

American College of Radiology

Annual Progress Report: 2009 Formula Grant

Reporting Period

July 1, 2013 – December 31, 2013

Formula Grant Overview

The American College of Radiology (ACR) received \$2,043,960 in formula funds for the grant award period January 1, 2010 through December 31, 2013. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Novel Methods for Cancer Clinical Trial Design and Analysis - Clinical trials provide the critical evidence necessary to advance treatment for cancer. With the ever growing number of promising interventions, there is a need for improvements in trial design in order to a) obtain answers more quickly, b) conserve and optimize resources, and c) make better choices of what treatments to pursue in further evaluation. In addition, as treatment regimens become more complex and multimodal, the ability to accurately characterize whether anticipated benefits with respect to specific disease event reduction have occurred requires extensions of standard analytic methods. To address these needs, we propose a series of methodological projects aimed at addressing current questions in clinical trial design and analysis. These projects encompass a range of needs that apply broadly to cancer clinical trials and research in general.

Duration of Project

1/1/2010 - 6/30/2013

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement C.U.R.E. Annual Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.

Research Project 2: Project Title and Purpose

Exploration of the RTOG Clinical Trial Database – Beyond Protocol-Specified Endpoints For over 40 years, the Radiation Therapy Oncology Group (RTOG) has been funded by the National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. Drawing upon this vast resource of demographic, treatment, outcome, and patient-reported data, the researchers will develop hypotheses and explore correlations that were not defined in the treatment protocols for patients with brain, cervix, gastrointestinal, head

and neck, lung, and prostate cancer. These analyses may lead to future protocols and/or better ways to identify high-risk subgroups and screen patients for specific treatment regimens.

Duration of Project

1/1/2010 - 12/31/2013

Project Overview

RTOG investigators complete analyses and report on the endpoints specified in each NCI-approved protocol. Frequently these analyses raise questions or point to other potential hypotheses that were not included in the original protocol. Likewise, current literature and new research may point to areas of interest or possible correlations that were unknown during the design of the original protocol. The broad objectives of this research proposal are to (i) generate hypotheses and explore correlations that may lead to more efficient clinical trials and more patient-targeted treatments, and (ii) explore novel ways of analyzing the demographic (age, gender, race), treatment (including dose, volume, duration), outcome (survival, disease-free survival, time-to-progression), and quality of life (frequency/severity of adverse events, patient-reported outcomes) data in the RTOG database to potentially develop new tools for determining the best treatment regimen for each patient based upon their personal profile.

Principal Investigator

Kathryn A. Winter, MS
RTOG Director, Statistics
Radiation Therapy Oncology Group
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Other Participating Researchers

Daniel Hunt, PhD, Jonathan Harris, MS, Jennifer Moughan, MS, Rebecca Paulus, MS, Wendy Seiferheld, MS – employed by American College of Radiology

Expected Research Outcomes and Benefits

The identification of pre-treatment patient characteristics and demographics associated with better or worse outcome for cancer patients may allow future researchers to generate new hypotheses to address outcome disparities due to age, race, ethnic origin or gender. Exploring the radiation therapy dose volume histogram data in more detail will help with better definitions of dose constraints in future trials. In addition to aiding in the conduct of clinical trials, this type of research may help to tailor treatments to individual patients based on their demographic and/or treatment characteristics profile.

Summary of Research Completed

Statistical Methods

This recursive partitioning analysis (RPA) considers models derived by five splitting methods for censored data described by Zhang and Singer and implemented by Zhang's free "stree" software, <http://c2s2.yale.edu/software/stree/>, for the overall survival of patients from six Radiation Therapy Oncology Group (RTOG) unresectable pancreas cancer studies. Each splitting method (likelihood, log-rank, Kaplan-Meier distance, adaptive normalization, and global normalization) provided a survival tree with patients grouped into as few as seven and as many as eleven mutually exclusive terminal nodes of the tree.

These patient groups were then combined in order to arrive at a simpler model with statistically significantly distinct groups, which are called RPA classes. In this process, overall survival was estimated using the Kaplan-Meier method and compared between groups with the log-rank test. Hazard ratios were derived from the Cox regression model. The final models were decided by taking the statistical and visual comparisons of the terminal node survival distributions into account, along with an attempt to group patients meaningfully when possible.

Statistical Analysis

This analysis used data from seven RTOG unresectable pancreas cancer studies which are described in Table 1: 8505, 8801, 9102, 9209, 9812, 0020, and 0411. All of the studies had treatments which included radiation (RT) and chemotherapy. The following variables were used: age (continuous), gender, t-stage (T1, T2, T3, T4, TX), n-stage (N0, N1, N2, NX), and Zubrod (0, 1). Percent weight loss, largest tumor dimension, and location of primary tumor were not included because they were not collected on all of the studies. For studies that collected Karnofsky performed status (KPS), it was converted to a Zubrod score. Twelve patients with Zubrod scores of 2 (or equivalent KPS scores) were excluded from the analysis, resulting in data on a total of 593 eligible patients. N-stage was categorized for the RPA as N0 vs. all others and one TX patient was grouped with unknown and missing t-stage patient for the purpose of the RPA.

Table 2 presents baseline characteristics and the distribution of patients across the studies.

Table 3 describes the final models achieved from the different RPA splitting methods. The table lists all variables appearing in the initial full tree, the number of classes in the final model, the hazard ratios and log-rank p-values comparing the ordered classes, and a description of each class with median survival time. In some cases both a two-class and three-class model is provided. Although one would prefer more than two distinct RPA classes, it did not appear possible for a majority of the models. The likelihood survival tree could not be reduced to statistically significantly distinct classes.

Table 1
Contributing RTOG Studies
(n*=593)

Study	n (%)	Title
8505	71 (12.0%)	Phase I/II Study of Intraoperative and External Radiotherapy plus 5-FU for Resectable, Unresectable, and Localized Adenocarcinoma of the Pancreas
8801	77 (13.0%)	Phase I/II Study of Prophylactic Hepatic Irradiation plus Local Irradiation and Systemic Chemotherapy with 5-FU in Patients with Unresectable Adenocarcinoma of the Pancreas
9102	27 (4.6%)	Phase III Randomized Trial of Chemoradiotherapy using 5-FU with vs without Electron-Beam Intraoperative Irradiation in Patients with Unresectable, Nonmetastatic Adenocarcinoma of the Pancreas
9209	47 (7.9%)	Phase I/II Study of Hyperfractionated External-Beam Radiotherapy, Prophylactic Hepatic Radiotherapy, and Concurrent 5-FU/Low-Dose CF in Patients with Unresectable Carcinoma of the Pancreas
9812	105 (17.7%)	A Phase II Trial of External Irradiation (50.4 GY) and Weekly Paclitaxel (Taxol) for Non-Metastatic, Unresectable Pancreatic Cancer
0020	184 (31.0%)	A Randomized Phase II Trial of Weekly Gemcitabine, Paclitaxel and External Irradiation (50.4 Gy) Followed by the Farnesyl Transferase Inhibitor R115777 (NSC #702818) for Locally Advanced Pancreatic Cancer
0411	82 (13.8%)	A Phase II Study of Bevacizumab with Concurrent Capecitabine and Radiation Followed by Maintenance Gemcitabine and Bevacizumab for Locally Advanced Pancreatic Cancer

*Eligible patients

Table 2
Pretreatment Characteristics
(n=593)

Age	
Median	62
Min - Max	29 - 84
Gender	
Male	310 (52.3%)
Female	283 (47.7%)
Zubrod	
0: Fully Active	292 (49.2%)
1: Restricted	301 (50.8%)
T-Stage	
T1	50 (8.4%)
T2	102 (17.2%)
T3	193 (32.5%)
T4	232 (39.1%)
TX	1 (0.2%)
Unknown/Missing	15 (2.5%)
N-Stage	
N0	346 (58.3%)
N1	161 (27.2%)
N2	2 (0.3%)
NX	68 (11.5%)
Unknown/Missing	16 (2.7%)
Percent Weight Loss	
None	23 (3.9%)
<=10%	104 (17.5%)
>10%	187 (31.5%)
Unknown/Missing	279 (47.0%)
Largest tumor dimension of primary	
<5cm	192 (32.4%)
>=5cm	158 (26.6%)
Unknown/Missing	243 (41.0%)
Primary Location	
Head	337 (56.8%)
Body,Tail,Neck,Body&Tail ,Head/Body,or Diffuse	172 (29.0%)
Unknown/Missing	84 (14.2%)

**Table 3
Summary of Final RPA Models**

Method	Full tree ¹	Groups	Comparison	HR ²	95% CI	p-value ³	RPA Classes					
							n	RPA I (best)	n	RPA II	n	RPA III
Adaptive Norm.	Age Zubrod T-stage Gender	3	II vs. I III vs. II	2.24 2.18	(1.06, 4.73) (1.58, 3.00)	0.0276 <0.0001	10	Z0, T1, age > 71 MST=12.9 mo.	525	Other MST=8.9 mo.	42	Z1, T3+, age > 63, female MST=3.5 mo.
		2	II vs. I	2.21	(1.60, 3.05)	<0.0001	535	Other MST=9.0 mo.	42	Z1, T3+, age > 63, female MST=4.5 mo.		N/A
Global Norm.	Age Zubrod T-stage	2	II vs. I	1.33	(1.09, 1.63)	0.0043	446	Other MST=9.3 mo.	138	Age > 63 & Z1 MST=6.4 mo.		N/A
Log-Rank	N-stage Age T-stage	2	II vs. I	1.46	(1.23, 1.75)	<0.0001	219	N0+T4 & age 53-67 or N1,N2,N3 & age 54-77 MST=11.3 mo.	357	Other MST=7.8 mo.		N/A
KM Distance	Age Gender N-stage	3	II vs. I III vs. II	1.28 1.72	(1.07, 1.53) (1.21, 2.46)	0.0061 0.0028	231	age 38<-41 or age 75<-77 or age 45<-73 & N1,N2,NX or age <=77 & female MST=9.8 mo.	315	Age <=38 or Age 73<-75 or Age 45<-73 & N0 MST=8.2 mo.	35	age>77 & female or age 41<-45 MST=4.7 mo.
		2	II vs. I	2.19	(1.40, 3.42)	0.0005	561	Other MST=8.8 mo.	20	Age>77, fem MST=4.4 mo.		N/A
Likelihood	Age N-stage T-stage	Could not find any clear separation of nodes.										

¹ All variables that appeared in the full RPA tree

² A hazard ratio greater than one for group A vs. B indicates an increased risk for group compared to group B.

³ Log-rank test

Research Project 3: Project Title and Purpose

Emerging Imaging Technology Clinical Trials in PA: Comparison of Full Field Digital Mammography with Digital Breast Tomosynthesis Imaging: Comparison of Recall Rates The purpose of this multi-center study, to be conducted as part of the American College of Radiology Imaging Network – Pennsylvania, is to evaluate the digital breast tomosynthesis screening recall rates compared to routine 2D projection digital mammography. The goal is to understand if a hybrid combination of 3D tomosynthesis and low dose 2D digital mammography can significantly reduce the recall rate of women from screening mammography without a concomitant reduction of sensitivity of cancer detection.

Duration of Project

1/1/2010 - 12/31/2013

Project Overview

Previous C.U.R.E. funding established a network of medical centers in Pennsylvania (ACRIN PA) with the broad goal of advancing the role of imaging in the detection and/or treatment of disease by conducting early stage imaging clinical trials. This project seeks to continue the work of that network. A multi-institutional clinical trial is proposed to evaluate the impact of breast tomosynthesis on the recall rate of screening mammography.

Study Hypothesis: Digital breast tomosynthesis (DBT) will improve the specificity of breast cancer screening as measured by a reduction in the recall rate while maintaining the sensitivity of cancer detection. This improved accuracy will be achieved by the optimization of the imaging sequence and number of views obtained at a capped radiation dose in the combined DBT and 2D screening sequence.

Principal Investigator

Mitchell D. Schnall, MD, PhD
Professor of Radiology
University of Pennsylvania
Dept. of Radiology
Hospital of the University of Pennsylvania
3400 Spruce St.
Philadelphia, PA 19104

Other Participating Researchers

Emily Conant, MD – employed by University of Pennsylvania
Andrew Maidment, PhD – employed by University of Pennsylvania
Constantine Gatsonis, PhD – employed by Brown University

Expected Research Outcomes and Benefits

Screening mammography has been extensively criticized for the high rate of false positive interpretations, a subgroup of which is the recall of patients for additional diagnostic imaging for “pseudolesions” or superimpositions of normal tissue, perceived on screening mammography to be potentially significant lesions that on additional imaging prove to be normal. With competing parameters of specificity and sensitivity, mammographic screening must both limit missed cancers and reduce false positive call-backs. Tomosynthesis, a new emerging technology that allows the 3D reconstruction of images, has shown early evidence suggesting that it could significantly reduce the rate of false positive recalls from screening without a loss of sensitivity or breast cancer detection.

There are few published trials on breast cancer screening with tomosynthesis partly because the optimal procedural metrics for tomosynthesis have not been fully defined. Manufacturers have different platforms that offer different views, different angles, and different dose and exposure levels. The exact number of tomosynthesis views of the mediolateral-oblique (MLO) view only or both MLO and cranio-caudal (CC) tomosynthesis views varies while the screening imaging sequence with or without 2D digital mammography remains controversial. This disparity in image number and image acquisition parameters may alter the balance between specificity and sensitivity and significantly affect radiation dose. The expected outcome of this research is to show that the incorporation of tomosynthesis in the screening paradigm can reduce the number of false positive interpretations without a loss of cancer detection. This improvement in screening specificity must be gained while limiting both the number of imaging views and the radiation dose to the patient.

Summary of Research Completed

Data Analysis

During the reporting period (July, 2013-December, 2013), additional evaluation continued on the call-back frequency and overall recommendations as compared between Full Field Digital Mammography (FFDM) and Digital Breast Tomosynthesis (DBT) as noted in Tables 1 and 2 below. There were 17 cases called back from both FFDM and DBT, 12 cases called back from FFDM only and 17 cases called back from DBT only. Of the 12 cases called back from FFDM only, 6 were thought to be due to “pseudolesions” seen on the 2-D imaging that were not seen on 3-D that on diagnostic imaging at call-back were normal. The other 6 cases were felt to be due to different levels of threshold for call-back between the readers of the FFDM and the DBT arms, or inter-reader variability. Of the 17 cases called back only from DBT, 11 cases had real lesions seen better on DBT (i.e., cyst, lymph nodes) that were benign. Five of the cases were thought to be due to reader variability and different thresholds for call-back. One patient called back from DBT but not from FFDM was lost to follow-up.

Results Reporting

Primary Aim

To compare recall rates of FFDM to the limited DBT set (digital breast two-view tomosynthesis with low-dose MLO) [Group A].

During the reporting period, discussion continued as to how best to publish the study results as the abstract submitted to the Radiological Society of North America (RSNA) was not accepted. A manuscript is presently being prepared for submission to *Academic Radiology* that will address the methodologic aspects of the trial, specifically the important step when evaluating a new modality that readers be recruited and trained and that the progress of the trial should be carefully monitored so that 1) readings between modalities are balanced and 2) an adequate number of cases are read by each individual reader so that any *difference between modality* will not be lost due to a larger variability *between readers*.

Secondary Aims

1. To calculate and compare the radiation dose of the FFDM and the DBT sets.
2. To identify the determinants of participant radiation dose and clinical image quality, including factors such as kVp, mAs, target/filter combination, and breast thickness and composition.

The following abstracts reported results at the Radiological Society of North America, Chicago, December 1-6, 2013.

- Kontas D, Choi J, Keller B, Conant E, Maidment A. Effect of Reduced Radiation Dose on Breast Density Estimation in Digital Mammography: Data from the ACRIN 4006 Trial.
- Thomas M, Matsutani Y, Conant E, Maidment A. ACRIN PA 4006: Effect of Device Technical Factors on Patient Dose in a Prospective Digital Breast Tomosynthesis Screening Trial

- Thomas M, Matsutani Y, Conant E, Maidment, A. ACRIN PA 4006: Comparison of Dose in Digital Breast Tomosynthesis and Standard Two-View Mammography for Prospective Breast Cancer Screening Trial
- Thomas M, Matsutani Y, Choi J, Kontos D, Conant E, Maidment, A. ACRIN PA 4006: Characterization of Mean Glandular Dose Adjusted to Volumetric Breast Density in a Prospective Digital Breast Tomosynthesis Screening Trial

Currently, manuscripts for submission to peer-reviewed journal are in preparation.

Table 1: Comparison of recommendations from FFDM versus DBT imaging

FFDM (OVERALL RECOMMENDATIONS)		TOMO (OVERALL RECOMMENDATIONS)		
Frequency		Recall for additional diagnostic imaging	Routine follow-up	Total
	Recall for additional diagnostic imaging	17	12	29
	Routine follow-up	17	455	472
Total		34	467	501

Table 2: Comparison of called back frequency from FFDM and DBT

Called Back		
type	Frequency	Cumulative Frequency
Mammo and Tomo	17	17
Mammo Only	12	29
Tomo Only	17	46
neither	455	501

Research Project 4: Project Title and Purpose

Investigation and Analyses of Patient Co-Morbidities in a Survey of Radiation Oncology Facilities in the USA and their Association with Treatment Decisions in Radiation Oncology -
 The purpose of this project is to describe the distribution of co-morbidities by socio-demographic characteristics such as age, race, geographic region, insurance status and socio-economic status

in patients diagnosed with cancer of the breast, cervix, stomach, lung and prostate, to investigate the association of the prevalence of co-morbidities with treatment decisions and variations in compliance with recommended disease management guidelines for such patients, and to examine the interaction of co-morbidities by site and stage of disease with gender, race, and age.

Duration of Project

1/1/2010 - 7/2/2012

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement C.U.R.E. Annual Reports on the Department's Tobacco Settlement/Act 77 web page at <http://www.health.state.pa.us/cure>.