American College of Radiology

Annual Progress Report: 2012 Formula Grant

Reporting Period

July 1, 2012 – June 30, 2013

Formula Grant Overview

The American College of Radiology received $1,851,408.00 in formula funds for the grant award period January 1, 2013 through December 31, 2016. Accomplishments for the reporting period are described below.

Research Project 1: 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, and outcome data, the researchers will test new hypotheses and explore associations that were not defined in the treatment protocols for patients with gynecologic, head and neck, lung, and prostate cancers. These analyses may inform and/or lead to future protocols.

Anticipated Duration of Project

7/1/2013 – 12/31/2016

Project Overview

This project aims to analyze data that have been collected in previous RTOG studies. The specific research objectives of this project relate to six data analysis efforts.

*Aim 1: Correlation of Radiation Therapy Dose Volume Histogram (DVH) Data with GI Toxicity in Post-Operative Cervical and Endometrial Cancer Patients Treated with IMRT: RTOG 0418* is a Phase II trial that evaluated the use of IMRT in post-operative cervical and endometrial cancer patients. Using data collected from this trial, we will correlate the radiation therapy DVH data, relative to the amount of bowel receiving radiation, with reported GI adverse events.

*Aim 2: Evaluation of the Impact of Treatment Time for Head and Neck Cancer Patients Treated with Radiation Therapy:* Using data collected from 3 RTOG Phase III Head and Neck Cancer Trials (RTOG 9003, 9111, and 9501), we will evaluate whether or not a longer radiotherapy treatment time is associated with a significantly worse clinical outcome.
Aim 3: Evaluation of Outcome in Squamous Cell Carcinoma of the Head and Neck (SCCHN) Based on Age: Using data collected from several RTOG combined modality Head and Neck cancer trials (RTOG 8527, 9003, 9111, 9703, 9903, 9914, 0129, and 0522), we will evaluate efficacy outcomes & Adverse Events (AE) by age categorizations: ≥ 70 vs. < 70 and ≤ 60 vs. 61-69 vs. ≥ 70.

Aim 4: Evaluation of Incidental Cardiac Irradiation on Toxicity and Survival in Stage IIIA/IIIB Non-Small Cell Lung Cancer (NSCLC) Patients Treated with Chemoradiotherapy: Using data from RTOG 0617, we will correlate the radiation therapy dose volume histogram data, relative to the amount of heart receiving radiation, with cardiac and pulmonary AEs and overall survival.

Aim 5: Evaluation of Hormone Therapy Length on Outcome for Intermediate Risk Prostate Cancer Patients: We will evaluate whether or not radiotherapy with long-term hormones (28 months) is associated with better outcome than radiotherapy with short-term hormones (4 months) for the RTOG 9202 subset of intermediate-risk prostate cancer patients.

Aim 6: Evaluation of Changes in Serum Testosterone Levels in Prostate Cancer Patients Treated with Radiotherapy Alone: We will evaluate associations between radiated area (prostate vs. whole pelvis) and changes in serum testosterone for the patients treated on the radiotherapy alone arm of RTOG 9408.

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Expected Research Outcomes and Benefits

Aim 1: Correlation of Radiation Therapy Dose Volume Histogram Data with GI Toxicity in Post-Operative Cervical and Endometrial Cancer Patients Treated with IMRT: Results from this aim will inform dose constraints for future IMRT GYN trials to help minimize GI adverse events.

Aim 2: Evaluation of the Impact of Treatment Time for Head and Neck Cancer Patients Treated with Radiation Therapy: Results from this aim may impact the approach to treatment breaks and will help to inform treatment time components of future trials.
Aim 3: Evaluation of Outcome in Squamous Cell Carcinoma of the Head and Neck (SCCHN) Based on Age: Results from this aim may identify subsets of patients by age that are associated with a benefit from certain treatment regimens and/or associated with significantly better/worse treatment adverse events. This will help to form the basis for future SCCHN clinical trials.

Aim 4: Evaluation of Incidental Cardiac Irradiation on Toxicity and Survival in Stage IIIA/IIIB Non-Small Cell Lung Cancer (NSCLC) Patients Treated with Chemoradiotherapy: Results from this aim will help to define critical anatomic cardiac structures and inform the dose constraints to be used on future lung and other trials where the heart is in the area of the radiation treatment field.

Aim 5: Evaluation of Hormone Therapy Length on Outcome for Intermediate Risk Prostate Cancer Patients: Results from this aim may lead to a trial to definitely evaluate radiotherapy with long-term hormones in the intermediate-risk prostate cancer patient population.

Aim 6: Evaluation of Changes in Serum Testosterone Levels in Prostate Cancer Patients Treated with Radiotherapy Alone: Results from this aim may lead to improvements in the amount of scatter radiation to the testes. This data may also serve as a control group for a future project to evaluate associations between radiotherapy modality and serum testosterone changes.

Summary of Research Completed

This new start date for this project is 7/1/2013. There were no funds spent and there is no information to report for 1/1/2013-6/30/2013.

Research Project 2: Project Title and Purpose

Community Learning of a Prediction Model for Treatment Outcome in Head and Neck Cancer Patients for Radiation Therapy Decision Support – Personalized medicine for head and neck cancer (HNC) is promising, but validated decision support systems are needed to make the promise a reality. A decision support system relies on a model to predict treatment outcome (e.g. survival, quality of life, toxicity). Such a model can be developed through a machine learning process using a well-organized database and query system that is designed for a community based rapid learning approach. This project aims to build such a model to guide head and neck radiotherapy treatment, and includes the development of an IT infrastructure for the Radiation Therapy Oncology Group (RTOG) to manage and deploy the clinical trial data needed for machine learning and building predictive models for radiotherapy treatment of HNC.

Anticipated Duration of Project

7/1/2013 – 12/31/2016

Project Overview

This project will test the hypothesis that it is feasible to build a decision support system to provide personalized radiotherapy treatment plans for head and neck cancer (HNC) patients. Three specific aims are proposed as follows:
Specific Aim 1. **Build an IT infrastructure for machine learning.** Clinical trial data used for machine learning requires full semantic interoperability so that the local data can be translated into a centralized database. The IT infrastructure also needs to support a community based rapid learning approach where routine patient data from many institutions in many countries is shared for learning. The design of the underlying technology will combine a local semantic interoperable environment with a distributed learning framework. When new patients (or new members) in the community become available an updated model can be learned.

Specific Aim 2. **Modeling of survival in HNC based on our previous study.** Utilizing an established machine learning system, a model that predicts the treatment outcome (including survival, toxicity, etc.) in HNC patients will be studied using the RTOG protocol 0522 clinical trial data. Classical approaches such as the logistic regression model as well as the so-called second-generation machine learning approaches such as Bayesian networks will be employed for modelling. The model performance is quantitatively evaluated.

Specific Aim 3. **Extend the model by including more predictive parameters to improve model performance.** Functional imaging procedures are employed more widely in cancer diagnosis and treatment. Large amounts of biological and molecular information become available as well with the advancement of sequencing technology. The project will explore these additional predictors in modeling to enhance the predictive performance of models.

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**Expected Research Outcomes and Benefits**

Extracting knowledge in the form of a prediction model can be used to change care delivery. Very specific questions like “what radiation dose should this head and neck cancer patient
receive for an expected survival of X% at two years” can be answered. These are the type of questions that are being posed at the point of care.

The predictive models are built from a machine learning system that learns and shares knowledge while leaving the data behind the firewalls of the institutions. This system will be established as we complete Specific Aim 1 of this project. The important next step is to prove the rapid learning hypothesis that knowledge can be extracted from coordinated databases of routine care and clinical trial data sources. Using this system, learning can be done without data leaving the institute that holds the data.

The machine learning infrastructure can also be used to study other types of disease. Once deployed, the system can be leveraged in multiple research projects targeted at specific treatment modalities and specific cancers. Also, the technology is such that it can easily be applied outside of cancer. An open source solution, using semantic web technology and machine learning techniques, will boost the use of rapid learning in health care in the United States. The predictive models based on machine learning will be used to provide decision support in the personalized medicine era to give patients the best outcome: longer survival and better quality of life.

**Summary of Research Completed**

Due to protracted contract negotiations, funds were not available to begin this project during this reporting period. The new start date for the project is July 1, 2013.

**Research Project 3: Project Title and Purpose**

_Discovery of Plasma Biomarkers of Doxorubicin and Trastuzumab Induced Cardiotoxicity in Breast Cancer_ – The overall objective of this proposal is to discover novel circulating biomarkers using powerful proteomic profiling methods to identify patients at increased risk for doxorubicin and trastuzumab-induced cardiotoxicity, before conventional decreases in ejection fraction or heart failure are evident. The key deliverables from this study are: 1) we will identify specific protein biomarkers indicative of early, subclinical cardiotoxicity; 2) we will gain insight into the mechanisms of doxorubicin and trastuzumab-induced cardiotoxicity, leading to new targeted therapies to prevent and treat this disease; and 3) we will build a multi-disciplinary collaboration for the study of cardiotoxicity biomarkers that we can expand to other cancer therapies.

**Anticipated Duration of Project**

1/1/2013 – 12/31/2016

**Project Overview**

Doxorubicin and trastuzumab (Herceptin®) are used widely in the treatment of breast cancer, are highly effective, and have led to important survival gains. However, these agents carry a substantial risk of cardiovascular morbidity and mortality. There is currently no adequate methodology to recognize patients at high risk for cardiac complications, prior to overt disease.
The overall objective of this proposal is to discover novel circulating biomarkers using powerful proteomic profiling methods to identify patients at increased risk for both doxorubicin and trastuzumab-induced cardiotoxicity. Basic studies suggest potential mechanisms for cardiac dysfunction include oxidative stress, altered neuregulin/ErbB signaling, and anti-angiogenesis, but the true relevance of these findings in humans and the precise mechanisms of cardiotoxicity remain to be elucidated. Furthermore, doxorubicin and trastuzumab cardiotoxicity are likely secondary to multiple altered and potentially differing pathways, and not one single mechanism. The broad working hypothesis of this proposal is that multiple circulating biomarkers, identified through discovery proteomics, will detect cancer therapy-induced cardiotoxicity in patients before conventional decreases in Left Ventricular Ejection Fraction (LVEF) or heart failure (HF) are evident. In breast cancer patients undergoing therapy with doxorubicin and trastuzumab, we will determine if patterns of change over time in protein markers differ between patients who experience cardiotoxicity and those who do not. In Aim 1, we will identify novel plasma biomarkers associated with cardiotoxicity in breast cancer patients treated with doxorubicin and trastuzumab. In Aim 2, we will verify the most promising biomarkers associated with doxorubicin and trastuzumab cardiotoxicity.

Principal Investigator

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Other Participating Researchers

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Expected Research Outcomes and Benefits

The key outcomes from this novel study that will advance the field of cardio-oncology and improve the overall cardiovascular and oncology care of a growing cancer population are as follows: we will determine the utility of discovery plasma proteomics in identifying patients at risk for doxorubicin and trastuzumab-induced cardiotoxicity; and we will identify specific protein biomarkers whose changes in abundance levels are indicative of the early-stage development of cardiotoxicity. These two results alone will substantially advance the field of cancer therapy cardiotoxicity risk prediction. We will gain specific insights into the mechanisms of cancer therapy induced cardiotoxicity which has the potential to lead to new targeted therapies to prevent and treat cardiotoxicity. This strong foundation of research has the potential to grow into multiple additional studies: 1) further verification and validation of the biomarkers identified herein; 2) pursuit of biologic mechanism leads; 3) development of new cardioprotective therapies indicated by the biologic leads; and 4) expansion of biomarker discovery and validation to additional cancers and cancer therapies. This work will serve as a critical launching pad to further build a cardio-oncology translational research program statewide and nationally, and strengthen collaborations between investigators at the University of...
Pennsylvania, Eastern Cooperative Oncology Group (ECOG), and American College of Radiology Imaging Network (ACRIN). It is anticipated, pending funding from other sources, a working group will be convened, comprised of cardiologists, oncologists, academic clinicians, and researchers, with the goals of developing strategies to enhance the detection of cardiotoxicity; innovative and cost-effective strategies for treatment and follow-up of cardiotoxicity; and recommendations for the management of cardiac comorbidities in cancer survivors. Health Research Funds from the Department of Health shall not be used to pay for expenses related to the work of this Committee.

Summary of Research Completed

This project was awarded on 4/15/2013. During the reporting period, April 15-June 30, efforts have focused on organizing study procedures, obtaining appropriate regulatory committee approvals, and negotiating contracts. Drs. Ky and Speicher and Lynn Beers have met multiple times (bimonthly) during this time period to review study procedures. Samples (cases and controls at longitudinal time points) have been carefully selected and provided to the Wistar Institute for analyses. The Wistar Institute has begun initial sample preparations in their lab for these analyses.

Research Project 4: Project Title and Purpose

Novel Statistical Analysis and Evaluation Methods for Multiple Endpoints in Cancer Clinical Trials – Clinical trials provide critical evidence necessary to advance clinical development in cancer research. The increasing number of promising new interventions mandates the improvement in clinical trial design and analysis, such that we can a) better understand disease progression; b) address clinical interests more quickly and efficiently; and c) conserve and optimize resources by terminating unpromising trials early. To address these needs, we propose a series of methodological projects aimed at addressing current questions in multiple endpoints in cancer clinical trials. These projects encompass a range of needs and challenges that apply broadly to cancer clinical trials and clinical research in general.

Anticipated Duration of Project

1/1/2013 – 12/31/2016

Project Overview

Aim 1: Assessment of correlation between PFS and OS based on a Weibull model: Progression-free survival (PFS) has been used as a surrogate marker for overall survival (OS) in oncology clinical trials. Accurate estimation of correlations between the two endpoints is important for trial design and outcome modeling. In previous work, an exponential model was considered for this purpose. However, observed hazard rates are often non-constant across time. In this research we aim to establish a Weibull correlation model which can provide more realistic estimates for this important quantity.
Aim 2: Estimating Hazard of Failure Over Time in Early Prostate Cancer – Typically, time to event data is summarized using aggregate measures such as time to event functions (i.e., survival curves, cumulative incidence curves) or cumulative hazards. The hazard function, being a dynamic time-varying process, may reveal features of the failure pattern over time that may have both biologic and clinical implications. However, hazard functions present challenges in terms of estimation and interpretation. In prostate cancer specifically, there are numerous questions regarding an individual’s risk of failures of different types (biochemical failure, frank clinical disease, prostate cancer death and competing cause death) that have bearing on clinical management, as well as on gaining a better understanding of the disease process. We will investigate and compare different recently developed hazard estimation methods, and apply these to practical questions in long-term follow-up after treatment for localized prostate cancer.

Aim 3: Evaluation of PFS and OS based on a progressive multistate model: In oncology clinical trials, PFS is often considered as a putative surrogate endpoint for OS due to its clinical relevance and correlation with OS. However, the high correlation between PFS and OS, as well as the improvement in PFS alone do not always translate into an improvement in OS directly, therefore systematic evaluation and appropriate statistical models for PFS and OS are needed to address this issue. We propose to investigate and identify factors that may influence statistical inference of OS with reference to that of PFS.

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Yimei Li, PhD – employed by Children’s Hospital of Philadelphia

Expected Research Outcomes and Benefits

Clinical trials are a critical component of cancer research to advance effective interventions to prolong the survival of patients and save lives, and it is only through systematic and comprehensive evaluation in a clinical trial setting that the risks and benefits of treatment options can be assessed. However, the process of cancer clinical research can be slower than expected and resources are limited, especially with the tremendous amount of information that needs to be collected. Meanwhile, for clarity and robustness, a single primary trial endpoint (outcome of interest) must be chosen. To improve the process of cancer clinical research, a better understanding of multiple types of failure endpoints (disease recurrence of different types, death
from cancer, death from other causes, etc.) experienced after cancer treatment is needed. This may offer additional pivotal insights into treatment efficacy, as well as inform trial design and analysis. These observations also provide information on disease natural history over time. A more efficient analysis and treatment evaluation strategy making use of all this information could improve both knowledge acquisition and patient care, which may rely heavily on our knowledge of the relationship between the multiple endpoints observed sequentially in cancer clinical trials. We propose three areas of statistical methodology research that have immediate practical implications for cancer clinical trials. These novel statistical methods can more directly assess risks, benefits and effects on investigative therapeutic agents, and will increase the trial operational efficiency and produce more informative outcomes. These investigations will provide a concrete demonstration of the worth of these innovative concepts and advance knowledge in cancer research and treatment.

Summary of Research Completed

Aim 1:
In the development of anti-cancer therapies the most commonly used endpoints are: overall survival (OS), time to progression (TTP) and progression free survival (PFS). OS is defined as the time from randomization until death from any causes or censoring at the last follow up. TTP is defined as the time from randomization until tumor progression, considering death as censoring. PFS includes both progression and death as events, and is defined as time from randomization to tumor progression or death whichever occurs first. Generally, OS is considered the most reliable clinical endpoint and is preferred by regulatory agencies because prolonging patient life is the ultimate goal. However, determination of OS may require a prolonged follow-up period and may be influenced by subsequent therapies after patients go off a given trial. On the other hand, the endpoints PFS and TTP can be reached faster, and sometimes are a more direct measure of clinical benefit. As potential surrogate endpoints for OS, PFS and TTP have become more acceptable, especially in the earlier phases of drug development, such as phase II trials.

To validate PFS or TTP as acceptable surrogates for OS, establishing their correlations is an important aspect. There have been some publications of empirical correlations between them in different cancers, but statistical models describing the dependence structures are very limited. Recently, Fleischer et al. proposed a statistical model that is mathematically tractable and shows some flexibility to describe the dependencies in a realistic way. Their model assumed Exponential distributions for TTP, OS before progression, and time to survival post progression. They derived the correlations among different survival outcomes and also the distribution of the overall survival induced by the model. However, in our attempt to apply their methods to data from some cancer clinical trials, we found that sometimes there is a discrepancy between the observed OS and their model based OS. Therefore, we are aiming to extend their approach by relaxing the Exponential distribution to Weibull distribution, which provides a more flexible model framework and potentially will fit better to real data.

During the current grant period, we have worked on the derivation of five theorems and wrote R codes for statistical estimation of survival distributions under the Exponential and Weibull
models. Both assumptions are tested using simulated data from: Exponential distribution, Weibull distribution with same shape parameters, Weibull distribution with different shape parameters, and log-logistic distribution. For all scenarios, Weibull distribution showed better fit to the data comparing the Exponential method.

We also identified two RTOG trial examples, RTOG 0214 and 9413. The first study is a phase III trial comparing prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer. The main result was published by Gore et al in the Journal of Clinical Oncology. The failure event of PFS was defined as the earliest event of any-cause death, local progression, regional metastasis, distant metastasis, or second primary. Though the original paper reported 2-year outcomes, we used 4-year data in our analyses as we now have longer follow up. The second study is a phase III trial that compares whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression. The failure of PFS was defined as the first occurrence of local progression, regional nodal failure, distant failure, or biochemical (PSA) failure or death due to any cause. In these two trials the overall survival was not significantly different between treatment arms and therefore in our following analyses we pooled the data across arms. All distribution parameters are estimated using the codes mentioned above and the correlations calculated using the newly derived five theorems under each model. Figure 1 shows the estimated Kaplan-Meier (KM) curve for OS together with the predicted OS based on Theorem 5 from both the Exponential model and Weibull model, for each of the two examples. We can see that in the first example, RTOG 0214, both predicted curves are almost overlapped with the observed KM curve, presumably because the data roughly met the Exponential distribution assumption. In the second example, RTOG 9413, the Weibull model seems to fit the data pretty well, but the Exponential model shows some lack of fit.

Table 1 presents the estimated correlations from Exponential model and Weibull model, by submitting maximum likelihood estimates into Theorems 2-4. As expected, in the first example the estimated correlations under two models are very close to each other. In the second example, the correlations estimated under Weibull model are somewhat larger than those under Exponential model.

The proposed statistical model induced the correlations among TTP, PFS and OS, which can be derived analytically. In our real clinical trial examples, we saw only small differences in the estimated correlations under the Weibull model and Exponential model, presumably because the estimated parameter was not too much away from 1, a parameter for the Exponential model, so that the advantage of the Weibull over Exponential model was not obvious. However, the difference of correlations under two models can be substantial in reality. Since the Weibull model is generally more flexible and fits data better than the Exponential model, the correlations under the Weibull model should be more accurate. Naively applying an Exponential model could potentially over or under estimate the true correlations.

We will continue to summarize results from simulations and clinical trial examples and start drafting the paper for future submission.
In Aim 2 of project 2 of the 2011 grant, we aim to predict when a certain number of events will occur for a primary endpoint - for example, overall survival. Therefore, the goal is to predict the time that, for instance, the 50th death happens in a trial. However, for this project, we want to estimate the correlation between two endpoints, progression free survival and overall survival, using all data observed in a study.

Aim 2: No progress to report.

Aim 3: No progress to report.

Figure 1: Comparison between Observed and Predicted OS Rates
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