

Radiation Therapy Oncology Group

Walter J. Curran, Jr., MD

RTOG Group Chair

RTOG Overview

- Organization & Administration
- Research Initiatives & Strategic Themes
- RTOG's Unique Characteristics

RTOG: An Introduction

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 Leadership Structure

- 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*

- Brain Tumors
 - Head & Neck Cancer
 - Lung Cancer
 - Gastrointestinal Cancer
 - Genitourinary Cancer
 - Breast Cancer*
 - Gynecologic Cancer*
 - Sarcoma*
- Minesh Mehta, MD
Kian Ang, MD
Hak Choy, MD
Christopher Willett, MD
Howard Sandler, MD
Julia White, MD
David Gaffney, MD, PhD
Burton Eisenberg, MD

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

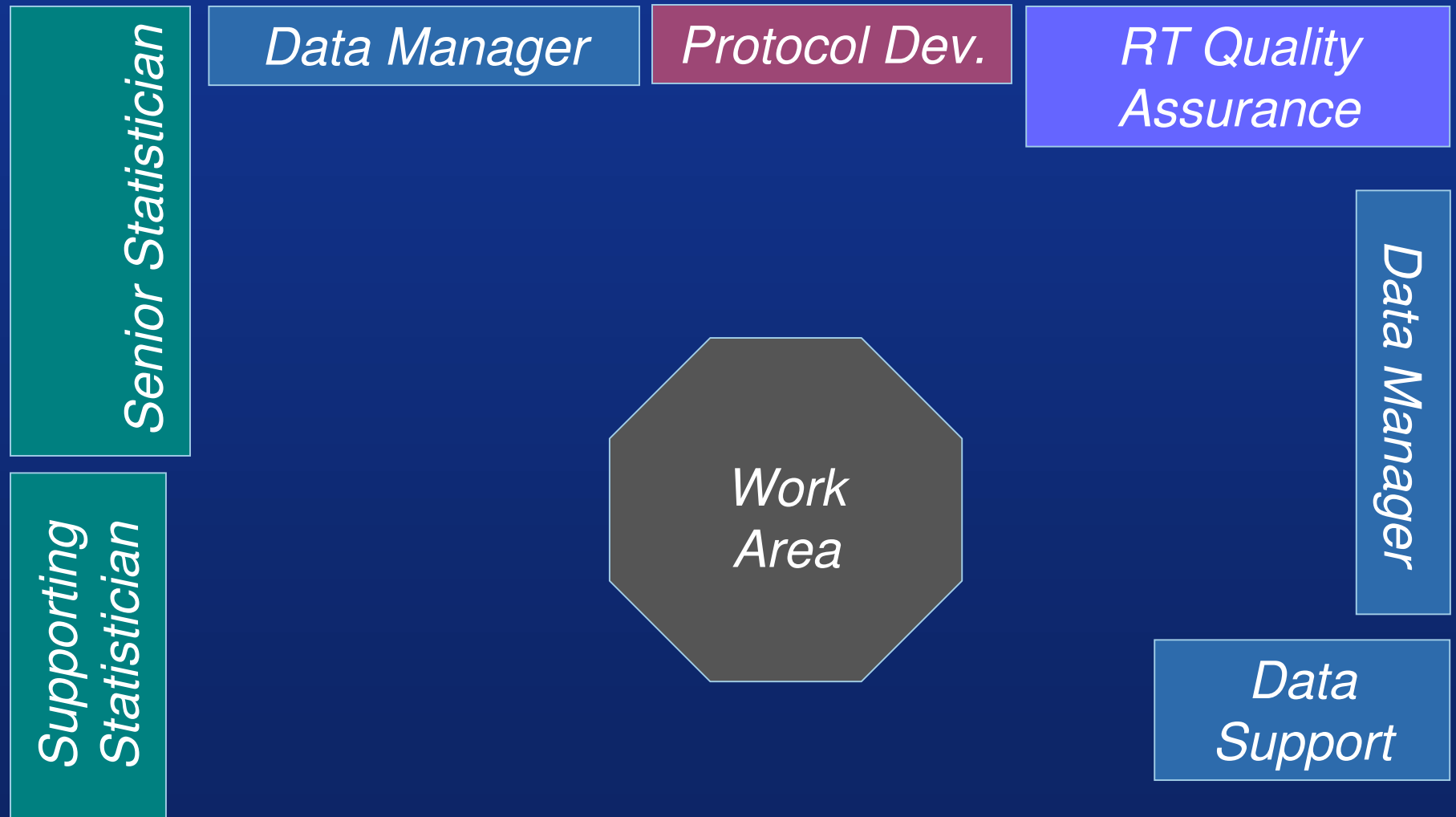
Scientific Core Committees

- Advanced Technology Integration
 - Health Services Research & Outcomes
 - Translational Research Program
 - Biospecimen Resource
 - Pathology
 - Medical Oncology
 - Medical Physics
 - Surgical Oncology
- Jeff Michalski, MD
Deborah W. Bruner, PhD
Adam Dicker, MD, PhD
Frederic Waldman, MD, PhD
Mahul Amin, MD
Corey Langer, MD
Michael Gillin, PhD
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 HQ Research Team Floor Plan



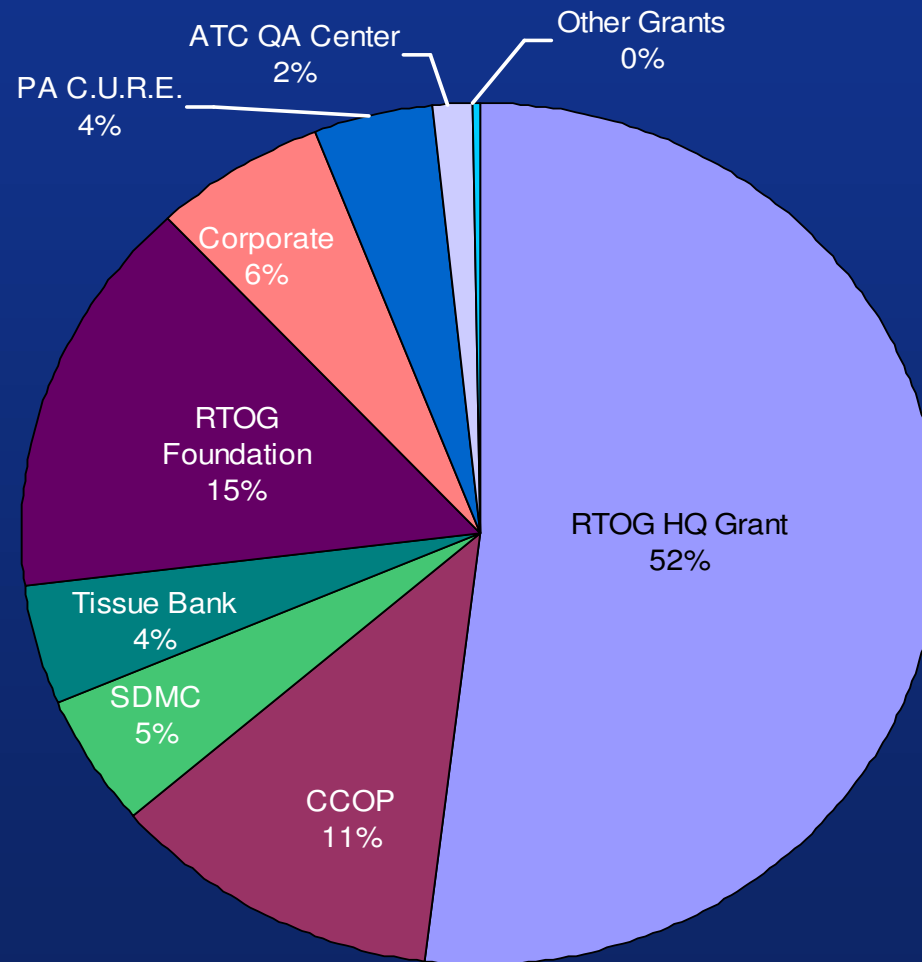
RTOG Prioritization Process

- 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



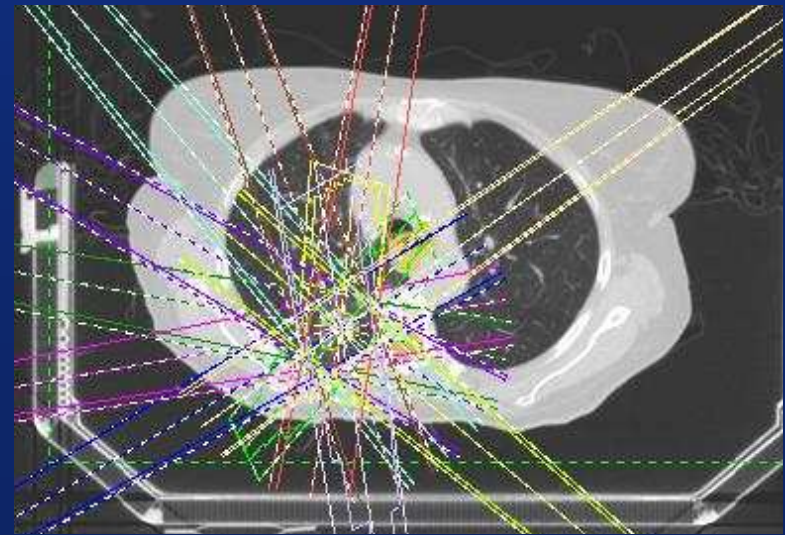
Research Initiatives & Strategic Themes

- 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



Physical Targeting

First Research Initiative & Strategic Theme

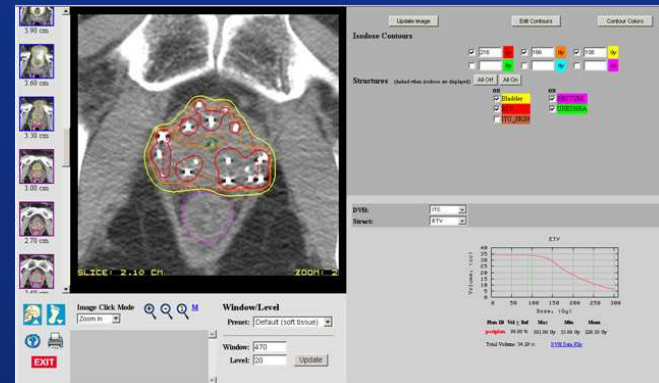
- RTOG will implement and test advances in imaging and high-precision radiation therapy planning and delivery technologies in clinical trials. This will lead to meaningful improvements in therapeutic ratio.

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 Concomittant 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

RTOG 0522

Eligible

Stage III & IV SCCHN

Stratify

IMRT

Site

N- vs. N+

KPS

R
A
N
D
O
M
I
Z
E

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

2. Chemoradiation
+ Cetuximab

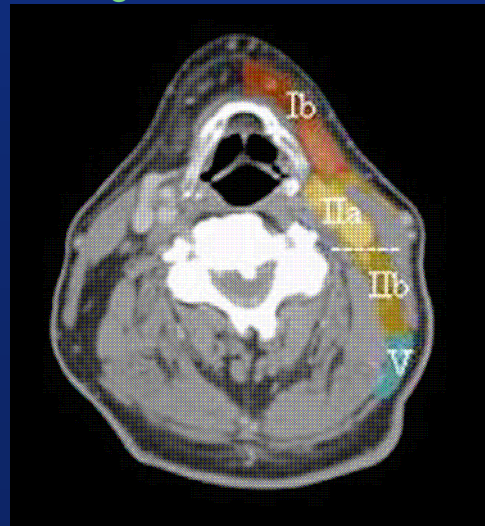


Phase III Trial in Locally Advanced HNSCC

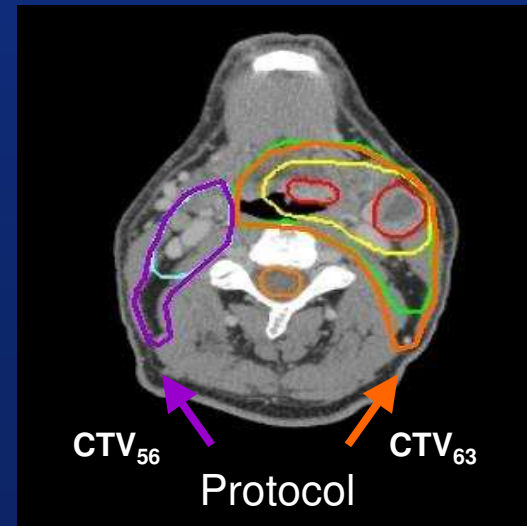
RTOG 0522 Illustrates all 3 RTOG Strategic Initiatives

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

Target Delineation Atlas



Online Review



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

Novel Agents with RT / ChemoRT

- 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

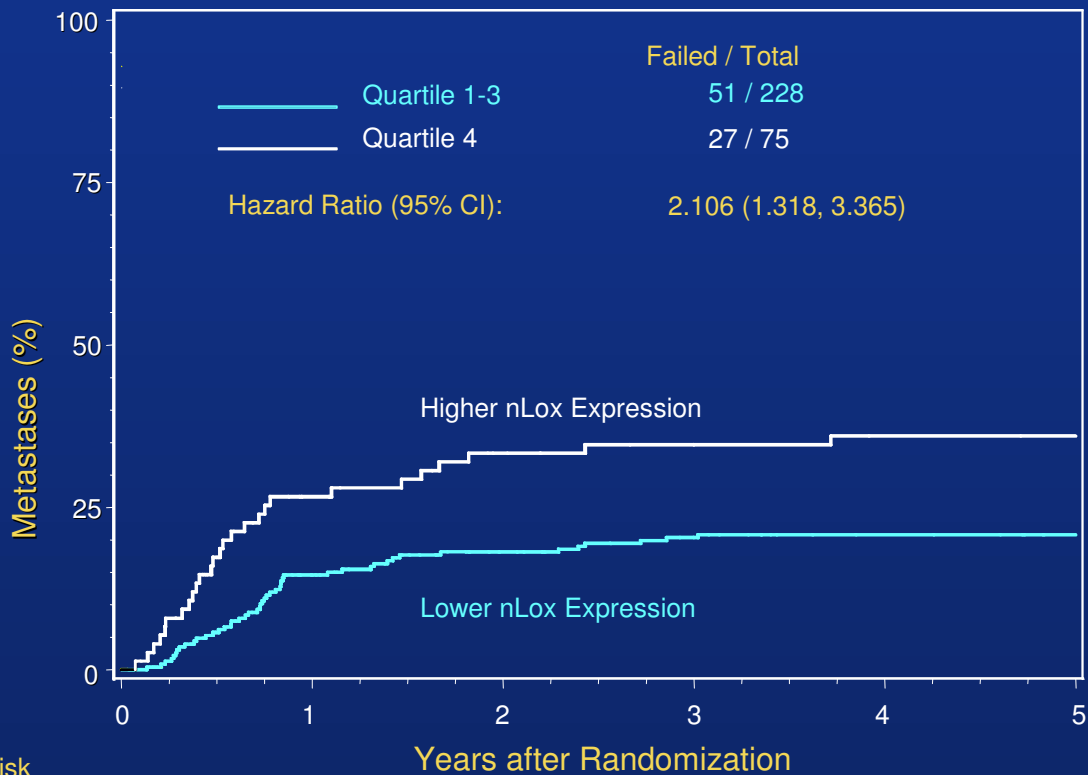
RTOG Phase III Head & Neck Cancer Trial

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- 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

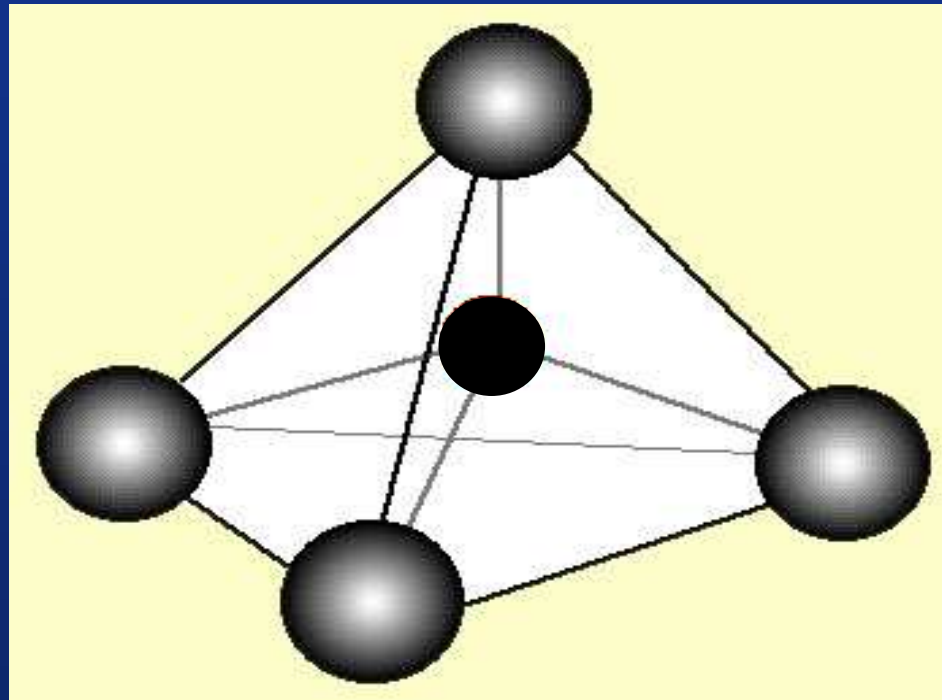
	0	1	2	3	4	5
Quartile 1-3	228	124	90	76	66	61
Quartile 4	75	32	20	15	12	11

(Q. Le et al, ASTRO 2008)

RTOG Outcomes Model (2009-2014)

Clinical

Survival, toxicity, symptoms



Physical

Image/dose parameters

Humanistic

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

Economic

Cost-effectiveness
cost-utility

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

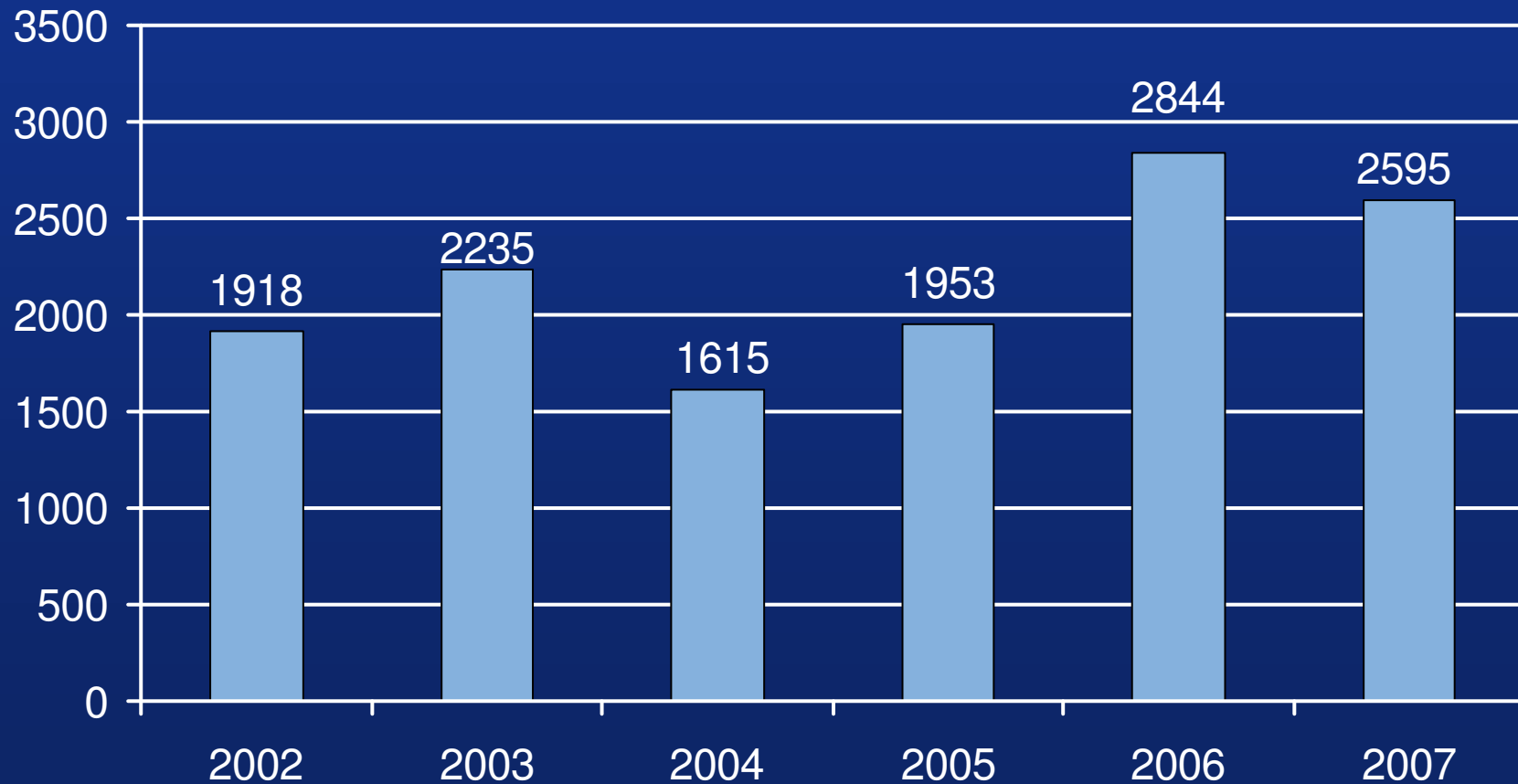
- Updated Group Bylaws
- 5 New Vice Chair Positions since 2006
- Multi-Disciplinary Leadership
- Outstanding Elected/Appointed Steering Committee
- Expedited Trial/Concept Review Process
- Scientific/Disease Site Committee Leadership
- Full Participation in New NCI Initiatives

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

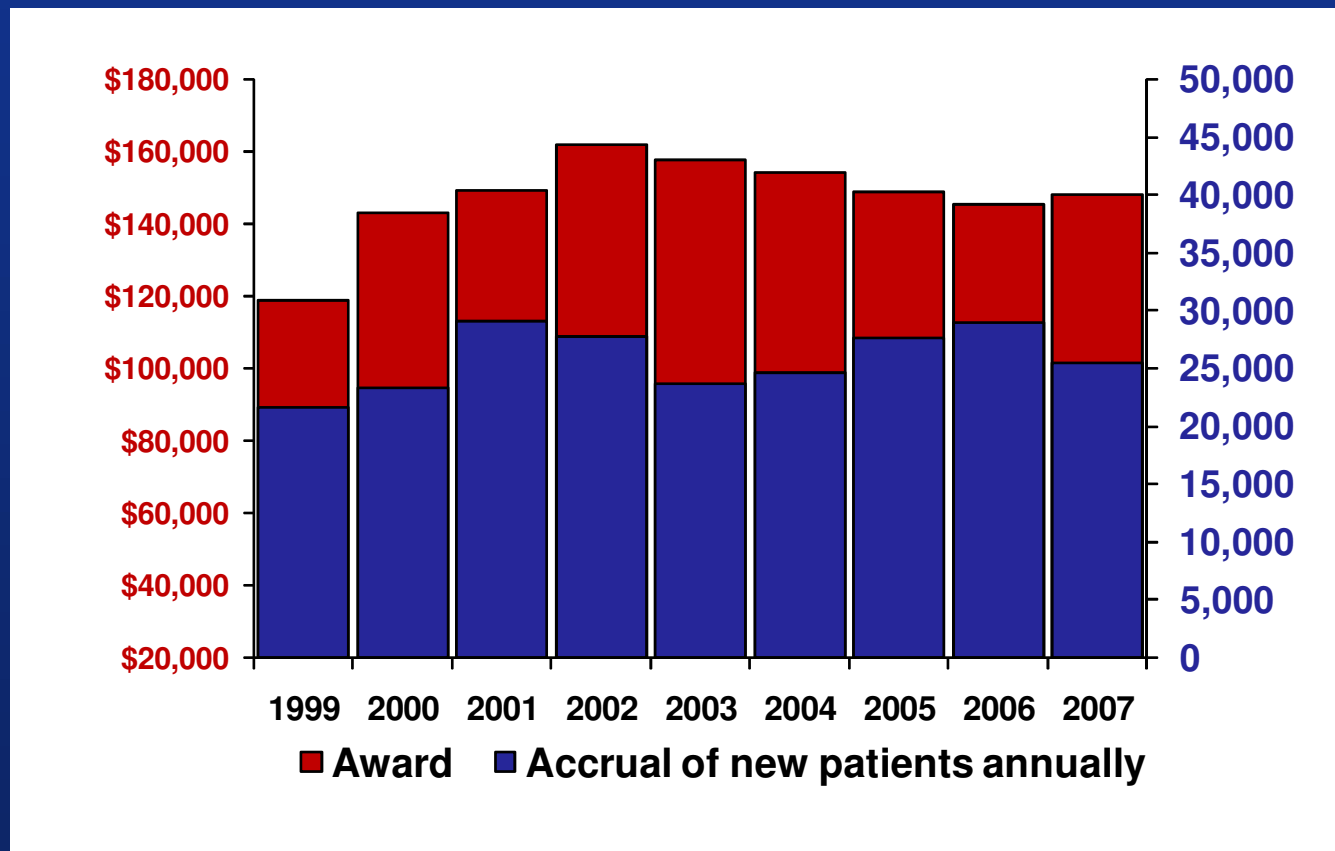
Accrual to RTOG CTEP Trials

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



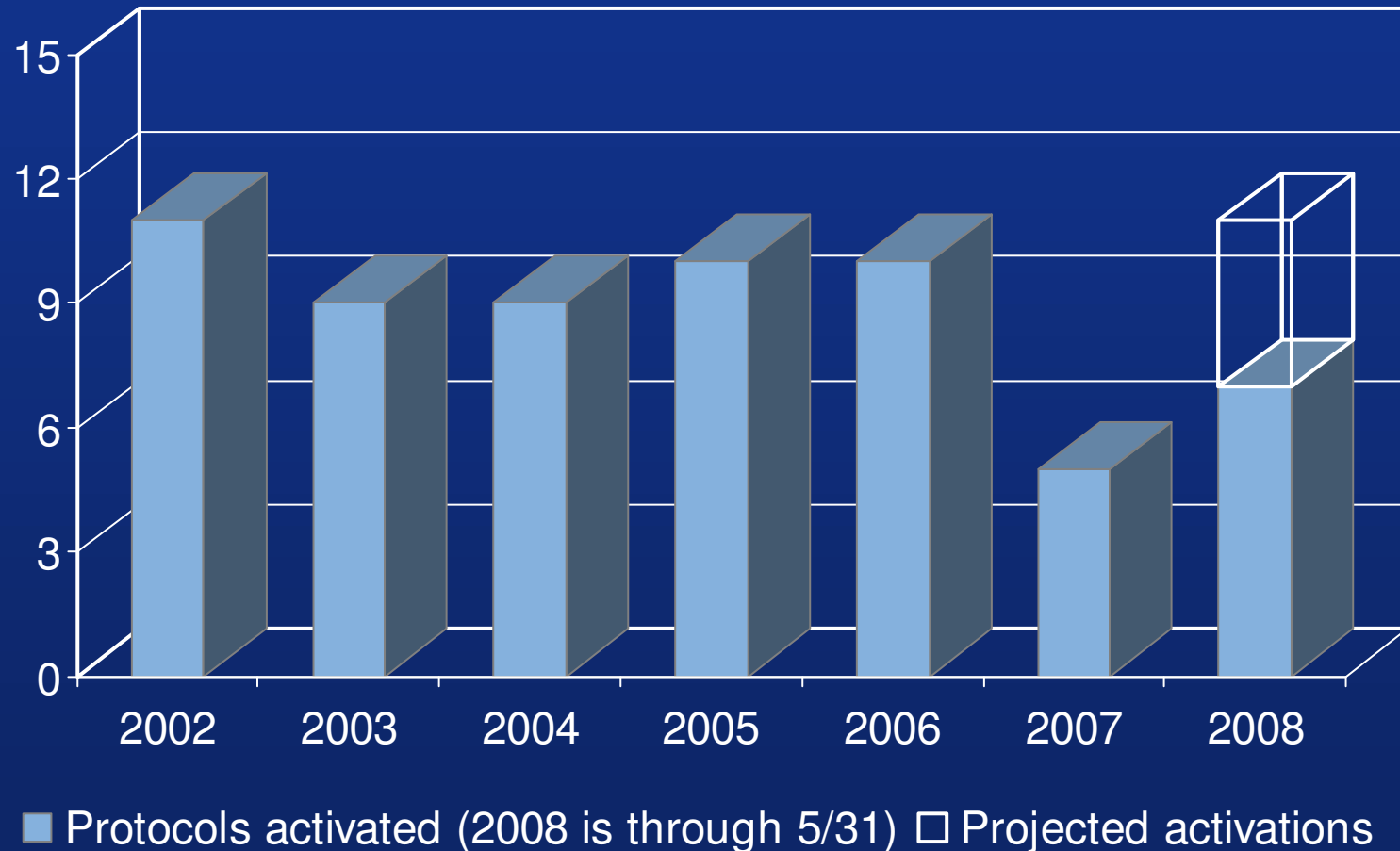
Cooperative Group Accrual/Awards

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



RTOG Protocol Activations

CTEP Protocols



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

Race	%
American Indian/ Alaska Native	0.5%
Asian	1.4%
Native Hawaiian/ Pacific Islander	0.2%
Black or African American	12.0%
White	83.3%
More than One Race	0.1%
Unknown or not Reported	1.6%
Prior to ethnicity; Race = Hispanic	0.9%

Non-Gender Specific Trials	%
Female	36.3%
Male	63.5%
Unknown	0.2%

Ethnicity	%
Hispanic or Latino	3.3%
Not Hispanic or Latino	92.4%
Unknown	4.3%

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!