Prospective Randomized Trials of Photon vs Proton in LA-NSCLC

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Shanghai, China
Association of OS and GTV, heart, and lung dose

Liao and Tucker, ASTRO, 2012
Impact of New Technologies: 3D CT & 3D CRT (318 pts) vs. 4D CT & IMRT (91 pts) for NSCLC

Freedom from $\geq$ Grade 3 Pneumonitis

Overall Survival (Local Control Similar)

IMRT as an advanced radiation delivery technology reduced dose and volume of the normal lung to radiation, decreased RP, and improved OS.

Why Protons?

• Have
  – Lower entrance dose
  – A finite range and a sharp falloff

• They stop
A Bayesian Randomized Trial of Image-Guided Adaptive Conformal Photon vs Proton Therapy, with Concurrent Chemotherapy, for Locally Advanced Non-Small Cell Lung Carcinoma: Treatment Related Pneumonitis and Locoregional Recurrence (clinicaltrials.gov identifier NCT00915005)

Protocol PI: Zhongxing Liao, M.D.
PI: MGH-N. Choi
Funded by NCI PO1 grant
PO1 PI: Thomas Delaney, CO-PI: Radhe Mohan
Hypothesis and Primary Objective

Hypothesis:
Proton therapy will reduce grade 3 TRP Equivalent LC

Primary objectives
Assess and compare the incidence and time to
- CTCAE v3.0 grade ≥ 3 TRP
- Local failure

Trial Design:
Adaptive randomization was used so that more patients can be offered the treatment that is found to be more effective.
Secondary Objectives

- Grade 3 Esophagitis
- MDASI
- OS, PFS
- Blood biomarkers
- Images studies – PET, weekly CT

Figure 1. Timeline of blood sample collection and image studies. RT, radiotherapy; FDG-PET, positron emission tomography scan; F/U, follow-up after completion of therapy.
Protocol 2008-1033, clinicaltrials.gov identifier NCT00915005

Study Flow Diagram

All treatments are with concurrent chemo

- Eligible Stage II IIB NSCLC patients; Informed consent
- 4D simulation; * Delineation of targets and normal tissues
- 74 CGE proton & photon plans achievable
- 66 CGE proton & photon plans achievable
- Randomize at achieved dose level
- Photons (Group 1)
- Protons (Group 2)
- During treatment
  • Weekly CT images
  • Re-planning if indicated
  • MDASI - Lung (optional)
  • Blood samples (optional)
- Follow-up (see table)
  • Monthly tox. Assessment
  • Tests on each follow-up visit
- *IMRT or 3D CRT

Insurance
- OK
- Denied

Modality that allows higher dose (Group 3)

Photons @ highest dose achievable (Group 4)
Accumulated patient enrolled and randomized in MDACC & MGH for 2008-0133

Number of patients

Randomization rate (%)

Number of patients

Enrolled

Randomized

Randomization rate (%)

Basic info on patients

- **Age (year):** 40-85
- **Gender:** M:59.4%, F:40.6%
- **Race:** White, 87%; other; 23%
- **Smoking:** ever 91.7%
- **ECOG:** ECOG 0, 32%
  ECOG 1, 68%
- **Histology:** SCC, 32%, Non SCC, 68%
- **Stage:** N2, 58%, N3, 22%, Stage IIIA/B, 78%
- **GTV (cc):** median: 85.8 (1.9-686.6)
- **Radiation dose:** 74 CGE: 83.7%
PSPT reduced Heart Dose

Both arms are doing better than expected
IMRT vs. PSPT – Lung V5

Moving Average of V5

Average V5 (%) vs. No. of patients

- IMRT V5
- PSPT V5
- 10 per. Mov. Avg. (IMRT V5)
- 10 per. Mov. Avg. (PSPT V5)
Overall Toxicity

Yearly Quarters from 2009 to 2014
Overall Lung and Esophagus Toxicities

Lung Toxicities

Esophagitis

Yearly Quarters from 2009 - 2014
Proton beam is sensitive to density change during radiation
Adaptive Planning during treatment
IMRT: 18.9%, PSPT: 52.5%
Case # 02-1-01ZL1 001 – Group 3

- 55-year-old man
  - CC: cough.
  - Came to MDACC
  - Induction Chemotherapy x 2
  - 74 Gy planned
  - IMRT not possible
  - Proton was able to deliver the prescription dose
RTOG 1308: Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Radiochemotherapy for Inoperable Stage II-IIIB NSCLC

PI: Zhongxing Liao
Co-Chairs

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Outcomes: Ben Movsas, MD, Henry Ford Health System
Comparative Cost Effectiveness:
Deborah Bruner, RN, PhD, Emory University
Gregory Russo, MD, Boston University School of Medicine
Primary Objective

To compare overall survival (OS) time between the 2 arms, defined as the time from randomization to the date of death of any cause.

Secondary Objectives

- Progression-free survival (PFS),
- Any grade 3 or higher adverse events
- PROs (MDASO-Lung, SOBQ, Health Utility [EQ5D])
- Cost-effectiveness
- Pulmonary function changes
- To explore the most appropriate and clinically relevant technological parameters to ensure quality and effectiveness (imaging, simulation, immobilization, target and critical structure definition, treatment planning, image guidance and delivery)
### RTOG 1308 Schema

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>Concurrent Chemotherapy Doublet Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. II</td>
<td>Squamous</td>
<td>1. Carboplatin/paclitaxel</td>
</tr>
<tr>
<td>2. IIIA</td>
<td>Non-Squamous</td>
<td>2. Cisplatin/etoposide</td>
</tr>
<tr>
<td>3. IIIB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Randomize**

| Arm 1: Photon dose—70 Gy*, at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy** |
| Arm 2: Proton dose—70 Gy (RBE), at 2 Gy once daily plus platinum-based doublet chemotherapy** |

Both Arms: Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel**

*The total prescribed dose will be 70 Gy (RBE) **without exceeding tolerance dose-volume limits of all critical normal structures**. If 70 Gy (RBE) is not achieved, plan will be reviewed, prescription dose will be lowered at 2 Gy decrements to as low as 60 Gy.
Statistical Consideration

• OS will be improved from 21 months (monthly hazard $\lambda=0.0330$) with photon therapy, 60-70 Gy, (Arm 1) to 28 months (monthly hazard $\lambda=0.0248$) with proton therapy, 60-70 REB, (Arm 2), i.e., hazard ratio (HR) equals to 0.75, which translates to a 25% relative hazard reduction.

• The statistical power is set as 80% and the significance level is 0.025 (one-sided).

• Three interim analyses will be performed when 25%, 50%, and 75% cumulative information for OS are available.

• A total of 504 analyzable patients are required to be accrued uniformly with 10 patients per monthly accrual.

• Guarding against up to a 10% ineligibility and lost to follow up rate, the final targeted accrual for this study will be 560 cases, which is projected to be accrued uniformly in 56 months and followed for an additional 24 months.
RTOG 1308:
A historical opportunity for our specialty!
Three patients enrolled!
Representative Plans

- Protons
- IMRT
Intensity modulated proton therapy with simultaneous integrated boost (SIB) 2011-1058

Dose distributions of IMRT 66 Gy and PSPT 66 Gy, and IMRT SIB (72 Gy), IMPT SIB (72 Gy) plans
Phase I/II trial of image guided pencil scanning beam IMPT proton therapy and simultaneous integrated boost (SIB) dose escalation to gross tumor volume (iGTV) with concurrent chemotherapy in stage II/III non-small cell lung cancer (NSCLC)

**Study Number:** MDACC 2011-1058

Protocol PIs: MDACC - Zhongxing Liao, M.D.
MGH - N. Choi, MD

Funded by NCI PO1 grant
PO1 PI: Thomas Delaney, CO-PI: Radhe Mohan
Phase II/III Randomized Trial of Simultaneous Integrated Boost IMRT vs. IMPT (optimized based on variable RBE) and Concurrent Chemoradiation

Eligibility:
Stage II-IIIB NSCLC
KPS >=70% or ECOG 0-1, wt loss <15% 3 month before IC
Tumor motion<=5mm
NO prior RT to chest
No tumor invasion to esophagus, heart, spinal cord, major nerve
Age >18 year
FEV1>=1.0 L
Adequate blood work

Primary Endpoints:
Phase II: Grade 3 toxicities, LRPFS
Phase III: OS

Secondary endpoints:
MDASI-plus
Toxicity
Dose response
Blood biomarkers
Image biomarkers
Cost effectiveness

IMRT SIB and platinum based chemotherapy
PTV dose = 60 Gy (RBE)/2Gy (RBE)/fraction over 30 fractions/6 weeks
SIBV dose: 66 – 81 Gy (RBE) at 2.4 – 2.7 Gy (RBE)/fraction over 30 fraction/6 weeks

IMPT SIB and platinum based chemotherapy
PTV dose = 60 Gy (RBE)/2Gy (RBE)/fraction over 30 fractions/6 weeks
SIBV dose: 66 – 81 Gy (RBE) at 2.4 – 2.7 Gy (RBE)/fraction over 30 fraction/6 weeks
Summary

• Prospective randomized trials comparing protons and photons can and should be done!

• The execution of the protocol has been a great learning experience for all involved in the trial

• Great opportunity to collaborate with all proton centers and establish guidelines in planning, QA, data analyses and reporting

• Identify new challenges, ask new questions, and generating new hypothesis for further research
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