American College of Radiology

Annual Progress Report: 2010 Formula Grant

Reporting Period

July 1, 2013 – June 30, 2014

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.

Duration of Project

1/1/2011 - 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.

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.

Principal Investigator

Mitchell Schnall, MD, PhD
Professor of Radiology
University of Pennsylvania School of Medicine
Department of Radiology
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104

Other Participating Researchers

Harold Litt, MD, PhD, Tessa Cook, MD, PhD – employed by University of Pennsylvania School of Medicine

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

Specific Aim 1:

- To survey the distribution of radiation doses received at CT at select practice sites across Pennsylvania.

A modified version of the Radimetrics eXposure software was developed and tested by Radimetrics personnel. It has been installed at the University of Pennsylvania Health System (UPHS), Geisinger Health System, Pennsylvania State U - Hershey Medical Center, and at the American College of Radiology Clinical Research Center in Philadelphia.

CT scan dose data collection began at The Hospital of the University of Pennsylvania, Penn Presbyterian Hospital and Pennsylvania Hospital on April 28, 2014 (12 scanners), and from Penn Community Radiology practices on May 28, 2014 (10 scanners). As of June 30, 2014, dose data for 13,500 examinations has been acquired from these sites, and the eXposure server has begun to pull older studies from the picture archiving and communications system (PACS) at UPHS to retrieve dose data for all scans performed since January 1, 2014. Figure 1 below shows the distribution of exams over the time since we began data acquisition.

Figure 2 shows a plot of Size Specific Dose Estimate (SSDE) versus patient diameter for 13500 scans acquired up to June 30, 2014. The SSDE is a derived value of radiation dose that attempts to compensate for differences in patient size, as an uncorrected dose measurement would show a direct correlation with patient size, which would overwhelm the contribution of other device, protocol, technologist or radiologist-related factors. Use of SSDE allows analysis of these other factors and their contribution to received patient doses. For example, Figure 3 shows a subgroup of studies from Figure 2, all of which were performed on a single type of CT scanner (Siemens Definition Flash) but at two different study sites (green vs. white markers). As can be seen from the figure, the site depicted with white markers had a large number of studies performed at a dose of >60 mGy for patient diameters between 100 and 200 mm (likely CT examinations of the head or cervical spine), while the site depicted with green markers had only 2 exams with a dose of >60 mGy. This suggests a systematic difference in the acquisition protocol for head CTs between the two institutions.

While this data does not provide information on differences in image or diagnostic quality between the two sites, it does show a potential avenue for dose optimization by comparing the protocols for the two different institutions. Alternatively, this may reflect a difference in disease demographics or study indications between the two sites, e.g. one site may do a larger number of cervical spine CTs for trauma or in patients with pre-existing spinal hardware, which may affect scan protocol design. This type of analysis is ongoing and provides the motivation for the on-site education to be performed at sites randomized to this intervention.

Dose data began to be recorded at Pennsylvania State University - Hershey Medical Center (6 scanners) on June 11, 2014 and Geisinger (23 scanners) began recording data on June 27, 2014. At present there are over 9,000 dose data records from Geisinger and 1,340 from Hershey, for a total of nearly 25,000 exams thus far. Retrospective dose data extraction back to January 1, 2014

will begin at other sites imminently.

It should be noted that a fourth site, University of Pittsburgh Medical Center (UPMC), has been unable to install the software due to contractual disagreements between Bayer, the company that purchased Radimetrics in November 2012, and UPMC legal staff. ACRIN officials and Dr. Litt have attempted to moderate the dispute, which concerns some specific legal language that UPMC requires in all of their vendor contracts related to human resource policies at the companies with whom they deal. UPMC leadership has been unwilling to compromise, so we have engaged with leadership at Bayer/Medtronic in Pittsburgh to determine if they can resolve the issue, and discussions are ongoing.

Specific Aim 2:

- To evaluate the impact of various strategies for providing dose reduction education to sites performing CT in Pennsylvania.

Interventions will begin at UPHS in July 2014 and at other sites once 6 months of dose data has been retrieved from the local PACS at each site.

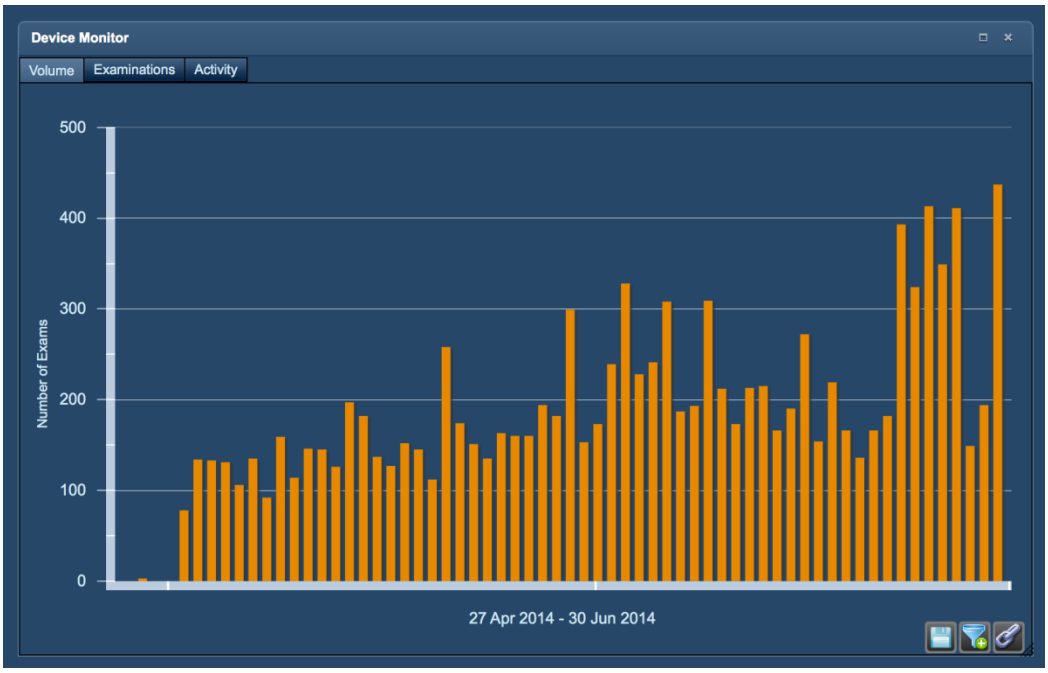

Figure 1: Plot of number of CT scans with dose data acquired from UPenn and Penn Community Radiology per day from April 27 to June 30, 2014

Figure 2: Plot of Size Specific Dose Estimate (SSDE) vs. Patient diameter for all CT scans with data acquired since April 27, 2014. Data are further divided by CT scanner (color of markers).

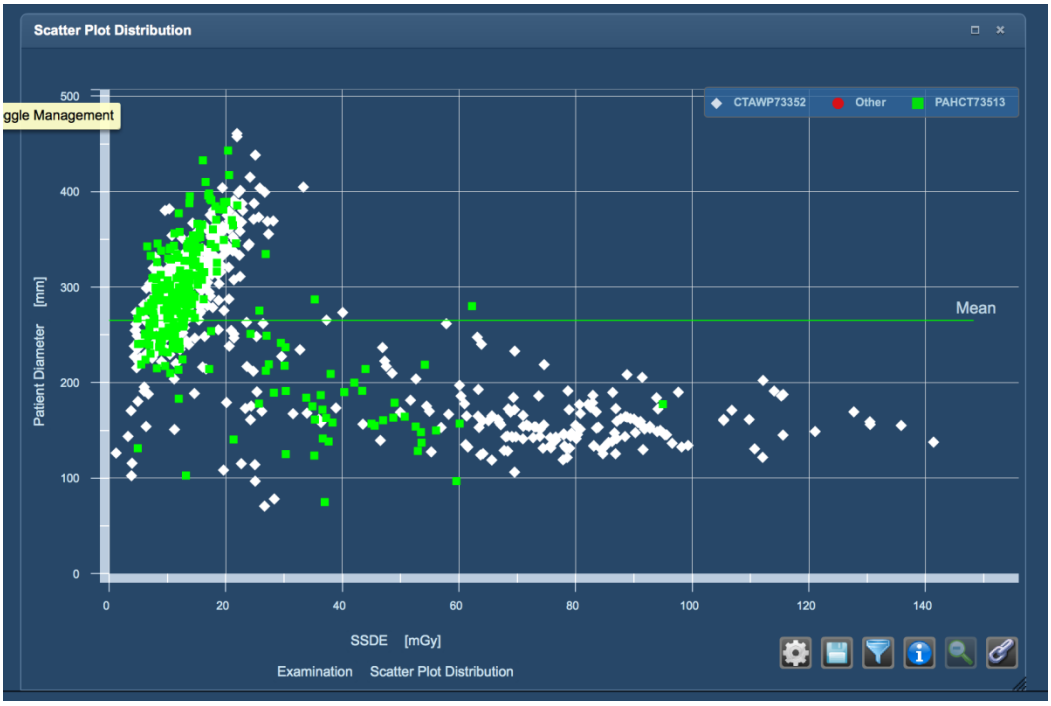

Figure 3: Plot of SSDE vs. Patient Diameter for scans performed on a single type of CT scanner (Siemens Definition Flash) at two different sites in the study (green vs. white markers). Note that the site in white had many more scans at higher doses (e.g. >60 mGy) than the site in green. See text for analysis.

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.

Principal Investigator

Kathryn A. Winter, MS
Director, RTOG Statistical and Data Management Center
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Other Participating Researchers

Adam Dicker, MD, PhD – employed by Thomas Jefferson University
Asha George, MS, Jen Moughan, MS, Fran Bradley, BA, Rebecca Paulus, MS – employed by American College of Radiology

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

Aim 1: TRP 173: No progress to report for this period.

Aim 2: TRP 165: No progress to report for this period.

Aim 3: TRP 167: Statistical analyses have begun and are summarized below.

Being able to identify heritable, germline polymorphic markers that are prognostic for or predictive of outcome and/or toxicity in resected pancreas patients is of interest. RTOG 9704 is a phase III randomized trial comparing fluorouracil versus gemcitabine before and after chemoradiotherapy as adjuvant therapy for patients with resected pancreatic cancer. The results revealed a non-significant improvement in survival for the gemcitabine arm. Pharmacogenetic studies can identify one or more genetic variations that are highly associated with, and therefore may predict for, either drug toxicity or efficacy. In addition, germline polymorphisms may be prognostic markers of outcome, independent of therapy.

Analyses done so far have focused on the amount of missing data for each polymorphic marker; allele frequencies, including the minor allele frequency; observed genotype numbers; expected genotype frequencies; expected genotype numbers; and an exact test for the Harvey-Weinberg Equilibrium (HWE).

Statistical comparisons to assess potential associations between baseline characteristics and those patients with and without polymorphic marker data were carried out using the chi-square test. The following baseline characteristics were dichotomized: pathological t-stage (T1, T2 vs. T3, T4) and American Joint Committee on Cancer (AJCC) stage (I, II vs. III, IV). Race was categorized as white vs. African American/other. Univariate analysis of overall (OS) and disease-free survival (DFS) comparing patients with and without polymorphic marker data was also performed. OS and DFS were estimated univariately with the Kaplan-Meier method and polymorphic marker status (with vs. without) were compared using the log-rank test. Cox proportional hazards models were utilized to identify the impact of patients with and without polymorphic marker data on OS and DFS. Given the numerous polymorphic markers and to adjust for multiple comparisons in this analysis, a p-value < 0.001 was considered statistically significant. A p-value < 0.001 denotes a violation of the HWE.

Patients who are not analyzable are more likely to have head of pancreas tumors, as compared to body/tail of pancreas tumors, than patients who are analyzable (89.0% vs. 81.5%. p=0.024). There were no other statistically significant differences seen in baseline characteristics. There were no statistically significant differences in OS or DFS between those who were analyzable and those who were not analyzable. Sixty-one markers were analyzed, 52 assessed in the lab by

the Sequenom assay, 5 by the SNaPshot assay, and 4 by the Sangar assay. Tables were created showing the observed genotype frequencies, the expected genotype frequencies, the calculated allele frequency, and the p-value for testing whether the results violate the HWE. Of the 61 markers analyzed, the HWE was only violated for two, both assessed by the SNaPshot assay, and those 2 markers will not be evaluated further. While these analyses were done for all 61 markers, due to space limitations in this progress report, only the table for the 5 markers done using the SNaPshot assay are shown below in Table 1.

Aim 4: TRP 169: Completed.

Aim 5: TRP 91: Completed.

Aim 3: Table 1
Genes and SNPs by SNaPshot Assay

Marker	RS #	Genotype	Observed Genotype n	Expected Genotype Frequency	Expected Genotype n*	Exact Test for HWE p-value
TP73	rs2273953	CC	103	0.6334	107	0.093
		CT	63	0.3249	54	
		TT	3	0.0417	7	
		Total	169			
		Allele Frequency	C=0.7959			
			T=0.2041	MAF		
		X (failed)	9 (5.1%)			
PMS2L3	rs794378	CC	0	0.1572	26	<0.0001
		CT	134	0.4786	80	
		TT	35	0.3643	61	
		Total	169			
		Allele Frequency	C=0.3964	MAF		
			T=0.6036			
		X (failed)	9 (5.1%)			
hENT1	rs9394992	CC	82	0.5201	85	0.18
		CT	74	0.4021	66	
		TT	9	0.0777	12	
		Total	165			
		Allele Frequency	C=0.7212			
			T=0.2788	MAF		
		X (failed)	13 (7.3%)			
PLCG2	rs4889426	CC	74	0.4314	72	0.73
		CT	74	0.4508	76	
		TT	21	0.1178	19	
		Total	169			
		Allele Frequency	C=0.6568			
			T=0.3432	MAF		
		X (failed)	9 (5.1%)			
PMS2	rs17420802	AA	9	0.2775	46	<0.0001
		GA	159	0.4986	83	
		GG	0	0.2239	37	
		Total	168			
		Allele Frequency	A=0.5268			
			G=0.4732	MAF		
		X (failed)	10 (5.6%)			

Abbreviations: MAF, minor allele frequency; HWE, Hardy Weinberg Equilibrium
*Note: The sum of the expected genotypes might not equal the total sample size due to rounding.

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.

Principal Investigator

Stephanie Shook Pugh, PhD
Senior Statistician
American College of Radiology
1818 Market St., Suite 1600
Philadelphia, PA 19103

Other Participating Researchers

Kathryn Winter, MS, Daniel Hunt, PhD, Ed Zhang, PhD, Jennifer Moughan, MS, Yan Yan, MD, MS, Jonathan Harris, MS – employed by American College of Radiology

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

Work on *Aims 1* and *2* was completed in a previous reporting period.

Aims 3, 4, and 6: Statistical analyses for this project have begun, including preliminary data cleaning and statistical programming.

Aim 5: Statistical analyses are still in progress.

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.

Principal Investigator

Benjamin Movsas, MD
Chairman, Radiation Oncology
Henry Ford Health System
2799 West Grand Blvd, M2
Detroit MI 48202

Other Participating Researchers

Stephanie Shook, PhD, Karan Boparai, BS, Roseann Bonnani, Jennifer James, MS – employed by American College of Radiology
Mitchell Machtay, MD – employed by Case Western University
Clement Gwede, MD – employed by Moffitt Cancer Center

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

During this past year, important milestones were accomplished on this project entitled "Improving the Collection of Patient-Reported Quality of Life (QOL) Data – Expansion of Web-based Quality QOL Collection Strategy". The Radiation Therapy Oncology Group (RTOG) study 0920, entitled "A Phase III Study Of Postoperative Intensity Modulated Radiation Therapy (IMRT) +/- Cetuximab For Locally-Advanced Resected Head And Neck Cancer " was opened to enrollment, including the amendment allowing for patients to complete their quality of life (QOL) forms using the electronic web-based technology (called VisionTree Optimal Care or VTOC). Moreover, this amendment to allow for the use of this HIPAA-compliant electronic system had to be approved by each individual Institutional Review Board (IRB). This process went well and this component of this study (with this amendment) was approved and opened at many RTOG institutions across North America.

Over the past year, 44 patients who consented to complete their quality of life on this study using VisionTree Optimal Care (VTOC) passed the one-year follow-up time point. This represented 43% of the patients who consented to participate in the QOL component of RTOG 0920. The pretreatment characteristics of the 44 patients who consented to use VTOC are as follows: The median age was 60.5 years, compared to 59 years among other patients in the study. 30 of the 44 patients (68%) were male (compared to 71% of the patients in the rest of the study). Similarly, the breakdown by race was also similar. 40 of the 44 patients (91%) were white compared to approximately 85% of the patients in the rest of the study. The remaining 4 patients (who consented to use VTOC) were Black or African-American (9%). This compared to 7% African-American or Black patients and another 7% Asian patients in the rest of the study. Of the 44 patients who consented to use VisionTree Optimal Care, 15 (34%) had an excellent Zubrod performance status of zero. This appeared somewhat lower than the rate of 56% of patients in the rest of the study who had a Zubrod performance status of zero. Due to the relatively small numbers so far accrued, it is too early to determine if this is of statistical significance. Overall, the smoking history was similar among patients who consented to use VTOC and the remaining patients. 17 of the 44 patients who consented to VTOC (39%) had never smoked, compared to 36% of patients in the rest of the study. 16% of the VisionTree Optimal Care patients had less

than 20 pack year history of smoking, 23% had 20 to 40 pack year of smoking, and 16% had a greater than 40 pack year history of smoking. The respective percentages in the remaining patients were 15%, 24%, and 24% (which is similar).

Overall, the pathologic staging using the American Joint Committee on Cancer staging system (AJCC) was also similar between patients who consented to use VisionTree Optimal Care (VTOC) and the remaining group. AJCC stages I, II, III, and IV among the VTOC patients was broken down as follows: 5%, 16%, 25%, and 52%, respectively. Among the remaining patients, the breakdown was: 5%, 14%, 15% and 66%, respectively. In both groups, the rate of perineural involvement was 84%. The breakdown by pathologic T-stage was also very similar. Among the patients who consented to VisionTree Optimal Care, the breakdown of T1, T2, T3 and T4 was 23%, 41%, 11% and 25%, respectively. In the remaining group, it was 20%, 41%, 12% and 27%, respectively. The breakdown by pathologic N-stage was as follows for N0, N1, and N2: for the VTOC group it was 41%, 23%, and 35%, respectively; in the remaining group it was 41%, 19%, and 39%, respectively. Thus, at this point in the study, the pretreatment characteristics for the patients who consented to use VisionTree Optimal Care (VTOC) were mostly as expected and overall comparable to the remaining group of patients in the study who did not choose to use VTOC.

By the one-year time point, two of the 44 patients (4.5%) who had consented to use VisionTree Optimal Care had passed away. Of the remaining 42 patients who were eligible to complete the validated Functional Assessment of Cancer Therapy – Head and Neck (FACT-HN) quality of life (QOL) form at one year, 23 patients (55%) did so within the QOL time window (of +/- 2 months). Another 2 patients completed the QOL form outside of this time window. None of the patients withdrew their consent prior to the 1-year time point period. Of the patients who did not complete the FACT-HN form at the 1-year time point, the following were the reasons provided for the lack of compliance: Six patients (14.3%) did not do so due to institutional error. One patient (2.4%) did not do so due to patient refusal. Three patients (7%) could not be contacted and one patient (2.4%) did not complete the QOL form for "other reason". Of note, for six patients (14.3%), the QOL form was not received and no reason was stated.

The hypothesis for this project was that the compliance rate for the validated Functional Assessment of Cancer Therapy – Head and Neck form (FACT-HN) at one year would be significantly increased from the baseline level of 50% (using paper forms in a prior study, RTOG 0522) to 65% using the electronic web-based technology, VisionTree Optimal Care (a 30% relative increase). Of note, the statistical design using 95% power would require 130 patients to show this difference. Thus, at this point, it is too early to make a statistical assessment regarding this hypothesis as, thus far, 44 patients who consented to using VTOC have completed radiation therapy at least one year ago. The information thus far suggests a trend in the right direction as 55% of the patients have completed the FACT-HN form at one year (and within the QOL time window). If one includes the additional 2 patients who completed the 1-year form outside of this time window, the 1-year compliance rate increases to 60%. Of note, there were 6 patients who did not complete the 1-year QOL form due to "institutional error". This may have been due to a learning curve in this study for using VisionTree Optimal Care. Indeed, one of the benefits of using VTOC (in a prior RTOG prostate cancer study) was that it was able to reduce the rate of institutional error compared to using paper forms. It is also important to note that there were 3

patients who could not be contacted, which is another opportunity for further improving compliance over time. If indeed, with further experience, the institutional error can be reduced, it is possible that the 1-year compliance rate could further increase over time. However, this remains to be determined and requires further follow-up, as planned.
In summary, the following important milestones were accomplished over the past year for this project. Patients were able to consent to using the electronic web-based technology, VisionTree Optimal Care (VTOC), with the appropriate IRB approval (as part of the RTOG study 0920). Moreover, the pretreatment characteristics of the patients appear similar to what would be expected compared to other patients enrolled in this study thus far. Finally, the 1-year validated Functional Assessment of Cancer Therapy – Head and Neck (FACT-HN) QOL compliance rate is tracking in the range expected and, as planned, further follow-up is needed to assess the hypothesis of this project.

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

7/1/2012 - 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.

Principal Investigator

Karen E Knudsen, PhD
Professor of Cancer Biology, Urology, & Radiation Oncology
Thomas Jefferson University
Kimmel Cancer Center
233 S. 10th St., BLSB 1008
Philadelphia, PA 19107

Other Participating Researchers

Adam Dicker, MD, PhD – employed by Thomas Jefferson University

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

Aim 1 Progress:

Because of protracted contract negotiations between ACR and Thomas Jefferson University, funds were significantly delayed for initiating the project, and the project components for Aim 1

were initiated, completed, and published using start-up funds provided to Dr. Knudsen. As a result, no grant funds were used for work on Aim 1 but we were able to advance what we had initially planned in terms of the timeline for Aim 2, which is a natural extension of the Aim 1 outcomes. Notably, these have significant translational potential.

Aim 2 Progress

We have also made substantial progress on this aim in the last year. For these studies, we built on our recent publication identifying AR as a major mediator of double-strand DNA break repair as mediated by the ability of AR to regulate the expression and activity of the DNAPK enzyme. The catalytic subunit of the DNA-dependent protein kinase (DNAPKcs) plays a major role in the non-homologous end joining (NHEJ) double strand break repair pathway and was demonstrated to be critical in the AR-mediated response to damage. Surprisingly, DNAPKcs also interacts with AR in a damage-independent fashion serving as a coactivator of AR transcriptional activity and forming a positive feedback circuit linking hormone action to the DNA damage response. This feedback circuit suggests that DNAPK may significantly impact global transcription in the absence of DNA damage.

New findings demonstrate that DNAPKcs expression is positively correlated with decreased freedom from metastases in prostatic adenocarcinoma (PCa) patients (Figure 1) suggesting that DNAPKcs may drive disease progression and metastatic phenotypes. As such, understanding how DNAPKcs drives metastases may be of significant clinical benefit. DNAPKcs was found to directly interact with AR, and this interaction was not disrupted after AR stimulation with DHT or DNAPKcs inhibition using a commercially available DNAPK inhibitor, NU7441 (Figure 2A). Chromatin immunoprecipitation (ChIP) analyses revealed that DNAPKcs resides at regulatory regions of well-characterized AR target genes under the same treatment conditions where direct interaction between AR and DNAPKcs was observed (Figure 2B), suggesting that DNAPKcs interaction with AR at regulatory regions may impact expression of AR target genes.

Given this finding and reports demonstrating DNAPKcs interaction with other transcription factors, we speculated that DNAPKcs may impact gene expression on a global scale. To test this hypothesis, PCa cells treated with DNAPKcs inhibitor or subject to DNAPKcs knockdown were subject to microarray analysis (Figure 3). Expression of numerous genes was either positively or negatively impacted by either DNAPKcs knockdown or inhibition (or both). Of interest, the family of UGT enzymes was shown to be significantly upregulated after diminished DNAPKcs expression. The UGT family of enzymes catalyzes glucuronidation reactions and plays important roles in small molecule metabolism. Specifically, UGT2B15 and UGT2B17, whose expression is impacted by AR, have been shown to glucuronidate and aid in metabolism of testosterone and DHT. Gene expression of both UGT2B15 and UGT2B17 were significantly upregulated in two castration-resistant (CRPC) lines after DNAPKcs depletion, while protein expression was only modestly upregulated (Figure 4A). ChIP analyses revealed the presence of AR and DNAPKcs at the promoter regions of UGT2B15 and UGT2B17, and AR recruitment was decreased in response to inhibitor treatment while DNAPKcs recruitment was not significantly altered (Figure 4B,C). Combined, these findings suggest that DNAPKcs impacts UGT2B15 and UGT2B17 gene expression, possibly by aiding in recruitment of AR to regulatory chromatin regions.

Excitingly, another pathway regulated by DNAPKcs was focal adhesion, and detailed analysis revealed decreased expression of numerous genes associated with metastasis after DNAPKcs knockdown or inhibition (Figure 5A). ChIP analyses of DNAPKcs recruitment to the promoters of P-REX1, ITGB4, and ROCK2 revealed the presence of DNAPKcs at these sites both endogenously and after inhibitor treatment, suggesting that the kinase activity of DNAPKcs aids in expression of these genes (Figure 5B). The biological consequence of DNAPKcs-mediated expression of metastasis-associated genes was investigated through migration and invasion assays, which revealed decreased migration and invasion of multiple PCa cell lines (both hormone therapy-sensitive and castration resistant) after DNAPKcs inhibitor treatment (Figure 5C). Combined, these studies demonstrate that DNAPKcs impacts expression of genes associated with metastasis, most likely through direct interaction at key transcriptional regulatory regions.

Combined, these exciting new studies reveal that DNAPKcs regulates genome wide transcriptional networks in the absence of exogenous damage. DNAPKcs impacts expression of canonical AR target genes, UGT enzymes involved in testosterone metabolism, and genes associated with metastasis, which may be the most important finding of all given the positive correlation between DNAPKcs expression and development of metastases seen in patients. These findings support investigation of targeting DNAPKcs as a novel therapeutic intervention in PCa, particularly since multiple DNAPKcs inhibitors are currently in different stages of clinical trials for treatment of solid tumors.

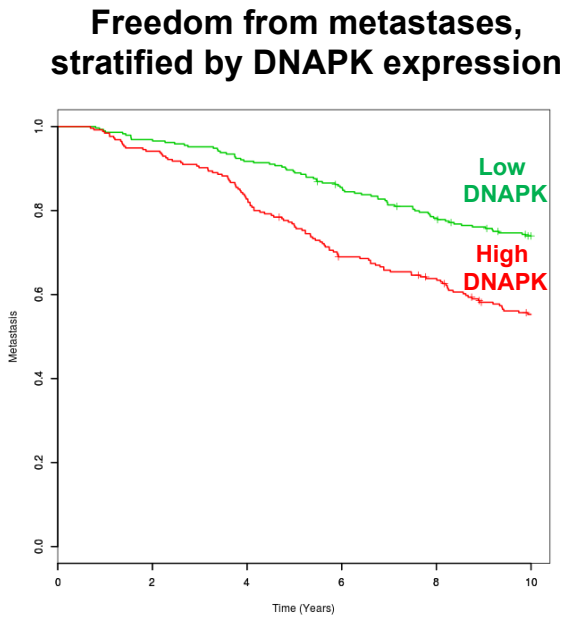

Figure 1. High DNAPK expression predicts for metastases in a cohort of PCa patients

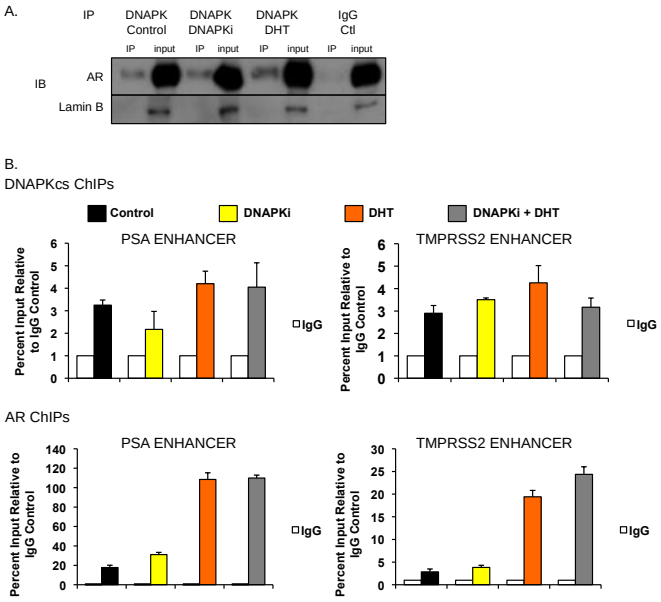

Figure 2. DNAPK binds
AR and regulates AR signaling. (A) DNAPK was immunoprecipitated 3 hours after 1uM NU7441 or 10nM DHT treatment and immunoblot analyses performed for AR and Lamin B. (B) DNAPK and AR ChIPs were performed at the PSA and TMPRSS2 enhancer after treatment with 1uM NU7441, 10nM DHT, or combination of both

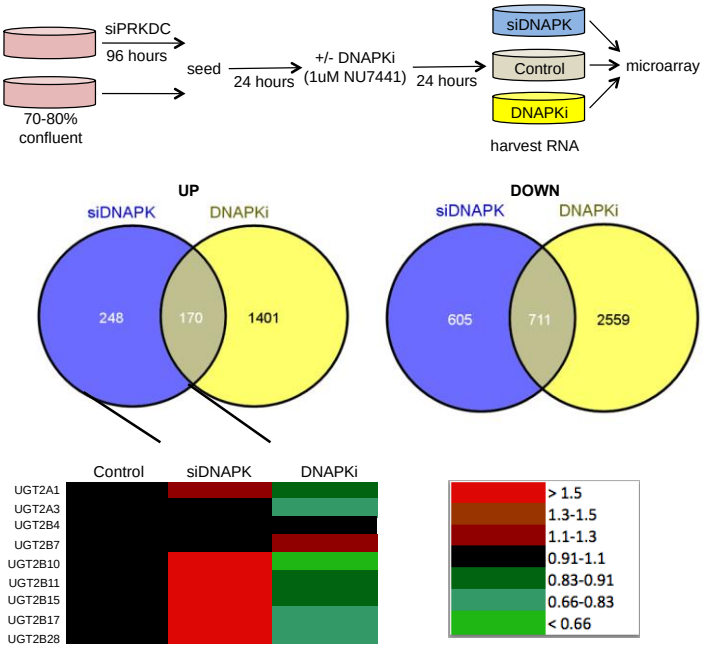

Figure 3. DNAPK impacts gene expression on a global scale.
CRPC cells subject to DNAPK knockdown or treated with DNAPK inhibitor were subject to microarray analysis. The UGT family of enzymes was identified to be significantly upregulated after DNAPK knockdown.

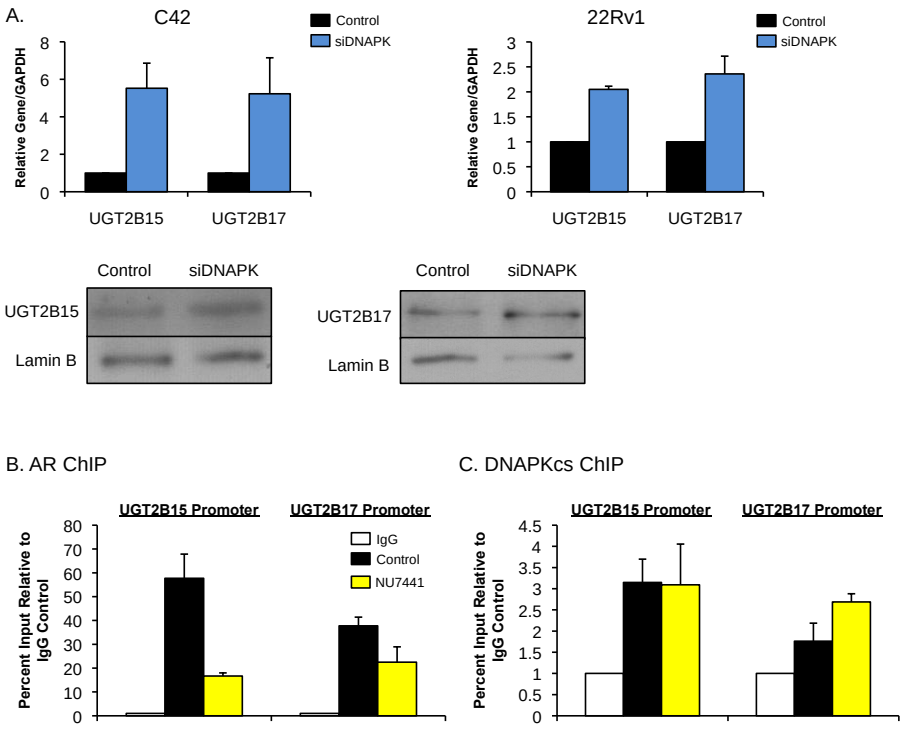

Figure 4. DNAPK regulates UGT2B15/17 in CRPC.
(A) Knockdown of DNAPK in CRPC cells results in elevated UGT2B15 and UGT2B 17 gene and protein expression. (B,C). ChIP analyses in CRPC cells shows that recruitment of AR to regulatory loci of UGT2B15 and 17 is reduced after inhibitor treatment, while DNAPKcs recruitment is not significantly altered.

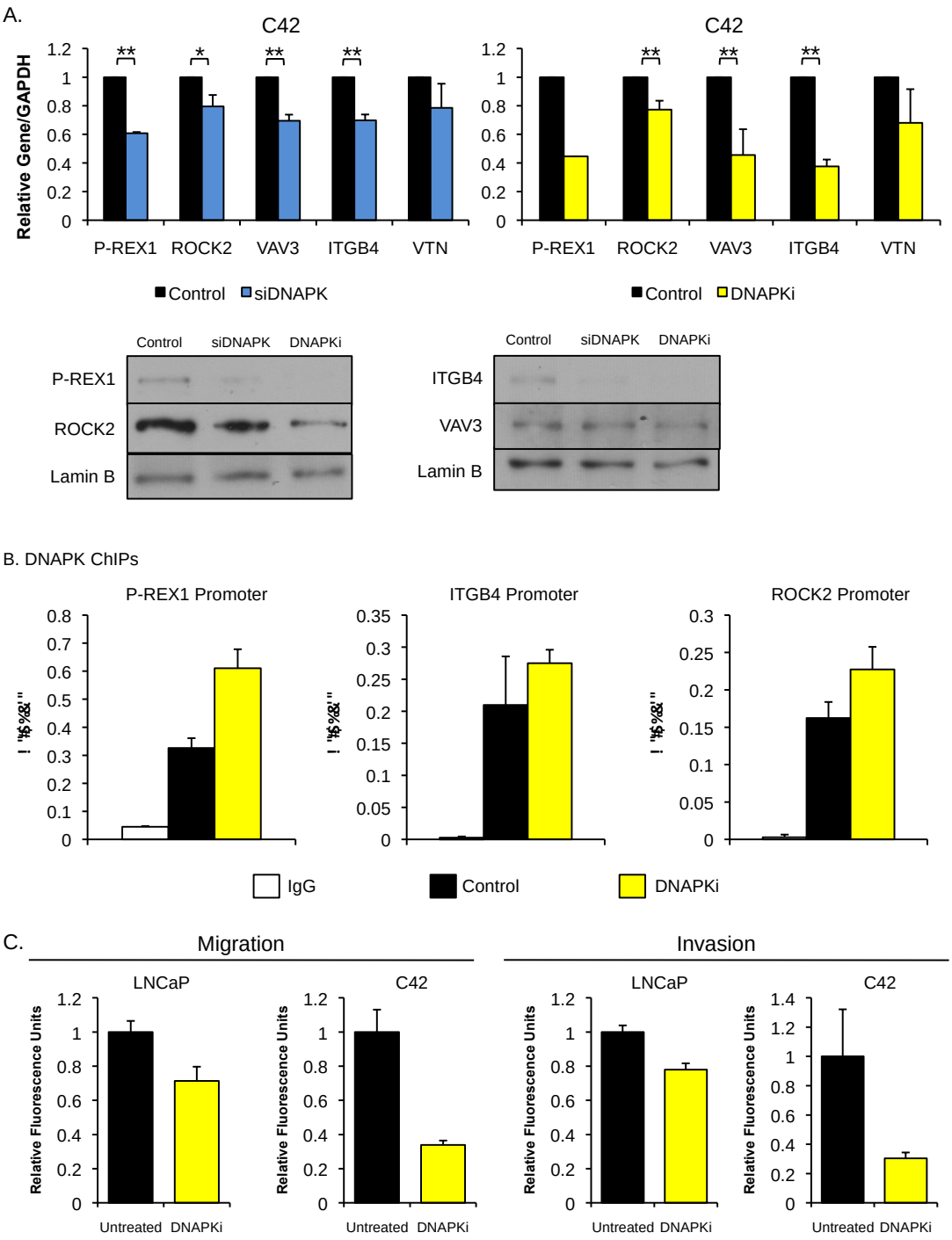

Figure 5. DNAPK promotes pro-metastatic signaling.
(A) Knockdown or inhibition of DNAPK results in decreased gene and protein expression of numerous genes associated with metastasis. (B) ChIPs demonstrate recruitment of DNAPKcs to regulatory loci of genes associated with metastasis endogenously and after inhibitor treatment. (C) DNAPK inhibition results in decreased migration and invasion in hormone-therapy sensitive and CRPC cells.