American College of Radiology

Annual Progress Report: 2005 Formula Grant

Reporting Period

July 1, 2009 – December 31, 2009

Formula Grant Overview

The American College of Radiology received $2,590,126 in formula funds for the grant award period January 1, 2006 through December 31, 2009. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Biomarkers for Prostate Cancer Treatment with Radiation and Hormone Therapy - Some men with prostate cancer have an excellent prognosis and do not need treatment, while others succumb to the disease in a relatively short period of time. Since 1 in 6 men will develop prostate cancer in their lifetime, the need to better understand the biology of the disease is imperative. The identification of biomarkers that predict prostate cancer response to therapy will facilitate more accurate selection of appropriate therapy, lead to a greater appreciation of the molecular mechanisms that govern response and guide the administration of newer "targeted" therapies that are currently under investigation. The objectives are to bring into more routine use measurements of MDM2, p53, Ki-67 and p16 expression at the protein level and a host of other potential genes measured at the RNA level.

Duration of Project

1/1/2006 - 12/31/2009

Project Overview

Prior studies from the Radiation Therapy Oncology Group (RTOG) have demonstrated that when prostate cancers over express MDM2, p53, Ki-67 and/or p16 at the protein level there is a propensity to develop distant metastasis and to die from the disease. Statistical analyses have revealed that these markers are independent of the conventional factors used today, namely Gleason score, PSA and stage, as well as the type of treatment administered. These findings are the most dramatic since the seminal observation by Dr. Gleason on the Gleason scoring system. The only reason that that these findings have not yet been promoted more widely is that they need to be repeated in one more large study. Confirmation of our findings has the potential to substantially alter clinical practice. Initial investigations were performed in tumor samples from patients treated on two large RTOG randomized trials, RTOG 86-10 and 92-02. In the latter trial, which is the more definitive, patients with locally-advanced disease were treated with radiotherapy (RT) plus short or long term hormone therapy (HT). Corroboration of these

findings will be made in samples from another major clinical trial, RTOG 94-13, which also involved treatment with RT+HT.

The methods used to quantify the protein levels of MDM2, p53, Ki-67 and p16 are well established, but limiting. Protein expression was measured by immunohistochemistry (IHC); the methods required significant amounts of tissue and only an average of 6-7 markers can be examined in each case. Newer techniques involving quantification of RNA, instead of protein, permit measurement of gene expression in hundreds to tens of thousands of genes in each case. We plan to refine a novel method for extracting and analyzing RNA from formalin-fixed needle biopsy specimens to measure expression in 380 genes simultaneously.

Specific Aims: The focus of the analyses proposed will be on preserved pretreatment prostate biopsy samples from men treated in RTOG 94-13. The specific aims are: 1) confirm and extend the prior protein-based gene expression results from RTOG 92-02 using previously acquired samples from RTOG 94-13; 2) measure the expression of an expanded set of 380 genes at the RNA level using a custom made card in 200 selected cases from RTOG-94-13; and 3) compare the protein and RNA results directly and with the protein expression results from RTOG trials 86-10, 92-02 and 94-06 (this is another trial being analyzed with independent funding at this time).

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Expected Research Outcomes and Benefits

Preliminary studies of the protein expression of MDM2, p53, Ki-67 and p16 in RTOG protocols 86-10 and 92-02 have been very promising. This line of research is now on the brink of translation into clinical practice on a broad scale. The project will allow for the implementation of the definitive experiments needed to solidify the significance of these markers, with the expectation that patients in Pennsylvania will immediately benefit from more accurate determination of prognosis. The plan is to confirm the results in an independent patient population, i.e., the cases in RTOG 94-13. Assuming our preliminary results are substantiated, the tests for MDM2, p53, Ki-67 and p16 gene expression at the protein level and the resultant predictive models will first be available to men in Pennsylvania. A mechanism is already being put in place to offer these tests through the Department of Pathology at Fox Chase Cancer Center (Fox Chase) in collaboration with the Principal Investigator's laboratory. The estimated timeline is that these investigations will be complete within two years.

The project will also broaden the molecular marker analysis by quantifying expression at the RNA level. Methods are in development to measure 380 genes in prostate needle biopsy tissue that has been fixed in formalin and stored. Preliminary results show that this is feasible, although not all genes are measurable in stored samples, as compared to flash frozen samples. The project will determine the limitations. An array of genes will be put together to complement the protein-based studies that have been done. The expectation is that these new associations will supplement or replace the observations at the protein level, providing a greater degree of precision in treatment selection, understanding of the mechanisms governing response to RT and HT and development of novel targeted therapies.

Summary of Research Completed

1. *Construct a model predictive of distant metastasis and/or cause specific mortality based on molecular marker expression by IHC and clinical factors.*

Since last year's report we have finalized a model that predicts for distant metastasis (DM) at 10 years and it will be submitting the paper in the near future. This model was presented at the American Society for therapeutic radiology and oncology in 2008 and was described in last year's annual report.

A paper was published on PKA overexpression, as it relates to patient outcome in RTOG 92-02.[1] This paper was in press at the time of the last annual report and the results described in that report.

2. *Quantify the expression of model selected biomarkers by IHC in samples from RTOG 94-13 and confirm that the model is predictive of outcome in this patient population.*

This project has finally gained some traction. We have all of the samples from 94-13 cut and they are ready for staining. Because of concerns with the staining of the first batch of slides, we have ordered, and now have received, our own autostainer in the Department of Radiation Oncology. The Pennsylvania Department of Health Grant was instrumental in getting this off the ground. In order to sustain the project and bring it to completion, we have obtained an R21 that will support the subsequent staining. Based on the results from Aim 1, we are focusing on Ki-67, MDM2, p16, Cox-2 and PKA.

We also ran into delays with our ChromaVision image analysis system. There is spotty support for this unit since the company was bought out by another group. However, the unit is now functioning properly and we can continue to use it. Comparative studies between ChromaVision have been done and the results are being compiled. Eventually we will have to migrate to the AQUA image analysis system.

We have assessed the samples in the RTOG tissue bank for study 94-13 and have over 500 cases available for IHC analysis, but have not started yet. The main reason is that there was concern about using up the tissue. As a result, we have spent some time to determine if the AQUA system, which is another image analysis platform that is available in my laboratory, could be

used to multiplex the analysis of biomarkers and preserve tissue. After several studies, we decided to proceed with the ChromaVision study, which is now in progress with additional funding from an R21 from the NIH.

3. *Establish a procedure for microarray analysis of mRNA from archival prostate cancer needle biopsy tissue and begin to apply this technology to selected cases from RTOG 94-13.*

We developed an IRB approved protocol to acquire prostate biopsies from patients with the goal of comparing fresh versus frozen material for mRNA and miRNA gene expression profiling. Everything was in place, but funds were exhausted. We originally included this Aim in the R21 that we have obtained, but the reviewers thought it was too preliminary and cut the funding for this project. We continue to look for alternative funds to support this avenue of research, which is high risk with potentially high reward, and certainly is worth doing. This was mentioned in the prior annual report, so nothing has changed.
Of note, we have begun to look at single nucleotide polymorphisms (SNPs) in pretreatment prostate diagnostic tissue, which is an offshoot of this project. Our efforts in this area have been recently funded.

References

1. Pollack A, Bae K, Khor LY, Al-Saleem T, Hammond ME, Venkatesan V, Byhardt RW, Asbell SO, Shipley WU, Sandler HM. The importance of protein kinase A in prostate cancer: relationship to patient outcome in Radiation Therapy Oncology Group trial 92-02. Clin Cancer Res 2009;15: 5478-84.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19706804

Research Project 2: Project Title and Purpose

Assessing the Value Added of PROs in Cooperative Group Oncology Clinical Trials - Quality of life (QOL) during and after treatment is ever more important as cancer patient survival increases. The value added of patient-reported outcomes (PROs) has been questioned. With this study, we will examine the degree to which toxicity data is redundant with PROs and the number of cases that would be considered to have a positive outcome by each assessment method.

Duration of Project

1/1/2006 – 6/30/2009

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 3: Project Title and Purpose

Identification of Barriers and Facilitators to RTOG Clinical Trials Recruitment - It is well documented that only about 3-5% of new cancer patients participate in clinical trials. Despite considerable time, effort, and expense, the proportion of patients recruited is frequently small. This study will assess barriers and facilitators to clinical trials recruitment within the context of patient-, clinician- and organizational-level factors. The data will provide evidence upon which to develop interventions for improvement of recruitment to Radiation Therapy Oncology Group (RTOG) clinical trials.

Duration of Project

1/1/2006 - 6/30/2009

Project Overview

Much observation, yet little scientific rigor, has been applied to the study of barriers to and methods for increasing recruitment to cancer clinical trials. However, without this obvious prerequisite to successful clinical trials completion, even the most innovative research is stymied. The 2005 Agency for Healthcare Research and Quality Report on recruitment to clinical trials found only nine studies of physician barriers and facilitators to clinical trials recruitment. Most of the studies found physician attitudes to be barriers and only one study found physician attitudes to facilitate clinical trials recruitment. None of the studies were specifically conducted in radiotherapy clinical trials where there may be additional misconceptions and barriers to clinical trials participation.

In order to improve recruitment and retention to clinical trials, the RTOG has developed a Recruitment Working Group to study barriers and test interventions to facilitate recruitment. The primary aim of this study is to assess clinician (physician and clinical research associates CRAs) level barriers and facilitators to recruitment to RTOG clinical trials. The secondary aims are as follows: 1) to assess patient and organizational-level barriers and facilitators to recruitment to RTOG clinical trials; 2) assess RTOG accrual by race, gender and age and compare to U.S. Census and SEER data; and 3) compare accrual based on type of institution (academic, community, freestanding) and by geographic location (which part of the country) and setting (urban, suburban, rural). Data gathered from the assessments will be used as pilot data for future funding for studies of specific interventions to address the barriers and augment the facilitators identified in this study.

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Expected Research Outcomes and Benefits

Clinical trials provide evidence that is formulated into recommendations for practice guidelines, but without improvements in recruitment, it is an ongoing concern that patients enrolled in trials may not be similar to those treated in routine practice. There is some evidence that clinical trials have a positive effect on patient outcomes and therefore, for reasons of social justice, all cancer patients should have access to the high-quality care, surveillance and availability of the latest treatments put forth in clinical trials. Identifying barriers to recruitment into a randomized clinical trial can help researchers adjust recruitment strategies to maximize enrollment. Data gathered from the assessments will be used as pilot data for future funding for studies of specific interventions to address the barriers and augment the facilitators of recruitment identified in this study. For example, if communication is found to be a major barrier to RTOG trial recruitment, scripted informed consent and/or video-taped examples of effective clinical trials presentation and informed consent could be developed and tested. If patient knowledge is found to be an issue in the pilot study, larger trials to assess the specific areas of misunderstanding could be designed and targeted education programs developed. And if organizational barriers such as CRA method for identification of eligible patients or recruitment methods are identified as barriers, improved methods and CRA training may be a solution that will be tested. If institution type is identified as a barrier, then clinician awareness and education may help to improve recruitment.

This work is a priority for the RTOG as demonstrated by the recent development of a Recruitment Working Group that focuses on improving recruitment plans for RTOG trials in general with an emphasis on minorities in particular. This work is also part of a program of research conducted by the PI of this study who has published on a conceptual framework to improve recruitment and successful strategies for African American recruitment in a single institution experience. The goal is to use the data from the trial to develop similar strategies on a national level for the RTOG.

Summary of Research Completed

Since the last progress report investigators have completed work related to Secondary Aim 1
Secondary Aim 1: to assess patient and organizational-level barriers and facilitators to recruitment to RTOG clinical trials

Patient-Level/Organizational-Level

Patient Survey

A survey of 42 patients at 5 RTOG sites was collected anonymously by the Clinical Research Associates (CRAs), i.e., no patient identifiers were collected. The survey was administered to the patients either via the telephone or face-to-face in the clinic.

The data obtained from the completed patient surveys was recently analyzed and accepted for presentation to the NCI-ASCO Cancer Trial Accrual Symposium: Science and Solutions taking place April 29-30, 2010, in Bethesda, MD. The abstract is below and the final manuscript is in development. The first author is a doctoral student at the University of Pennsylvania, a mentee of the PI, Dr. Bruner. She has been added to the scientific team after the funding was complete but is working on this as part of an independent study.

Identification of Patient Level Barriers and Facilitators to RTOG Clinical Trials Recruitment

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Abstract:
Background/Purpose: It has been well documented that only about 5% of new cancer patients participate in clinical trials despite significant recruitment effort, time and expense. There are many gaps in the existing literature on barriers and facilitators to clinical trial recruitment and almost no data regarding recruitment to clinical trials involving radiation therapy. This pilot study begins to identify barriers and facilitators to Radiation Therapy Oncology Group (RTOG) clinical trials from a patient perspective. Identifying patient level barriers to recruitment will help researchers adjust recruitment strategies to maximize enrollment to clinical trials.
Objective: The primary objective of this pilot study was to assess patient level barriers and facilitators to Radiation Therapy Oncology Group (RTOG) clinical trials in order to develop improved patient recruitment strategies.
Methods: Twenty one patients who had previously participated in an RTOG clinical trial and 21 eligible patients who refused participation in an RTOG clinical trial were randomly selected by senior research associates at five sites. A Likert-based, semi-structured, IRB approved survey was administered to each participant during a routine clinical visit. The Fisher Freeman-Halton extension of the Fisher exact test was used to evaluate response differences between the two groups at a significance level of 0.05.

Results: Patients who participated in an RTOG study were significantly more likely to disagree that participating in a clinical trial would take up too much of their time (p=.001). RTOG study participants were also significantly more likely to agree to participate in a clinical trial to help others whom they may or may not know (p=.0002), including family members who may get cancer in the future (p=.014). Patients who refused participation in an RTOG trial were significantly more likely to agree that taking part in a clinical trial made him or her feel like a "guinea pig" (p=.006).
Conclusion: Barriers to RTOG clinical trials recruitment include what some patients consider as too large a time commitment to warrant participation as well as feelings of being a "guinea pig". Possible facilitators to trial recruitment are patient's altruistic attitudes. Future recruitment efforts should consider strategies to streamline study processes and procedures to minimize time constraints for patients. Strategies should also seek to frame clinical trial discussions with patients to maximize their understanding of altruistic benefits and openly explore whether fears of being an experimental subject are actual fears or rather misunderstandings of treatment received on clinical trials.
(Rearden, J., James, J., Thomas, T., Gaffney, D., Neading, J., Neimanis, D., Stern, J., Consoli, J., Hanisch, L., Bruner, D. W. Identification of Patient Level Barriers and Facilitators to RTOG Clinical Trials Recruitment. Accepted for presentation at the NCI-ASCO Cancer Trial Accrual Symposium: Science and Solutions taking place April 29-30, 2010, in Bethesda, MD.)

Research Project 4: Project Title and Purpose

Missing Quality of Life Assessments in Radiation Therapy Oncology Group Studies - Quality of life (QOL) during and after treatment is ever more important as cancer patient survival increases. A major issue in QOL is missing assessments that complicate the analysis and interpretation of results. This project will describe patterns of missing QOL assessments in clinical trials that include radiotherapy and then investigate patient and disease characteristics that predict this.

Duration of Project

1/1/2006 - 12/31/2009

Project Overview

The broad objective is to describe patterns of missing QOL assessments and to investigate patient and disease characteristics for predictive value for missing QOL assessments in cancer clinical trials including radiation therapy. Specific aims for this objective are to describe the amount and timing of missing QOL assessments by disease site and type of QOL instrument; to evaluate similarities and differences in the patterns of missing assessments that provide insight to optimal selection of forms and collection schedules; and to determine the statistical strength and direction of associations of pre-selected patient and disease characteristics with missing QOL assessments, including investigating synergy between pairs of characteristics. The research design and methods for this objective will use data from brain tumor and head & neck, lung, breast, and gastrointestinal cancer trials to describe the patterns of missing QOL. Next, the project team will select patient and disease characteristics to analyze for statistical association with missing QOL assessments. The project team will explore confirmatory techniques, in

which the data are randomly split and each result is developed in one half of the data and tested with the other, to ensure the robustness of the results and subgroup analyses.

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Expected Research Outcomes and Benefits

Quality of life is an important component of cancer research and allows fuller appraisal of the costs and benefits of treatments to patients. Benefits of this project are that the results of this analysis can make QOL research more focused and meaningful. Cancer patients will be able to get the most appropriate and effective treatment based not only on clinical outcomes such as progression and survival but also on the QOL implications of the treatment regimen.

This project will shed light on how successful the RTOG has been in collecting the QOL information necessary to determine how cancer treatment affects the quality of life for cancer patients and how to be more successful. The importance of QOL makes this research timely because the collection of multiple measurements over time is difficult, especially in a patient population undergoing radiation therapy as part of their treatment for cancer. Knowledge gained in this project will allow study chairs to select the best possible QOL instruments and collection schedule.

Summary of Research Completed

We focused on describing the patterns and reasons of missing The Mini Mental Status Exam (MMSE) measurements across all RTOG brain tumor studies in which it was employed. Our initial results were presented at the American Society of Clinical Oncology Annual Meeting in 2008. Since then we have refined our analysis, preformed additional analyses, and drafted a manuscript that will be submitted to a peer-reviewed journal. Below is a draft of this the methods and results section of the manuscript. It is currently undergoing review by the RTOG Publications Committee and upon their approval it will be submitted for publication.

The evaluation of cancer treatments has changed as improvements in therapies prolong survival. The assessment of treatments is no longer limited to traditional clinical outcomes such as survival or response rates, but also includes the consequences of these treatments as measured by

adverse health events, as well as impact on quality of life (QoL) in general. In patients with brain cancer, neurocognitive effects of radiation therapy (RT) and their impact on quality of life have become important considerations due to the potential for radiation-related neurotoxic side effects. To capture these side effects, neurocognitive assessments have become common measures in brain cancer clinical trials. However, the collection of this data over time is difficult, especially in a patient population where disease progression may be rapid.

The Radiation Therapy Oncology Group (RTOG), a National Cancer Institute sponsored cancer clinical trials cooperative group, has frequently utilized the Mini Mental Status Exam (MMSE) as a parsimonious screening tool to assess neurocognitive changes in brain cancer patients treated on RT clinical trials. The MMSE was developed in 1975 by Folstein et. al, and has been validated and extensively used in both clinical practice and research. The MMSE instrument is administered by the clinician and usually takes less than 10 minutes to complete, rendering it practical to use repeatedly and routinely. Although not designed as an instrument to follow patients exposed to potentially neurotoxic therapy, this test is effective for screening to separate patients with and without cognitive impairment. It has also been used to measure changes in cognitive status that may benefit from intervention.

Despite the positive attributes of the MMSE, assessments that are incomplete relative to the planned ascertainment schedule are common. Evaluating similarities and differences in the patterns of missing MMSE as well as the amount and timing of missing MMSE can provide insight into predictors of missingness and optimal MMSE collection schedules in brain cancer trials. Knowledge about the reasons and patterns of missing measurements would allow researchers to better select the most feasible neurocognitive function data collection schedule. Knowledge of factors associated with missing measurements and the ability to minimize missing measurements in cancer patients treated with RT will lead to more and better quality information of the side-effects of treatment. This will also allow oncologists to include the side effects in their discussion of treatment options with patients. An additional outgrowth will be better monitoring and intervention of signs and symptoms of neurocognitive decline. In this study, we investigate missing data patterns in MMSE data collected during the conduct of eight RTOG prospective clinical trials evaluating RT for brain cancer.

MATERIALS AND METHODS

Summary of Instrument and Trials

The MMSE is a brief 11 question quantitative measure of neurocognitive function that can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. The measure tests five areas of cognitive function: orientation (total score of 10 from 2 items), registration (a score of 3 from 1 item), attention and calculation (a score of 5 from 1 item), recall (a score of 3 from 1 item), and language (a total score of 9 from 6 items). A final item to assess level of consciousness concluded the test (Alert, Drowsy, Stupor, and Coma). The higher the score on the MMSE the better the mental status with the "normal" range differing by study population (e.g., Alzheimer's, depression, etc.) and scores from 24 to 30 have been defined as "normal". In a study of patients

with low grade-gliomas treated with RT, the “normal” range, based on quartile scores was defined as 27 to 30 and "abnormal" scores were defined as patients with a MMSE of 26 or less, and a longitudinal change of more than 3 MMSE points was considered clinically significant.

The RTOG has frequently used the MMSE to assess mental status of brain cancer patients treated with radiation therapy. For this investigation, MMSE data from patients who participated in one of 8 brain cancer trials consisting of 10 distinct treatment arms were included. MMSE participation was not mandatory for all studies.

Statistical Methods

A patient who was protocol eligible, consented to participate in the MMSE portion (if applicable), and alive was defined as expected to be evaluated at a given time point. Thus, the number of expected evaluations was defined as the total number of evaluations that should have been submitted according to the protocol schedule, taking into account patient death prior to scheduled evaluations. Compliance rates were defined as the proportion of evaluations submitted among those expected to be submitted. The patterns of missing data in combined as well as individual trials are categorized as *Complete* if the patient is evaluated at all scheduled time points, *Monotone drop-out* if the patient is not evaluated at a given time point or any subsequent time points but is evaluated at all the previous time points*, All missing* if the patient is not evaluated at any time point*, and Mixed* for any patterns other than above three patterns (for example, present at baseline, missing a 3-month assessment but appearing at 6 months). The following pretreatment characteristics were considered; age (< 53 (median age) vs. ≥ 53), gender (male vs. female), treatment (observation vs. RT only vs. RT +others), race (White vs. black vs. others), Zubrod performance status (ZPS) (0 vs. 1 vs. 2), and the highest education (≤ high school vs. > high school).

The chi-squared test, Fisher’s exact test, and Kruskal-Wallis test (for continuous variable) were used to evaluate differences among four missing patterns with respect to the pretreatment characteristics. For the three missing pattern categories with observations (complete, monotone drop-out, mixed), descriptive statistics of baseline MMSE scores and change scores from baseline at the end of RT, and the last scheduled time point were calculated. The Kruskal-Wallis and Wilcoxon-rank sum tests were used for comparing the mean baseline and changes scores of difference missing patterns, followed by pairwise comparisons when the overall comparison result indicated a significant difference. Parametric counterparts (i.e., ANOVA and t-tests) yielded similar results, and subsequently linear models with MMSE scores as the independent variable were used to test the effect of missing pattern and other factors simultaneously and to test for interactions between missing pattern and other factors. For MMSE baseline scores and changes from baseline between groups, we consider differences of 1 point or more to be materially important. All testing was done at an overall significance level of 0.05, with Bonferroni method used to account for multiple testing. Statistical Analysis System (SAS Institute, Cary, NC) software was used for all statistical analyses.

RESULTS

MMSE data were available for 1,957 eligible patients from among the 8 brain cancer trials used for this analysis. The pretreatment characteristics of patients as they vary by the MMSE missing patterns (Complete, Monotone drop-out, Mixed, and All missing patterns) are shown in Table 1. Overall, the median age of patients was 53 years (range: 18-90) and 56% were male. Fifty-two percent were treated by RT only, 88% were white, 60% had ZPS of 0 and 50% had a higher than high school education. Almost half (49%) of patients fell into the Monotone drop-out pattern, while the complete pattern was the least frequent category (7%). The distribution of patients by age, treatment modality, ZPS, and highest education differed significantly among the four missing patterns. In the Complete pattern, 74% of patients have ZPS of 0, a higher proportion than any of the other patterns. Patients with the Complete pattern also tended to be younger and more educated (> high school) compared to the other patterns. Among patients with the Complete pattern, 55% received RT only, similar to those in the Monotone drop-out pattern (52%).

Each trial collected the MMSE at different time points with a total of 2-7 times during and after treatment in addition to the baseline assessment. Six of the eight trials had ≥ 90% compliance rate at baseline. Overall, only 8% were not evaluated at any time point (All missing). Thus, 92% had at least one evaluation, and 89% of patients were evaluated at baseline. However, 85% (49% Monotone drop-out, 36% Mixed pattern) of patients were not evaluated at all scheduled times, and 26% were evaluated only at baseline. Table 2 presents the distribution of MMSE compliance at baseline, at the end of RT (4 months after randomization for observation group), and the last scheduled time point (excluding long term follow-up) by treatment modality. The compliance rates at the last scheduled time point ranged from 41%-50%, compared to a baseline range of 71%-93%. The RT+others modality has the lowest compliance rate, possibly indicating that more aggressive treatment may contribute to patient attrition. The MMSE baseline scores were significantly different among the three treatment modalities (observation vs. RT only vs. RT +other modalities; p-value <0.0001). For the observation only treatment group, mean MMSE was roughly two points higher than those of the other two modalities, likely because these patients had less severe disease (low-grade glioma). While the RT and RT+others groups differed statistically, there is no clinically meaningful difference in mean MMSE between these groups.

In the RTOG trials, information on the reasons for an MMSE evaluation not being performed at a scheduled time point was requested to be reported. This information may have been provided by patients, practitioners, or family members. Table 3 shows the summary of reasons at the first missing time point in the Monotone drop-out and All missing patterns by treatment modality. Among the 778 patients in the Monotone drop-out pattern, more than half (71%) did not report the reason for missing. Institutional error (9%) and requests not to be contacted (9%) were the leading reasons for missing evaluation. Among the 147 patients in the all missing pattern, most (85%) did not have a specified reason for missing and 11% were missing due to institutional error. Similar distributions for missing reason were found in the RT only and RT+others modality.

Baseline MMSE scores is shown in Table 4 for the three missing patterns with data (All Missing pattern omitted). Overall, the mean baseline score is 27.63 (standard deviation (STD) =3.40). The baseline mean score from the Complete pattern (mean=28.61, STD= 1.95) was approximately 1 point higher than the Monotone drop-out (mean = 27.34, STD=3.50) and Mixed pattern (mean =27.83, STD=3.40), suggesting that those who begin with a higher score may be less likely to drop out. Unadjusted overall and pair-wise differences were statistically significant (results are not shown). However, after adjustment for other patient factors, means did not differ significantly by missing pattern. Other factors significantly associated with MMSE score in the multivariable model include age at randomization, gender, highest education level, and ZPS. As expected, patients who were younger at diagnosis, had better ZPS, and higher education have higher baseline scores in all patterns. Females tended to have higher baseline MMSE scores than males and blacks had lower baseline scores than other race groups. Those who were under observation only had higher scores, likely reflecting the lower disease burden of those participating in trials with an observation only treatment arm. Overall, differences in baseline MMSE scores across missing patterns were small (1 point or less) within each factor category, suggesting that missingness pattern may not be strongly related to patient characteristics. One exception is ZPS 1, where those with missing assessments have lower baseline scores, possibly due to greater deterioration of health status after treatment initiation in these patients. The baseline mean MMSE scores of trials for low-grade brain cancer (RTOG 9402 and 9802) were higher than trials with higher grade brain cancer, further supporting an association between baseline severity and MMSE (results are not shown).

Table 5 shows mean change scores between baseline and at the end of RT by the same factors as in Table 5. For 37% (732/1957) of patients, both baseline and end of RT MMSE scores are available. A significantly higher percentage of those with both assessments are from the Complete pattern (83%) group, compared to the Monotone drop-out (41%) and Mixed patterns (29%). Those with Complete patterns (mean =0 and STD=1.99) had smaller changes than those of the other two patterns (Monotone: mean = -.56, STD=3.66, Mixed: mean = 0.01, STD=3.72). The unadjusted overall comparison result was of nominal statistical significance, possibly in part due to the large standard deviations of scores relative to the mean scores, and the changes within each group were far smaller than that which could be considered clinically meaningful. Similar to baseline MMSE score, missing pattern was not a statistically significant factor with respect to change in MMSE score when adjusted for other factors (p =0.43). There were similar patterns to the baseline scores, in that those with more favorable baseline scores had smaller changes, with the exception of gender, where females had somewhat greater declines in scores. Overall, changes from baseline to the end of RT were small and not notably different by missing pattern. Age was the only statistically significant factor, with older patients having greater declines.

Table 1
Pretreatment Characteristics by Missing Patterns
(n= 1957)

Variable	Missing Pattern: Complete (n = 143)	Monotone (n = 955)	Mixed (n = 711)	All missing (n = 161)	Total (n=1957)	p-value*
Age						
Median	49	57	48	55	53	
Range	19 - 79	18 - 90	18 – 82	19 - 83	18 - 90	<.0001[↑]
Gender						
Male	81(57%)	549(57%)	386(54%)	78(53%)	1094(56%)	
Female	62(43%)	406(43%)	325(46%)	70(47%)	863(44%)	0.4994
Treatment Modality						
RT only	79(55%)	494(52%)	351(49%)	95(64%)	1019(52%)	
RT + others	45(32%)	421(44%)	321(45%)	40(27%)	827(42%)	
Observation	19(13%)	40(4%)	39(6%)	13(9%)	111(6%)	< 0.0001[↑]
Race						
White	132(92%)	837(88%)	628(88%)	122(82%)	1719(88%)	
Black	4(3%)	79(8%)	50(7%)	15(10%)	148(8%)	
Others	7(5%)	39(4%)	33(5%)	11(8%)	90(5%)	0.1365
ZPS**						
0	106(74%)	506(53%)	475(67%)	83(56%)	1167(60%)	
1	37(26%)	426(45%)	230(32%)	62(42%)	754(39%)	<0.0001[↑, ↑↑]
2	0	23(2.41%)	6(1%)	3(2%)	32(2%)	
Highest Education***						
<= High school	55(41%)	406(48%)	231(39%)	42(38%)	734(44%)	
> High school	73(54%)	388(46%)	325(55%)	56(51%)	842(50%)	0.0037[↑↑]
Prefer not answer	6(4%)	46(5%)	38(6%)	12(11%)	102(6%)	

* All except for age from Chi-square test statistic. If any expected cell count was less than 5, then Fisher's exact test was used. For age, Kruskal-Wallis Test was used.
** Zubrod Performance Status
[↑] It is significant at the 0.05 level
[↑↑] Comparison between only two groups: ZPS (0 vs. 1) and Education (<= high school and > high school.)

Table 2
The Compliance of MMSE by Treatment Modality
(n = 1957)

Treatment Modality	Scheduled Time points		
Observation (n=111)	Baseline	4 months after randomization	Last Scheduled Time point
# of expected evaluations[†]	111	111	109
# of death occurred	0	0	2
# of missing evaluation[*]	32	61	59
# of evaluation (%[**])	79 (71%)	50 (45%)	50 (46%)
Baseline MMSE mean (SD)	29.33 (1.13)		
RT only (n=1019)	Baseline	End of RT	Last Scheduled Time point
# of expected evaluations[†]	1019	933	443
# of death occurred	0	86	576
# of missing evaluation[*]	119	497	216
# of evaluation (%[**])	900 (88%)	436 (47%)	221 (50%)
Baseline MMSE mean (SD)	27.37 (3.55)		
RT+ Others (n=827)	Baseline	End of RT	Last Scheduled Time point
# of expected evaluations[†]	827	791	556
# of death occurred	0	36	271
# of missing evaluation[*]	59	402	323
# of evaluation (%[**])	768 (93%)	389 (49%)	228 (41%)
Baseline MMSE mean (SD)	27.75 (3.32)		
Comparison of Baseline MMSE	Overall p-value[††] = <0.0001 Pairwise p-value[†††] Observation vs. RT only = <.0001 Observation vs. RT+others = <.0001 RT only vs. RT+others = 0.0081		

[†] "Expected" is defined as MMSE from a alive patient at each time point and is eligible at baseline
* "Missing" is defined as a MMSE evaluation was not collected from a patient alive at each time.
** The compliance rate is calculated by dividing # of evaluation by # of expected.
[††] From Kruskal-Wallis Test to compare the baseline MMSE among the treatment modality
[†††] From Wilcoxon-rank sum test and is significant at 0.05/3=0.016

Table 3
Reasons for Missing MMSE by Treatment Modality

Missing Pattern	Reasons for Missing	Observation	RT only	RT+ Others	Total
Monotone*		n=40	n=433	n=305	n = 778
	Due to illness	0	13 (3%)	12 (4%)	25(3%)
	Refusal to complete any items	0	6 (1%)	1(0%)	7(1%)
	Request to not be contacted	8(20%)	30 (7%)	33 (11 %)	71(9%)
	Institution error	10(25%)	31 (7%)	31 (10%)	72(9%)
	Other	9(23 %)	25 (6%)	18 (6%)	52(7%)
	missing or unknown	13(32%)	328 (76%)	210 (69%)	551(71%)
All missing		n = 13	n=97	n=37	n = 147
	Due to illness	0	0	0	0
	Refusal to complete any items	1(8%)	0	1 (3%)	2(1%)
	Request to not be contacted	2(15%)	0	0	2(1%)
	Institution error	5(38%)	7 (7%)	4 (11%)	16(11%)
	Other	1(8%)	0	0	1(1%)
	missing or unknown	4(31%)	90 (93%)	32 (86%)	126(85%)

* The reason for missing is from the first missing time point after the last evaluation.
† The reason for missing is from the baseline

Table 4
Distribution of Baseline MMSE Score by Missing Pattern
(n=1758)

	Complete (n = 143)	Monotone (n = 955)	Mixed (n = 711)	Total (n=1758)	p-value[†]
Variable	n Mean(STD*)	n Mean(STD*)	n Mean(STD*)	n Mean(STD*)	
Available MMSE	143	955	649*	1747*	0.15[††]
Mean Baseline Score (STD)	28.61 (1.95)	27.34 (3.50)	27.83 (3.45)	27.63 (3.40)	
Age					
< 53	89 29.03 (1.51)	376 28.36 (2.64)	401 28.31 (2.84)	866 28.40 (2.65)	<.0001
≥53	54 27.91 (2.37)	579 26.68 (3.83)	248 27.05 (4.15)	881 26.86 (3.86)	
Gender					
Male	81 28.35 (2.00)	549 27.15 (3.76)	360 27.50 (4.01)	990 27.38 (3.76)	0.0093
Female	62 28.95 (1.84)	406 27.59 (3.11)	289 28.23 (2.54)	757 27.95 (2.84)	
Treatment Modality					
RT only	79 28.53 (1.90)	494 27.14 (3.61)	327 27.44 (3.71)	900 27.37 (3.55)	0.2710
RT + others	45 28.42 (2.28)	421 27.40 (3.48)	302 28.14 (3.19)	768 27.75 (3.32)	
Observation	19 29.11 (1.20)	40 29.23 (1.17)	20 29.50 (1.24)	79 29.33 (1.13)	
Race					
White	132 28.61 (1.98)	837 27.38 (3.54)	572 27.88 (3.47)	1541 27.67 (3.43)	0.9040
Black	4 28.50 (1.29)	79 26.57 (3.43)	48 26.75 (3.78)	131 26.69 (3.52)	
Others	7 28.57 (1.81)	39 28.05 (2.55)	29 28.55 (1.76)	75 28.29 (2.20)	
ZPS					
0	106 28.79 (1.76)	506 28.15 (2.52)	436 28.49 (2.14)	1048 28.36 (2.31)	<.0001
1	37 28.08 (2.37)	426 26.65 (3.74)	207 26.62 (4.57)	670 26.72 (3.96)	
2	0	23 22.13 (7.99)	6 21.17 (11.50)	29 21.93 (8.60)	
Highest Education					
<= High school	55 27.87 (2.60)	406 26.97 (3.45)	210 27.18 (3.46)	671 27.11 (3.39)	<.0001
> High school	73 29.15 (1.16)	388 27.98 (3.14)	301 28.57 (2.80)	762 28.33 (2.90)	
Prefer not answer	6 29.00 (1.26)	46 26.83 (3.65)	33 27.88 (3.13)	85 27.39 (3.38)	

*STD=standard deviation [†] Comparison of means by variable categories, from regression model including missing pattern and the other factors as shown in the table (race was specified as white vs. black+others, ZPS 0 vs. 1/2 education level excluding preferred not to answer) [††] Comparison of means by missing category, from regression model including the other factors; * Some patients in the Mixed pattern do not have baseline assessments

Table 5
Distribution of MMSE Change Score at the end of RT by Missing Pattern
(n=732)

Variable	Complete (n =120) n Mean (STD*)	Monotone (n =399) n Mean (STD*)	Mixed (n =213) n Mean (STD*)	Total (n=732) n Mean (STD*)	p-value[†]
Mean change score (STD)	0.00 (1.99)	-0.56 (3.66)	0.01 (3.72)	-0.30 (3.47)	0.4279[††]
Age					
< 53	67 0.07 (1.25)	145 0.02 (2.48)	130 0.25 (3.58)	342 0.12 (2.79)	0.0160
≥53	53 -0.09 (2.65)	254 -0.89 (4.15)	83 -0.35 (3.93)	390 -0.67 (3.94)	
Gender					
Male	71 0.13 (1.49)	236 -0.50 (3.57)	114 -0.03 (4.17)	421 -0.27 (3.50)	0.4660
Female	49 -0.18 (2.55)	163 -0.65 (3.79)	99 0.06 (3.15)	311 -0.35 (3.43)	
Treatment Modality					
RT only	79 -0.28 (2.11)	214 -0.53 (3.46)	127 0.15 (2.79)	420 -0.28 (3.06)	0.6453
RT + others	41 0.54 (1.61)	185 -0.59 (3.88)	86 -0.19 (4.78)	312 -0.33 (3.96)	
Race					
White	113 0.14 (1.92)	349 -0.52 (3.66)	189 0.06 (3.83)	651 -0.23 (3.49)	0.1641
Black	3 -1.33 (2.08)	37 -0.97 (4.19)	18 -0.50 (2.96)	58 -0.84 (3.73)	
Others	4 -3.00 (1.41)	13 -0.62 (1.56)	6 0.00 (1.90)	23 -0.87 (1.87)	
ZPS					
0	84 0.26 (1.42)	215 -0.47 (3.10)	131 0.10 (2.73)	430 -0.15 (2.75)	0.8169
1	36 -0.61 (2.84)	176 -0.89 (4.10)	78 0.36 (3.93)	290 -0.52 (3.95)	
2	-	8 4.00 (4.50)	4 -9.50 (11.56)	12 -0.50 (9.67)	
Highest Education					
<= High school	51 0.06 (2.05)	190 -0.77 (4.40)	72 0.28 (4.19)	313 -0.40 (4.08)	0.8220
> High school	57 0.25 (1.06)	169 -0.30 (2.83)	100 -0.43 (3.63)	326 -0.25 (2.90)	
Prefer not answer	4 -1.00 (1.15)	17 -0.71 (3.00)	10 1.30 (3.06)	31 -0.10 (2.95)	

*STD=standard deviation [†] Comparison of means by variable categories, from regression model including missing pattern and the other factors as shown in the table, except race (coded white vs. black+others), ZPS (0 vs. 1/2) education (excluding preferred not to answer) [††] Comparison of means by missing category, from regression model including the other factors.

Research Project 5: Project Title and Purpose

Dynamic Tumor Volumetric Regression Response Using Cone-Beam and PET/CT in NSCLC - To evaluate tumor response for non-small cell lung cancer (NSCLC) patients using PET/CT and Cone-Beam CT (CBCT) and determine parameters needed for adaptive radiotherapy. There are 6 parameters of interest. 1) Relationship between volumes determined using PET/CT and CBCT to determine which imaging modality is better to calculate clinical target volumes (CTV). 2) Volume of target (CTV) as a function of dose and time. 3) Three-dimensional motion of the target as a function of dose and time. 4) Margin needed for PTV as a function of dose and time. 5) Lung function after treatment with pulmonary function tests, including diffusion capacity (DL_{CO}). 6) Correlation of imaging response with serum protein and peptide profiles with emphasis on signature effects of ionizing radiation.

Duration of Project

1/1/2006 - 12/31/2009

Project Overview

Published studies suggest that dose escalation in NSCLC is feasible and may offer improved control rates. However, dose escalation can only be achieved with careful assessment of normal tissues irradiation in order to avoid untoward toxicities including radiation pneumonitis, esophagitis and carditis. For intra-thoracic tumors, compensation for physiologic organ motion is critical for radiation therapy planning in order to avoid overdosing adjacent critical organs or underdosing the disease. The introduction of computer controlled linear accelerators with integrated imaging devices such as cone-beam CT coupled with 4D-CT scanning capabilities now offer the possibilities of establishing the three-dimensional size, shape and motion of CTVs as a function of dose and time. The capability to evaluate each of these characteristics has led to the opportunity to establish margins for planning target volumes (PTV) as a function of dose and time and with the expressed intent of enabling routine adaptive radiotherapy. The proposed study seeks to elucidate a clear relationship among all these parameters.

Studies will be performed for 10 inoperable stages IIA/B, IIIA/B NSCLC patients using the following method:

- A pre-treatment PET/CT study will be undertaken to determine the clinical target volume (CTV).
- 4D-CT studies will be performed at the beginning, middle and end of the treatment to determine the motion of the target and reproducibility of intra-fraction target and organ motion.
- Treatment planning will be performed for all patients to ensure conformal dose coverage.
- Gated treatment delivery will be performed if the target motion is more than 5 mm. Otherwise, all treatments will be delivered using non-gated treatment.
- CBCT CTV data will be acquired at the beginning of the treatment and weekly thereafter.
- Analysis of CTV (in cc), size and shape of CTV will be performed from each of these studies and a 3D model will be constructed.

- Analysis of lung function and total lung volumes will be performed along with the target analysis pre- and post-treatment.
- A PET/CT study of the target volume will be performed 8 weeks after treatment to assess response.
- A time dependent analysis of the CTV will be performed using both the PET/CT and CBCT data

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Expected Research Outcomes and Benefits

- CBCT can be used as a predictor of trend in target volume change as a function of dose and time.
- CTVs determined using PET/CT and CBCT may be strongly correlated. If they are not strongly correlated then this study may give guidance to selection of alternate surrogates for tumor regression modeling.
- The use of adaptive radiotherapy may spare more normal tissues to improve patient lung functionality and may enable dose escalation regimens to improve local tumor control.
- The proposed serum-based markers, including proteins and peptide profiles, will be confirmed to be markers of radiation stress response and may correlate with tumor response to ionizing radiation.

Summary of Research Completed

The project was submitted to the IRB for review shortly after the last submitted progress report after having had delays in technology, radiation safety items, and timing of imaging. There were several critiques of the project, mainly revolving around the establishment of the primary endpoint, the CBCT dose clarification.

We carefully and meticulously responded to each of the comments from the Protocol Review Committee (PRC) and Institutional Review Board and met with the Chair of the PRC to review the endpoints of this exploratory trial. The results of these close consultations with the PRC has

resulted in greater understanding by the PRC of the objectives, technologies and endpoint of this project.

Specifically, we made the evaluation of the mid-point PET-CT and its correlation with the first post-treatment PET-CT the primary endpoint of this trial. We streamlined the laboratory correlates of the metabolomics proposed to coincide with their other weekly blood work, which are standard of care (SOC).

The project was reviewed by the PRC in their August 2009 meeting and approval of the protocol was achieved in November 2009. We had anticipated rather rapid accrual to this clinical trial given that the majority of the project is standard of care. When the project was originally proposed, only 1 center in our network had the capability & technology to accrue patients on this trial. There are now 5 centers that are prepared to participate and as a result, we expected to fully accrue to this project by June 2010.

No grant funds were spent on this project.

Research Project 6: Project Title and Purpose

Assessing Evidence to Support Quality Indicators for Radiation Oncology - The purpose of this project is to define quality indicators likely to be useful in measuring good quality care for patients treated with radiation oncology for cancer in several major sites and to use existing databases of national survey data to assess the strength of the evidence that these indicators actually show variations that can measure quality.

Duration of Project

1/1/2006 - 12/31/2009

Project Overview

Overall Goal

The overall objective of this project is to assess the existing evidence base for measuring proposed quality indicators across all types of practice. Many organizations, most notably the Institute of Medicine, have asserted in recent years that the quality of medical care delivered in this country should be improved and have proposed quality indicators as a way of measuring the quality of care. These indicators may be used to reward high quality providers and to seek to improve poorer quality providers. This project will analyze data in an existing database to assess the usefulness of proposed quality indicators in identifying differences in the quality of care.

Specific Aims

1. Define in detail proposed quality indicators for radiation treatment of cancer of the breast, prostate, lung, and cervix. These quality indicators are derived from guidelines and standards that are widely disseminated and based on the best available evidence in the scientific literature.

2. Using an existing national survey database of patterns of care, analyze variations in compliance with quality indicators for all types of practice, as well as by key practice and patient demographic subgroups.
3. Make recommendations regarding the adequacy of the proposed quality indicators, areas in which radiation oncology practice should seek to improve, or areas needing further research.

Principal Investigator

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Other Participating Researchers

None

Expected Research Outcomes and Benefits

In recent years many participants in the American health care system have begun to demand higher standards of cancer care. The first step seeks to reach consensus around valid sets of quality indicators, which are expected to eventually cover the vast spectrum of services required by cancer patients. Much work remains to be done to accomplish the ambitious goal of determining the overall quality of cancer care. Most projects that seek to cover the entire spectrum of cancer care have not demonstrated an ability to assess radiation oncology processes of care in any significant detail.

This project will test the validity and usefulness of specific proposed quality indicators against a national survey database of patients treated in all types of practice. The results will help validate these indicators and lead to recommendations for new indicators or the development of additional data sources to help validate indicators.

Summary of Research Completed

During the last six months of this project, investigators completed work to address the Specific Aims and used the results to improve measurement of quality of care in radiation oncology by defining detailed evidence-based measures, mapping the required data elements to those in an existing database, identifying gaps in required elements, and incorporating knowledge into a new survey for another project funded by the National Cancer Institute.

Specific Aim 1 was achieved successfully. Quality indicators were defined in detail as Clinical Performance Measures (CPM) for radiation treatment of cancer of the breast, prostate, lung, and cervix, based on guidelines, such as those of the National Comprehensive Cancer Network (NCCN), that are evidence-based and widely disseminated.

For Specific Aim 2 investigators analyzed data from the Patterns of Care Study database by mapping the data elements required for the detailed CPMs to the data elements of the survey database. Although many of the needed data elements were present in the database, some important data elements, such as measures of patient comorbidities, were not available. The CPMs were computed for the existing database, but uncertainty remained because the unavailable elements made it difficult to define acceptable benchmarks or to make conclusive comparisons across groups.

These results led to recommendations under Specific Aim 3 for the addition of the needed data elements to future surveys. For example, investigators evaluated measures of comorbidities and selected the Adult Comorbidity Evaluation Index (ACE-27) developed by Piccirillo, to be used in future surveys. The addition of these other data elements would make possible measures that can be applied to all practices with solid benchmarks from a comprehensive survey. After this project started investigators obtained funding from the National Cancer Institute for a new national survey of quality of care in radiation oncology and data collection is underway. The recommendations based on this C.U.R.E. project were very useful in designing survey forms for the new national survey and identifying data elements that should be added to the survey to provide benchmark data for detailed quality indicators. They will also be useful in future research and Quality Improvement Projects.

Results

Investigators developed detailed Clinical Performance Measures (CPM) for radiation treatment of cancer of the breast, prostate, lung, and cervix, derived from evidence-based guidelines that have been widely disseminated, reviewed, and accepted. They also developed Emerging CPMs for new technologies that are being widely used throughout the national practice, often with little scientific testing. The detailed CPMs for each disease site included precise definitions, justifications, and mapping to data elements to allow measurement.

These CPMs are being used to guide data collection in a new national survey that will provide benchmark data that will allow radiation oncologists to assess the quality of care in their own practices by measuring quality indicators (QIs) and comparing individual with national practice. Results from the national survey database for patients treated in 1998 and 1999 were reviewed and additional analyses conducted to assess data adequacy to measure compliance with these clinical performance measures.

In one cervical cancer indicator the percentage of patients with cervical cancer receiving definitive irradiation who also receive concurrent Cisplatin-containing chemotherapy was measured. In 1999 a National Cancer Institute (NCI) clinical alert established the need for concurrent chemotherapy which has become a standard of practice. QRRO Process survey results, not including the current denominator exclusion for comorbidities, showed that only 16% of patients treated from 1996 to 1998 had Cisplatin-containing chemotherapy concurrently with radiation therapy (RT). For the year 1999 the results were 64%. The new survey with the denominator exclusion for comorbidities is expected to reach the 90th percentile and establish a true level of current practice compliance.

Another example of an indicator for lung cancer is based upon the NCCN guidelines for Stage III non-small cell lung cancer (NSCLC) which recommends a radiation therapy daily total dose of up to 74 Gray in a concurrent chemoradiation setting. However, some conditions will mediate the total dose delivered e.g., if RT is stopped early due to complications, non-compliance or death, or if treatment includes surgery or if the patient is on an Institutional Review Board (IRB)-approved protocol. Data from the 1999 survey of NSCLC were used to demonstrate that adjustments at this level of detail can be made. Investigators also evaluated an emerging quality indicator/clinical performance measure derived from NCCN guidelines regarding the roles of Positron Emission Tomography (PET) scan or bone scan and brain Computerized Tomography (CT)/ Magnetic Resonance Imaging (MRI) in the staging work-up evaluation of patients receiving combined modality therapy for stage III NSCLC. Data for NSCLC patients with no distant metastases or pleural effusion treated in 1998-1999 were analyzed. Of the 180 patients with stage III NSCLC, 132 patients received concurrent chemoradiation, of which 57 patients were excluded for conditions that might mitigate total dose as described above. Analysis showed that 88% of the patients received a total dose in the recommended range of 59-74 Gray (median dose of 63 Gray). Of note, recommended brain MRI/CT and PET or Bone scans were performed in only 42% of the patients.

These measures are used as part of the Practice Quality Improvement (PQI) project that has been approved by the American Board of Radiology (ABR) under its Maintenance of Certification (MOC) requirements for radiation oncology and radiation physics.

During this time period one abstract was presented at the Annual Meeting of the American Society for Radiation Oncology:

1. N. Khalid, B. Movsas, J. Owen, C. Crozier and J. Wilson: QRRO: Estimating National Benchmarks for Quality Indicators for Non-Small Cell Lung Cancer (NSCLC). *Int J Radiat Oncol Biol Phys* [75]:S444-445, 2009.

Research Project 7: Project Title and Purpose

Emerging Imaging Technology Clinical Trials in PA: Part II – This project represents the development and completion of clinical research trials involving the use of emerging imaging technology at selected Pennsylvania academic medical centers, aimed at advancing the role of imaging in the detection and/or treatment of disease. This research will evaluate the role of Dynamic Contrast Enhanced MRI (DCE-MRI) in assessing the effectiveness of drug interventions targeted at tumor vascularity. This clinical research trial, designed and developed through protocol approval by the American College of Radiology Institutional Review Board under the 2004 formula grant, will be activated and conducted through 12 month follow up under this award. In addition, clinical trial design will be completed to evaluate the role of Positron Emission Tomography (PET) and the classification ability of two novel imaging compounds to distinguish Alzheimer's disease from cognitively normal subjects.

Duration of Project

1/1/2006 - 12/31/2009

Project Overview

The broad objective is to develop and operationalize a clinical trials network to perform imaging studies of early phase technology at academic medical centers in Pennsylvania. The network will initially consist of the University of Pennsylvania, University of Pittsburgh, Pennsylvania State University (Hershey Medical Center), Thomas Jefferson University and Fox Chase Cancer Center. The overall project is three-pronged with clinical research proposed in the following areas: 1) the role of MRI in measuring the functional integrity of articular cartilage for the purpose of assessing the progress of arthritis; 2) the role of Dynamic Contrast Enhanced MRI (DCE-MRI) in assessing the effectiveness of drug interventions targeted at tumor vascularity; and 3) the role of Positron Emission Tomography (PET)) and the classification ability of two novel imaging compounds to distinguish Alzheimer's disease from cognitively normal subjects. The initial project (Part I) was awarded in 2004-2005 as Emerging Imaging Technology Clinical Trials in PA. This project (Part II) extends the scope of work consistent with the overall aims.

The aforementioned three areas of focus were awarded support in the 2004-2005 Health Formula funding with the goal of developing two clinical trials, specifically the DCE-MRI and Alzheimer's trials. However, a change in personnel required a delay in the Alzheimer's work, allowing the osteoarthritis research to begin earlier than anticipated. Furthermore, due to the complexity of the image analysis phase, it is anticipated that the osteoarthritis clinical trial will consume the majority of the funding allocated in the 2004 formula grant. It is anticipated that the 2005 funding (1/1/06-12/31/09) will support the activation and conduct of the study involving DCE-MRI's role in assessing drug intervention. In addition, initial discussions among the Alzheimer's researchers will be funded and culminate in the development of an IRB approved clinical research trial.

Specific aims funded through this project consist of the activation and conduct of a clinical trial which involves the application and refinement of a novel approach to Dynamic Contrast Enhanced MRI (DCE-MRI) to function as a non-invasive measure of tumor vascularity. This study will entail use of a sophisticated technique using DCE-MRI to evaluate the response of tumors to drugs targeted at the vascular structure of the tumor. The technique will first be validated across the network's participating institutions through the use of a phantom image system. Once validated, the technique will be applied in a clinical trial involving approximately 50 patients undergoing chemotherapy of advanced cancer. MRI exams will be conducted twice prior to treatment in order to assess reproducibility of results and then early and late in the treatment course. DCE-MRI images will be collected and data will be fit using the Tofts model. Consequently, tumor cell characteristics, specifically the Ktrans values and extracellular space, will be mapped and density profiles modeled. Statistical analysis will be conducted to correlate Ktrans values and extracellular space as determined at various time points (pre-treatment, early during treatment, late during treatment) to the tumor's response as indicated by post-treatment tumor size through a 12-month follow up period.

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Chet Mathis, PhD, James M. Mountz, MD, PhD- employed by University of Pittsburgh

Expected Research Outcomes and Benefits

The proposed study involving use of DCE-MRI to evaluate changes in tumor vascularity resulting from chemotherapy is expected to determine the role of this imaging technology as a reliable early indicator of the drug's effectiveness. If proven effective, this will enable better monitoring of the response of cancerous tumors to therapy targeted at disrupting blood flow to the tumor (anti-angiogenic therapy), thereby resulting in better patient selection for this course of therapy and also resulting in support for the continued therapeutic development of anti-angiogenic agents. The second study will use novel imaging agents to enable imaging of proteins associated with Alzheimer's disease (Amyloid plaque). If proven effective, these agents will enable early clinical diagnosis (and therefore treatment) of Alzheimer's disease as well as provide an important method for quantifying the extent of disease and, in turn, support more advanced research in determining the effectiveness of new drugs for this debilitating condition.

Summary of Research Completed

ACRIN PA 4002: Angle Interleaved Projection Reconstruction with K-Space Weighted Image Reconstruction for Dynamic Contrast MRI of Cancer Therapy Response

During this reporting period, the amended and ACR IRB-approved protocol was distributed to the sites for subsequent submission to their local IRBs. The summary of changes clearly detailed the modification, noting that it included the addition of a study arm with less restrictive eligibility criteria, allowing for enrollment of subjects with malignant liver lesions arising from any index cancer (not just colorectal) and requiring only two DCE-MRI scans prior to treatment. Furthermore, specific therapy treatment was not defined for this arm (Arm B) nor was follow up required. The intent was to focus on the primary objective of DCE-MRI reproducibility and it was successful resulting in a 6-fold increase from 1 subject to 6 subjects by the time the study closed on December 31.

ACRIN PA 4003/4004: Evaluation of the Ability of a Novel ^{18}F Amyloid Ligand to Distinguish Patients with a Clinical Diagnosis of Alzheimer's Disease from Cognitively Normal Elderly Individuals

The eligibility criteria were reviewed during the reporting period and changed to allow a cognitive dementia rating of .5 with a consensus diagnosis of Alzheimer's disease. Concurrently, a change to the mini mental state evaluation was suggested, but rejected after discussion with the statistician.

Note: The development of the Alzheimer's trial is funded by this grant (2005FY) per March 2009 discussion with the Department of Health; the activation and conduct of the trial is funded by the 2006FY grant.

Table I: ACRIN PA 4002 DCE MRI Site Status and Subject Enrollment (July 2009-December, 2009)

Site	Status	Enrollment
University of Pennsylvania	Open	1
Thomas Jefferson U. Hospital	Open	4
Fox Chase Cancer Center	Open	0
Pennsylvania State/Hershey Medical Ctr	Open	1
University of Pittsburgh Medical Ctr	Open	0