American College of Radiology

Annual Progress Report: 2010 Formula Grant

Reporting Period

July 1, 2010 – June 30, 2011

Formula Grant Overview

The American College of Radiology received $1,700,785 in formula funds for the grant award period January 1, 2011 through December 31, 2014. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Socio-demographic Factors, Workup, and Treatment for Cancer Patients in an Enhanced National Survey - The purpose of this project is to test hypotheses relating to quality of care and differences in socio-demographic factors for patients treated with radiation therapy for cancer of the breast, cervix, stomach, lung and prostate. Quality of care is defined by compliance with detailed clinical performance measures that include the patterns and sequence of particular types of surgery, radiation therapy, chemotherapy, hormonal therapy. Based on these findings we will make recommendations for improvement in the care of these groups of patients.

Anticipated Duration of Project

1/1/2011 - 12/31/2014

Project Overview

The objective of this project is to test hypotheses regarding the relationship between quality of care and differences in socio-demographic factors for cancer patients treated with radiation therapy.

The Specific Aims:

1. To link national survey data with census data based on the patient's zip code and to describe the distribution of socio-demographic characteristics in patients diagnosed with cancer of the breast, cervix, stomach, lung and prostate.

2. To test hypotheses that the quality of care received by patients treated for these cancers varies by socio-demographic factors. For each disease site at least four detailed clinical performance measures (CPM) will be calculated to assess quality of care. Hypotheses will test whether compliance with these CPMs is different for groups of patients based on measures of socio-demographic factors.

3. To test hypotheses that patterns of use and sequence of treatment modalities, including surgery, radiation therapy, chemotherapy, and hormonal therapy are different for patients with different socio-demographic factors. The particular patterns to be tested will be those that may represent over-treatment or under-treatment as compared to appropriate treatment for the diseases.

Using data from the Quality Research in Radiation Oncology (QRRO) data set, this project will address research questions regarding quality of care as they relate to socio-demographic factors. The QRRO database will be used for information on patient and tumor characteristics, imaging, treatment planning, surgery, radiation and systemic therapy. Socio-demographic factors will be obtained by linking and matching each patient's zip code to data in the 2000 United States Census.

To test the hypothesis that compliance with CPMs varies by socio-demographic measures, at least four CPMs for each disease site will be used as the basis for measuring quality of care. The primary outcome measure for each disease site will be compliance with all of those CPMs. Secondary outcome measures will be compliance with individual CPMs.

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Expected Research Outcomes and Benefits

This project will identify the relationship between socio-demographic factors and the consequential disparities in the care provided to patients as it relates to detailed clinical performance measures for radiation oncology workup and treatment. By identifying this association between both the socio-demographic and socio-economic factors and the consequential disparities in the provision of care we will be able to develop recommendations for reducing the disparities. This will lead to future improvements in the health status of patients with similar socio-demographic characteristics.

Summary of Research Completed

In the six months since the start of the project, we performed the following:

(1) Data on patients with breast, cervix, stomach, lung and prostate cancer were extracted from ACR QRRO central database. This database stored information from the survey

which was begun in 2007 and completed in 2010. For each disease site, a dataset was created combining patient demographic, workup, diagnosis and treatment information and the patient's zip code information so that the resulting dataset could be merged with Census data correctly.

(2) Since information on socio-demographic factors appeared on more than one US Census data file, a literature review has been conducted focusing on identifying appropriate census data files to be used and extracted for this project.

(3) Census 2000 Summary File 3 (SF 3) was used and data were obtained by ZIP Code Tabulation Area (ZCTA) for Census 2000 SF3. As described in American FactFinder website (http://factfinder.census.gov), the SF3 summary file contains "in-depth population and housing data collected on a sample basis from the Census 2000 long form questionnaire (also known as Sample Data), as well as variables from the short form for which there are 100-percent data (age, race, sex, Hispanic or Latino origin, tenure and vacancy status). Data were in tabulation format and were divided into social, demographic, economic, and housing characteristics. Data from population tables P5 (Urban and Rural), P37 (Sex by Educational Attainment for the Population 25 Years and Over), P43 (Sex by Employment Status for the Population 16 Years and Over), P53 (Median Household Income in 1999), and P87 (Poverty Status in 1999 by Age) were downloaded from the U.S. Census Bureau website: http://factfinder.census.gov/home/saff/main.html?_lang=en.

(4) Since all Census data are in tabulation formats, specific data from each population table were identified and extracted using Statistical Analysis System (SAS version 9.2, SAS Institute). All Census data were then merged with our QRRO national survey database by zip code and were ready for the analytic stage for this project.

(5) Preliminary basic descriptive statistics for cervical cancer cases were performed and presented in Tables 1-3.

In summary, during the first 6-month period of funding for this project, we made progress in completing the first milestone(s) for 1/1/2011-6/30/2011, namely identified key data fields in census data at the zip code level data, downloaded data, and merged with patient level data from the survey for each of the five disease sites to create analytic files. Furthermore, descriptive statistics of patient characteristics for the first disease site (cervical cancer) were done and presented in this report. This progress will facilitate the process and completion of the 2nd milestone(s) for 7/1/2011-6/30/2012.

Table 1: Characteristics of Patient Population – Cervical Cancer Study

Characteristics	Estimate (%)*	Weighted no. of Patients	Unweighted no. of Patients
Total (N)	100.0	10400	261
Age at Start of Radiotherapy (RT)			
<=40 yrs	21.1	2191	61
41-60 yrs	48.6	5058	127
>60 yrs	30.3	3151	73
Race/Ethnicity			
White	58.9	6125	143
African American	19.5	2026	59
Hispanic	15.1	1572	39
Others	6.5	677	20
Treatment Facility/Institution			
Academic	23.9	2487	124
Large Non-Academic	32.7	3399	89
Medium Non-Academic	21.4	2229	25
Small Non-Academic	22.0	2285	23
FIGO Stage (1988)			
Stage IA	0.6	60	3
Stage IB	27.4	2853	67
Stage IIA	8.7	903	24
Stage IIB	30.0	3126	86
Stage IIIA	3.3	340	9
Stage IIIB	23.5	2444	57
Stage IVA	4.7	488	11
Not Det/Unk	1.8	186	4
Histology			
Squamous Cell	78.7	8183	209
Adeno-/Adenosquamous	17.0	1769	42
Other/Unknown	4.3	448	10
CT scan			
Not Done	9.8	1019	25
Done	89.6	9323	234
Unknown	0.6	58	2
Lymph-Angiogram			
Not Done	98.7	10262	255
Unknown	1.3	138	6
MRI			
Not Done	81.8	8508	205
Done	17.1	1774	51
Unknown	1.1	118	5
PET Scan			
Not Done	57.7	6004	138
Done	38.6	4016	112
Unknown	3.7	380	11
Nodal Biopsy			
Not Done	89.4	9294	225
Done	9.7	1008	32
Unknown	0.9	98	4
Surgical Staging			
Not Done	96.1	9996	247
Done	2.8	286	9
Unknown	1.1	118	5

(*) Percentages based on weighted number of patients

Table 2: Patient Treatment Information – Cervical Cancer Study

Characteristics	Estimate (%)*	Weighted no. of Patients	Unweighted no. of Patients
Total (N)	100.0	10439	261
Treatment Goal			
Curative	84.7	8809	225
Palliative	5.3	549	12
Unknown	10.0	1042	24
External Beam RT (EBRT)			
Yes, at Other Facility (A)	5.5	575	18
Yes, at This Facility (B)	89.9	9353	233
Yes, at Both (A) & (B)	4.6	472	10
Brachytherapy (BT)			
No	14.5	1507	32
Yes, Intracavitary (ICRT)	83.3	8669	224
Yes, Interstitial Implant	0.6	58	2
Unknown	1.6	166	3
Chemotherapy			
No	17.9	1864	39
Yes	80.7	8389	219
Unknown	1.4	147	3

(*) Percentages based on weighted number of patients

Table 3: Socio-demographic Information from Census 2000 by Treatment Facility – Cervical Cancer Study

Census Data	Academic (Mean ± SE)*	Large Non-Academic (Mean ± SE)*	Medium Non-Academic (Mean ± SE)*	Small Non-Academic (Mean ± SE)*
% persons living in Urban Areas	100.0 ± 0.0	97.9 ± 1.2	90.2 ± 2.8	91.0 ± 3.5
% persons <= 9th Grade in Education	8.3 ± 0.7	17.9 ± 1.9	15.2 ± 2.3	4.2 ± 0.9
% persons > 9th Grade in Education	29.7 ± 1.9	35.5 ± 1.0	38.0 ± 3.0	30.1 ± 1.2
% persons with College	62.0 ± 2.5	46.6 ± 2.1	46.7 ± 4.1	65.7 ± 2.0
% persons unemployed	10.5 ± 0.7	8.8 ± 0.5	7.9 ± 0.5	5.0 ± 0.3
Median Household Income (US$)	28316 ± 1591	30840 ± 1116	38773 ± 4460	58476 ± 2991

(*) Weighted mean and SE

Research Project 2: Project Title and Purpose

Pennsylvania CT Dose Registry and Reduction Project - This project aims to study the effects of various interventions on radiation dose received by patients undergoing Computed Tomography (CT) scans at American College of Radiology Imaging Network – Pennsylvania (ACRIN PA) healthcare delivery sites in Pennsylvania. Dose data for all CT scans performed at the sites will be collected during a 6-month baseline period and analyzed to provide insight into practice variations resulting in different rates of exposure. Sites will then be randomized to one of several strategies for education and implementation of CT dose reduction techniques during a 6-month intervention period, and dose data recorded for a one-year follow-up period. It is hypothesized that the average radiation dose delivered subsequent to the intervention will be lower than the dose delivered prior to the intervention.

Anticipated Duration of Project

1/1/2011 - 12/31/2014

Project Overview

Four ACRIN Pennsylvania Network sites, which include community hospitals and outpatient clinics, performing CT in Pennsylvania will be identified to participate in the project. CT scan dose information will be collected from participating sites over a 6-month observational period. Sites will then be randomized to one of several dose reduction strategies and interventions will be implemented accordingly. Following the intervention, CT dose rate data will be collected for another year to determine how effective the intervention was in lowering dose.

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Expected Research Outcomes and Benefits

Knowledge of the current distribution of doses within this patient sample will allow more accurate analysis of and prediction of the amount of radiation received at CT and may provide

background information for subsequent trials of larger scale which would enable more discrete analysis of variations (by manufacturer, scanner type, procedure, age, gender, etc).

Evaluation of different dose reduction strategies will allow identification of best practices and implementation of strategies for reducing radiation exposure to Pennsylvanians, thereby reducing risk of radiation induced illnesses and cancers.

Summary of Research Completed

The notice of award was received in April 2011 and funding was received in June 2011. Several organizational efforts were initiated once the notice of award was received in May 2011, including:

- Pre-Award Meeting: The ACRIN Administrator, PI, and Project Manager met May 12, 2011 to discuss the project and revise the implementation timeline and milestones. Plans to address the milestones for the initial 6-month project period were discussed: confirming participating sites, developing a budget and plan for purchasing and installing computer hardware, and establishing a research team assigned to develop a full protocol, including methodology and statistical design.
- Establish Project Team: A project manager, protocol associate, and statistician were assigned to the project. A plan to engage PhD-level statistical oversight was implemented.
- Protocol Development: The Protocol Associate inserted the project proposal as submitted in the PA DOH application into the ACRIN PA protocol template for initial review and development.
- Site identification: The PI contacted the Department of Radiology Chair at the 4 PA health systems (University of Pittsburgh, Hershey Medical Center, Geisinger Health System, and University of Pennsylvania) that will participate in the project. The contact served as a notification of funding for the project, summary of the project, and next steps, including a request for information about the IT infrastructure, equipment, and personnel at their facility.

Research Project 3: Project Title and Purpose

The Evaluation of Translational Research Program (TRP) Projects - The Radiation Therapy Oncology Group (RTOG), a National Cancer Institute funded multi-institutional clinical cooperative group has been collecting and banking biospecimens (biopsies, blood, urine, etc.) from patients enrolled on its clinical trials for decades. Often these specimens are collected without a pre-identified analysis – they are "banked" for future use. As technology and new biomarkers are developed, investigators request permission to use the specimens for research to identify new biomarkers or validate new procedures. These "secondary" analyses are not required by the original protocol, and may not be funded as part of that protocol. This project will allow for the investigation, including the statistical analysis, of five specified translational research program (TRP) projects.

Anticipated Duration of Project

1/1/2011 - 12/31/2014

Project Overview

This project aims to use biomarkers and tissue specimens that have been collected in previous RTOG studies to advance current knowledge regarding the treatment and prognosis of cancer patients. The specific research objectives of this project relate to five TRP requests that will contribute to the overall project.

Aim 1: TRP 173: DPC-4 Status in pancreatic cancer patients: RTOG 9704, a Phase III trial of patients with resected pancreatic cancer, is a study that has resulted in several requests from investigators. For this project, the investigators will examine a patient's resected pancreatic cancer with intact DPC-4 to see if there's a local or incompetent metastatic phenotype as well as the correlation of DPC-4 loss with distant tumor recurrence using data collected in RTOG 9704. There will also be an investigation into DPC-4 status that is prognostic for overall survival.

Aim 2: TRP 165: Caveolin-1 and GSK3β in pancreatic cancer patients: Using data and samples collected in RTOG 9704, this project looks to determine whether Caveolin-1, GSK3β and related signaling molecules are prognostic biomarkers with regard to overall survival, disease-free survival, local failure-free survival and distant failure-free survival and correlate Cav-1 expression and pre-operative CA 19-9 levels.

Aim 3: TRP 167: Pharmacogenetic correlative science: The final project using data from RTOG 9704 has an overall goal to identify heritable, germline polymorphic markers that are prognostic and predictive of toxicity in pancreatic cancer patients. Efficacy and toxicity of previously identified putative germline genetic polymorphisms in this patient population will be examined.

Aim 4: TRP 169: Ribonucleotide reductase in cervix cancers: This project restricts its data to two cervical cancer trials: RTOG 0116 and 0128. The aim is to associate ribonucleotide reductase (RNR) M2 and p53R2 expression with survival.

Aim 5: TRP 91: Expression of receptors in bladder cancers: The final project utilizes multiple RTOG bladder sparing trials, particularly muscle-invasive bladder cancers treated with selective bladder preservation. The objective is to correlate the level of expression with the primary tumor site by immunohistochemical staining of VEGF and VEGF receptors, Flt-1 and Flk-1, with response, recurrence and survival.

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Expected Research Outcomes and Benefits

There are many benefits that will arise from these five TRP projects. The identification of new biomarkers will lead to changes in how RTOG designs studies, assigns protocol therapy, and analyzes the results of its clinical trials. This research project will provide valuable information to aid future investigators in the design and conduct of radiation therapy-based oncology research.

Aim 1: TRP 173: DPC-4 Status in pancreatic cancer patients: This project may aid in the approval of a future RTOG proposal concerning a biologically directed technique for patients with intact DPC-4 and novel chemotherapy for patients with DPC loss.

Aim 2: TRP 165: Caveolin-1 and GSK3β in pancreatic cancer patients: Expanded knowledge of the current roles of Cav-1 and the GSK3β/β-catenin pathway obtained from TRP 165 will improve the prognosis of patients, discover new objectives for therapy and improve the development of trials for locally advanced pancreatic cancer.

Aim 3: TRP 167: Pharmacogenetic correlative science: TRP 167 will identify putative germline polymorphic prognostic and predictive markers to validate in this a large phase III study of pancreatic cancer.

Aim 4: TRP 169: Ribonucleotide reductase (RNR) in cervix cancers: TRP 169 will determine RNR inhibition following radiation as a therapeutic strategy as well as allow for future screens of candidate proteins identified in the DNA damage response pathway.

Aim 5: TRP 91: Expression of receptors in bladder cancers: There have been no reports concerning the correlation of cancer control with levels of VEGF and VEGF receptors in patients with muscle invading bladder cancer whose primary tumor has been treated by external irradiation or concurrent radiation and radiosensitizing chemotherapy, providing a rationale for TRP 91.

Summary of Research Completed

The analyses for Aim 5: TRP 91: Expression of receptors in bladder cancers was started in this progress report period. This analysis is investigating molecular markers on the VEGF angiogenesis pathway as potential biomarkers pooling several Radiation Therapy Oncology Group (RTOG) bladder cancer trials. An abstract from this analysis was submitted to the 2011 American Society of Therapeutic Radiation Oncology (ASTRO) annual meeting and has been accepted for oral presentation at the ASTRO annual meeting in October 2011.

Research Project 4: Project Title and Purpose

The Evaluation of Quality of Life (QOL) Endpoints in RTOG Studies - The Radiation Therapy Oncology Group (RTOG), a National Cancer Institute funded multi-institutional clinical cooperative group, conducts clinical trials with the goal of improving the survival and quality of life (QOL) of patients with cancer. RTOG has collected QOL data from both caregivers and patients for many of its trials. QOL outcomes are often not listed as a primary endpoint of the trial and therefore not funded by the original protocol. This project will allow for the evaluation of QOL of cancer patients receiving treatment in six specified RTOG protocols. The results of these assessments will provide valuable information regarding the treatments under study as well as the basis for the design of future studies.

Anticipated Duration of Project

1/1/2011 - 12/31/2014

Project Overview

This research project aims to advance knowledge of quality of life in cancer patients. Due to the broad range of the effects of cancer and its treatment among the various disease sites, six specific research aims are proposed.

Aim 1: RTOG 9408: Patient's perception of quality of sexual function: This is a randomized Phase III trial investigating the effect of the combination of Zoladex and flutamide used prior to and during definitive radiation therapy on the patient's perception of quality of sexual function. A secondary objective is to determine the effect of the treatment on sexual function for patients in good prognosis with locally confined adenocarcinoma of the prostate.

Aim 2: RTOG 0247: Assessment of QOL changes from combined modality therapy: This is a randomized Phase II study evaluating neoadjuvant combined modality therapy for locally advanced rectal cancer. Changes in both overall and colorectal cancer-specific QOL concerns are of interest.

Aim 3: RTOG 0630: Exploring QOL in soft tissue sarcomas (STS): A Phase II trial, RTOG 0630 follows two cohorts of patients diagnosed with STS of the extremity on different image guided preoperative radiotherapy schedules This study explores late radiation morbidity, sexual and physical function and QOL.

Aim 4: RTOG 0129: Evaluation of radiation specific QOL: RTOG 0129 is a Phase III trial comparing two concurrent radiation and chemotherapy regimens for advanced head and neck squamous cell carcinomas. This study looks to evaluate whether there are differences in patient's QOL using a radiation specific QOL measure, performance status, health utilities and perception of side effects between each treatment arm.

Aim 5: RTOG 0522: Assessment of QOL, performance and health utilities: RTOG 0522 is a randomized Phase III trial designed to assess the impact of the addition of cetuximab to a

concurrent radiation-cisplatin regimen for stage III and IV head and neck squamous cell carcinomas (HNSCC). QOL, performance and health utilities are measured up to 5 years post treatment, providing crucial long-term outcomes on this patient population.

Aim 6: RTOG 0244: Preventing xerostomia and improving QOL: This is a Phase II study of investigating the use of submandibular salivary gland transfer in head and neck cancer patients. Of main interest is the effectiveness of this treatment in preventing radiation-induced xerostomia as well as its impact, and possible improvement, on QOL since radiation therapy is one of the leading modalities for treating this population.

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Expected Research Outcomes and Benefits

For cancer patients QOL is a critical aspect to any treatment, especially if two treatments offer similar survival probabilities. QOL may then be the determining factor on choosing a treatment. Each of these aims will contribute to present knowledge regarding QOL in cancer patients. Better understanding of a patient's QOL will benefit the patients and aid investigators in the development and administration of new treatments.

Aim 1: RTOG 9408: Patient's perception of quality of sexual function: QOL is especially important in the realm of prostate cancer, where the treatment has a direct impact on the patient's sexual function. When investigating new treatments for prostate cancer, QOL must be taken into account as related to the patient's sexuality.

Aim 2: RTOG 0247: Assessment of QOL changes from combined modality therapy: Due to the lack of research on QOL in patients with rectal cancer, the QOL objectives in RTOG 0247 will provide information and estimates for the purposes of planning future Phase III trials.

Aim 3: RTOG 0630: Exploring QOL in soft tissue sarcomas (STS): In the disease site of sarcoma, current data is variable regarding QOL. Hence, the QOL component of this study will be a critical addition to current knowledge.

Aim 4:RTOG 0129: Evaluation of radiation specific QOL, Aim 5: RTOG 0522: Assessment of QOL, performance and health utilities & Aim 6: *RTOG 0244: Preventing xerostomia and*

improving QOL: Treatment of cancer found in the head and neck, along with the cancer itself, can greatly impact a person's ability to eat, speak and socialize which adversely affects a patient's QOL. Therefore, studies like RTOG 0129, 0522 and 0244 need to incorporate a QOL component in order to measure how these difficulties affect a patient's life. Many other side effects of treatment for head and neck cancer have not been thoroughly studied so these three RTOG studies would provide further insight into this area where we have minimal data related to QOL.

Summary of Research Completed

RTOG 0247 is a randomized phase II trial for patients with locally advanced rectal cancer receiving neoadjuvant chemoradiation. The secondary endpoint in 0247 assesses whether the combined modality therapy produces changes in general QOL and patient-reported bowel function from baseline to three time points (completion of chemoradiation, completion of post-operative chemotherapy [approximately one year] and two years). The analysis for this secondary endpoint has been completed and its abstract accepted for an oral presentation at ASTRO 2011 in Miami, Florida. Once a manuscript is written and published, detailed results will be included in the progress report.

RTOG 9408 is a phase III trial looking at endocrine therapy used as a cytoreductive and cytostatic agent prior to radiation therapy in cancer patients with a good prognosis of locally confined adenocarcinoma of the prostate. The secondary QOL endpoint measures the effect of this treatment on sexual function as measured by the Sexual Adjustment Questionnaire (SAQ). This analysis was carried out earlier this year. The manuscript for the primary endpoint was recently accepted by the New England Journal of Medicine (NEJM) with only pretreatment and 1-year results of erectile dysfunction in both treatment arms. Since this manuscript has been accepted for publication, detailed results of the QOL analysis, specifically erectile dysfunction, will be included in the next annual progress report.

Research Project 5: Project Title and Purpose

Improving the Collection of Patient-Reported Quality of Life Data - Expansion of Web-based QOL Collection Strategy - The purpose of this project is to test a novel strategy to reduce missing quality of life (QOL) data in clinical studies. While QOL is recognized as a key endpoint that provides direct patient reported outcomes, missing QOL data is a critical problem that plagues many clinical trials. Unlike other endpoints, such as survival, QOL data cannot be collected retrospectively. Typically, QOL forms are filled out on "hard" (paper) copies. This project will collect QOL using a real-time, privacy-secure, user-friendly, web-based software system such that patients can conveniently fill out their QOL forms on-line. The study will involve head and neck cancer patients with the goal of improving compliance of QOL data collection in this challenging population.

Anticipated Duration of Project

7/1/2011 - 12/31/2014

Project Overview

The broad research objective is to rigorously test a new approach for collecting patient-reported quality of life (QOL) data in clinical trials in order to significantly reduce the challenge of missing QOL data. Patient-reported outcomes, such as QOL, are recognized as key endpoints in clinical trials. Yet, missing data is an ongoing problem that limits the clinical relevance of many QOL studies. One of the most common reasons for missing QOL forms in multi-institutional studies is "institutional error", which might be something as simple the staff neglecting to provide patients with the QOL instruments at the proper time point. Recently, a novel web-based privacy-secure software system has been developed that enables patients to fill out their QOL forms on-line at their own convenience and provides real-time reminders. A preliminary pilot study in prostate cancer patients showed that this strategy significantly improved the QOL compliance at 6 months.

The primary aim of this project is to test this new software system in a more challenging patient population, specifically patients with head and neck (H&N) cancers. While the small pilot study in about 50 prostate cancer patients was encouraging, this was a relatively healthy group of patients. A more relevant test of this strategy is to determine its benefit in a population of H&N cancer patients, who typically have more involved symptoms and QOL challenges. Moreover, the primary time point in this project will be extended out to one year, rather than six months. If this project demonstrates that this strategy for collecting QOL can be successful in this more difficult setting, this approach could then be extended to a much broader group of cancer patients across many clinical oncology trials.

The main QOL instrument in this study is the validated Functional Assessment of Cancer Therapy (FACT)-H&N form. This QOL instrument was used in RTOG 0522, a phase III trial testing the addition of cetuximab to chemoradiation in a similar patient population. Based on this study using paper forms, the QOL compliance rate in H&N studies was about 50% at one year. Using this novel software system, the hypothesis is that this compliance rate at one year will be significantly increased to >65% (a 30% relative increase). The statistical design using 95% power would require 138 patients to show this difference. The study also has a 3-month QOL time point which would also be analyzed as part of this project.

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Expected Research Outcomes and Benefits

The expected outcome of this research project is to demonstrate that a web-based technology can significantly improve compliance regarding quality of life (QOL) as measured by completions rates within a clinical oncology trial. More and more, QOL is appreciated as a critical endpoint in clinical oncology studies. Indeed, the potential benefit of an intensive treatment is often counterbalanced by the increased rate of side effects. The optimal way to accurately assess the impact of these side effects is to collect QOL information directly from the patients (i.e., patient-reported outcomes). However, QOL studies are typically limited due to missing data, which must be collected at the appropriate time points. This project will test a promising strategy to enable patients to conveniently fill out QOL forms on-line using privacy-secure software. A prior pilot study in prostate cancer suggests that this approach can help improve the QOL collection rate. The expected outcome of this project is to expand this finding to a more diverse and complex group of patients with head and neck cancer.

The benefits of this project are potentially far-reaching. QOL is collected in many clinical trials and this project could change how these studies are done to make them more relevant and beneficial. Currently, most studies use paper copies of QOL forms; however, patients sometimes do not receive these forms or forget to fill them out. This novel web-based technology makes this process user-friendly for patients and allows for real-time tracking, such that an upcoming QOL time point that might have otherwise gone missing can instead be captured with reminders before the appropriate time window closes. Thus, this project has the potential to dramatically change and improve how QOL studies are performed and monitored.

Summary of Research Completed

The project will start July 1, 2011 and the start date has been amended in this report.

Research Project 6: Project Title and Purpose

Leveraging the Androgen Receptor Axis to Improve Treatment of Locally Advanced Prostate Cancer - Treatment of locally advanced prostate cancer remains a major clinical challenge. New studies in our laboratory indicate that the androgen receptor (AR) axis can be manipulated to enhance the response to radiotherapy. The goal of this project is to develop a means for optimizing combinatorial therapy for locally advanced prostate cancer. Multiple *in vitro* and *in vivo* approaches will be utilized so as to provide the foundation for new clinical trials.

Anticipated Duration of Project

7/1/2011 - 12/31/2014

Project Overview

Prostate cancer is the second leading cause of death due to cancer for American men. The current non-surgical standard of care for locally advanced prostate cancer involves a combination of radiation therapy and hormone-based, androgen-deprivation therapy (ADT). While ADT is intended to suppress the androgen receptor (AR) function through depletion of ligand, new studies in our laboratory indicate that alternate or adjuvant means to more robustly suppress AR signaling are likely to be of significant therapeutic benefit.

Preliminary data suggest the ***hypothesis*** that consideration and manipulation of the AR axis can be leveraged to improve treatment of men with locally advanced prostate cancer. This project will:
(Aim 1) Define means of targeting AR-mediate mTOR activity and sensitize prostate cancers to radiotherapy,
(Aim 2) Delineate the impact of newly identified AR antagonists on radiotherapy response.

Both aims of the project will utilize *in vitro* and *in vivo* analyses of human tumors, and the impact of combination therapy will be monitored using markers of clinical progression (e.g., prostate specific antigen (PSA), kinetics), apoptotic indices, proliferative indices, and measures of tumor growth. From these studies, it is expected that the knowledge gained will provide the basis for new RTOG clinical trials designed to optimally suppress AR and improve prostate cancer patient survival after radiation therapy.

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Expected Research Outcomes and Benefits

The standard of care for men with locally advanced prostate cancer utilizes a combination of androgen deprivation therapy (ADT) and radiotherapy. Our preliminary data indicate that targeting the androgen receptor (AR) axis directly would be of significant clinical benefit, and can act in concert with ADT to improve treatment outcomes for men with locally-advanced disease. This project will examine this hypothesis as follows:

1. It has previously been shown that AR utilizes the mTOR-cyclin D1 axis to promote cancer cell proliferation and survival. New studies in the lab indicate that antagonizing mTOR activity

using existing experimental therapeutics not only suppresses AR activity but also sensitizes prostate cancer cells to radiotherapy. The subproject described in Aim 1 will determine the efficacy of mTOR inhibitors in human prostate cancer cells and tumors as a means to improve the therapeutic response to radiotherapy.

2. New studies show that direct AR antagonists can act in concert with ADT to improve the cellular response to radiation therapy. Aim 2 of this project will assess the relevance of this concept under conditions associated with advanced disease.

The results from Aims 1 and 2 are expected to provide the foundation for new clinical trials designed to improve outcomes for men treated for locally advanced prostate cancer. If successful, the present project could lead to dramatic improvements in the clinical management of locally advanced prostate cancer.

Summary of Research Completed

The project will start July 1, 2011 and the start date has been amended in this report.