SITEMAN CANCER CENTER

Leveraging Innovation to Design Future Clinical Trials

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A National Cancer Institute Comprehensive Cancer Center
BARNES-JEWISH Hospital
Washington University in St. Louis School of Medicine

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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)

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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

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National Clinical Trial Network

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

NCI Cooperative Group Restructuring

NRG	ECOG-ACRIN	Alliance	SWOG	COG
NSABP: National Surgical Adjuvant Breast and Bowel Project **RTOG:** Radiation Therapy Oncology Group **GOG:** Gynecologic Oncology Group	**ECOG:** Eastern Cooperative Oncology Group **ACRIN:** American College of Radiology Imaging Network	**NCCTG:** North Central Cancer Treatment Group **CALGB:** Cancer and Leukemia Group-B **ACOSOG:** American College of Surgeons Oncology Group	**SWOG:** Southwest Oncology Group	**COG:** Children's Oncology Group *Formerly:* *CCG* *POG* *NWTS* *IRSG*

IROC IMAGING AND RADIATION ONCOLOGY CORE

Global Leaders in Clinical Trial Quality Assurance

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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

Imaging and Radiation Oncology Core Group

IROC
IMAGING AND RADIATION ONCOLOGY CORE
Global Leaders in Clinical Trial Quality Assurance
ACR

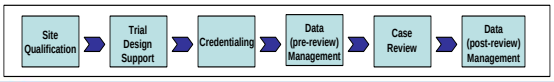
IROC's Definition
Who Are WE?

Imaging and Radiation Oncology Core (IROC) QA Consortium

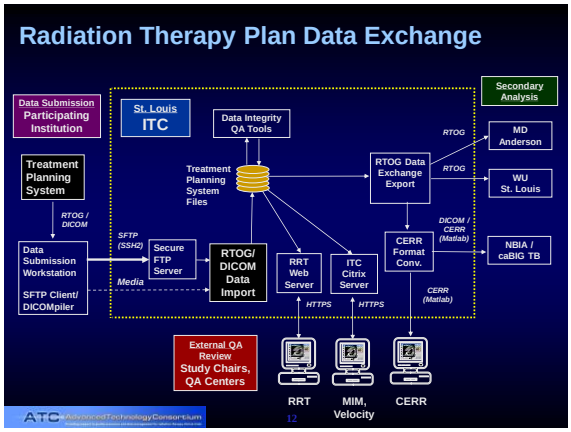
- New clinical trials Quality Assurance organization comprised of 6 QA Centers with individual PIs
- IROC RT and Imaging Centers have an extensive experience, knowledge and infrastructure to improve the quality of clinical trials

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)



IROC IMAGING AND RADIATION ONCOLOGY CORE — Global Leaders in Clinical Trial Quality Assurance



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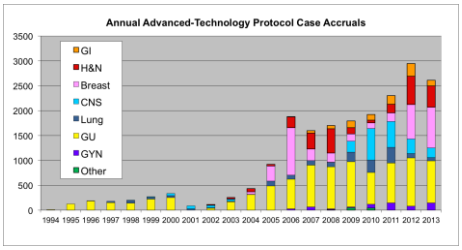
Protocol Case Submissions to ATC



- More than 20,000 complete, volumetric datasets have been collected at ITC from >750 institutions, using 12 commercial TPS as of 10/15/13.

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QA infrastructure as a resource

- Uses of RT data to improve outcomes
  - Treatment plan database (0617)
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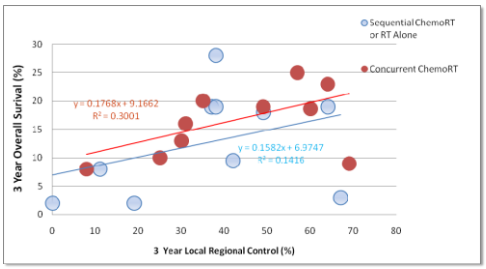
NSCLC Local control = Survival



RTOG 0617

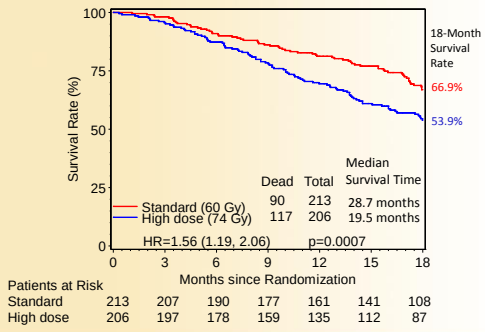
A Randomized Phase III Comparison of Standard-Dose (60 Gy) Versus High-Dose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab In Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer (NSCLC)

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

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

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

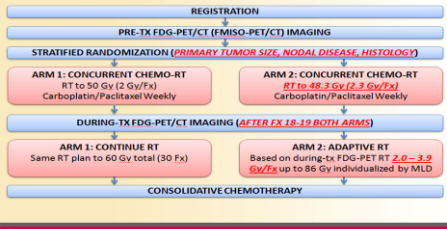
Contouring scores for TVs, OARs, DVA of TVs, OARs, elapsed days were reviewed

QA measure	Standard Dose 60Gy Per Protocol	High Dose 74Gy Per Protocol	p-value
Overall RT Review	82.9%	73.9%	0.02
Elapsed RT days	89.9%	83.0%	0.04
PTV Contour	92.8%	86.0%	0.03
Brachial plexus contour	92.3%	85.5%	0.03

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



NRG ONCOLOGY™

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

SCHEMA

STRATIFY

Stage
1. II
2. IIIA
3. IIIB

Histology
1. Squamous
2. Non-Squamous

Concurrent Chemotherapy Doublet Type
1. Carboplatin/paclitaxel
2. Cisplatin/etoposide

RANDOMIZE

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

Arm 2: Proton dose—70 Gy (RBE), at 2 Gy (RBE) 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 (RBE) without exceeding tolerance dose-volume limits of all critical normal structures.**

NRG ONCOLOGY™

PI: Zhongxing Liao, MD

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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 followup
  - Secondary goal is identifying patients who may benefit from early salvage or additional treatments
- 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.

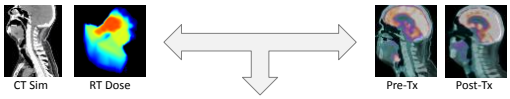
NRG ONCOLOGY

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			
	1. Larynx			**8-9 Weeks Post-Treatment**
	2. Non-Larynx			
			[b]**Arm 1**	
	Nodal Status		Accelerated Fractionation	**Reassessment**
S	1. N0	[a]**R**	by Concomitant Boost	Required CT scan
T	2. N1, N2a, N2b	**A**	(AFX-CB) or IMRT	or MRI for N2-N3[c]
R	3. N2c, N3	**N**	plus cisplatin	and N1-N2c patients[c]
A		**D**		
T	**Zubrod Status**	**O**		These patients also
I	1. 0	**M**		can receive post-treatment PET/CT
F	2. 1	**I**	[b]**Arm 2**	
Y		**Z**	Accelerated Fractionation	scan
	Use of IMRT	**E**	by Concomitant Boost	
	1. No		(AFX-CB) or IMRT	If suspicion of relapse:
	2. Yes		plus cisplatin	Directed biopsy
			plus cetuximab	
	Pre-Treatment PET/CT			
	1. No			
	2. Yes			

RTOG 0522

Data Integration



ITC DB
RTOG 0522

VelocityAI Integration

ACRIN DB
ACRIN 4500

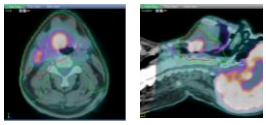
RTOG 0522

- Diagnostic PET registered to Planning CT using deformation
- Choose isodose values from RT Dose object

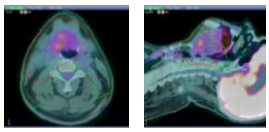
RTOG 0522

- 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



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Advancing RT – Adaptive

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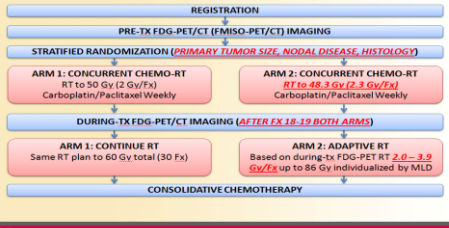

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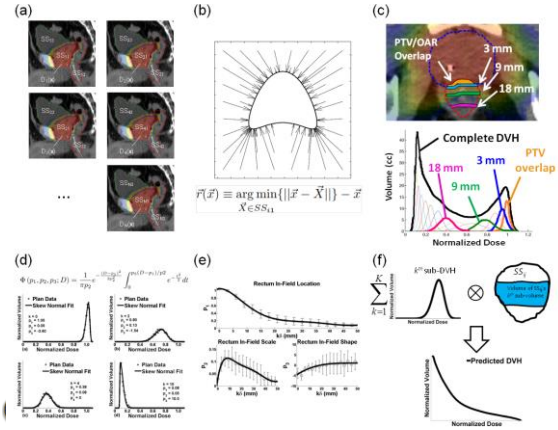
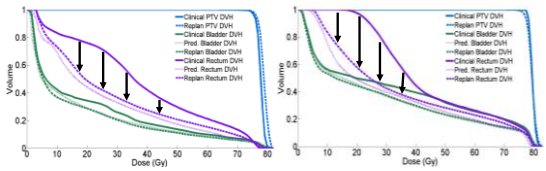


Inter-institutional QC at a small radiotherapy clinic

Average Reduction in V65 and V40 for Rectum and Bladder				
Organ	V65(orig)-V65(replan)	dV65	V40(orig)-V40(replan)	dV40
Rectum	4.8%±2.3%	0.9%±1.1%	17.9%±10.3%	0.7%±1.4%
Bladder	3.4%±2.1%	0.4%±0.5%	6.0%±2.8%	0.6%±0.9%



Appenzoller et. al. AAPM 2013 (BEST IN PHYSICS) 33

RTOG 0126: study schema

STRATIFY

1. Risk Group
   - Gleason Score 6 and PSA 10-20
   - Gleason Score 7 and PSA ≤15
2. Treatment
   - 3DCRT
   - IMRT

RANDOMIZE

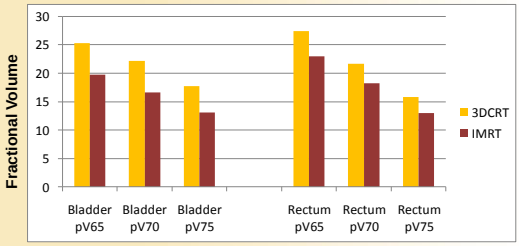
Arm 1
Minimum PTV prescription 70.2Gy in 39 fractions

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

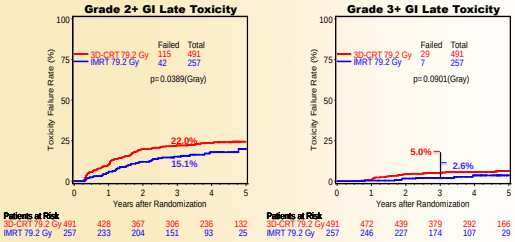
RTOG 34

IMRT vs 3DCRT Dosimetric comparison



All differences statistically significant p<0.0001

Time to Late GI Toxicity



Grade 2+ GI Late Toxicity – Multivariate Analysis

Stratified variables	variables categories	HR	95%CI	p-value
RT method	3D-CRT 79.2Gy	RL		
	IMRT 79.2Gy	0.728	(0.511, 1.035)	0.077
Age	≤ 70	RL		
	> 70	1.126	(0.820, 1.547)	0.460
Race	White	RL		
	Non-white	0.364	(0.202, 0.655)	0.001†

*Fine-Gray statistics. † Statistical significant at 0.05.

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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

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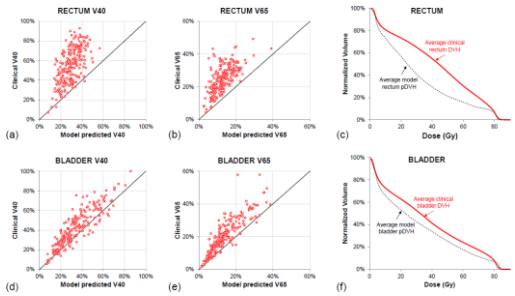
RTOG 0126 analysis-210 cases



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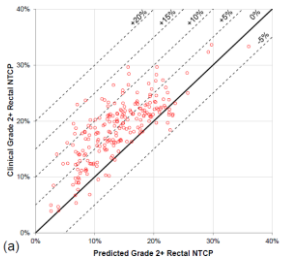
NTCP model: Excess risk of toxicity?



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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