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

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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

Klopp et al IJROBP 2008

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

- NSCLC is relatively radioresistant
- Surrounding critical organs are relatively radiosensitive
- Uninvolved lung is often dysfunctional *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)

PROBABILITY

Tumor Control

Toxicity

Treatment Intensity

Tumor Control

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)

Treatment Intensification (more RT; more chemo; more surgery)

Multivariate Cox Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Dead/Total Group 1</th>
<th>Dead/Total Group 2</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>151/206</td>
<td>156/192</td>
<td>1.54 (1.01, 2.35)</td>
<td>0.0442</td>
</tr>
<tr>
<td>Maximum related esophagitis/dysphagia grade</td>
<td>Maximum grade ≥ 3 (RL) vs. esophagitis/dysphagia grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of PTV</td>
<td>Continuous</td>
<td>257/407</td>
<td>1.000 (1.000, 1.000)</td>
<td>0.7579</td>
<td></td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>257/407</td>
<td>1.002 (1.000, 1.004)</td>
<td>0.0035</td>
<td></td>
</tr>
<tr>
<td>PET Staging</td>
<td>No (RL) vs. Yes</td>
<td>30/39</td>
<td>227/368</td>
<td>0.70 (0.52, 1.13)</td>
<td>0.1766</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (RL) vs. Female</td>
<td>153/240</td>
<td>164/167</td>
<td>0.97 (0.74, 1.26)</td>
<td>0.7975</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-Squamous (RL) vs. Squamous</td>
<td>167/258</td>
<td>111/175</td>
<td>1.10 (0.86, 1.39)</td>
<td>0.3900</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Non-smoker/former light smoker (RL) vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Former heavy/current smoker vs. Unknown</td>
<td>256/328</td>
<td>1.14 (0.80, 1.63)</td>
<td>0.4617</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>12/19</td>
<td>1.44 (0.74, 2.80)</td>
<td>0.2776</td>
<td></td>
</tr>
</tbody>
</table>

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

- Tumor control
- Toxicity

Widening of the Therapeutic Ratio
Proton Beam

DOSE OF RADIATION

PROBABILITY

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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”
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
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.

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Randomization Schema

**Eligible Stage II-IIIb, IV NSCLC patients; Informed consent:**

- **4D simulation:** Delineation of targets and normal tissues

  - Yes

    - 74 CGE proton & photon plans achievable

  - No

    - 66 CGE proton & photon plans achievable

- **Randomize at achieved dose level**

  - **Insurance**
    - OK
      - Protons (Group 2)
      - Photons (Group 1)
    - Denied
      - Photons (group 4)

- **Modality that allows higher dose**

  - Defend

**Peer reviewed contours and plans**

**Endpoint evaluation:**

- Internal Outcomes Review Committee
- External Expert Review Committee – reviewed all RPs

**During treatment**

- Weekly CT images
- Re-planning if indicated
- MDASI - Lung (optional)
- Blood samples (optional)

**Follow-up**

- Monthly tox. Assessment
- Tests on each follow-up visit
Lung, Esophagus and Heart Mean Dose

![Box plot showing mean dose comparison between IMRT and 3DPT](image)

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

<table>
<thead>
<tr>
<th>Protocol Failure</th>
<th>Grade ≥3 TRP</th>
<th>Local Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph showing protocol failure comparison" /></td>
<td><img src="image" alt="Graph showing grade ≥3 TRP comparison" /></td>
<td><img src="image" alt="Graph showing local failure comparison" /></td>
</tr>
</tbody>
</table>

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>Histology</th>
<th>Concurrent Chemotherapy Doublet Type</th>
<th>Arm 1: Photon dose—70 Gy*(RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**</th>
<th>Arm 2: Proton dose—70 Gy (RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**</th>
<th>Both Arms: Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Squamous</td>
<td>Carboplatin/paclitaxel</td>
<td>Randomize</td>
<td>Randomize</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Non-Squamous</td>
<td>Carboplatin/paclitaxel</td>
<td>Randomize</td>
<td>Randomize</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>Carboplatin/paclitaxel</td>
<td>Randomize</td>
<td>Randomize</td>
<td></td>
</tr>
</tbody>
</table>
Does moving from 60 to 70+Gy translate into improved local control?

Local Control: The Role of Dose Escalation

- Standard (60 Gy) vs. High dose (74 Gy)
- Local Progression Rate (%)
- Months since Randomization
- Patients at Risk
- Months: 0, 3, 6, 9, 12, 15, 18
- Fail: 65, 81
- Total: 213, 206
- HR = 1.37 (0.99, 1.89)
- P = NS
- Standard: 213, 205, 187, 165, 137, 113, 85
- High dose: 206, 197, 170, 134, 105, 80, 62
PBS for a moving target

PBS for a moving target: phantom data
Dose Profile

Stationary

Red: measured
Green: planned

Tumor size: 430 cc
Tumor motion (estimated by 4DCT): ~ 15 mm

Max hot (%) Max cold (%) Gamma passing rate (3mm/3%)

<table>
<thead>
<tr>
<th></th>
<th>Stationary</th>
<th>Motion (15mm)</th>
<th>Motion+10 layer repainting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max hot (%)</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Max cold (%)</td>
<td>-2%</td>
<td>-17%</td>
<td>-5%</td>
</tr>
<tr>
<td>Gamma passing rate</td>
<td>98.3%</td>
<td>81.1%</td>
<td>92.3%</td>
</tr>
</tbody>
</table>

Can toxicity mitigation alone without an improvement in local control translate into improve overall survival?
The value of toxicity mitigation

- 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.

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

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

- Expanded enthusiasm for supportive oncology

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

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

SPECT/CT for Functional Lung Definition

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>[99mTc]MAA Perfusion SPECT/CT</td>
<td>[99mTc]DTPA Ventilation SPECT/CT</td>
<td>Functional Avoidance Regions</td>
</tr>
</tbody>
</table>

Courtesy of Stephen Bowen, PhD
Response Adaptive Dose Escalation

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

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

FLARE RT Phase I/II Trial

- 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?

RBE under the Bragg Peak

- 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

(physical dose)

Courtesy Rui Zhang (LSU)

RBE-Weighted Dose

(low dose RBE_{SF})

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

Local Progression Rate (%)

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Standard (60 Gy)</th>
<th>High dose (74 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>213</td>
<td>206</td>
</tr>
<tr>
<td>6</td>
<td>205</td>
<td>197</td>
</tr>
<tr>
<td>9</td>
<td>187</td>
<td>170</td>
</tr>
<tr>
<td>12</td>
<td>165</td>
<td>134</td>
</tr>
<tr>
<td>15</td>
<td>137</td>
<td>105</td>
</tr>
<tr>
<td>18</td>
<td>113</td>
<td>80</td>
</tr>
<tr>
<td>21</td>
<td>85</td>
<td>62</td>
</tr>
</tbody>
</table>

HR=1.37 (0.99, 1.89)
P=NS

MDACC Proton Trial 20.1%

Experimental Small Animal Proton Beam

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

Model of Ring-Shaped Dose Distribution
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
  - 4/23/07 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 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

- STANDARD DOSE CHEMORT
  - FAVORABLE FDG RESPONSE
  - UNFAVORABLE FDG RESPONSE
  - 3 MO

- PROTON DOSE ESCALATION
  - FAVORABLE TME RESPONSE
  - UNFAVORABLE TME RESPONSE
  - SURGERY?
    - CHEMO/HIGH LET RT?
    - 3 MO
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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