Establishing A Stereotactic Body Radiation Therapy (SBRT) Clinical Program Part II: Clinical and Radiobiological Considerations

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Disclosures
- UVA has a research relationship with Tomotherapy and has been provided with a subsidized research planning cluster and research software and we have grant funding for clinical translational projects including a proposal to develop a STAT-SBRT program.
- I serve on a Helical Tomotherapy Grant Review Committee for industry-sponsored clinical translational trials.

Educational Objectives
- Clinical Questions for developing an SBRT program
- Clinical Trials Process and Design
- Review of Current National Lung SBRT Protocols
- Organ Tolerances
- Development of the UVA SBRT program as a Physician-Physics team approach

Developing an SBRT Program?
Basic Questions to Consider:
- What types of patients do you intend to treat (lung, spine, liver, other)?
- What patient volume do you anticipate?
- How will surgeons be included in your process?
- What equipment do you have and what do you need for simulation, respiratory motion management, immobilization, and treatment delivery?
- How will you standardize the contouring of target volumes and OARs and what constraints on OARS will you use?
- How will all essential personnel be trained?
- Will SBRT be paid for by regional third party payers?
SBRT-capable Treatment Units

Clinical Trials Process: monitoring process

DMSC: Data Monitoring Safety Committee
In the United States oncology clinical trials are monitored by DMSCs whose primary responsibility is to determine if the studies are properly conducted, and to recommend any changes to the treatment protocol.

1) Adverse Events: defined as any sign or symptom that a patient reports, which is not listed in the protocol-specific forms and graded as to severity, and as to whether this was related or unrelated to the treatment.

2) Protocol Violations: defined as non-compliance with the clinical trial specifications and guidelines and generally characterized as minor and major violations.

The DMSC can make recommendations to the PRC to modify the consent form or suspend or discontinue patient accrual to any oncology clinical trial based on:

1) toxicity analysis showing the study has reached protocol specified stopping rule threshold.
2) the discovery of significant unexpected toxicities.
3) repeated protocol violations.

In the United States oncology clinical trials are approved for patient enrollment by at least two independent institutional committees whose main goal is to ensure that trials are as safe as possible and ethically conducted in the best interests of the patients. These committees may have overlap of jurisdiction and oversight depending on institution-specific committee guidelines.

- PRC: Peer Review Committee
  Institutional committee generally consisting of oncologists and statisticians whose primary responsibility is to review and determine the scientific merit, rationale, and statistical design of proposed investigator-initiated and industry-sponsored oncology clinical trials.

- IRB: Institutional Review Committee
  Institutional committee generally consisting of a wide range of health care professionals whose primary responsibility is to review and ensure patient safety and proper informed consent of all oncology clinical trials including national cooperative trials.

* Clinical trials can take months to get through these committees.

Institutional Clinical Trial Organization

Institutional Clinical Trial Organization

PRC  DMSC  IRB

approval  monitoring
**Simplified Clinical Trial Classification**

- **Phase I:** Dose escalation study with dose limiting toxicity criteria that trigger stopping rules to determine the maximally tolerated dose of a study agent. Generally single arm and non-randomized.

- **Phase II:** Efficacy study powered to determine if an investigational treatment meets a specified response in a target-study population. Generally single arm and non-randomized, but not always (example placebo controlled).

- **Phase III:** If the phase II efficacy data meets or exceeds current standard of care efficacy data a phase III randomized study is performed to compare the study treatment with the standard of care treatment to determine which is superior.

Depending on the required follow up period for endpoint determination this process can span well over a decade. To date no phase III randomized SBRT national cooperative trials have been opened.

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**Lung SBRT as a Model for SBRT Clinical Translational Research**

- Clear Rationale for SBRT development from failure of conventionally fractionated dose escalation studies

- Curative treatment of early primary lung cancers

- Tumor motion incorporated into treatment planning and/or delivery

- Existing Phase I and II national cooperative group trials

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**Surgical Outcomes for Operable Early Non-small Cell Lung Cancer**

Surgical resection with lobectomy, the best surgical procedure, results in local control rates of 90%.

However, patients whose lung function is too poor to undergo lobectomy were offered a wedge resection which resulted in reported local control rates of 50-85%.


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**Historical Early Non-small Cell Lung Cancer Radiation Therapy Outcomes for Inoperable Patients**

- Patients with medically inoperable T1-T2N0 lung cancer treated with conventionally fractionated radiation therapy to 60–70 Gy had historical reported local control rates of 30–50%.

- MSKCC and University of Michigan initiated institutional phase I dose escalation studies to 84 and 102.9 Gy respectively to improve local control.

- These studies were followed by RTOG 9311, a multi-institutional phase I/II dose escalation study for inoperable lung cancer patients treated with radiation alone or following induction chemotherapy with a maximum permissible dose of 83.8 Gy while keeping the total volume of lung receiving 20 Gy < 25%.

- Despite dose escalation, the 2-year loco-regional control rate for the group that received 83.8 Gy was only 55%.

Why did these studies fail to significantly improve local control for these patients?

In separate reported analysis, Mehta and Machtay, reported that prolongation of the treatment time in lung cancer resulted in poorer survival. With prolongation beyond 5-6 weeks patients lose 1-2% survival per day thought to be secondary to clonagen repopulation.


Phase I dose escalation early NSCL SBRT trial: University of Indiana

- 47 patients were stratified into 3 groups based on tumor size (<3 cm, 3-5 cm, 5-7 cm).
- Dose escalation in cohorts of 3 patients with all patients receiving 3 fractions of 3D conformal radiation and starting at 8 Gy per fraction.
- The maximal tolerated dose was not reached for the 2 smaller tumor subgroups despite treating to 60-66 Gy and was 66 Gy for the largest tumor subgroup.
- The reported 2-year local control rate for patients treated with 18-24 Gy x 3 fractions was 90%.


Dose Response Curve


Phase II early NSCL SBRT trial: University of Indiana

- 70 patients stratified for size with patients with smaller tumors, 5 cm or less treated with 60 Gy/3 fractions and larger tumors treated with 66 Gy/3 fractions (n=35 for each stratification).
- The actual 2-year local control rate was 95% with a 56% overall survival with death mostly from comorbid illness.
- Dose limiting toxicity (grade 3) was reported to be 11 times greater for patients treated with central tumors compared to peripheral tumors.

Summary of Three Recent/Current RTOG Lung SBRT Trials

- **RTOG 0236** phase II closed n = 52
- **RTOG 0618** phase II open n = 33
- **RTOG 0813** phase I/II open n = 94

**RTOG 0236**
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

- Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 medically inoperable non-small cell lung cancer; patients with T3 tumors chest wall primary tumors only; no patients with tumors of any T-stage in the zone of the proximal bronchial tree.
- Treatment: Stereotactic Body Radiation Therapy (SBRT), 20 Gy per fraction for 3 fractions over 1½ to 2 weeks, for a total of 60 Gy.
- Multi-institutional national trial to determine if the excellent institutional phase II trial local control data could be reproduced in a multi-institutional trial setting.

**RTOG 0618**
A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer

- Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 medically inoperable non-small cell lung cancer; patients with T3 tumors chest wall primary tumors only; no patients with tumors of any T-stage in the zone of the proximal bronchial tree.
- Treatment: Stereotactic Body Radiation Therapy (SBRT), 20 Gy per fraction for 3 fractions over 1½ to 2 weeks, for a total of 60 Gy.
- Similar eligibility and treatment as RTOG 0236 except for operable patients and post-radiation adjuvant chemotherapy is recommended for patients with T2 tumors > 4 cm and all T3 tumors.
- This trial would potentially provide preliminary data for a phase III trial comparing surgical resection vs. lung SBRT.

**RTOG 0813**
PHASE I/II STUDY OF STEREOTACTIC LUNG RADIOTHERAPY (SBRT) FOR EARLY STAGE, CENTRALLY LOCATED, NON-SMALL CELL LUNG CANCER (NSCLC) IN MEDICALLY INOPERABLE PATIENTS

- Patients with stage T1-2N0M0, non-small cell lung cancer, tumor size ≤ 5 cm, who are not candidates for a complete surgical resection in the opinion of a thoracic surgeon; only patients with tumors within or touching the zone of the proximal bronchial tree or adjacent to mediastinal or pericardial pleura.
- This study will determine the maximally tolerated dose and efficacy of SBRT for centrally located tumors.
Japanese Lung SBRT experience

- Uematsu reported a 94% 3-year local control rate for patients treated with 50-60 Gy in 5-6 fractions.
- Nagata reported a 98% local control rate at 30 months for patients treated with 48 Gy in 4 fractions.
- Onishi reported a retrospective study involving 245 patients treated at 13 institutions with a 92% 2-year median local control rate for patients treated to a biologic effective dose of at least 100 Gy.


JCOG 0403

- Single arm phase II study for patients with stage 1A lung cancer
- Primary endpoint is 3-year overall survival
- Study will stratify patients based on medically operable (n=65) and medically inoperable (n=100)
- Treatment is 48 Gy/4 fractions prescribed to the isocenter.

OAR Dose Tolerances for RTOG 0236 and 0618

<table>
<thead>
<tr>
<th>OAR</th>
<th>RTOG 0236</th>
<th>RTOG 0618</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>54 Gy</td>
<td>40 Gy</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>30 Gy</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>24 Gy</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Kidneys</td>
<td>30 Gy</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Stomach</td>
<td>35 Gy</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>45 Gy</td>
<td>45 Gy</td>
</tr>
</tbody>
</table>

Summary of reported local control rates for early lung cancer patients treated with SBRT (80-95%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Local Control Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uematsu</td>
<td>1A</td>
<td>94%</td>
</tr>
<tr>
<td>Nagata</td>
<td>1A</td>
<td>98%</td>
</tr>
<tr>
<td>Onishi</td>
<td>1A</td>
<td>92%</td>
</tr>
</tbody>
</table>

Timmerman’s Lung SBRT Conclusions

1. The maximal tolerated dose for peripheral primary tumors less than 7 cm is 60 to 66 Gy in three fractions.
2. The maximal tolerated dose for centrally located primary tumors less than 7 cm is unknown but is exceeded by doses of 60 to 66 Gy in three fractions.
3. A prescription dose less than 54 Gy in three fractions is associated with maximal local control of approximately 70% to 80% for patients treated in prospective trials with adequate follow-up in North America and Europe.
4. A prescription dose of 54 Gy or more in three fractions has been demonstrated to achieve local control in more than 90% of treated tumors in prospective testing.
5. Despite clinical staging, isolated hilar and mediastinal nodal failures occur in less than 5% of patients after SBRT.
6. Despite staging with whole body PET scans, approximately 20% of patients develop distant metastatic disease.
7. Although it is well-accepted that toxicity after large dose per fraction treatment occurs late, it is also recognized that tumor recurrence frequently occurs late after treatment with the median time to recurrence of 16 to 24 months after therapy.
8. Despite excellent local control after SBRT, patient survival for medically inoperable early-stage lung cancer is very poor, mainly due to severe and life-threatening coexisting morbidities and the eventual appearance of metastatic disease.

Literature Review of SBRT Related Chest Wall Toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Number Patients</th>
<th>Dose</th>
<th>Fractionation</th>
<th>Chest Wall Pain</th>
<th>Rib Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norihisa et al.</td>
<td>34</td>
<td>48-60 Gy</td>
<td>3-5</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Zimmermann et al.</td>
<td>68</td>
<td>37.5 Gy</td>
<td>3-5</td>
<td>N/A</td>
<td>3%</td>
</tr>
<tr>
<td>Fritz et al.</td>
<td>40</td>
<td>30 Gy</td>
<td>1</td>
<td>N/A</td>
<td>5%</td>
</tr>
<tr>
<td>Princess Margaret</td>
<td>76</td>
<td>48-60 Gy</td>
<td>3-5</td>
<td>23%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Unexpected Lung Toxicity: UVA Patient with IPF treated with lung SBRT

How do we account for organ function in our dose tolerance constraints? Are DVH and maximum point doses constraints adequate?

Lung Motion Determination Using Dynamic MRI: Pilot Study to test the reproducibility of breathing


Results: 3D Displacement with hyperpolarized gas grid tagging

Given lung motion we really don’t have an accurately determined lung DVH

Additional Excellent References to aid in starting an SBRT program

Liver SBRT Phase I/II Trials

Normal Organ Tolerances for 1,3,5 fraction SBRT from Univ. of Texas Southwestern

Spinal Radiosurgery
UVA SBRT Development

- Developed as a clinical translational research program with close physician–physicist collaboration with institutional grant funding
- Goal was to build a Helical TomoTherapy-based SBRT program as our other 2 linacs were over 10 years old.
- We acquired the 12th clinical Helical TomoTherapy Unit
- We had a single slice CT simulator and a fluoroscopic simulator.
- Basic Dosimetric feasibility studies began in 2004
- First patient was treated in 2/2005

Motion Phantom to determine how motion effects the dose distribution

- Designed by Ke Sheng, Ph.D. and fabricated at UVA
- Programmable step motor allows for computer driven lung motion profiles

Lung Phantom SBRT Dosimetry

- Designed by Ke Sheng, Ph.D. and fabricated at UVA
- Programmable step motor allows for computer driven lung motion profiles

Effect of Respiratory Amplitude and Periodicity on PTV Coverage

- Designed by Ke Sheng, Ph.D. and fabricated at UVA
- Programmable step motor allows for computer driven lung motion profiles
Dosimetric study to determine the HT maximal permissible lung SBRT PTV dose

- Dosimetric Criteria of RTOG 0236
  - Heart, Trachea, Ipsilateral Bronchus: max pt dose 30 Gy
  - Esophagus: max pt dose 27 Gy
  - Brachial Plexus: max pt dose 24 Gy
  - Spinal Cord: max point dose 18 Gy
  - No deviation V20 Gy less than 10% of lung
  - Minor deviation V20 Gy less than 15% of lung
  - Different Lung Volumes used
    - Volumes of 2000-5000 cc used
    - GTVs from 1-6 cm with 5 mm radial and 1 cm craniocaudal expansions for the PTV

Maximal permissible dose to meet RTOG 0236 Criteria: V20 Gy to < 10% lung

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>PTV Vol (cc)</th>
<th>GTV Size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>5000</td>
<td>4</td>
</tr>
<tr>
<td>45</td>
<td>4500</td>
<td>4</td>
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<tr>
<td>25</td>
<td>2500</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>2000</td>
<td>4</td>
</tr>
</tbody>
</table>

Regression analysis and equations to determine the maximal permissible HT lung SBRT PTV dose for initial treatment planning

- Regression equation for V20 < 15% of lung:
  \[
  \text{Dose} = 0.0056 \times \text{Lung Vol} - 0.094 \times \text{PTV} + 46
  \]
  For V20 < 15% of lung

- Regression equation for V20 < 10% of lung:
  \[
  \text{Dose} = 0.0025 \times \text{Lung Vol} - 0.024 \times \text{PTV} + 56
  \]
  For V20 < 10% of lung

Regression analysis and equations to determine the maximal permissible HT liver SBRT PTV dose


Dynamic MRI and dynamic MRI data rebinned and resorted as a 4DCT simulation

Correlation between the respiratory variability and the error in tumor ITA (ITV) determined from the simulated 4DCT

Real Time Adaptive SBRT treatment planning and delivery
Proposed New Work Flow and Patient Care

STAT SBRT and Linac-based SBRT

Proposed Work Flow

Existing Work Flow

Dose volume histogram (DVH) comparison between STAT RT and TomoHelical for a SBRT of a typical liver lesion (3 iterations)

Representative isodose plans for treating a 23 cc liver lesion PTV with TomoHelical and StatRT.
Dose volume histogram (DVH) comparison between STAT RT and TomoHelical for SBRT of a peripheral lung lesion (3 iterations)

Special Thanks

- Dr. Ke-Sheng PhD
- Dr. James Larner MD
- Dr. Stanley Benedict PhD
- Dr. Jing Cai, PhD
- Dr. Alyson McIntosh, MD
- Dr. Neal Dunlap, MD
- Dr. Neal Shoup, MD
- Dr. Brian Kavanaugh
- Tomotherapy Collaborators
- UVA Cancer Center