Radiation Therapy Oncology Group

Walter J. Curran, Jr., MD

RTOG Group Chair

www.rtog.org
RTOG Overview

- Organization & Administration
- Research Initiatives & Strategic Themes
- RTOG’s Unique Characteristics
Who is the RTOG?

- The leading multicenter organization systematically testing novel radiotherapy approaches against cancer and pursuing fully integrated translational research to support and further this effort.
RTOG History

3 Lines on RTOG History

- Forty Years of Continuous NCI Funding
- Four Group Chairs
- Administered via American College of Radiology
RTOG Scientific & Administrative Structure

- Elected Chair & Elected/Appointed Vice Chairs
- Steering and Executive Committees
- Disease Site Committees and Working Groups
- Scientific Core Committees
• RTOG Steering Committee: 15 Members
  – 5 Elected (by Full Member PIs) & 10 Appointed Members
  – Serves as RTOG Foundation Board
  – Meets Monthly via Conference Call

• RTOG Executive Committee: 13 Additional Members
  – 2 Elected (by Full Member PIs) & 11 Appointed Members
  – Meets at Semiannual Meetings
  – Steering Committee is Subcommittee of Executive Committee
# Disease Site Committees/Working Groups*

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Leader</th>
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<tbody>
<tr>
<td>Brain Tumors</td>
<td>Minesh Mehta, MD</td>
</tr>
<tr>
<td>Head &amp; Neck Cancer</td>
<td>Kian Ang, MD</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>Hak Choy, MD</td>
</tr>
<tr>
<td>Gastrointestinal Cancer</td>
<td>Christopher Willett, MD</td>
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<tr>
<td>Genitourinary Cancer</td>
<td>Howard Sandler, MD</td>
</tr>
<tr>
<td>Breast Cancer*</td>
<td>Julia White, MD</td>
</tr>
<tr>
<td>Gynecologic Cancer*</td>
<td>David Gaffney, MD, PhD</td>
</tr>
<tr>
<td>Sarcoma*</td>
<td>Burton Eisenberg, MD</td>
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RTOG Working Groups

*Breast Cancer*, *Gynecologic Cancer*, *Sarcoma*

- Each with Focused Mission
- Critical to the 3 RTOG Strategic Themes
- None Slated to Become Full Committee
- “Other Disease Sites” Committee to be Formed
Scientific Core Committees

• Advanced Technology Integration  Jeff Michalski, MD
• Health Services Research & Outcomes  Deborah W. Bruner, PhD
• Translational Research Program  Adam Dicker, MD, PhD
• Biospecimen Resource  Frederic Waldman, MD, PhD
• Pathology  Mahul Amin, MD
• Medical Oncology  Corey Langer, MD
• Medical Physics  Michael Gillin, PhD
• Surgical Oncology  Peter Pisters, MD
RTOG Administrative Structure

- ACR Philadelphia Office is Home to
  - RTOG Biostatisticians
  - Data Management
  - RT Quality Assurance Center
  - Headquarters Staff
  - Group Chair’s Office

- Uniquely Integrated Office Layout with Team-Based Architecture
RTOG Prioritization Process

• **How are Decisions Made?**
  – Study/Research Priorities
  – Resource Allocation

• **How are Priorities Established?**

• **How is Input Sought?**
RTOG Prioritization Process

- Disease Site Committees & WGs Define Research Priorities
- Input from Relevant Scientific Core Committees
- RTOG Steering Committee
  - Reviews & Approves all Research Proposals
  - Adjudicates Among Competing Research Priorities
- RTOG Administrative Leadership Executes Priorities:
  - W Curran, M Machtay, W Hoffman, R Sadek, K Winters
- RTOG Steering Committee Reviews Resource Allocation
  - As RTOG Foundation Board
RTOG Funding

- RTOG HQ Grant: 52%
- RTOG Foundation: 15%
- CCOP: 11%
- SDMC: 5%
- Tissue Bank: 4%
- Corporate: 6%
- PA C.U.R.E.: 4%
- ATC QA Center: 2%
- Other Grants: 0%
Research Initiatives & Strategic Themes

- Physical Targeting
- Molecular Targeting with RT or ChemoRT
- Translational and Analytic Research
Research Initiatives & Strategic Themes

*RTOG Competitive Renewal*

- Physical Targeting
- Molecular Targeting with RT or ChemoRT
- Translational and Analytic Research
• RTOG will implement and test advances in imaging and high-precision radiation therapy planning and delivery technologies in clinical trials. This will lead to meaningful improvements in therapeutic ratio.
Physical Targeting

Background

Tremendous Biophysical Advances!

- Functional Imaging
- Image-Guided RT
- RT Planning & Delivery
- Data Transfer & Analysis
- Operational Characteristics of RT
Enhanced Infrastructure

Physical Targeting

• Advanced Technology Integration Committee (ATIC)
  – New Name, New Missions
• Effective Liaisons between Disease Site, ATIC, and Medical Physics Committees
• Co-Development of Trials with ACRIN
• Creation of RT Core Lab at RTOG HQ
• Increase in Resources for New Technology Accreditation
Physical Targeting

Selected Achievements: Completed Trials

- Survival Benefit of SRS for Brain Metastases
- No Benefit of SRS for Glioblastoma
- Execution of 3 H&N Cancer IMRT Trials
- Phase II SRT for Unresectable Lung Cancer
- Phase III RT Dose Trial for Prostate Cancer
- Phase II RT Dose Trials for NSCLC & SCLC
- Phase III Concommittant Boost for H&N Cancer
Physical Targeting

Ongoing Initiatives

- Integration of IMRT in Prostate Cancer Trials
- Phase III Partial Breast RT Trial with NSABP
- Phase III RT Dose Trial in Stage III NSCLC
- Phase II SRS for Hepatic Lesions
- Phase III Prostate Brachy ± External Beam
- Phase II PET Scans in Response Assessment
Phase III Trial in Locally Advanced HNSCC

Eligible
- Stage III & IV SCCHN

Stratify
- IMRT Site
- N- vs. N+
- KPS

1. Chemoradiation (70 Gy/6 wks) + cddP
2. Chemoradiation + Cetuximab

RTOG 0522
Phase III Trial in Locally Advanced HNSCC

*RTOG 0522 Illustrates all 3 RTOG Strategic Initiatives*

- **Physical Targeting**
  - First Phase III H/N Trial to Allow IMRT
  - Prospective Assessment of PET Imaging

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**Target Delineation Atlas**

**Online Review**

- $CTV_{56}$
- $CTV_{63}$
- Protocol
Primary Endpoint: Toxicity Reduction

Physical Targeting

- Anal Cancer IMRT Trial
- Rectal Cancer IMRT Trial
- Nasopharyngeal Cancer IMRT Trial
- Cervix/Endometrial Cancer IMRT Trial
Primary Endpoint: Enhanced Tumor Control

Physical Targeting

• Stereotactic Radiation NSCLC
• Higher Dose RT
  – NSCLC
  – Prostate Cancer
  – SCLC
• Concomitant Boost RT in H&N Cancer
Physical Targeting

Future Initiatives

- Greater Integration with Other Research Themes
- Expansion of Anatomic Atlases
- Initiative with ACRIN on Brain Tumors
- Proton Beam Research Strategy
Research Initiatives & Strategic Themes

**RTOG Competitive Renewal**

- Physical Targeting
- Molecular Targeting with RT or ChemoRT
- Translational and Analytic Research
• RTOG will design and conduct hypothesis-driven trials testing the integration of new classes of molecular targeted anti-cancer agents with optimized radiation or chemoradiation.
Background

Builds on RTOG-Generated Level 1 Evidence for Combined Modality Therapy

- Cervix Cancer
- Localized/Locally Advanced Prostate Cancer
- Stage III NSCLC
- Head and Neck Cancer
- GI Cancer (Anal & Pancreatic)
- Brain Tumors
Selected Landmark Trials in Grant Period

**Combined Modality Testing**

- Role of Gemcitabine in Pancreatic Cancer (*JAMA* 2008)
- Optimal ChemoRT for Anal Cancer (*JAMA* 2008)
- ChemoRT for High Risk Resected H&N Cancer (*NEJM* 2004)
- Role of Surgery in N2 NSCLC (Under *Lancet* Review)
- Chemo Role in Anaplastic Gliomas (*JCO* 2006, ASTRO 2008)
Novel Agents & ChemoRT

New Initiatives in the Combined Modality Setting

- EGFR-Targeting Therapy (10 Trials)
- Vascular-Targeting Therapy (8 Trials)
- Other Targeted Approaches (4 Trials)
Criteria for Selecting Agents for Testing

- Scientific Rationale
- Pre-Clinical Synergism with RT (CURE Funding)
- Antitumor “Activity” without RT in Given Disease?
- Meaningful Opportunity to Improve Tumor Control
- Low Likelihood of High Toxicity
- Availability of Agent for Testing

- Use Optimized RT!
Novel Agents and ChemoRT

Future Directions

• Concurrent Novel Agent(s) with RT Regimens
  – No Concurrent Chemotherapy
  – Reduced Toxicity?

• Link with Pre-Clinical/Early Clinical Programs in Industry, Cancer Centers, and SPORES

• “Personalized” Testing of Novel Agents with RT?
  – Biomarkers
  – Prognostic Features
RTOG Phase III Head & Neck Cancer Trial

*RTOG 0522 Involves all 3 RTOG Strategic Initiatives*

- **Physical Targeting**
  - First Phase III H/N Trial to Allow IMRT
  - Prospective Assessment of PET Imaging

- **Novel Agents and ChemoRT and/or RT**
  - Primary Trial Endpoint: Addition of Cetuximab
  - Assessment of Efficacy as well as Toxicity
Research Initiatives & Strategic Themes

*RTOG Competitive Renewal*

- Physical Targeting
- Molecular Targeting with RT or ChemoRT
- Translational and Analytic Research
Translational and Analytic Research

- The RTOG has unique and inter-linked clinical, biophysical, biologic, and outcomes databases. RTOG will develop and implement powerful biostatistical and medical informatics approaches that will facilitate hypothesis-driven analyses of these resources.
Selected Achievements

Translational and Analytic Research

- Addition of Biomarkers to RTOG Brain Tumor RPA (IJROBP 2005)
- New Adverse Event System for H&N Cancer (Lancet Oncology 2007)
- New RTOG/ASTRO PSA Failure Definition (IJROBP 2006)
- Economic Analysis of RTOG H&N Ca Trial Using CMS (PASCO 2006)
- Biomarker Analysis in All Disease Sites
RTOG Phase III Head & Neck Cancer Trial

*RTOG 0522 Involves all 3 RTOG Strategic Initiatives*

- **Physical Targeting**
  - First Phase III H&N Trial to Allow IMRT
  - Prospective Assessment of PET Imaging

- **Novel Agents and ChemoRT/RT**
  - Primary Trial Endpoint: Addition of Cetuximab
  - Assessment of Efficacy as well as Toxicity

- **Translational and Analytic Research**
  - Correlate EGFR & Downstream Molecules with Outcome
  - Quality of Life and Health Utilities Evaluation
AQUA nLox & Time to Metastasis in HNC

**RTOG 9003**

- **Patients at Risk**
  - Quartile 1-3: 228
  - Quartile 4: 75

- **Years after Randomization**
  - Year 0: 228, 75
  - Year 1: 124, 32
  - Year 2: 90, 20
  - Year 3: 76, 15
  - Year 4: 66, 12
  - Year 5: 61, 11

- **Failed / Total**
  - Quartile 1-3: 51 / 228
  - Quartile 4: 27 / 75

- **Hazard Ratio (95% CI):** 2.106 (1.318, 3.365)

*(Q. Le et al, ASTRO 2008)*
RTOG Outcomes Model (2009-2014)

**Clinical**
Survival, toxicity, symptoms

**Economic**
Cost-effectiveness, cost-utility

**Physical**
Image/dose parameters

**Humanistic**
PROs (QOL, utilities, symptoms), neurocognitive, behavioral

**Biological**
Genetic, transcriptome, cytokines, protein signatures
RTOG’s Unique Characteristics

- Group Focus & Vision
- Outstanding Facilities
- Organizational Capabilities
- Collaboration with other Research Entities
- Broad Commitment
- Group Leadership
RTOG’s Unique Focus & Vision

• 3 Strategic Themes Not Duplicated Elsewhere
• Growing Evidence of the Value of these Initiatives
• Evolving Focus and Themes over 40 Years
• Lead Cooperative Group Studying Patients with
  – Primary and Secondary Brain Tumors
  – Head and Neck Cancer
  – Localized/Locally Advanced Prostate Cancer
• RTOG Investigators at Nearly Every Academic Center
  – US and Canada
Selected Facilities Enhancement

- New RTOG Administrative Offices Since 2005
- Optimized Office Design
- New Biospecimen Resource at UCSF
- ACR Department of Clinical Informatics
- Enhanced RT Object Management Facility
- Remote PI and QA Reviews
- New RT QA Core Facility 2009
Organizational Capabilities Highlights

• Reorganized RTOG Steering Committee Processes
• New RTOG Senior Director Position (W Hoffman)
• Enhanced Liaison Positions among Committees
• Creation of *Clinical Trials Education and Recruitment Working Group*
• Enhanced RA Quality Control and Mentor Program
• Formalized RTOG Phase I/II DSMB Committee
Collaboration with Other Research Entities

- Partnership with EORTC et al on Brain Tumor Trials
- NSABP Co-Leadership in Partial Breast RT Trial
- Co-Development of Trials with SWOG, CALGB, & ACRIN
- SPORE & Cancer Center Research Links
- International Membership Initiative (Corn et al JCO 2008)
Broad Commitment 2002-2008

- CURE Funding from Pennsylvania ($2.51 M)
- RTOG Trial-Specific Corporate Support ($10.8 M)
- RTOG Foundation Increase from $2.4 to 4.7 M
- Expanding Membership: US/Canada/ROW
- Expanding Volunteer Member Efforts
RTOG Group Leadership

• Updated Group Bylaws
• 5 New Vice Chair Positions since 2006
• Multi-Disciplinary Leadership
• Outstanding Elected/Appointed Steering Committee
• Expedited Trial/Concept Review Process
• Scientific/Disease Site Committee Leadership
• Full Participation in New NCI Initiatives
Selected Results of Administrative Changes

- Increase in Accrual: 28% Over Grant Period
- Increase in Member Institutions
- Full Compliance with all CTEP & CIRB Deadlines
- Increase in Number of Publication & Abstracts
- Favorable Time Line for Activation (per Dr. Dilts)
- First Trial Approved by NCI GI Steering Committee
Accrual to RTOG CTEP Trials

28% Increase in Accrual from 2002-2004 to 2005-2007!!

Accrual (subjects) by year:
- 2002: 1918
- 2003: 2235
- 2004: 1615
- 2005: 1953
- 2006: 2844
- 2007: 2595
Cooperative Group Accrual/Awards

5.5% Increase in non-RTOG Accrual 2002-4 to 2005-7*

*Accrual of new patients annually
RTOG Protocol Activations

CTEP Protocols

- Protocols activated (2008 is through 5/31)
- Projected activations
Minorities/Women Recruitment

- NCI Cancer Disparities Research Partnership
  - Dr. Dwight Heron, PI on RTOG Executive Committee
- RTOG Health Services Research Committee
- Clinical Trials Education & Recruitment Committee
- 36% Female Enrollment (Up 44% from prior grant)
- 12% African American Enrollment
- 2.2% Native American, Asian, Pacific Islander
- 1% Hispanic
### Race / Gender / Ethnicity Accrual – Current Grant Period 2002-2007

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<tr>
<th>Race</th>
<th>%</th>
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<tr>
<td>American Indian/Alaska Native</td>
<td>0.5%</td>
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<tr>
<td>Asian</td>
<td>1.4%</td>
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<tr>
<td>Native Hawaiian/Pacific Islander</td>
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<tr>
<td>Black or African American</td>
<td>12.0%</td>
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<tr>
<td>White</td>
<td>83.3%</td>
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<tr>
<td>More than One Race</td>
<td>0.1%</td>
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<tr>
<td>Unknown or not Reported</td>
<td>1.6%</td>
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<tr>
<td>Prior to ethnicity; Race = Hispanic</td>
<td>0.9%</td>
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<table>
<thead>
<tr>
<th>Non-Gender Specific Trials</th>
<th>%</th>
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<tr>
<td>Female</td>
<td>36.3%</td>
</tr>
<tr>
<td>Male</td>
<td>63.5%</td>
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<tr>
<td>Unknown</td>
<td>0.2%</td>
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<table>
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<tr>
<th>Ethnicity</th>
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<tr>
<td>Hispanic or Latino</td>
<td>3.3%</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>92.4%</td>
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<tr>
<td>Unknown</td>
<td>4.3%</td>
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RTOG Trial Completion Issues

Trial Accrual Failure Rate Reported at RTOG Site Visits:

- 1996 33%
- 2001 10%
- 2008 9%
Next Generation Investigator Award

- Jeffrey Bradley, MD *Washington U*
- Arnab Chakravarti, MD *Mass General*
- Christine Chung, MD *Vanderbilt*
- Christopher H. Crane, MD *MD Anderson*
- Elizabeth M. Gore, MD *MCW*
- Gregory Videtic, MD *Cleveland Clinic*
- Stuart J. Wong, MD *MCW*
- Wendy A. Woodward, MD, PhD *MD Anderson*
Next Generation Investigator Award

• Laura Dawson, MD *Princess Margaret*
• Lisa Kachnic, MD *Boston University*
• Jean M. Moran, PhD *U Michigan*
• Geoffrey A. Porter, MD, MSc *Dalhousie U*
• John J. Coen, MD *Mass General*
• Deborah Citrin, MD *NCI*
• Howard Safran, MD *Brown U*
• Anuja Jhingran, MD *MD Anderson*
• Norissa Honea, PhD *Arizona Oncology*
RTOG: Summary

- Organization Customized to its Mission
- Unique Niche Among Cooperative Groups
- Diversified Funding Model
- Reliance on Investigator Volunteerism
- International Members of Growing Importance
- Next Generation Investigators in Place!