee, M.D.
## Control Rates by $\text{BED}_{10}$ For All Patients

<table>
<thead>
<tr>
<th>Total cases</th>
<th>$\text{BED} &lt; 100 \text{ Gy}$</th>
<th>$\text{BED} \geq 100 \text{ Gy}$</th>
<th>$p$</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local tumor</td>
<td>36/257 (14.0%)</td>
<td>18/42 (42.9%)</td>
<td>18/215 (8.4%)</td>
<td>$&lt;0.01$</td>
<td>20/164 (12.2%)</td>
<td>16/93 (17.2%)</td>
</tr>
<tr>
<td>Regional nodal metastasis</td>
<td>29/257 (11.3%)</td>
<td>9/42 (21.4%)</td>
<td>20/215 (9.3%)</td>
<td>$&lt;0.05$</td>
<td>17/164 (10.4%)</td>
<td>12/93 (12.9%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>51/257 (19.8%)</td>
<td>11/42 (26.2%)</td>
<td>40/215 (18.6%)</td>
<td>0.3</td>
<td>32/164 (19.5%)</td>
<td>19/93 (20.4%)</td>
</tr>
</tbody>
</table>

BED, biological effective dose.

5y overall survival

| 19.7% | 53.9% | sig |

Onishi, H, JTO, 2007
OPTIMAL DOSE FOR PERIPHERAL TUMORS?

5 yr. OS by $\text{BED}_{10}$ in Medically Operable Patients

\[ \text{BED} = \text{nd}(1 + d/\alpha/\beta) \]

\begin{align*}
\geq 100 \text{ Gy} & \quad 3\text{y} 80.4\%, 5\text{y} 70.8\% \\
< 100\text{ Gy} & \quad 3\text{y} \sim 65\%, 5\text{y} \sim 50\%
\end{align*}

**Schemes > 100 Gy:**
- $16 \text{ Gy} \times 3 = 48 \text{ Gy}$
- $12 \text{ Gy} \times 4 = 48 \text{ Gy}$
- $10 \text{ Gy} \times 5 = 50 \text{ Gy}$

**FIGURE 4.** Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.
• 411 stage I NSCLC patients, 434 tumors
• 2-year LF of 15% for low BED vs. 4% for high BED

Grills, I et al., JTO, 2012
Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control

Niraj Mehta MD, Christopher R. King MD, PhD, Nzhde Agazaryan PhD, Michael Steinberg MD, Amanda Hua BA, Percy Lee MD*

Department of Radiation Oncology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California
DOSE RESPONSE LUNG SBRT

PURPOSE:

- Is there a relationship between tumor control probability (TCP) and the Biological Effective Dose (BED) in Stage I NSCLC?
- Is there evidence for further dose escalation?
- Are we really doing better than before (SBRT vs. 3DCRT)?

N. Mehta and P. Lee et al., PRO, 2012
METHODS

- 42 PUBLISHED STUDIES (48 DATA POINTS) – Heterogeneous!
- July 1988-March 2010
- Crude Local Control (TC) ≥ 2 years as a function of BED
- Scatter plot TC vs. BED
- TCP = \( \exp(\frac{[d-TCD_{50}]/k}{1+\exp(\frac{[d-TCD_{50}]/k})}) \)
- Daily fraction size ≥ 6 Gy considered SBRT - Assumptions!

N. Mehta and P. Lee et al., PRO, 2012
RESULTS

- 2696 patients (SBRT: 1640; 3D-CRT: 1050)
- 704 adenoCA, 847 SCC, 1145 NOS
- Daily fx size 1.2 – 4 Gy (total dose: 48-103) for 3D-CRT
- Daily fx size 6-26 Gy (total dose 20-66) for SBRT
- Median aBED 105.6 Gy (59.6 – 286.6)

N. Mehta and P. Lee et al., PRO, 2012
**RESULTS**

![Graph showing tumor control probability vs. BED (Gy)]

<table>
<thead>
<tr>
<th>Table 3: Demographics, radiation therapy details, and tumor control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>NOS</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>NOS</td>
</tr>
<tr>
<td><strong>Operable</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
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<tr>
<td><strong>RT technique</strong></td>
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<tr>
<td>3D-CRT</td>
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<tr>
<td>SBRT</td>
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<tr>
<td><strong>Absolute dose range, Gy</strong></td>
</tr>
<tr>
<td>3D-CRT</td>
</tr>
<tr>
<td>SBRT</td>
</tr>
<tr>
<td><strong>No. of fractions, range</strong></td>
</tr>
<tr>
<td>3D-CRT</td>
</tr>
<tr>
<td>SBRT</td>
</tr>
<tr>
<td><strong>Median aBED, Gy</strong></td>
</tr>
<tr>
<td><strong>aBED range, Gy</strong></td>
</tr>
</tbody>
</table>

*3D-CRT, 3-dimensional conformal radiation therapy; aBED, average biological effective dose; NOS, not otherwise specified; RT, radiation therapy; SBRT, stereotactic body radiation therapy.*
Largest meta-analysis to model TCP as a function of BED for curative radiotherapy for stage I NSCLC

Near plateau, TCP is $\geq 90\%$ with BED $\geq 124$ Gy (USC)

Corresponds to 53 Gy in 3 fractions at isocenter (48 Gy in 3 fractions at periphery)

N. Mehta and P. Lee et al., PRO, 2012
Dose escalation, not “new biology”, can account for the efficacy of SBRT with NSCLC

J. Martin Brown, PhD¹, David J. Brenner, PhD², and David J. Carlson, PhD³
¹Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305
²Center for Radiological Research, Columbia University Medical Center, 630 W 168th St, New York, NY 10032
³Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT 06520
NEW BIOLOGY

OLD BIOLOGY
OLD BIOLOGY VS. NEW BIOLOGY

- Brown et al. argues for a monotonic relationship between TCP and BED
- We avoided Old vs. New Biology
  - Equation is poor man way to normalize the dose
  - Unknown (model ≠ mechanism)
- As dose increase, TC asymptote to 100%
- BED is derived from LQ/USC models, flawed; Circular argument
- Abscopal and vascular effects of SBRT?
- Timing of normal tissue effects: e.g., pneumonitis
  - different between 3DCRT and SBRT
Critical Review

The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?

J. Martin Brown, PhD.*, David J. Carlson, PhD.,† and David J. Brenner, PhD.‡

*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California; †Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut, and ‡Center for Radiological Research, Columbia University Medical Center, New York, New York

Received May 9, 2013, and in revised form Jul 14, 2013. Accepted for publication Jul 17, 2013

Percy Lee, M.D.
Counter Arguments

COMMENTS

Dose Escalation, Not “New Biology,” Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer

In Regard to Brown et al

Shyam S. Rao, MD, PhD
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

Jung Hun Oh, PhD
Andrew Jackson, PhD
Joseph O. Deasy, PhD
Department of Medical Physics
Memorial Sloan-Kettering Cancer Center
New York, New York
OTHER FACTORS THAT MIGHT INFLUENCE TUMOR CONTROL

**Patient Factors:**
- Age, histology (in situ vs. invasive), tumor size/volume, tumor location, tumor doubling time, lung function?

**Treatment Factors:**
- Total dose, dose per fraction, number of fractions?
- Length of treatment? Time effects (BED 100 can be achieved with 3DCRT but takes many weeks). Tumor cell repopulation?
- Treatment techniques, margins, image-guidance, etc.?
- Prescription standards? Normalized to isocenter as best as possible
Working Group on Biological Effects of Hypofractionated Radiotherapy/SBRT (WGSBRT)
WGSBRT Organization

- Five top-level groups:
  - Tumor Control Probability (TCP)
  - Normal Tissue Complication Probability (NTCP)
  - Radiobiology
  - Rationale for Prescription Schemes
  - Reporting Standards
The TCP and NTCP groups have divided into six anatomical subgroup:

- Cranial
- Head & Neck
- Thoracic
- Abdominal
- Pelvic
- Spine
Methodology:
- 118 clinical studies reviewed on SBRT for lung cancer
- Reviews by 12 members of the Thoracic TCP Working Group – primary data
- Selected re-review by group co-chairs for consistency
- Data modeling by Allen Li and his group (KM/actuarial figure digitized).

Objectives:
- Better model than LQ, USC for thoracic SBRT TCP?
- More accurate predictions for tumor control by biological and physical dose
- Discern intrinsic radio sensitivity of lung tumors to SBRT (α/β)
## Sample Data Review Sheet for Consistent Data Collection

<table>
<thead>
<tr>
<th>Study</th>
<th>N Pts</th>
<th>N Tumors</th>
<th>Pt Dose (Gy)</th>
<th>mNv</th>
<th>Rate 2yr</th>
<th>Rate 5yr</th>
<th>Rate 10yr</th>
<th>Rate 15yr</th>
<th>Rate 20yr</th>
<th>Rate 25yr</th>
<th>Rate 30yr</th>
<th>Rate 35yr</th>
<th>Rate 40yr</th>
<th>Rate 45yr</th>
<th>Rate 50yr</th>
<th>Rate 55yr</th>
<th>Rate 60yr</th>
<th>Rate 65yr</th>
<th>Rate 70yr</th>
<th>Rate 75yr</th>
<th>Rate 80yr</th>
<th>Rate 85yr</th>
<th>Rate 90yr</th>
<th>Rate 95yr</th>
<th>Rate 100yr</th>
<th>Median LC (yrs)</th>
<th>Median CSS (yrs)</th>
<th>Regional or Involved Lobe Control</th>
<th>Median Control (yrs)</th>
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</thead>
<tbody>
<tr>
<td>Faltas2008 T1</td>
<td>34</td>
<td>60</td>
<td>3</td>
<td></td>
<td>4.10</td>
<td></td>
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<td>2.23</td>
<td>83.4%</td>
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<tr>
<td>Faltas2008 T2</td>
<td>36</td>
<td>68</td>
<td>3</td>
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<td>4.10</td>
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<td></td>
<td>2.04</td>
<td>67.0%</td>
<td>70.0%</td>
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</tr>
<tr>
<td>Solace2008 OS vs time for different stages</td>
<td>402</td>
<td>40</td>
<td>4</td>
<td>62.1%</td>
<td>3.17</td>
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<tr>
<td>Solace2008 Stage I</td>
<td>60</td>
<td>40</td>
<td>4</td>
<td>58.2%</td>
<td>3.17</td>
<td>73.0%</td>
<td>62.0%</td>
<td>47.0%</td>
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<td></td>
<td>67.0%</td>
<td>82.0%</td>
<td>70.0%</td>
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<tr>
<td>Solace2008 Stage II</td>
<td>30</td>
<td>40</td>
<td>4</td>
<td>63.0%</td>
<td>3.17</td>
<td>73.0%</td>
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<tr>
<td>Umetate 2001</td>
<td>50</td>
<td>50</td>
<td>50 Gy for ne prior RT; 45-50 Gy for prior RT cases</td>
<td>Str 10 Fix</td>
<td>1.67</td>
<td>100%</td>
<td>77.0%</td>
<td>66% (40)</td>
<td>88% in operable pts</td>
<td>15%</td>
<td>11%</td>
<td>80%</td>
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</table>
Thank you - Acknowledgments

- WGSBRT – TCP Group
  - Allen Li – Co-chair
  - Billy Loo – Co-chair
  - Jimm Grimm
  - Ellen Yorke
  - Tithi Biswas
  - Issam El Naqa
  - Timothy Solberg
  - George Ding
  - Andy Jackson
  - Spring Kong
  - Moyed Miften
  - Chang Song
  - Tamara LaCouture