American College of Radiology

Annual Progress Report: 2014 Formula Grant

Reporting Period

January 1, 2015 – June 30, 2015

Formula Grant Overview

The American College of Radiology received $1,268,999 in formula funds for the grant award period January 1, 2015 through December 31, 2018. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Using the RTOG Legacy Clinical Trials Database to Investigate Non Protocol-Specified Research Questions – For over 40 years, the Radiation Therapy Oncology Group (RTOG) was funded by the National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. RTOG's research has been incorporated into a newly funded NCI clinical trials program, NRG Oncology, which is a member of the NCI National Clinical Trials Network. Drawing upon this vast resource of demographic, treatment, biospecimen, and outcome data from RTOG trials, the researchers will develop hypotheses and explore associations that were not defined in the treatment protocols for patients with brain tumors, head and neck, lung, pancreas, and prostate cancers, which may inform and/or lead to future protocols.

Anticipated Duration of Project

1/1/2015 – 12/31/2018

Project Overview

Aim 1: Correlation of the Number of Recorded Lymph Nodes with Efficacy Outcomes in Post-Operative Advanced Squamous Cell of the Head and Neck Cancer Patients: Using data from trials RTOG 0234 and RTOG 9501, this aim will correlate the number of recorded lymph nodes with overall survival and regional relapse, while controlling for patient, tumor, and treatment factors.

Aim 2: Correlation of Diabetes and Insulin Use with Overall Survival in Adjuvant Pancreas Cancer Patients. Using data from RTOG 9704, this aim will determine if there is a correlation between diabetes and/or insulin use and overall survival, while adjusting for other patient, tumor, and treatment factors.

Note: This project is funded, in part, under a grant with the Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analyses, interpretations or conclusions.

Aim 3: Correlation of prostate-specific antigen (PSA) Response to Neoadjuvant Androgen Deprivation Therapy (ADT) with Efficacy in Prostate Cancer Patients: Using data from RTOG studies 9202, 9408, 9413, and 9910, this aim will evaluate if the post neoadjuvant PSA level is correlated with efficacy outcomes.

Aim 4: Evaluating the Impact of Short Delays in Initiation of Radiation Therapy in Glioblastoma (GBM) Patients Treated with Chemoradiation. This aim will assess if concurrent temozolomide (TMZ) will in effect "level the playing field" for overall survival due to a synergistic/radiosensitizing mechanism with RT, making RT timing less of a significant factor.

Aim 5: Genetic and Epigenetic Analysis with Respect to Short vs Long Term Survivors for Patients with Anaplastic Oligodendroglial Tumors Treated on RTOG 9402. This aim will evaluate if patients with 1p/19q co-deleted anaplastic oligodendrogliomas who have long survival after the addition of chemotherapy (PCV) to radiation (RT) are associated with a distinctly different genetic profile than those who have short survival.

Aim 6: Assessing Cognitive Function and Quality of Life in Long Term Survivors of RTOG 9402: This aim will compare cognitive function (MMSE) and quality of life (QLC-B30) by therapy (PCV+RT vs. RT) in patients who lived 10 years or longer, specifically looking for a difference in MMSE and QLC-B30 between PCV + RT and RT alone in these patients.

Aim 7: Correlation of Kirsten Rat Sarcoma (KRAS) variant and Efficacy in Non-Small Cell Lung Cancer (NSCLC): Using data from RTOG 0617, this aim will evaluate if the KRAS variant is correlated with efficacy outcomes.

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Expected Research Outcomes and Benefits

Aim 1: Correlation of the Number of Recorded Lymph Nodes with Efficacy Outcomes in Post-Operative Advanced Squamous Cell of the Head and Neck Cancer Patients: Results from this aim may provide a cut point for the number of lymph nodes recorded that could be used as a stratification factor in future clinical trials.

Aim 2: Correlation of Diabetes and Insulin Use with Overall Survival in Adjuvant Pancreas Cancer Patients. Results from this aim will provide data on the potential prognostic significance of diabetes and/or insulin use.

Aim 3: Correlation of prostate-specific antigen (PSA) Response to Neoadjuvant Androgen Deprivation Therapy (ADT) with Efficacy in Prostate Cancer Patients: Results from this aim may provide guidance for future prostate clinical trials.

Aim 4: Evaluating the Impact of Short Delays in Initiation of Radiation Therapy in Glioblastoma (GBM) Patients Treated with Chemoradiation. Results from this analysis may alleviate concerns regarding short delays in the start of radiation.

Aim 5: Genetic and Epigenetic Analysis with Respect to Short vs Long Term Survivors for Patients with Anaplastic Oligodendroglial Tumors Treated on RTOG 9402. Results from this aim may provide guidance for genetically targeted treatments.

Aim 6: Assessing Cognitive Function and Quality of Life in Long Term Survivors of RTOG 9402: Results from this analysis may provide guidance regarding tradeoffs between prolonged survival and neurocognitive functioning.

Aim 7: Correlation of KRAS variant and Efficacy in NSCLC: Results from this aim may provide information to identify subgroups of NSCLC that respond better than others to radiation and or cetuximab.

Summary of Research Completed

Aim 1: Statistical analyses were done and an abstract of the results was submitted to and presented at the 2015 ASCO Annual Meeting. Results are summarized below.

Quality of head and neck surgery has thus far focused on adherence to clinical national guidelines and margin status. For other solid tumors, an association has been found between lymph node counts from regional nodal dissection and overall survival; as such, lymph node counts have been proposed as measure of quality. Yet, for neck dissection, no prospective metrics for the surgical quality have been established for patients with head and neck squamous cell carcinoma. The purpose of this analysis is to investigate the association between lymph node counts from primary neck dissection, local-regional recurrence, and overall survival.

A secondary analysis of patients that were enrolled in two post-operative head and neck trials, RTOG 9501 (Phase III Intergroup Trial of Surgery Followed by (1) Radiotherapy vs. (2) Radiochemotherapy for Resectable High Risk Squamous Cell Carcinoma of the Head and Neck) and RTOG 0234 (A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (cetuximab) for Advanced Squamous Cell Carcinoma of the Head and Neck) was performed. The number of lymph nodes counted from regional nodal dissection was evaluated for its prognostic impact on overall survival using a multivariate Cox model adjusted for

demographic, tumor, and lymph node data, and stratified by postoperative treatment group: (1) radiation or (2) chemoradiation on RTOG 9501 or (3) chemoradiation and cetuximab on RTOG 0234. Models were compared by Akaike Information Criterion (AIC).

572 patients were analyzed. Median follow-up for surviving patients was 8 years. Median number of lymph nodes recorded on the left and right sides were 24 and 25. Fewer than 18 nodes was associated with significantly worse overall survival relative to ≥18 nodes (hazard ratio (HR) 1.38, 95%CI 1.09-1.74, p=0.007). The model with this cut point had minimum AIC of all possible models. The difference appears to be driven by local-regional failure (HR 1.46, 95%CI 1.02-2.08, p=0.04) but not distant metastasis (HR 1.08, 95%CI 0.77-1.53, p=0.65). Limited to RTOG 0234, adding p16 status to the model does not affect the HR for sampled nodes and the effect of nodes is not different by p16 status (p-value for interaction 0.99).

Identifying 18 or more sampled lymph nodes was associated with improved overall survival and lower rates of local-regional failure. The benefit was seen in both p16-positive and p16-negative patients from this analysis. The removal and identification of at least 18 lymph nodes should be considered as a measure of quality in neck dissections for mucosal squamous cell carcinoma. Surgeon and pathologist can play important roles in achieving this objective.

Aim 2: No progress to report.

Aim 3: Statistical analyses were done and an abstract of the results was submitted to the 2015 ASTRO Annual Meeting. Results are summarized below.

Many RTOG prostate trials have evaluated the giving of and the length of androgen suppression (AS), and provide a rich database for asking secondary questions. The purpose of this analysis is to evaluate the association between pre-radiation therapy (RT) nadir prostate specific antigen (nPSA) and long-term outcomes after short-term AS + RT in prostate cancer patients.

This analysis was performed on patients from four randomized Phase III RTOG prostate trials, RTOG 9202, 9408, 9413, and 9910. All 3962 patient assigned to neoadjuvant AS (neoAS) prior to RT + concurrent AS (without post-RT AS) in these trials were selected. Pre-specified exclusions were no PSA between neoAS and RT start date (n=1432), or lack of AS (n=57) or RT (n=69) reporting, yielding 2404 evaluable pts for this analysis. nPSA was assessed as a pre-defined dichotomized variable (≤0.1 vs. >0.1 ng/mL) and as a continuous variable. Pearson correlation coefficient or chi-square test was used to assess the homogeneities between baseline/treatment factors and nPSA. Univariate (UVA) and multivariate (MVA) Cox proportional hazard models were used to test the association between nPSA and overall survival (OS). Gray's method, UVA and MVA Fine-Gray models were applied to evaluate the relationships between nPSA and nadir+2 biochemical failure (BF), local failure (LF), distant failure (DF), and cause-specific mortality (CSM) under the competing risk approach. MVA models included age, race, protocol, T-stage, N-stage, baseline PSA, Gleason score (GS), neoAS duration, RT target (prostate vs. pelvis+prostate), and RT dose as covariates. Hazard ratios (HR) and 95% confidence intervals (CI) were determined with a significance level at $p<0.05$.

Median (interquartile range [IQR]) follow-up for surviving pts was 9.4 years (IQR 8.5-10.7). Median interval from neoAS start to nPSA date was 56 days (IQR 53-154) and from nPSA to RT start was 6 days (IQR 1-13). Median nPSA was 0.3 ng/mL (IQR 0.1-0.7), and it was ≤0.1 in 32% of patients. Race, GS, T-stage, N-stage, baseline (pre-AS) PSA, and duration of neoAS were associated with nPSA (≤0.1 vs. >0.1). On UVA models, nPSA >0.1 was associated with increased BF (HR 2.08, 95% CI 1.75-2.49, p<0.0001), LF (HR 2.78, 95% CI 1.93-4.03, p<0.0001), DF (HR 1.78, 95% CI 1.27-2.48, p=0.0004), CSM (HR 2.45, 95% CI 1.60-3.74, p<0.0001), and OS (HR 1.30, 95% CI 1.12-1.51, p=0.0005). On MVA models, nPSA (continuous or dichotomized) was not associated (p>0.05) with any of these clinical outcomes.

Patients with nPSA ≤0.1 ng/mL after neoAS had more favorable outcomes. However, nPSA was not independently predictive of long-term clinical outcomes in this large and diverse study cohort when prognostic variables, RT parameters, and duration of neoAS were also taken into account.

Aim 4: Statistical analyses were done and an abstract of the results was submitted to the 2015 SNO Annual Meeting. Results are summarized below.

The study investigators had previously reported the unexpected finding that better survival was significantly associated with patients with newly-diagnosed GBM when radiation therapy (RT) was initiated later (>4 weeks post-op) compared to earlier (≤2 weeks post-op). That analysis included 2855 patients from 16 RTOG trials conducted prior to the era of concurrent temozolomide (TMZ) with RT. This analysis reports on patients from two Phase III RTOG trials involving newly-diagnosed GBM, treated with RT and concurrent TMZ followed by adjuvant TMZ. The hypothesis is that concurrent TMZ has a synergistic/radiosensitizing mechanism, making RT timing less significant.

Data from 1127 patients on both arms of RTOG 0525 and the placebo arm of RTOG 0825 were analyzed to determine whether there was still an impact on survival by delaying RT in the RT+TMZ era. Overall survival was investigated using the Cox proportional hazard model. Early progression progressive disease from time of diagnosis to 30 days after finishing RT) was analyzed using the Chi-square test.

Given the small number of patients who started RT early, comparisons were made between >4 and ≤4 weeks delay of radiation following surgery. There was no statistically significant difference for overall survival (p-value=0.29; HR=0.93; 95% CI: 0.80-1.07) after adjusting for recursive partitional analysis (RPA) grouping and O(6)-methylguanine-DNA methyltransferase (MGMT) methylation status. Similarly, the rate of early progression did not differ significantly (p-value=0.59).

The previously seen significant prognostic influence of delaying radiation was not observed when given concurrently with TMZ for newly-diagnosed GBM. TMZ may "level the playing field" for patients treated with chemoradiation and offset the effect of RT-delay that was seen when RT was given alone.

Aim 5: No progress to report.

Aim 6: No progress to report.

Aim 7: The full statistical analysis plan has been created and the lab analyses for the marker are underway.

Research Project 2: Project Title and Purpose

Improving Quantitative Imaging Biomarker Methods to Accelerate the Development of Effective Cancer Therapies – This project will leverage the unique and extensive biomarker trial data sets that the American College of Radiology Imaging Network (ACRIN), based in Philadelphia, has collected from clinical trials evaluating cancer therapies. Using the ACRIN expertise in cancer biomarkers, as well as image analysis, we will test and develop improved methods of image analysis and quantification for cancer imaging biomarkers. The project will leverage the functionality of ACR's Data Archive and Research Toolkit (DART) to access, share, and analyze data more efficiently. Successful completion of the project will be improved imaging biomarkers that will improve the efficiency and quality of therapeutic cancer trials and help direct individualized cancer therapy.

Anticipated Duration of Project

1/1/2015 – 12/31/2018

Project Overview

The overarching goal of this project is to develop quantitative cancer imaging biomarkers to conduct more informative and efficient cancer clinical trials, and eventually to direct more individualized cancer treatment in the clinic. The specific goals of our project are to enhance methods for extracting information from novel molecular imaging biomarkers using images and data collected in several completed ACRIN trials. These trials are some of the first multi-center trials of novel imaging methods that address key biologic factors in cancer including tumor proliferation, tissue hypoxia, and normal tissue repair. By refining the approach to the analysis of these powerful but costly imaging assays, we will enhance their benefit to clinical trials and ultimately to patients, providing tools to maximize the benefits of cancer care for patients and avoid treatments unlikely to be effective.

The Specific Aims of the project are as follows:

Aim 1. Expand the capabilities of the American College of Radiology Data Archive and Research Toolkit (DART) to create a virtual environment where researchers can share data efficiently.

Aim 2. Leverage the results of research from select ACRIN studies to further develop advanced PET quantitative imaging methods for standardized use in future clinical research trials.

For these tasks, we will use images from completed trials where patient therapeutic outcome (e.g., disease-free survival) is known and serves as the reference standard for testing methods to optimize the predictive value of the biomarkers. The proposed approaches will leverage and test the ACR data archive and framework for combining imaging and clinical data, which will be used in the proposed studies. Expertise from the ACR/ACRIN Imaging Core Laboratory and its affiliate academic sites, especially the University of Pennsylvania, will provide the expertise in advance image analysis methods. The end result will be improved methods for cancer biomarkers in clinical trials, leading to more efficient cancer drug development and testing, and improved outcomes for cancer patients.

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Expected Research Outcomes and Benefits

The impact of this project will be improved cancer imaging biomarkers that will provide key tools for future trials of cancer therapy that improve patient selection, provide proof-of-mechanism for targeted cancer therapy, and improve the efficiency of drug testing in clinical trials. These same tests can then be used to direct more effective cancer treatment in the clinic. The resulting impact of successful completion of the proposed work on cancer treatment and cancer patients will be significant and would positively impact a high fraction of patients treated for cancer.

Current and future researchers will benefit from the availability of access to a system which combines data aggregation and feature extraction in one platform.

Summary of Research Completed

This project was awarded on April 30, 2015; we are reporting on activities during May and June, 2015.

Aim 1: Our activities toward this aim included beginning preparations for defining the study procedures, identifying a team, and drafting data share agreements.

Aim 2:
Our activities toward this aim included completing a review of pertinent datasets, and beginning preparations to develop plans to make them more broadly accessible for subsequent analysis.