CyberKnife Radiosurgery in the Treatment of Lung Cancer

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Medical Director, CyberKnife Radiosurgery Center
Medstar Franklin Square Medical Center
Definitions

- SRS – Stereotactic Radiosurgery
- SBRT – Stereotactic Body Radiation Therapy
- SABR – Stereotactic Ablative Radiotherapy
- Cyberknife
- Gammaknife
- Trilogy, VMAT, BrainLab, RapidArc etc.
Definitions

- Very High Dose
- Very Tightly Conformal
- 5 treatments or less
SRS concept—
high target dose conformity
low dose to proximal normal tissues
Definitions

- **Gy (Gray)** – absorbed dose of ionizing radiation
- **Biologic Equivalent Dose (BED)** – a way to compare different dose/fraction combinations

How do we compare

- $1.8\text{Gy} \times 40 = 72 \text{ Gy}$
- $20.0\text{Gy} \times 3 = 60 \text{ Gy}$
Synchrony™ camera
Linear Accelerator (source of high energy x-rays)
Targeting System
X-ray sources
Manipulator
Robotic Delivery System
Image detectors
Gold Fiducial Markers
Synchrony™ Respiratory Tracking System

- Synchrony camera
- Synchrony tracking markers (LEDs)
- Tracks patient’s respiratory motion
- Tumor motion tracked via fiducials
Seamless integration of the Xsight Lung Tracking System into the MultiPlan® Treatment Planning System demonstrating a contoured right upper lobe lung tumor.
NSCLC Left Upper Lung

RESULTS:

- Radiographic complete response in 15 weeks.
- A follow-up PET/CT scan at ten months post treatment was negative at the site of the primary tumor and showed no evidence of disease.

Case provided courtesy of St. Joseph’s Hospital, Phoenix, Arizona (USA)
CyberKnife® Treatment with Synchrony™

Two Month Response
Four Month Response
SBRT for Early Stage Lung Cancer

- Surgery is the standard of care
- Inoperable patients have historically been offered external beam radiation for 20-35 outpatient treatments
  - EBRT - local control rates – 30-40%
  - EBRT - 3 year survival – 20-35%
Timeline of how SBRT for Lung Cancer has evolved

- 2003 – Phase I study dose escalation study showing that very high doses were tolerated
- 2005 – Update of Phase I study showing maximum tolerated dose for tumors >3cm was 66 Gy in 3 fractions
Timeline of how SBRT for Lung Cancer has evolved

- 2006 - Phase II study 60Gy in 3 fractions – 17 Month follow up
  - 95% local control
  - Excessive toxicity seen in patients with centrally located tumors
    - Grade 3-5 Toxicity
      - 17% peripheral
      - 46% central
  - Proximal Bronchial Tree map
Timeline of how SBRT for Lung Cancer has evolved

- Phase II study Update – 4.2 year follow up
  - 3 year Local Control – 88% *(30-40% - EBRT)*
  - Nodal Failure – 9%
  - DM – 13%
  - 3 year OS – 43% *(20-35% - EBRT)*
  - CSS – 82%
  - Toxicity update – Grade 3+
    - Peripheral – 10%
    - Central – 27%
Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

Robert Timmerman; Rebecca Paulus; James Galvin; et al.


http://jama.ama-assn.org/content/full/303/11/1070

PRELIMINARY

COMMUNICATION

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

Robert Timmerman, MD
Rebecca Paulus, BS
James Galvin, PhD
Jeffrey Michalski, MD
William Straube, PhD
Jeffrey Bradley, MD
Arabella Fraker, MD
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Gregory Velebit, MD
David Johnstone, MD
Jack Fowler, MD
Elizabeth Gore, MD
Hal Choy, MD

While anatomical resection is the standard treatment for early stage lung cancer, some patients cannot tolerate surgery due to comorbidities such as emphysema and heart disease. These patients are deemed medically inoperable and are generally offered conventional radiotherapy (most commonly given during 30-35 outpatient treatments) or observed without specific cancer therapy. Outcomes are not ideal with either approach. Conventional radiotherapy fails to discordantly control the primary lung tumor in 60% to 70% of patients, more than half of patients ultimately die specifically from progressive lung cancer with observation and 2-year survival is less than 40% with either approach.

Stereotactic body radiation therapy (SBRT) is a noninvasive cancer treatment in which numerous small, highly focused, and accurate radiation beams are used to deliver potent doses in 1 to 5 treatments to tumor targets in extra-

Conclusions

Patients with early stage but medically inoperable lung cancer have a poor rate of primary tumor control (20%-40%) and a high rate of mortality (5-year survival, 20%-50%) with current management.

Objective

To evaluate the toxicity and efficacy of stereotactic body radiation therapy in a high-risk population of patients with early stage but medically inoperable lung cancer.

Design, Setting, and Patients

Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral 1-2 cm diameter non–small cell tumors (measuring ≤5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction × 3 fractions (54 Gy total) with a median treatment lasting between 11 and 2 weeks. The study opened May 26, 2004, and closed October 13, 2006; data were analyzed through August 31, 2009.

Main Outcome Measures

The primary end point was 2-year actuarial primary tumor control, secondary and tertiary endpoints were disease-free survival, primary tumor, involved lobe, regional, and disseminated recurrence, treatment-related toxicity, and overall survival.

Results

A total of 59 patients accrued of which 56 were evaluable (44 patients with 71 tumors and 11 patients with 12 tumors) with a median follow-up of 24.4 months (range, 4.8-49.9 months). Only 1 patient had a primary tumor failure; the estimated 2-year primary tumor control rate was 97.6% (95% confidence interval, 84.3%-99.7%). Three patients had recurrence within the involved lobe, the 2-year primary tumor and involved lobe (local) control rate was 96.6% (95% CI, 76.0%-96.5%). Two patients experienced regional failure, the local-regional control rate was 87% (95% CI, 71.6%-94.7%). Eleven patients experienced distant failure, the 2-year rate of distant failure was 22.1% (95% CI, 12.3%-37.8%). The rates for disease-free survival and overall survival at 3 years were 88.3% (95% CI, 84.1%-92.8%) and 56.8% (95% CI, 41.0%-71.3%), respectively. The median overall survival was 48.7 months (95% CI, 29.6 months to 59.7 months). Protocol-specified treatment-related grade 3 adverse events were reported for 2 patients (4.7%; 95% CI, 0.6%-8.8%); grade 4 adverse events were reported in 2 patients (3.6%; 95% CI, 0.7%-9.4%). No grade 5 adverse events were reported.

Conclusion

Patients with inoperable non–small cell lung cancer who received stereotactic body radiation therapy had a survival rate of 55.8% at 3 years, higher rates of local tumor control, and moderate treatment-related morbidity.
Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

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Jack Fowler, PhD
Elizabeth Gore, MD
Hak Choy, MD

Context Patients with early stage but medically inoperable lung cancer have a poor rate of primary tumor control (30%-40%) and a high rate of mortality (3-year survival, 20%-35%) with current management.

Objective To evaluate the toxicity and efficacy of stereotactic body radiation therapy in a high-risk population of patients with early stage but medically inoperable lung cancer.

Design, Setting, and Patients Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small cell tumors (measuring <5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction × 3 fractions (54 Gy total) with entire treatment lasting between 1½ and 2 weeks. The study opened May 26, 2004, and closed October 13, 2006; data were analyzed through August 31, 2009.

Main Outcome Measures The primary end point was 2-year actuarial primary tumor control; secondary end points were disease-free survival (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and overall survival.

Results A total of 59 patients accrued, of which 55 were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had a primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% confidence interval [CI], 84.3%-99.7%). Three patients had recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0%-96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI, 71.0%-94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3%-37.8%). The rates for disease-free survival and overall survival at 3 years were 48.3% (95% CI, 34.4%-60.8%) and 55.8% (95% CI, 41.6%-67.9%), respectively. The median overall survival was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade 3 adverse events were reported in 7 patients (12.7%; 95% CI, 9.6%-15.8%), grade 4 adverse events were reported in 2 patients (3.6%; 95% CI, 2.7%-4.5%). No grade 5 adverse events were reported.
RTOG 0236

- Phase II trial
- Eligible Patients: T1-T2No Peripheral NSCLC (<5cm) with medical conditions precluding surgical treatment
- 18Gy x 3 (54Gy total) over 1.5 to 2 weeks
RTOG 0236

- 59 patients
- 34.4 month median follow up
- Only 1 patient had primary tumor failure
  - LOCAL CONTROL – 97.6%
- 3 Patients had recurrence within the involved lobe
  - INVOLVED LOBE LC – 90.6%
- 2 Patients had locoregional recurrence
  - Local-regional LC – 87.2%
- 11 Patients formed Distant Metastatic Disease
  - 22.1%
RTOG 0236

- 3 year Disease Free Survival
  - 48.3%
- 3 year Overall Survival
  - 55.8%
- Median Overall Survival
  - 48.1 months
- Toxicity
  - Grade 3 – 12.7%
  - Grade 4 – 3.6%
  - Grade 5 – 0%
## Modality Comparison

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>EBRT</th>
<th>Early SBRT experience</th>
<th>RTOG 0236 SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Control</strong></td>
<td>95%</td>
<td>30-40%</td>
<td>82%</td>
<td>97.2%*</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td>70-80%</td>
<td>20-35%</td>
<td>43%</td>
<td>55.8%</td>
</tr>
</tbody>
</table>
# SRS FOR LUNG CANCER

## Literature Summary

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>STAGE</th>
<th># OF PTS</th>
<th>TUMOR CONTROL %</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hof H. et al</td>
<td>I-II</td>
<td>42</td>
<td>89.5</td>
<td>15 m</td>
</tr>
<tr>
<td>Hiraoka M. et al</td>
<td>I</td>
<td>43</td>
<td>100</td>
<td>----</td>
</tr>
<tr>
<td>Nyman J. et al</td>
<td>I-I</td>
<td>45</td>
<td>91</td>
<td>43 m</td>
</tr>
<tr>
<td>Nagata Y. et al</td>
<td>I</td>
<td>45</td>
<td>98</td>
<td>30 m</td>
</tr>
<tr>
<td>Zimmerman FB et al</td>
<td>I</td>
<td>68</td>
<td>94</td>
<td>----</td>
</tr>
<tr>
<td>Timmerman R. et al</td>
<td>I-I</td>
<td>70</td>
<td>95</td>
<td>17.5 m</td>
</tr>
<tr>
<td>Onishi H. et al</td>
<td>I</td>
<td>257</td>
<td>86</td>
<td>38 m</td>
</tr>
<tr>
<td>Bauman P. et al</td>
<td>I</td>
<td>138</td>
<td>88</td>
<td>33 m</td>
</tr>
<tr>
<td>Fukumoto S. et al</td>
<td>I</td>
<td>22</td>
<td>94</td>
<td>24 m</td>
</tr>
<tr>
<td>Xia T. et al</td>
<td>I-I</td>
<td>43</td>
<td>95</td>
<td>27 m</td>
</tr>
</tbody>
</table>
Top 10 Enrolling Centers in 2014

1. Barnabas Health, Toms River, NJ
2. St. John's Radiosurgery Center, Springfield, MO
3. Penrose Cancer Center, Colorado Springs, CO
4. St. Francis Hospital, Memphis, TN
5. Sir Charles Gairdner Hospital, Perth, Australia
6. St. Joseph/Candler, Savannah, GA
7. Mission Hospitals, Asheville, NC
8. Franklin Square Hospital Center, Baltimore, MD
9. Memorial Hospital West, Hollywood, FL
10. Pennsylvania Hospital, Philadelphia, PA
Stereotactic body radiotherapy for early-stage non-small cell lung cancer: clinical outcomes from a National Patient Registry

Joanne N. Davis • Clinton Medbery III • Sanjeev Sharma • David Perry • John Pablo • David J. D’Ambrosio • Heidi McKellar • Frank C. Kimsey • Paul N. Chomiak • Anand Mahadevan

Received: 16 October 2014/Accepted: 18 December 2014/Published online: 31 January 2015
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<table>
<thead>
<tr>
<th>CLINICAL ASSESSMENT</th>
<th>PRETREATMENT EVALUATION</th>
<th>INITIAL TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA (peripheral T1ab, N0)</td>
<td>PFTs (if not previously done)</td>
<td>Operable</td>
</tr>
<tr>
<td></td>
<td>Bronchoscopy (intraoperative preferred)</td>
<td>Operable</td>
</tr>
<tr>
<td></td>
<td>Pathologic mediastinal lymph node evaluation</td>
<td>Negative mediastinal nodes</td>
</tr>
<tr>
<td></td>
<td>FDG PET/CT scan (if not previously done)</td>
<td>Positive mediastinal nodes</td>
</tr>
<tr>
<td>Stage IB (peripheral T2a, N0)</td>
<td>PFTs (if not previously done)</td>
<td>Operable</td>
</tr>
<tr>
<td>Stage I (central T1ab–T2a, N0)</td>
<td>Bronchoscopy</td>
<td>Operable</td>
</tr>
<tr>
<td>Stage II (T1ab–2ab, N1; T2b, N0)</td>
<td>Pathologic mediastinal lymph node evaluation</td>
<td>Negative mediastinal nodes</td>
</tr>
<tr>
<td>Stage IIIB (T3, N0)</td>
<td>FDG PET/CT scan (if not previously done)</td>
<td>Positive mediastinal nodes</td>
</tr>
<tr>
<td>Stage IIIA (T3, N1)</td>
<td>Brain MRI with contrast (Stage II, IIIA)</td>
<td>See Stage IIIA (NSCL-7) or Stage IIIB (NSCL-11)</td>
</tr>
</tbody>
</table>
SABR is recommended for patients who are medically inoperable or who refuse surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and overall survival, comparable to lobectomy and higher than 3D-CRT in nonrandomized and population based comparisons in medically inoperable or older patients.
SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥ 75 years], poor lung function). SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.
A combined analysis of two randomized trials (that individually did not complete accrual) of SABR vs. lobectomy in operable patients found similar cancer-specific outcomes and improved toxicity profile and survival for SABR compared to surgery.

Chang et al Lancet Oncology 2015, 16:630-637
This analysis does **not** provide sufficient data to change the standard of care for good surgical candidates **but** strengthens the indication for SABR in patients with relative contraindications for surgery or who refuse surgery.
## RCT’s of SABR vs surgery

<table>
<thead>
<tr>
<th></th>
<th>ROSEL</th>
<th>STARS</th>
<th>Z4099</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility criteria</td>
<td>Operable non-central stage IA</td>
<td>Operable stage IA, IB (≤ 4 cm)</td>
<td>‘Borderline’ operable, stage I &lt;3cm</td>
</tr>
<tr>
<td>Primary end-point</td>
<td>Local &amp; regional control, QoL treatment costs at 2- and 5-years</td>
<td>OS at 3 years</td>
<td>OS at 3 years</td>
</tr>
<tr>
<td>Secondary end-points</td>
<td>OS, pulmonary functions, QALYs, total costs</td>
<td>DSS at 3 years; toxicities</td>
<td>LRR, DFS, toxicities, pulmonary function</td>
</tr>
<tr>
<td></td>
<td>CLOSED</td>
<td>CLOSED</td>
<td>CLOSED</td>
</tr>
<tr>
<td>Total enrolled</td>
<td>22 (of 920)</td>
<td>36 (of 1030)</td>
<td>10 (of 420)</td>
</tr>
<tr>
<td>Planned RCT’s of SABR vs surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>POSTLIV</strong>&lt;br&gt;(NCT01753414&lt;br&gt;F-M Kong)</td>
<td><strong>VALOR</strong>&lt;br&gt;(D Moghanaki &amp; T Karas)</td>
<td><strong>UK trial</strong>&lt;br&gt;(K Franks)</td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Tumor ≤3 cm, fit for lobectomy or pneumonectomy</td>
<td>Tumor ≤5cm (peripheral and central)</td>
<td>High-risk operable, Tumor ≤5cm, peripheral</td>
</tr>
<tr>
<td>Primary end-point</td>
<td>2-year local-regional control</td>
<td>5-year overall survival</td>
<td>Average recruitment rate of 3 pts/month for a 15 mo period</td>
</tr>
<tr>
<td>Secondary end-points</td>
<td>OS, DFS, site-specific failure, Time to LR failure and DM</td>
<td>QoL, patterns of failure, cause of death</td>
<td>'Limited participation study' Feasibility trial (4 sites)</td>
</tr>
<tr>
<td>Planned enrolment</td>
<td>76 pts</td>
<td>800 pts</td>
<td>54 pts</td>
</tr>
<tr>
<td>Male:Female</td>
<td>487 (61%):314 (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>73 years (range 41-93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1a (&lt;2cm)</td>
<td>233 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1b (2-3cm)</td>
<td>242 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2a (3-5cm)</td>
<td>276 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2b (5-7cm)</td>
<td>50 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SABR 3 x 18 Gy (3 x 20 Gy PB)</td>
<td>284 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SABR 5 x 11 Gy (5 x 12 Gy PB)</td>
<td>341 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SABR 8 x 7.5 Gy</td>
<td>176 (22%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### VUmc Update (n=801; single lesions only)

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological verification</td>
<td>274 (34%)</td>
</tr>
<tr>
<td>No pathological verification</td>
<td>527 (66%)</td>
</tr>
<tr>
<td>(Risk of malignancy of FDG-PET positive new or growing lesion is around 95% in the Dutch population)</td>
<td></td>
</tr>
<tr>
<td>Medically inoperable</td>
<td>590 (74%)</td>
</tr>
<tr>
<td>Refusal/Preference</td>
<td>211 (26%)</td>
</tr>
<tr>
<td>Patient setup &amp; Static fields</td>
<td>458 (57%)</td>
</tr>
<tr>
<td>Tumor setup &amp; RapidArc</td>
<td>343 (43%)</td>
</tr>
</tbody>
</table>
Survival and local failure (n=801)

**Overall survival**
- @2 years 66.3%
- @5 years 34.3%

**Local failure**
- @2 years 4.2%
- @5 years 8.3%
Regional and distant failure (n=801)

**Regional failure**
- @2 years 9.0%
- @5 years 14.7%

**Distant failure**
- @2 years 16.5%
- @5 years 21.1%
## Toxicity

<table>
<thead>
<tr>
<th>Early toxicity</th>
<th>Incidence</th>
<th></th>
<th>Late toxicity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>25%</td>
<td></td>
<td>Rib fracture</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>14%</td>
<td></td>
<td>Chest wall pain</td>
<td>3%</td>
</tr>
<tr>
<td>Chest wall pain</td>
<td>11%</td>
<td></td>
<td>Radiation pneumonitis</td>
<td>2%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10%</td>
<td></td>
<td>Pleural effusion</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin erythema</td>
<td>3%</td>
<td></td>
<td></td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Early toxicity</th>
<th>CTCAE grade</th>
<th></th>
<th>Late toxicity</th>
<th>CTC-AE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>52%</td>
<td></td>
<td>None</td>
<td>77%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>35%</td>
<td></td>
<td>Grade 1</td>
<td>12%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>12%</td>
<td></td>
<td>Grade 2</td>
<td>6%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1%</td>
<td></td>
<td>Grade 3</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 4</td>
<td>1%</td>
</tr>
</tbody>
</table>
Medically inoperable, biopsy proven early stage T1, T2 (< 5 cm) NSCLC patients; clinically node negative by PET, with peripherally located tumors (> 2 cm in all directions around the proximal bronchial tree; see figure below)
Lung SBRT

Rusthoven, JCO, 27, 2009
Clinical Investigation: Thoracic Cancer

Stereotactic Ablative Radiation Therapy for Centrally Located Early Stage or Isolated Parenchymal Recurrences of Non-Small Cell Lung Cancer: How to Fly in a “No Fly Zone”

Joe Y. Chang, MD, PhD,* Qiao-Qiao Li, MD,* Qing-Yong Xu, MD,* Pamela K. Allen, PhD,* Neal Rebueno, CMS,* Daniel R. Gomez, MD,* Peter Balter, PhD,† Ritsuko Komaki, MD,* Reza Mehran, MD,† Stephen G. Swisher, MD,‡ and Jack A. Roth, MD‡

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Received Dec 10, 2013, and in revised form Jan 7, 2014. Accepted for publication Jan 16, 2014.
Stereotactic body radiotherapy for centrally located early-stage non-small cell lung cancer or lung metastases from the RSSearch® patient registry

Joanne N. Davis¹, Clinton Medbery², Sanjeev Sharma³, John Pablo⁴, Frank Kimsey⁵, David Perry⁶, Alexander Muacevic⁷ and Anand Mahadevan⁸*
Clinical Investigation: Thoracic Cancer

Stereotactic Body Radiation Therapy for Re-irradiation of Persistent or Recurrent Non-Small Cell Lung Cancer

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Received Nov 14, 2013, and in revised form Jan 4, 2014. Accepted for publication Jan 8, 2014.
Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Lung Metastases

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ABSTRACT

Purpose
To evaluate the efficacy and tolerability of high-dose stereotactic body radiation therapy (SBRT) for the treatment of patients with one to three lung metastases.

Patients and Methods
Patients with one to three lung metastases with cumulative maximum tumor diameter smaller than 7 cm were enrolled and treated on a multi-institutional phase I/II clinical trial in which they received SBRT delivered in 3 fractions. In phase I, the total dose was safely escalated from 48 to 60 Gy. The phase II dose was 60 Gy. The primary end point was local control. Lesions with at least 6 months of radiographic follow-up were considered assessable for local control. Secondary end points included toxicity and survival.

Results
Thirty-eight patients with 63 lesions were enrolled and treated at three participating institutions. Seventy-one percent had received at least one prior systemic regimen for metastatic disease and 34% had received at least two prior regimens (range, zero to five). Two patients had local recurrence after prior surgical resection. There was no grade 4 toxicity. The incidence of any grade 3 toxicity was 8% (three of 38). Symptomatic pneumonitis occurred in one patient (2.6%). Fifty lesions were assessable for local control. Median follow-up for assessable lesions was 15.4 months (range, 6 to 48 months). The median gross tumor volume was 4.2 mL (range, 0.2 to 52.3 mL). Actuarial local control at one and two years after SBRT was 100% and 96%, respectively. Local progression occurred in one patient, 13 months after SBRT. Median survival was 19 months.

Conclusion
This multi-institutional phase I/II trial demonstrates that high-dose SBRT is safe and effective for the treatment of patients with one to three lung metastases.

J Clin Oncol 27:1579-1584. © 2009 by American Society of Clinical Oncology
Extracranial Oligometastases: A Subset of Metastases Curable With Stereotactic Radiotherapy

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CyberKnife with tumor tracking: an effective treatment for high-risk surgical patients with single peripheral lung metastases

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Standard treatment for operable patients with single peripheral lung metastases is metastasectomy. We report mature CyberKnife outcomes for high-risk surgical patients with biopsy proven single peripheral lung metastases. Twenty-four patients (median age 73 years) with a mean maximum tumor diameter of 2.5 cm (range, 0.8–4.5 cm) were treated over a 6-year period extending from September 2004 to September 2010 and followed for a minimum of 1 year or until death. A mean dose of 52 Gy (range, 45–60 Gy) was delivered to the prescription isodose line in three fractions over a 3–11 day period (mean, 7 days). At a median follow-up of 20 months, the 2-year Kaplan–Meier local control and overall survival rates were 87 and 50%, respectively. CyberKnife with fiducial tracking is an effective treatment for high-risk surgical patients with single small peripheral lung metastases. Trials comparing CyberKnife with metastasectomy for operable patients are necessary to confirm equivalence.

Keywords: lung metastases, CyberKnife, SBRT, metastasectomy
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

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Alexander M. Lesokhin, M.D., Sacha Gnajatic, Ph.D.,
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Review Article

The Confluence of Stereotactic Ablative Radiotherapy and Tumor Immunology

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Received 25 August 2011; Accepted 5 September 2011
**Figure 1: Confluence of SABR and Immunotherapy.** Apoptosis can be initiated by SABR-induced DNA damage and upregulation of the p53 tumor suppressor gene. In addition, apoptosis can be triggered by SABR-induced damage to the cellular lipid membrane, which can induce ceramide formation and activate the SAPK/JNK signaling pathway. Thus, SAPK/JNK can upregulate PKR expression, which can induce MHC and cytokines via NF-κB. SABR can induce cellular expression of MHC Class I, adhesion molecules, costimulatory molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines, and death receptors.
Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

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See accompanying editorial on page 3794
Future Directions

- Comparison of operable patients – Surgery vs SBRT
- Integrating the use of SBRT and systemic therapy in oligometastatic patients
- Improving our understanding of which patients can be salvaged with SBRT after EBRT or SBRT failures