The role of particle beam therapy in the management of non-small cell lung cancer

Ramesh Rengan, M.D. Ph.D.
Professor, Department of Radiation Oncology
University of Washington School of Medicine
Associate Member, Clinical Research Division
Fred Hutchinson Cancer Research Center
Medical Director, SCCA Proton Therapy
1959 NE Pacific Street
Seattle, WA 98195-6043
206-598-4100 office
rengan@uw.edu

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Disclosures

- Medical director SCCA proton therapy center
- IBA, travel expenses
- Astra-Zeneca Immuno Oncology, Consultant
Local control in locally advanced NSCLC is poor
Le Chevalier evaluated tumor control with bronchoscopic biopsies in NSCLC patients treated to 65 Gy:
- 20% local control at three months
- 17% local control at one year

Does Local Control Matter in NSCLC?
Local Control and Overall Survival in LA-NSCLC

- Phase III Trial of dose-intensified (54Gy in 1.8TID over 12 consecutive days) vs conventionally fractionated (60Gy in 30 daily fractions) radiotherapy alone in locally advanced NSCLC
  - 2-year local control improved from 15 to 23%
  - 2-year survival improved from 20 to 29%

What are the barriers to dose escalation in locally advanced NSCLC?
Treatment Intensification

- Tumor control versus Toxicity

Probabilities and Dose of Radiation

Treatment Intensification in NSCLC: Considerations

- NSCLC is relatively radioresistant
- Surrounding critical organs are relatively radiosensitive
- Uninvolved lung is often dysfunctional \textit{a priori} due to comorbid disease
Local Control: The Role of Dose Escalation

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

We may have reached a therapeutic plateau for treatment intensification in locally advanced disease (More RT- 0617; Induction chemo-CALGB 39801; Consolidation chemo- HOG; Surgery- INT-0139)

Introduction: Therapeutic Index

Tumor Control

Toxicity

Treatment Intensity

PROBABILITY

Multivariate Cox Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Dead/Total</th>
<th>Dead/Total</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Level</td>
<td>Standard Dose (RL) vs. High Dose</td>
<td>141/286</td>
<td>126/1392</td>
<td>1.23 (1.04, 1.47)</td>
<td>0.0247</td>
</tr>
<tr>
<td></td>
<td>Maximum grade &gt; 3 (RL) vs. esophagitis/dysphagia grade</td>
<td>210/349</td>
<td>47/58</td>
<td>1.54 (1.11, 2.15)</td>
<td>0.0102</td>
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<tr>
<td>Volumen of PTV</td>
<td>Continuous</td>
<td>257/407</td>
<td>1,000 (1,000, 1,003)</td>
<td>0.0759</td>
<td></td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>257/407</td>
<td>1,000 (1,000, 1,003)</td>
<td>0.0759</td>
<td></td>
</tr>
<tr>
<td>Zifedal PM</td>
<td>0 (RL) vs. 1</td>
<td>156/240</td>
<td>106/167</td>
<td>1.14 (0.89, 1.47)</td>
<td>0.3045</td>
</tr>
<tr>
<td>PET Staging</td>
<td>No (RL) vs. Yes</td>
<td>156/240</td>
<td>106/167</td>
<td>0.77 (0.52, 1.13)</td>
<td>0.1766</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (RL) vs. Female</td>
<td>156/240</td>
<td>106/167</td>
<td>0.97 (0.74, 1.25)</td>
<td>0.7975</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-Squamous (RL) vs. Squamous</td>
<td>156/240</td>
<td>106/167</td>
<td>1.10 (0.78, 1.53)</td>
<td>0.3300</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Non-smoker/former light smoker vs. (RL) vs. Former heavy/current smoker vs. Unknown</td>
<td>206/328</td>
<td>12/19</td>
<td>1.14 (0.80, 1.63)</td>
<td>0.4617</td>
</tr>
</tbody>
</table>

RL = reference level, HR = hazard ratio, CI = confidence interval
*Two-sided log-rank p-value
17 patients are missing dose-volume and/or smoking history information and are excluded from this model
Therapeutic Index: Protons

Tumor control

Widening of the Therapeutic Ratio

Proton Beam

Toxicity

PROBABILITY

DOSE OF RADIATION

The Physics of Protons

Depth dose curves for protons and photons.

10 MeV photons

Additional Dose outside the target delivered with Photons

Proton “Spread Out Bragg Peak”
The Physics of Protons

IMRT

Comparative plans of adjuvant mediastinal radiation


Clinical Data to Date with Protons: NSCLC

- 44 patients with Stage III NSCLC treated to 74Gy with concurrent chemotherapy
- Median survival of 29.4 months
- Median survival in 0617 for 74Gy arm was 19.5 months
- Median survival in 0617 for 60Gy arm was 28.7 months

Phase II Study of High-Dose Proton Therapy With Concurrent Chemotherapy for Unresectable Stage III Nonsmall Cell Lung Cancer

Survival Rate (%)

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Patients at Risk</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>213</td>
<td>90</td>
<td>206</td>
</tr>
</tbody>
</table>

HR = 1.56 (1.19, 2.06) p = 0.0007
A Bayesian Randomization Trial of Intensity Modulated Radiation Therapy (IMRT) vs. 3-Dimensional Passively Scattered Proton Therapy (3DPT) for Locally Advanced Non-Small Cell Lung Carcinoma

(clinicaltrials.gov identifier NCT00915005)


Supported in part by NCI grants P01 CA021230 and U19 CA021239.

Hypothesis

Proton therapy will

– Reduce irradiated lung volume, hence reduce radiation pneumonitis (RP)
– Achieve same local control (LC) with same biological effective radiation dose (Proton relative biological equivalence=1.1)
Primary Objective

Protocol Failure (Dual endpoints):

- RP grade ≥ 3 (CTCAE 3.0)
  - IMRT = 15%
  - 3DPT = 5%

- Local failure (PET, CT, biopsy):
  - IMRT = 3DPT
  - 15% 6mo, 25% 12mo.

Randomization Schema

Peer reviewed contours and plans
Endpoint evaluation:
- Internal Outcomes Review Committee
- External Expert Review Committee – reviewed all RPs
Lung, Esophagus and Heart Mean Dose

Note: Analysis carried out using the Wilcoxon rank-sum test (also known as Mann-Whitney Two Sample Statistic)

Protocol Failure - Randomized and Treated According to Protocol

Protocol Failure (Dual endpoints):
- RP grade ≥ 3 (CTCAE 3.0)
- IMRT = 15% vs. 6.5%
- 3DPT = 5% vs. 10.5%

Local Failure at 12 month (PET, CT, biopsy):
- IMRT = 3DPT = 25% vs. 10.7%
Interpretations

- This phase II trial as designed suggests no difference in local control or high grade TRP with protons vs photons in unselected stage II to IIIB NSCLC
- 19 patients denied protons due to insurance
  - 57 of the 76 patients randomized to protons received this modality
- 26/92 (21%) patients for whom IMRT were the only acceptable plan
- 13/57 (23%) patients for whom protons were the only acceptable plan
- Clear learning curve with protons
  - Patients enrolled after the midpoint of enrollment did not experience ANY grade 3 or higher RT (all in the early group)
  - No such difference observed with IMRT
- Perhaps a “one size” approach is not appropriate in NSCLC

RTOG 1308

RTOG 1308
Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC

**SCHEMA**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Randomize</th>
<th>Arm 1: Photon dose—70 Gy*(RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. II</td>
<td></td>
<td>Both Arms: Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***</td>
</tr>
<tr>
<td>2. IIIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. IIIB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Arm 2: Photon dose—70 Gy (RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td></td>
</tr>
<tr>
<td>Non-Squamous</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Concurrent Chemotherapy Doublet Type</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>1. Carboplatin/paclitaxel</td>
<td></td>
</tr>
<tr>
<td>2. Carboplatin/etoposide</td>
<td></td>
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</tbody>
</table>
Does moving from 60 to 70+Gy translate into improved local control?

**Local Control: The Role of Dose Escalation**

- **Standard (60 Gy)**: 65 Fail, 213 Total
- **High dose (74 Gy)**: 81 Fail, 206 Total

**HR=1.37 (0.99, 1.89)**

**P=NS**
PBS for a moving target

PBS for a moving target: phantom data
Can toxicity mitigation alone without an improvement in local control translate into improve overall survival?
The value of toxicity mitigation

1. 151 patients with metastatic lung cancer randomized to standard oncologic care or early palliative care, focused on symptom control and psychosocial support for patients and families, together with standard oncologic care.

2. Among patients with metastatic non–small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood.

3. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival.

4. Expanded enthusiasm for supportive oncology

Can we be smarter with how we deliver our proton beam?
Plan Comparison:

QA-CT (at 25\textsuperscript{th} fx) and planning CT for the patient receiving 60 Gy (RBE) in 30 fx.

SPECT/CT for Functional Lung Definition

Patient 1  Patient 2  Patient 3

\textsuperscript{99m}Tc\textsubscript{MAA} Perfusion SPECT/CT
\textsuperscript{99m}Tc\textsubscript{DTPA} Ventilation SPECT/CT

Functional Avoidance Regions

Courtesy of Stephen Bowen, PhD
Response Adaptive Dose Escalation

Non-responder
- 10% decrease in $SUV_{\text{max}}$
- Escalate dose to 74 Gy
- ~40% Stage III NSCLC

Responserd
- 60% decrease in $SUV_{\text{max}}$
- Standard dose to 60 Gy
- ~60% Stage III NSCLC

FLARE RT Phase I/II Trial
PI: Zeng

<table>
<thead>
<tr>
<th>FLARE RT Phase I/II Trial</th>
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<tbody>
<tr>
<td><strong>Patients:</strong> IIB-IIIB NSCLC Eligible for Definitive RT</td>
</tr>
<tr>
<td><strong>Pre RT:</strong> Cancer Imaging + Functional Imaging</td>
</tr>
<tr>
<td><strong>Week 1 RT</strong></td>
</tr>
<tr>
<td><strong>Week 2 RT</strong></td>
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<tr>
<td><strong>Week 3 RT:</strong> Cancer Imaging + Functional Imaging</td>
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<tr>
<td><strong>Week 4 RT</strong></td>
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<tr>
<td><strong>Week 5 RT</strong></td>
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<td><strong>Week 6 RT</strong></td>
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<td><strong>Week 7 RT</strong></td>
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<tr>
<td><strong>Week 8 RT</strong></td>
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<td><strong>Week 9 RT</strong></td>
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<tr>
<td><strong>Responder:</strong> Functional Avoidance RT 60 Gy total in 30 fx</td>
</tr>
<tr>
<td><strong>Non-responder:</strong> FLARE-RT FDG PET-guided dose escalation to 74 Gy total in 30 fx</td>
</tr>
</tbody>
</table>

- All patients get advanced imaging based high-precision RT → potential quality of life benefit
- Only high local failure risk patients get FDG PET-guided dose escalation → potential survival benefit

PI: Zeng
What is the next frontier with particle beam therapy?

- Emerging preclinical data that RBE under the Bragg peak may be greater than 1.1
- What is the clinical consequence of this phenomenon?
- Can we use this to our advantage?
Proton Therapy Plan

\textit{(physical dose)}

![Proton Therapy Plan Image]

Courtesy Rui Zhang (LSU)

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RBE-Weighted Dose

\textit{(low dose $\text{RBE}_{\text{SF}}$)}

![RBE-Weighted Dose Image]

Courtesy Rui Zhang (LSU)
Local Control: The Role of Dose Escalation

- **Local Progression Rate (%):**
  - Months since Randomization: 0 3 6 9 12 15 18
  - Patients at Risk:
    - Standard (60 Gy): 213
    - High dose (74 Gy): 206
  - Fail: 65
  - Total: 213
  - HR=1.37 (0.99, 1.89)
  - P=NS

- **Local Control:**
  - Standard (60 Gy): 18-Month Local Progression Rate: 25.1%
  - High dose (74 Gy): 34.3%
  - P=NS

Experimental Small Animal Proton Beam

- **Precision Image-Guided Radiation Platform**
  - PI: Eric Ford, George Sandison, Nina Mayr

- **Models and Images:**
  - CT Planning and Image-Guided Proton Delivery
  - Proton-Activated PET Imaging
What are new clinical paradigms that we should consider with protons in NSCLC?

“In the field of surgical (radiation) oncology tumor biology is king, patient selection is queen, and technical maneuvers are the prince and princess who try, but usually fail, to usurp the throne.” B Cady Archives of Surgery 1997
The risk of “one size fits all”

- 4/8/07: New diagnosis of NSCLC. Undergoes bronchoscopy for debulking and mediastinal staging and diagnostic thoracentesis
- 4/18/07 Seen in RadOnc by me. Undergoes PET/CT
  - 4.5 x 3.8 intensely FDG-avid mediastinal nodal conglomerate
  - RLL primary tumor; small non-FDG avid nodules in RML
  - Simulated for RT to encompass mediastinal nodes and RLL tumor
- 4/22/07 Presents to ED with hemoptysis. Repeat bronch shows complete recurrence of right BI tumor
- 4/23 started RT to mediastinal conglomerate and dominant RLL mass

Post-RT CT of Chest rt change only- no residual disease

NED 12/11/17

Dose received: 250 x 14 (3500cGy) from 4/23-5/11 2007

Bio-adaptive Particle Therapy

TME IMAGING
FDG-PET
CHEMORT TO 45Gy
TME IMAGING (F-MISO)
STANDARD DOSE CHEMORT
FAVORABLE FDG RESPONSE
3 MO
FAVORABLE TME RESPONSE
SURGERY?
CHEMO/HIGH LET RT?
3 MO
UNFAVORABLE TME RESPONSE
PROTON DOSE ESCALATION
3 MO
UNFAVORABLE FDG RESPONSE
Conclusions

- Particle beam therapy is potentially a powerful tool for improving the therapeutic ratio for subsets of patients with NSCLC
- Clinical data to date suggests that protons can provide control of disease and deliver effective doses with acceptable toxicity for these patients
- Prospective trials are underway to further evaluate the true value of particle beam radiotherapy in this clinical setting

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