Leveraging Innovation to Design Future Clinical Trials

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The Carlos A Perez Distinguished Professor of Radiation Oncology

Outline

• National Clinical Trial Network
  • Transition from prior cooperative groups
• Infrastructure for radiation therapy QA
  • Transition from prior QA facilities
• Uses of RT data to improve outcomes
  • Treatment plan database (0617)
  • Analyses to understand unexpected result
• Correlative imaging science (0522)
• Prospective plan optimization (0126)

Multi-Institutional Research

• Tests science in real world
• Bridges gap between efficacy and effectiveness
• Facilitates dissemination of science into the community
• QA infrastructure
  • Maintains high level of treatment
  • Becomes a resource for investigations
National Clinical Trial Network

- Replaces prior cooperative groups
- Consolidates 10 groups to 5
- Consolidates QA and Imaging resources

NCI Cooperative Group Restructuring

<table>
<thead>
<tr>
<th>NRG</th>
<th>ECOG-ACRIN</th>
<th>Alliance</th>
<th>SWOG</th>
<th>COG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP: National Surgical Adjuvant Breast and Bowel Project</td>
<td>ECOG: Eastern Cooperative Oncology Group</td>
<td>SWOG: Southwest Oncology Group</td>
<td>COG: Children’s Oncology Group</td>
<td></td>
</tr>
<tr>
<td>RTOG: Radiation Therapy Oncology Group</td>
<td>ACRIN: American College of Radiology Imaging Network</td>
<td>CALGB: Cancer and Leukemia Group-B</td>
<td>Formerly: CCO  POB  APOA</td>
<td></td>
</tr>
<tr>
<td>GOG: Gynecologic Oncology Group</td>
<td>ACGOG: American College of Surgeons Oncology Group</td>
<td>COG:</td>
<td>COG:</td>
<td></td>
</tr>
</tbody>
</table>

The Advanced Technology Consortium for Clinical Trials QA

National Cancer Institute U24 Grant
Consortium of clinical trial QA centers:
- Image-Guided Therapy QA Center
- Radiation Therapy Oncology Group – RT QA
- Radiological Physics Center
- Quality Assurance Review Center
IROC’s Definition

Who Are WE?

Imaging and Radiation Oncology Core (IROC) QA Consortium

- New clinical trials Quality Assurance organization comprised of 6 QA Centers with individual PIs
- IROC RT and Imaging Centers have an extensive experience, knowledge and infrastructure to improve the quality of clinical trials

IROC’s 5 General NCTN Core Services

1. Site Qualification
   (FQs, ongoing QA, proton approval, resources)
2. Trial Design Support/Assistance
   (protocol review, templates, help desk, key contact QA centers)
3. Credentialing
   (tiered system to minimize institution effort)
4. Data Management
   (pre-review, use of TRIAD, post-review for analysis)
5. Case Review
   (Pre-, On-, Post-Treatment, facilitate review logistics for clinical reviews)
More than 20,000 complete, volumetric datasets have been collected at ITC from >750 institutions, using 12 commercial TPS as of 10/15/13.

Uses of RT data to improve outcomes
- Treatment plan database (0617)
  - Analyses to understand unexpected result
- Correlative imaging science (0522)
- Prospective plan optimization (0126)
RTOG 0617
A Randomized Phase III Comparison of Standard-Dose (60 Gy) Versus High-Dose (74 Gy)
Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/-
Cetuximab In Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer (NSCLC)

Principal Investigator: Jeffrey D. Bradley, MD

NCI Sponsored Cooperative Groups:
RTOG, NCCTG, CALGB

Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory A. Masters, Kenneth Forster, Steven E. Schild, Jeffrey Bogart, Yolanda I. Garces, Samir Narayan, Vivek Kavadi, Lucien A Nedzi, Jeff M. Michalski, Douglas Johnson, Robert M MacRae, Walter J Curran, and Hak Choy

Overall Survival
### Multivariate Cox Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison (RL)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation dose</td>
<td>60 Gy v 74 Gy</td>
<td>1.51 (1.12, 2.04)</td>
<td>0.007</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squam v Squam</td>
<td>1.31 (0.99, 1.75)</td>
<td>0.061</td>
</tr>
<tr>
<td>Max esophagitis grade</td>
<td>2 &gt; 3 vs ≤3</td>
<td>1.52 (1.06, 2.20)</td>
<td>0.024</td>
</tr>
<tr>
<td>Heart Contour</td>
<td>Per Protocol vs. Not per protocol</td>
<td>0.67 (0.47, 0.96)</td>
<td>0.029</td>
</tr>
<tr>
<td>GTV</td>
<td>Continuous</td>
<td>1.001 (1.000, 1.002)</td>
<td>0.038</td>
</tr>
<tr>
<td>Heart V50(%)</td>
<td>Continuous</td>
<td>1.017 (1.004, 1.030)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Backwards Selection: Exit criteria p>0.10
Two-sided p-values
Removed from model: Age (continuous), overall RT review (per protocol vs. not per protocol), and lung V5 (continuous)

### 0617 Quality Assurance

**Measures differing between arms**

Contouring scores for TVs, OARs, DVA of TVs, OARs, elapsed days were reviewed

<table>
<thead>
<tr>
<th>QA measure</th>
<th>Standard Dose 600Gy Per Protocol</th>
<th>High Dose 740Gy Per Protocol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall RT Review</td>
<td>82.9%</td>
<td>73.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Elapsed RT days</td>
<td>89.9%</td>
<td>83.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>PTV Contour</td>
<td>92.8%</td>
<td>86.0%</td>
<td>0.03</td>
</tr>
<tr>
<td>Brachial plexus contour</td>
<td>92.3%</td>
<td>85.5%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

An unplanned subset analysis strongly suggests that radiation therapy compliance was not the cause for the poor performance of the high-dose group

### Advancing RT – Adaptive

**RTOG 1106 – Pi Kong**

**Registration**

- Pre-RT/RT PET/CT Imaging

**Schedules**

- Arm 1: Concurrent Chemo-RT RT to 50 Gy (6.5 Gy/Fr) Carboplatin (IV weekly)
- Arm 2: Concurrent Chemo-RT RT to 50 Gy (6.5 Gy/Fr) Carboplatin (IV weekly)

**Outcomes**

- Arm 3: Continue RT Same RT plan to 50 Gy (5 Fr)
- Arm 2: Adaptive RT Based on during RT TPS RT 3.0 – 3.5 Gy, ≥5 Gy individualized by MLD

**Other**

- Complete Concurrent Chemotherapy

January 2015 accrual 62/138
RTOG 1308: PHASE III RANDOMIZED TRIAL COMPARING OVERALL SURVIVAL AFTER PHOTON VERSUS PROTON CHEMORADIOThERAPY FOR INOPERABLE STAGE II-IIIb NSCLC

*The total prescribed dose will be 70 (RBE) without exceeding tolerance dose-volume limits of all critical normal structures.

Pt: Zhongxing Liao, MD

• Uses of RT data to improve outcomes
  • Treatment plan database (0617)
  • Analyses to understand unexpected results
  • Correlative imaging science (0522)
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NRG Clinical Imaging Priorities
• Investigate the role of imaging as a **biomarker for predicting response** to local and systemic therapies.
• Investigate that imaging is an early biomarker of response and **surrogate for established endpoints** such as local control or survival.
  – Long term goal is to replace distant endpoints that require long follow-up
  – Secondary goal is identifying patients who may benefit from early salvage or additional treatment
• Investigate the role of imaging to select and stratify patients for specific therapies (**integral biomarker**).
• Enhance and evaluate the use of molecular, physiological, morphological imaging to define **dynamic targets** for image-guided local therapies.
RTOG 0522 — A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) for Stage III and IV Head and Neck Carcinomas (Kian Ang, PI)

### Primary Site

<table>
<thead>
<tr>
<th>Larynx</th>
<th>8-9 Weeks Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>Treatment</td>
</tr>
</tbody>
</table>

### Nodal Status

<table>
<thead>
<tr>
<th>Node</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Acceleration/Fractionation

- **NS:** Concurrent Boost
- **CR:** Reassess CT scan
- **AR:** Plus cisplatin
- **ACR:** Plus C225

### Use of IMRT

- **No:** IMRT (C225) on MRI or MRI for BI-CL
- **Yes:** IMRT (C225) plus C225

### Pre-Treatment PET/CT

- **No:**
- **Yes:**

RTOG 0522 — Data Integration

- CT Sim
- RT Dose
- Pre-Tx
- Post-Tx
- ITC DB
- RTOG 0522
- VelocityAI Integration
- ACRIN DB
- ACRIN 4500

RTOG 0522 — Diagnostic PET registered to Planning CT using deformation

- Choose isodose values from RT Dose object

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RTOG 0522

- Therapy response assessment using RT specific data with PET-CT pre-treatment and post-treatment images

Pre-Tx PET fused w/ Planning CT and Dose

Post-Tx PET fused w/ Planning CT and Dose

Advancing RT – Adaptive

RTOG 1106 – PI Kong

January 2015 accrual 62/138

- Uses of RT data to improve outcomes
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Step 1 • Identify a set of site similar training patients
Step 2 • Generate pDVH model from training cohort
Step 3 • Utilize pDVH model to obtain DVH prediction for new patient

Inter-institutional QC at a small radiotherapy clinic

<table>
<thead>
<tr>
<th>Organ</th>
<th>V65(orig)-V65(replan)</th>
<th>dV65</th>
<th>V40(orig)-V40(replan)</th>
<th>dV40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>4.8%±2.2%</td>
<td>0.9%±1.1%</td>
<td>17.9%±10.3%</td>
<td>0.7%±1.4%</td>
</tr>
<tr>
<td>Bladder</td>
<td>3.4%±2.1%</td>
<td>0.3%±0.5%</td>
<td>6.0%±2.8%</td>
<td>0.6%±0.9%</td>
</tr>
</tbody>
</table>

Table 3. Average Reduction in V65 and V40 for Rectum and Bladder

RTOG 0126: study schema

1. Risk Group
   - Gleason Score 6 and PSA 10-20
   - Gleason Score 7 and PSA ≤15

2. Treatment
   - 3DCRT
   - IMRT

Arm 1
   - Minimum PTV prescription 70.2Gy in 39 fractions

Arm 2
   - Minimum PTV prescription 79.2Gy in 44 fractions

• Maximum dose variation
  - None: No more than 7% to ≤2% of PTV
  - Minor: 7%–10% to ≤2% of PTV
  - Major: More than 10% to ≤2% of PTV

• Minimum dose variation
  - None: Rx covers ≥98% of PTV
  - Minor: Rx covers 95%-98% of PTV
  - Major: Rx covers <95% of PTV or <100% of CTV
**IMRT vs 3DCRT**

Dosimetric comparison

All differences statistically significant p<0.0001

**Time to Late GI Toxicity**

Grade 2+ GI Late Toxicity

Grade 3+ GI Late Toxicity

**Grade 2+ GI Late Toxicity – Multivariate Analysis**

<table>
<thead>
<tr>
<th>Stratified variables</th>
<th>variables categories</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT method</td>
<td>3D-CRT 79.2Gy</td>
<td>RL</td>
<td></td>
<td>0.728</td>
</tr>
<tr>
<td></td>
<td>IMRT 79.2Gy</td>
<td>RL</td>
<td>(0.511, 1.035)</td>
<td>0.077</td>
</tr>
<tr>
<td>Age</td>
<td>≤ 70</td>
<td>RL</td>
<td></td>
<td>1.126</td>
</tr>
<tr>
<td></td>
<td>&gt; 70</td>
<td>RL</td>
<td>(0.820, 1.547)</td>
<td>0.460</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>RL</td>
<td></td>
<td>0.364</td>
</tr>
<tr>
<td></td>
<td>Non-white</td>
<td>RL</td>
<td>(0.202, 0.655)</td>
<td>0.001†</td>
</tr>
</tbody>
</table>

*Fine-Gray statistics. † Statistical significant at 0.05.
Would results have been different if "best" IMRT were utilized?

- Dose constraints defined based on prior experience
  - e.g. Rectal V70 < 25%
- Treatment planners not incentivized to continue optimization after constraints met
- Objective optimization prediction tools may set a patient specific target

RTOG 0126 analysis-210 cases

NTCP model: Excess risk of toxicity?
Concluding Remarks

- Multi-Institutional Technology Trials are facilitated by an infrastructure for plan quality assurance
- The data acquired for plan QA can serve as a reusable resource for supplemental investigations
- Future trials can be built upon knowledge gained from secondary analyses