American College of Radiology

Annual Progress Report: 2008 Formula Grant

Reporting Period

July 1, 2010 – June 30, 2011

Formula Grant Overview

The American College of Radiology received $2,144,345 in formula funds for the grant award period January 1, 2009 through December 31, 2012. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Methods and Strategies to Incorporate Radiotherapy Delivery Uncertainties in Clinical Trials Outcome Analysis - Randomized clinical trials provide evidence-based medicine that has become the foundation of radiation oncology. Numerous technologies are being used to deliver targeted radiotherapy. These technologies all have their own operational characteristics and uncertainties. Significant variations also exist in individual implementation of these technologies. These uncertainties may influence, to a critical extent, the outcome of clinical trials. However, they have not been addressed so far in a systematic manner in the outcome analysis. This study aims at bridging this gap with theoretical methodologies for critical assessment and propagation of uncertainties of radiation deliveries as a complement to current clinical trial analysis. Our hypothesis is that by properly accounting for the delivery uncertainties, we will allow better prediction of outcome.

Anticipated Duration of Project

1/1/2009 - 12/31/2012

Project Overview

The objective of this study is to bridge a gap between present radiotherapy related clinical trials, where essential delivery uncertainties are not included in the outcome analysis, and computational implementation that has the ability to propagate these uncertainties through the analysis process.

These methodologies will have the ability to propagate the uncertainties that arise from the treatment unit calibration, throughout the treatment process to the outcome. The quantitative analysis model will employ algorithms that enable self-adaptation, definability, and extendibility. The analysis process can also be reversed to create quality assurance guidance for limiting these uncertainties of radiotherapy delivery. Specifically, the tasks include the following:

A. To quantify the uncertainties associated with radiation therapy delivery process with accumulated data, which include identification of key components of the process, such as radiation calibration,

patient setup, etc., where potential variation can occur, uncertainties associated with each component and the accumulative effect from all.

B. To investigate the optimal statistical methods for propagating these uncertainties in outcome analysis modeling. Extensive research has been carried out in the mathematical methods in the uncertainty modeling and the propagation methods. We intend to evaluate the various strategies and algorithms and select the optimum ones that best suit our process.

C. To implement these mathematical methods into established biological modeling open source software system available for radiotherapy researchers. Ample considerations will be given for further extension and adaptation of the open software.

D. To develop a reverse process that can start from the endpoint of the outcome and predict the limit for uncertainties, thereby offering outcome based quality assurance guidelines for the delivery technologies, benefiting future design of clinical trials.

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Expected Research Outcomes and Benefits

Randomized clinical trials have been the foundation of modern medicine. They are the cornerstone of radiation therapy development. A large portion of recent development of radiotherapy treatment strategies and techniques is the direct or indirect result from these randomized clinical trials. Collection of appropriate data associated with these clinical trials and the analysis of the data with the most accurate and suitable tools are essential elements to the success of these trials.

There are uncertainties associated with all the processes of the radiotherapy treatments and data collection. The outcome analysis should consider these uncertainties. Many of these uncertainties are addressed in various ways. Among these, the heterogeneity of reporting has been addressed in guidelines and standards for reporting the results from clinical trials. The uncertainty of radiotherapy delivery, with a disconcerting amount of discrepancies reported from institutions (around 30% failure rate from a radiological physics center head and neck phantom test), is however generally not considered in the outcome analysis. These discrepancies and deviation could reach such an extent that they steer the clinical trial outcome, namely, the difference in outcome is found not due to the medical technique difference for which the clinical trial is designed, but due to the deviation from the

trial protocol. There were reports that deviation from radiotherapy protocol had a major negative impact on outcome.

It is therefore essential to access and quantify the uncertainties associated with the individual process of the execution of the clinical trials and evaluate the impact of these uncertainties on outcomes. This is the main focus of this study.

Summary of Research Completed

We have made progress in addressing the first three aims in the studies described below: To quantify the uncertainties associated with radiation therapy delivery process; To investigate the optimal statistical methods for dealing with these uncertainties from data analysis; and to implement these mathematical methods.

I. Dose/volume/outcome data

In 1991 Emami et al published a comprehensive review of the available dose/volume/outcome data. Since the publication of this classic paper, there have been numerous studies providing dose/volume/outcome data. In 2010 the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) reviews provide focused summaries of the dose/volume/outcome information for many organs. Not only are these reviews excellent resources to assist physicians and treatment planners in determining acceptable dose/volume constraints, but also provide excellent references and resources of multi-institutional toxicity data for further physical and statistical analysis. However, the QUANTEC papers also pointed out the shortcomings of current predictive models, the limitations and even inconsistency of the data, and suggested that the information in the reviews could be updated and improved with the help of new physical and statistical techniques.

II. A new method for multi-institutional clinical data analysis

We applied a useful mathematical theory - evidence theory - for multi-institutional clinical data analysis. Evidence theory, also known as Dempster-Shafer theory, is a mathematical theory of evidence and plausible reasoning. It offers a powerful mathematical tool to handle practical data with uncertainties and inconsistency. It has been successfully used in several other fields such as reliability engineering, meteorology, as well as ecology and management. In some evidence theory resource medical examples have been widely used to illustrate the idea behind the theory. Radiation therapy practice is based upon all levels of evidence. With all of this sometimes consistent, sometimes inconsistent, even conflicting evidence, it is essential to apply appropriate methods for combining the evidence for clinical guidance.

We believe that evidence theory is a potentially useful tool for the evaluation of dose-volume effects because precise predictions of radiation effects on patients are impossible and also different physicians have different opinions of dose effects. In such situations, uncertainties and inconsistency are inevitably introduced into the system and ultimately reflected in the outcomes of data analysis. These problems can be readily solved in the frame of evidence theory. In order to represent uncertainties, the theory has its unique ability to allocate probability masses to sets or intervals. With the help of the theory's valuable combination rules evidence from multiple sources can be readily fused, and the inconsistency between them can be quantified and modeled. A case study of the

"degree of belief" and "plausibility" in regard to the occurrence of radiation pneumonitis (RP) is implemented as an example to demonstrate our application of evidence theory, and the values of belief and plausibility functions are fitted by using Lyman-Kutcher-Burman (LKB) model. The parameters obtained from the LKB model curve fitting are compared with those in Emami and Bruman's papers, and we found that Emami and Bruman's parameters are within the probability range we calculated by evidence theory.

III. Combination of multi-institutional toxicity data describing dose response for radiation pneumonitis (RP)

In the QUANTEC review, the authors studied the radiation dose-volume effects for lung cancer treatments and presented the probability of radiation pneumonitis (RP) as a function of mean lung dose (MLD) in Fig. 2(a) of that review. As pointed out in it, the results from different institutions are inconsistent and some of the variation around the fitted curve is possibly explained by differences in patient selection as well as differences in the grade of RP reported in the various studies, in addition to all the other contributing factors such as those from radiation dose delivery variations. All these imply that conflict exists between the data from different sources, and in order to combine this information evidence theory and Yager's rule is applied.

We selected dose response data from four institutions: Memorial Sloan-Kettering Cancer Center (MSKCC) (Yorke et al 2005), Duke University (Hernando et al 2001), M.D. Anderson Cancer Center (Wang et al 2006) and University of Michigan (Kong et al 2006), and study the probability of RP as a function of mean lung dose at four dose points. The outlines of the individual papers we used in this study are given below and the dose response information is presented in Table 1, cf. Marks et al 2010 Fig. 2.

Yorke et al 2005 (MSKCC). Radiation Therapy Oncology Group (RTOG) Grade ≥3 in 78 patients from a Phase I dose escalation study (1991–2003) of three-dimensional conformal radiation therapy (3D-CRT) of non–small-cell-lung cancer (NSCLC). See Yorke et al 2005 Fig. 4a & Marks et al 2010 Fig. 2.

Hernando et al 2001 (Duke). Common Toxicity Criteria (CTC) Grade ≥1 in 318 patients undergoing 3D-CRT between 1991 and 1999. See Hernando et al 2001 Table 4 & Marks et al 2010 Fig. 2.

Kong et al 2006 (Michigan). Southwest Oncology Group (SWOG) Grade ≥2 in 109 patients with NSCLC undergoing 3D-CRT between 1992 and 2000. See Kong et al 2006 Table 4 and Fig. 2a & Marks et al 2010 Fig. 2.

Wang et al 2006 (M.D. Anderson). Common Terminology Criteria (CTC) Grade ≥3 in 223 patients with NSCLC treated with definitive concurrent chemoradiotherapy and 3D-CRT between 2001 and 2003. See Wang et al 2006 Fig. 2 & Marks et al 2010 Fig. 2.

Table 1. Radiation pneumonitis probability ranges at four different doses(Gy) from four institutions and the fused result by using evidence theory.

Dose(Gy)	8	15	20	25
MSKCC	0% ~ 6%	4% ~ 16%	15% ~ 35%	-----
Duke	0.05% ~ 2.4%	2.5% ~ 8.8%	8.9% ~ 18%	19% ~ 79%
MD Anderson	-----	10% ~ 24%	23% ~ 39%	26% ~ 45%
Michigan	0% ~ 7.3%	-----	-----	60% ~ 96%
Fused by Yager's rule	0.002% ~ 0.06%	0.23% ~ 15.9%	2.2% ~ 40.7%	30% ~ 80.1%

In Fig. 1, the values of the belief function are plotted as the black dots and those of the plausibility functions as the blue dots. The Lyman-Kutcher-Burman (LKB) model is used to fit the values of the belief and plausibility functions to obtain two boundary sigmoid curves, see Fig. 1. The LKB model is the most widely used normal tissue complication probability (NTCP) model for RP, with three fitted parameters: a position parameter, TD50; a steepness parameter, ms; and the volume exponent, n (when n = 1 the model reverts to mean lung dose [MLD]). In our calculation we use MLD which is widely considered in the literatures owing to its simplicity and effectiveness. By fitting the values of the belief and plausibility functions, we obtain two sets of values of TD50 and ms, see Table 2. For comparison we also list these two values from the well-known papers of Emami and Bruman and plot the sigmoid curve generated from their parameters in Fig. 2.

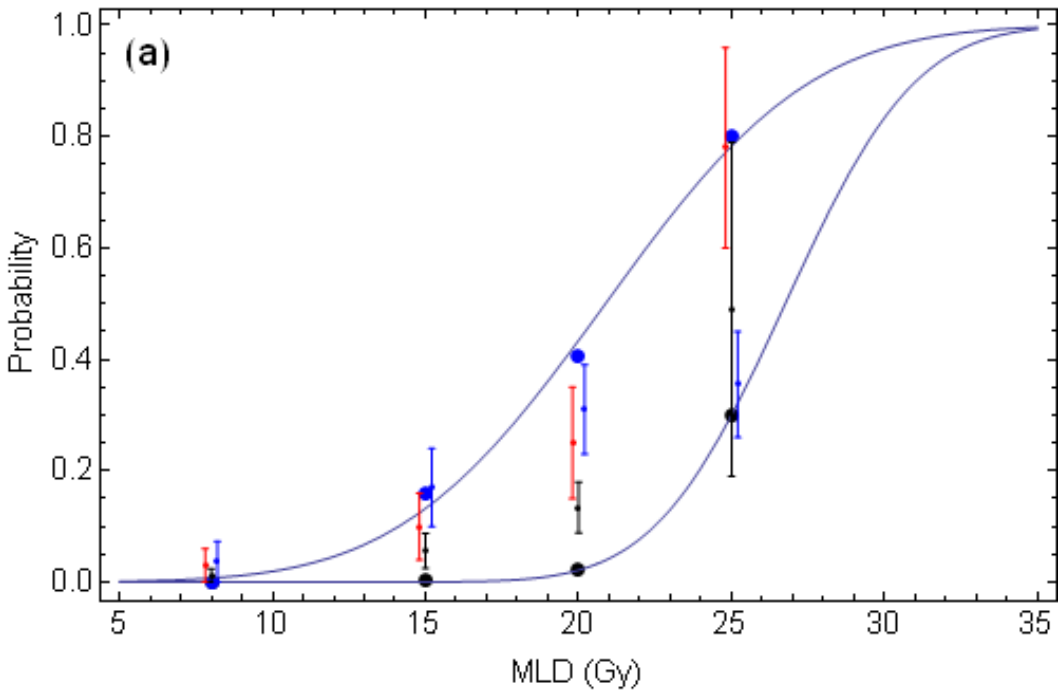

Figure 1. The values of the belief (black dot) and plausibility (blue dot) functions obtained from Yager's rule as function of mean lung dose (MLD). The error bars are from the clinical data of MSKCC (Yorke et al 2005), Duke University (Hernando et al 2001), M.D. Anderson (Wang et al 2006) and University of Michigan (Kong et al 2006). The curves are the fits for the values of the belief and plausibility functions by using LKB model.

Table 2. LKB parameters from evidence theory and Emami & Bruman's papers.

	TD_{50} (Gy)	m
Belief function	26.75	0.125
Plausibility function	20.87	0.252
Emami and Bruman	24.5	0.18

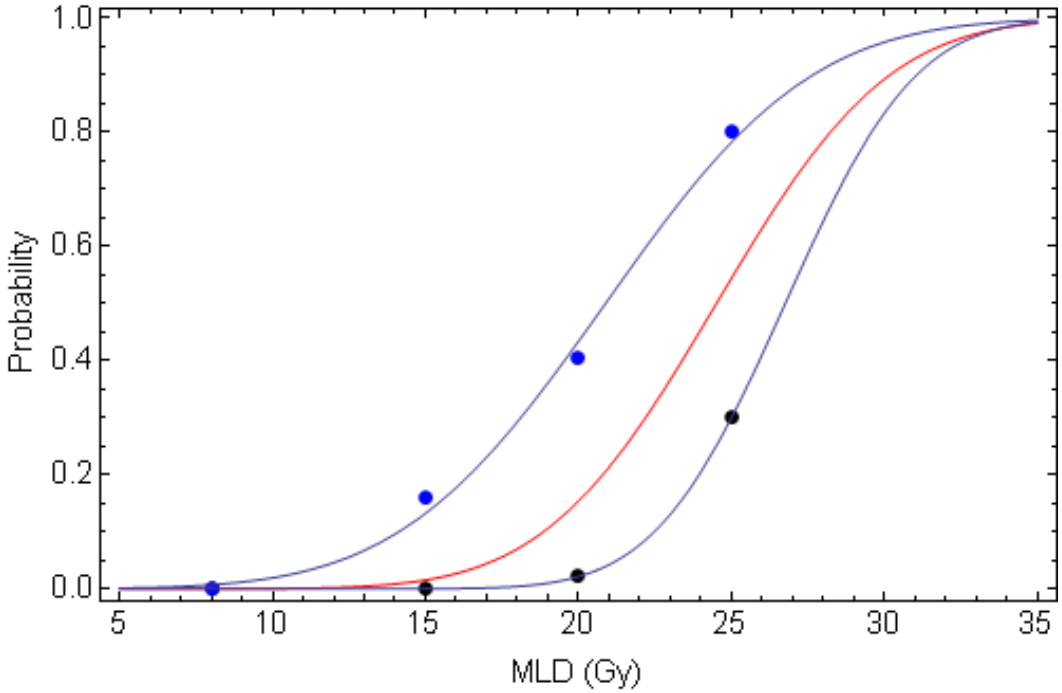

Figure 2. The sigmoid curves of LKB model. The upper one is the fit of the plausibility function, the middle one (red) is generated from Emami & Bruman's parameters, and the lower one is the fit of the belief function.

Research Project 2: Project Title and Purpose

Development and Analysis of an Infrastructure for Review of Modern Clinical Trials that Include Radiotherapy - Cooperative group protocols have greatly increased in complexity over the past 15 years. At least for the radiotherapy component of these protocols, this dramatic change has created considerable difficulty when reviewing dose distributions to determine whether protocol requirements have been met. Much of the difficulty is due to the time it takes to review advanced technology protocols. This research study is designed to demonstrate that analysis tools are now available that can shorten the time for case review to the extent that accuracy is not lost in a tradeoff with efficiency. This study will also provide information for designing the review tools needed for future cooperative group protocols that might include one or more advanced technologies such as IMRT, IGRT, SBRT, 4D respiratory control, or deformable image registration using PET and/or MRI.

Anticipated Duration of Project

1/1/2009 - 12/31/2012

Project Overview

The Radiation Therapy Oncology Group (RTOG) has, over the past years, gathered state-of-the-art equipment that allows detailed review of radiotherapy dose distributions. However, during a similar time period, there has been a tremendous increase in both the complexity of dose distributions and the overall amount of data that must be analyzed to determine if protocol requirements have been met.

These changes place considerable stress on the protocol Principal Investigators (PIs) to review submissions in a timely manner. This research project will compare 2D review techniques (i.e., sequential 2D cross-sectional review to accomplish 3D analysis) used for older 3D-CRT protocols with newer methodologies that allow multi-planar (e.g., coronal, sagittal, and cross-sectional) review of advanced technology protocols. Advanced technology protocols are studies that include Stereotactic Body Radiation Therapy (SBRT) treatments that use a large number of beam directions to achieve highly conformal dose distributions, dose-painting methodologies that include Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), 4D Respiration Controlled treatment, and the use of deformable fusion. The comparison will be accomplished by simply comparing the average review time for protocols that use the Advanced Technology Consortium (ATC) remote review tool (called QuASA^{2}R for Quality Assurance Submission, Archive, Analysis, and Review System) to the average review time for protocols that use more versatile tools that potentially shorten the review time. Another possible limitation in the ability of PIs to rapidly review large numbers of submitted cases is the firewalls that are established by most institutions to protect information. This is the case for both the American College of Radiology (ACR) and the Image-Guided Therapy QA Center (ITC), the institutions holding the data for the RTOG. Such firewalls hamper the ability of a PI to review cases at will, and it is common practice to instead place data in a secure area for a limited amount of time at the request of the PI. Improvements in the area of data dissemination for review purposes will be investigated as part of this research.

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Expected Research Outcomes and Benefits

Many recent advanced technology treatment modalities have matured to the point where they are being used as part of large Phase III studies that are aimed at accruing in excess of 1,000 patients. Additionally, some studies use more than one advanced technology. For example, there is currently at least one Phase III trial that allows both IMRT and IGRT. The incorporation of these and other advanced technologies in large Phase III studies makes the research described here extremely important. As the number of cases requiring review increases dramatically, there is the possibility that the quality of review could be compromised. In order to avoid a decrease in the level of review for a particular study, it is necessary to improve the efficiency of the review process while maintaining quality. This is the aim of the research plan described here. One way of accomplishing this goal is to identify and implement more efficient case review tools. Another way is to create a case review environment that optimizes the use of existing equipment. In addition, remote review capabilities can be improved to allow for situations where it is not possible for one or more individuals to be involved in a central review process. Thus, this research will study the case review

process with the goal of implementing and testing the improvements needed to meet the demands of the cooperative group protocols that utilize advanced technologies.

Summary of Research Completed

Aim: Investigate methods to improve information management capabilities, data analysis tools, and educational facilities for personnel involved in clinical trials so that the overall quality and efficiency of trial execution and outcome analysis is improved.

During this past reporting period, we've focused our service efforts for this research project on the evaluation of systems to support clinical trials. We upgraded the Velocity Advanced Imaging Informatics Software System with image registration and contouring capabilities and launched XenApp for web-based access to Core Lab applications. The XenApp platform is the latest Citrix technology for distributed, web-based access. It enables cross-platform delivery (access from desktops, laptops, PDAs). It leverages local graphics processor, multi-monitor and 5.8 megapixel display.

For a Phase II trial of Hippocampal Avoidance during whole Brain Radiotheapy for BrainMetastases, we evaluated these systems: MiMvista, Velocity AI, MOSAIQ, and CERR for functions for contouring evaluation and dose/volume evaluation. We've identified the systems for the review process and software tools development. See Figure1

For a Phase III trial evaluating both Erlotinib and Chemoradiaiton as adjuvant treatment for patients with resected head of Pancreas Adenocarcinoma we evaluated these systems: MiMvista, Velocity AI, MOSAIQ, and CERR for functions for contouring evaluation and dose/volume evaluation. We've identified the system for the review process. See Figure 2

For an Image Guided approval process, we evaluated systems: MiMvista, Velocity AI, MOSAIQ, and CERR for functions for 3D and 2D registration accuracy. See Figure 3
For a Randomized Phase II trial of Individualized Adaptive Radiation used during treatment FDG-PET/CT and modern Radiation Technology to dose escalated in locally advanced Non-Small Cell Lung Cancer (NSCLC), we evaluated: Pinnacle, XiO, Eclipse and CERR for contour evaluation, planning technique and optimization. See Figure 4

We've updated the IGRT Review instructions that we send out to physicists to use Mim 5.1 on the XenApp platform. With the IT infrastructure, we have integrated imaging/RT systems for onsite and remote usage and the evaluation of devices and systems with physician and medical physics support to further scientific investigation.

There were two abstracts accepted for the American Society for Therapeutic Radiology (ASTRO) Annual Meeting:
<u>Using During-RT PET to Individualize Adaptive RT for Patients with Stage III NSCLC: A RTOG Planning Study</u>

<u>Background:</u> RTOG1106 is to individualize adaptive radiotherapy (RT) based on PET response during concurrent chemoRT for stage III NSCLC. This study aimed to examine the consistency

across institutions of: 1) PET-based metabolic tumor volume (MTV) versus CT-based gross tumor volume (GTV); and 2) the feasibility of generating during-RT PET based adaptive plans.
Materials and Methods: Eleven RTOG lung committee member Institutes participated with this study on pre-RT and during-RT PET-CT scans of one T4N2M0 NSCLC of the right lower lobe. The initial plan (A) based on pre-RT PET-CT was to 74 Gy. An adaptive plan (B) used during-RT PET-CT to create an adapted boost, after 50 Gy to the initial planning target volume (PTV). The final adaptive plan limited total mean lung dose (MLD) to 20 Gy, and other organs at risk (OARs) to institutional or RTOG0617 criteria. Target/OAR volumes and doses and doses to 95% of PTV were compared between centers.

Results: The variations in PET-MTVs were not significantly different from CT-GTVs of primary tumors and nodal diseases either pre- or during-RT (P=NS). However, variations of these volumes were remarkable, ranging 1.4 to 9.2 fold of maximum over minimum for individual targets. Nodal CT-GTV pre-RT and CT-GTVs during-RT had the greatest variation, with a magnitude above 5 fold of maximum over minimum. During-RT GTV and MTV had greater variations than those of pre-RT ones, with during-RT CT-GTV having the greatest difference from one physician to another. There were also remarkable variations in OAR volumes, with maximum up to 4 fold greater than minimum for one structure.

Using during-RT PET and with some individual instruction, 11/11 centers were capable of generating adaptive plan to escalate PTV doses. Plan A generated a mean PTV dose of 73.3 Gy (95% CI 73.2-74.2) with MLD of 20.3 (95% CI 19.3-21.3) Gy. Plan Bs PTV dose was escalated to a mean of 83 Gy (95% CI 81-85), with a MLD of 19.0 Gy (95% CI 18.3-19.2). Plan B reduced the means of mean esophageal, heart V40, esophageal V60, and maximum cord doses, with a small increase (0.8 Gy) increase in the maximum esophageal dose. All adaptive had MLD<20 Gy.

Conclusions: Although significant variations between target and OAR volumes, there is no significant differences in variations between CT-GTVs and PET-MTVs on either pre- or during-RT scans. Adaptive planning is feasible among RTOG centers to provide relative consistent PTV dose escalation and OAR dose reduction. See Figure 5

Initial Experience With A Pre-Clinical Trial Process for A Dosimetric Feasibility Study of Adaptive Radiotherapy for Patients With Stage III NSCLC

Purpose/Objective(s): Protocol development is such an important starting process of any clinical trials that the eventual success lies in the comprehensive design and layout of the details of the trials. It is essential to have balanced radiotherapy objectives to ensure quality of the treatments and at the same time allowing sufficient enrollment for statistical significance. To have detailed technical guidance for achieving these objectives is also imperative. In this study, we have setup a data collection and analysis process at RTOG core laboratory for a potential trial on adaptive radiotherapy for patients with stage III NSCLC, and will report on the initial data analysis and associated recommendations.

Materials/Methods: [Data preparation] De-identified “before radiotherapy” (pre-RT), “during-RT” DICOM CT and FDG-PET scans of one T4N2M0 NSCLC of the right lower lobe are uploaded to the secured database that is set up for the project.[Data exchange] An FTPS server with high data transfer rates is the chosen data exchange method. 14 institutions downloaded these datasets with instructions

for contouring and planning, and uploaded delineations of targets and organs-at-risk (OAR), RT plans and dose matrices in DICOM RT format. Planning and delivery parameters are also submitted. [Data analysis] Most analysis of the data is performed centrally with tools from RTOG core laboratory, which guarantees a uniform analysis method. Targets and OARs are analyzed with simultaneous truth and performance level estimation (STAPLE), with sensitivity/specificity reported.

Results: Sensitivity/specificity ranges for all targets and OARs from STAPLE analysis are [0.32-098]/[0.98-0.99], pointing to a need to have atlas contour sets and more specific contour instructions. With OAR objectives from RTOG 0617 generally achievable, PTV dose can be escalated from 74 Gy to 82 Gy (79-84 Gy, 95% confidence level (CL)) with mean conformality index 0.47 (0.35-0.60,95% CL) for adaptive plans, suggesting a need for planning training. Treatment plans are created with 3D CRT, static IMRT, rapidArc, when applicable with 3-7 beam angles and multiple arcs. Manual beam weight adjustments are used in addition to inverse optimization with weighted DVH/biological objectives and dose gradient objectives. Total physics/dosimetry time spent averages 401 minutes (215-710 minutes).

Conclusions: A database and analysis infrastructure has been established for a process to assist pre-clinical trial protocol development. Data from such a process will form the basis for technical component of the protocol.

Grafts/Figures/Charts/Tables

Figure 1 displays the MiMvista contouring software used for contouring evaluation and dose/volume evaluation for a Phase II trial of Hippocampal Avoidance during whole Brain Radiotheapy for BrainMetastases.

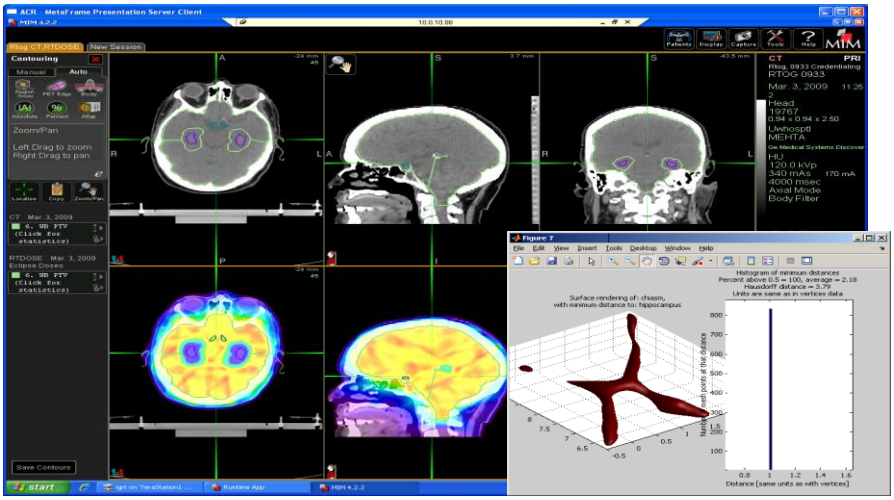


Figure 2 shows the MiMvista software for contouring evaluation and the dose volume analysis for QA review for specific parameters for a Phase III trial evaluating both Erlotinib and Chemoradiaiton as adjuvant treatment for patients with resected head of Pancreas Adenocarcinoma.

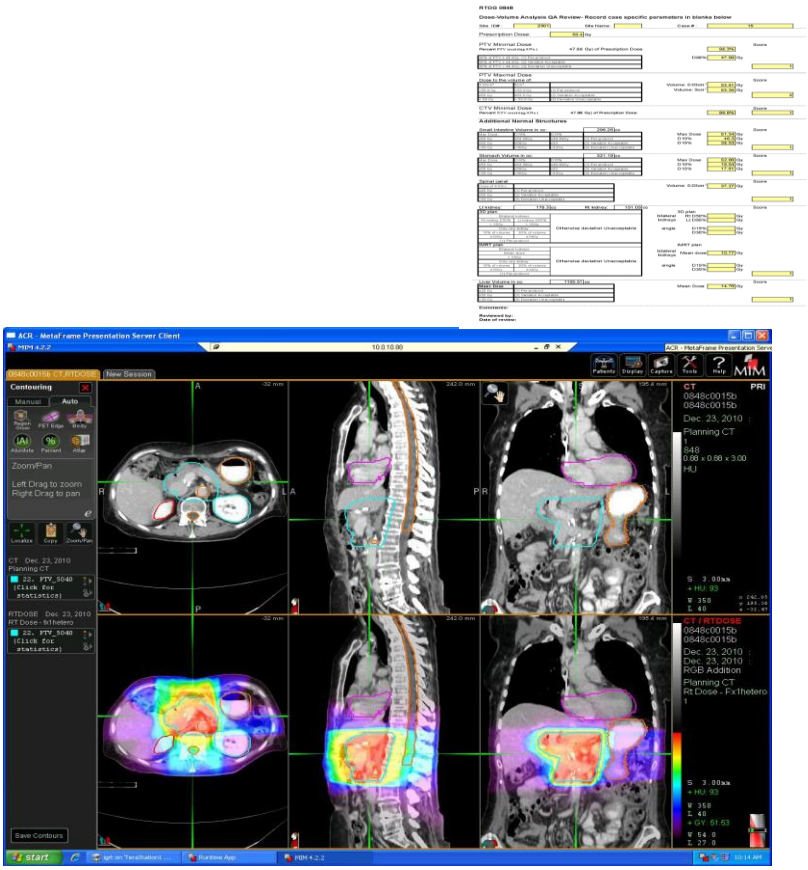


Figure 3 (left side) displays the MiMvista software used to evaluate the Image Guided Radiation Therapy delivery for a Lung cancer trial and the CERR software for functions for 3D and 2 D registration accuracy of treatment delivery.

Figure 4 (right side) displays the Pinnacle and CERR software used for contour evaluation, planning technique and optimization for a Randomized Phase II trial of Individualized Adaptive Radiation used during treatment FDG-PET/CT and modern Radiation Technology to dose escalated in locally advanced Non-Small Cell Lung Cancer (NSCLC).

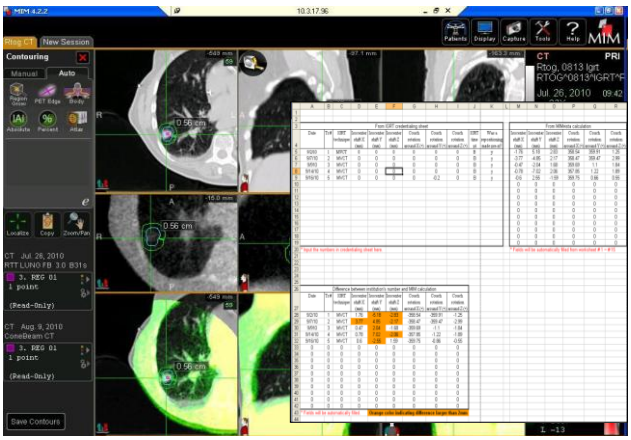
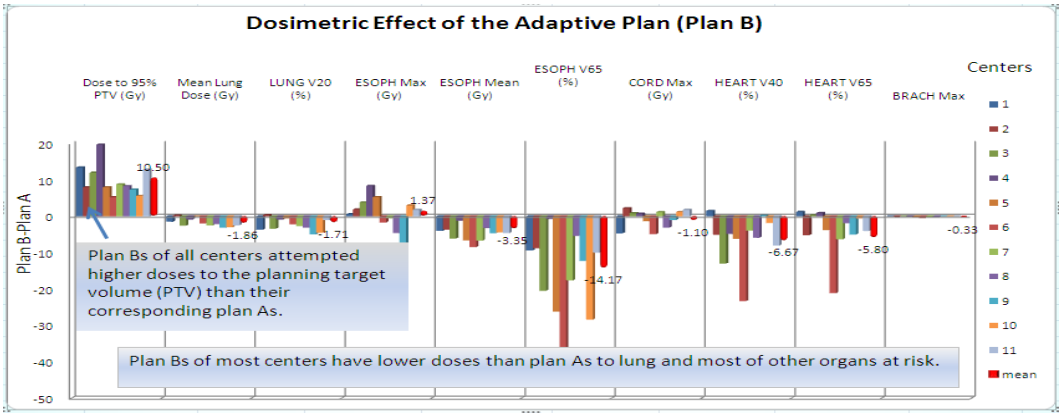


Figure 5 shows the detailed dosimetric differences between plan Bs and As of all individual centers.



Research Project 3: Project Title and Purpose

Screening For Depression and Referral for Treatment of Cancer Patients - The first purpose of this project is to determine the usefulness of screening for depression among cancer patients receiving radiation therapy, in terms of the proportion of patients who are identified as depressed and who are not currently receiving mental health treatment. Patients who are found to be depressed will be offered a referral to a mental health professional or primary care physician, depending on their preference. Three months later, they will receive a follow up telephone interview. The goal is to evaluate the efficiency of screening and to identify and find ways of overcoming the significant barriers to cancer patients receiving care for depression.

Anticipated Duration of Project

1/1/2009 - 12/31/2012

Project Overview

Objective – Depression is common among cancer patients, but often goes unrecognized and untreated, unnecessarily compounding patients' suffering and further compromising their quality of life. Screening with brief depression questionnaires is widely seen as providing a means of improving detection of depression among cancer patients and facilitating their referral to treatment in either mental health or primary care settings. Yet, questions remain as to whether screening is efficient: most patients who screen positive will not be found to be depressed upon interviewing, and an unknown proportion who are depressed will already be receiving treatment. Evidence is limited, but there is also a concern that many patients who are provided with referrals either do not complete them or encounter significant barriers that prevent them from receiving acceptable, effective care.

Specific Aims – To understand the rates of patients who screen positive on a questionnaire are actually found to be depressed in a psychiatric interview and secondly, the proportion who are not already receiving treatment. Third, to provide referrals for treatment to those depressed persons not already in treatment and follow up with them three months later to determine whether they have completed the referral and experienced an improvement.

Design, Methods – Four hundred patients who score positive on a measure of depression while they are receiving radiation treatment for cancer will receive telephone interviews to ascertain whether they are depressed, whether they have sought treatment, and, if they are not currently receiving treatment, their treatment preferences, i.e., antidepressants or psychotherapy. They will be provided with an appropriate referral. Three months later, a follow up telephone interview will ascertain if they have completed the referral and whether they have experienced an improvement in their level of depression. If they have not completed the referral or not received effective treatment, the nature of the barriers they encountered and how these could have been overcome will be assessed.

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Expected Research Outcomes and Benefits

A full range of effective treatments for depression are available, but the challenges lie in detecting depression in medical patients in a timely fashion and ensuring that they access these effective treatments. Depression is too often missed or not given the priority it deserves. Problems in detecting and treating depression are compounded for cancer patients who are contending with often debilitating treatment for their life-threatening condition. The American health care system is fragmented and the pathways to care for depression are not well mapped, but it is generally understood there are significant barriers to patients accessing care, particularly when they are uninsured or underinsured. Screening with brief questionnaires is seen as one way of identifying depression that would otherwise be missed, but screening does not alleviate depression if it does not lead to completed referrals to effective care. The first outcome of the proposed research will be scientific papers documenting the efficiency of screening for depression in terms of the rates of the disorder that are uncovered. The second outcome will be papers documenting the rate of referrals for treatment, what makes for effective referrals, and what can be done to improve the process, particularly for uninsured, underinsured, and members of minorities. The most important outcome of the project is that its results will serve as pilot work for an application for a more ambitious federally funded (National Cancer Institute) project evaluating means of addressing barriers to care and improving the completion of referrals and the assurance of effective treatment for depression.

Summary of Research Completed

RTOG 0841 is an observational study intended to guide development of an intervention robustly applicable in a multi-institutional setting. RTOG 0841 accrued 463 patients during active accrual periods from May 2009 through March 2011 averaging 58 patients per month. Patients were screened for depressive symptoms using two questionnaires: Hopkins Symptom Checklist (HSCL-25) and the 9-item Patient Health Questionnaire (PHQ-9). Patients then had a telephone diagnostic evaluation of major depression by trained clinical interviewers utilizing the Structured Clinical Interview for Diagnosis–DSM-IV (SCID). Patients diagnosed with depression were provided with a list of local mental health resources and had a follow-up telephone reassessment after 3 months. Patients with persistent major depression were provided with treatment options and resources.

The study is in follow-up, including the end-point analyses of the number of participants diagnosed with depression, those provided with a list of local mental health resources and the number of participants that completed the follow up telephone re-assessment.

Research Project 4: Project Title and Purpose

Assessment of Methods to Increase Latino Enrollment into Cancer Clinical Trials - Despite national initiatives to increase the enrollment of racial and ethnic minorities into cancer clinical trials, participation by Latinos remains low. The Radiation Therapy Oncology Group (RTOG), which conducts cancer clinical trials involving radiotherapy, will develop and evaluate evidence-based, cuturally and linguistically appropriate patient education materials and investigator training programs to increase the enrollment of Latinos into cancer clinical trials in Pennsylvania and nationally. We will also use cartographic modeling techniques to do a gap analysis through identification of current RTOG sites and their Latino population density compared to high density areas of Pennsylvania and the United States where we do not have RTOG sites. This will help us strategically identify sites to recruit into the RTOG that will facilitate Latino access to state-of-the-art cancer clinical trials.

Anticipated Duration of Project

1/1/2009 - 12/31/2012

Project Overview

Research Objectives: 1) The RTOG will develop and evaluate evidence-based, cuturally and linguistically appropriate education and awarness programs and recruitment materials to increase the enrollment of Latinos into cancer clinical trials in Pennsylvania and nationally. We will identify 4 RTOG clinical trials to target and evaluate. 2) We will develop and assess cultural competency training for RTOG investigators and research staff. 3) We will conduct a gap analysis of current RTOG sites with high density Latino populations and areas of the Commonwealth of Pennsylvania and the country with high density populations where we do not have RTOG sites. This will help us strategically identify sites to recruit into the RTOG that will facilitate Latino access to state-of-the-art cancer clinical trials.

Methods: 1) In consultation with our RTOG investigators and patient advocates, we will identify four protocols and use certified Spanish translators who will do back-forth translations of the informed consents and the study specific and general clinical trials and radiation therapy patient materials. Materials will be developed by our investigators and our in house marketing staff with input from patient advocates. 2) RTOG will develop a Latino Cultural Competency and Recruitment Training Program for physicians and clinical research associates (CRAs) who have primary contact with cancer patients and are located at facilities in geographic regions with Latino populations. The training program will instruct the caregivers in the barriers, myths, beliefs, and norms within the Latino culture that may impede clinical trial enrollment and provide strategies for overcoming these barriers. Video recordings of the training sessions will be made available for subsequent reinforcement of course material and for physicians and CRAs unable to attend in person. An interactive program with role playing will be used in the training sessions. Culturally appropriate Spanish language patient information brochures, posters, and Spanish translations of patient consent forms for RTOG's larger randomized trials will be developed and provided to enrolling facilities. Pre and post knowledge tests will assess effectiveness of the training in enhancing cultural competence. 3) We will use cartographic modeling techniques to do a gap analysis to assist with the identification

of current RTOG sites with high density Latino populations and areas of Pennsylvania and the country with high density populations where we do not have RTOG sites.

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Expected Research Outcomes and Benefits

This research is designed to address the underrepresentation of Latinos in cancer clinical trials. The primary outcome will be a 10% increase in Latino recruitment by year 3 but we will continue to evaluate recruitment annually past the end of this study. We need to recognize the multifactorial nature of barriers to minority recruitment and that this study is only the beginning of testing evidence-based methods to begin to improve recruitment. Improvements are expected to be incremental with identification of evidence-based methods that show increased awareness, informed consent and accrual to research. RTOG will leverage this funding to continue to support the methods that show efficacy in increasing Latino recruitment. Increased minority recruitment to clinical trials provides the ability to generalize results to the Latino population which is the fastest growing minority in Pennsylvania and the United States. These strategies also enhance social justice by facilitating Latino access to state-of-the-art cancer clinical trials.

Summary of Research Completed

Research objectives 1 and 2 were addressed over the reporting period through the following study: Evaluation of the Effect of a Cultural Competency Training Program for Radiation Therapy Oncology Group (RTOG) Physician Investigators and Clinical Research Associates (CRAs) on the Recruitment of Minority Patients into Radiation Therapy Clinical Trials

Background/Purpose: Despite national initiatives to increase the enrollment of racial and ethnic minorities into cancer clinical trials, participation by Latino and African American populations remains low. Clinical trials provide evidence that is formulated into recommendations for practice guidelines, however, without improvements in recruitment 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. While clinical trials accrual for all adult cancer patients is small, at only about 5 to 8%,

Caucasian patients make up the majority of trial participants at approximately 86%. Latinos and African Americans constitute a much lower percentage of participants at only about 3.1% and 9.2%, respectively. Despite low accrual rates, research has shown that with equal access Latinos appear to have similar clinical trials participation rates with Whites. A recent study has also concluded that efforts to increase minority participation in health research should focus on ensuring access to health research for all groups, rather than changing minority attitudes. However, to provide clinical trials access to minorities, cultural as well as language differences and barriers to clinical trial enrollment must be addressed. This study proposes to develop and empirically test methods to improve Latino and African American recruitment to RTOG clinical trials.

Objectives: The primary objectives of this project are 1) To develop a Cultural Competency and Recruitment Training Program for physician investigators and clinical research associates (CRAs) who have primary contact with cancer patients and are located at facilities in geographic regions with Latino and African American populations, 2) To modify the Cultural Competency Assessment (CCA) tool to be utilized by physician investigators and clinical research associates within a clinical research setting, 3) To perform psychometric testing on this adapted CCA tool, 4) To determine if a Cultural Competency and Recruitment Training Program increases cultural competency scores among physician investigators and clinical research associates (CRAs). Secondary objectives include 1) To determine the impact of the Cultural Competency and Recruitment Training Program on Latino and African American patient recruitment into RTOG clinical trials at one and two years post training, 2) To determine whether post-training cultural competency scores correlate with post-training minority accrual to RTOG clinical trials, and 3) To assess differences in cultural competency scores between the in-person and video cultural competency training programs.

Methods: In order to develop the Cultural Competency and Recruitment Training Program, we drew on the work of Leininger (1991) and utilized the Cultural Competency Model that suggests the importance of an interconnection between (a) cultural diversity, (b) cultural awareness, (c) cultural sensitivity, and (d) cultural competence behaviors among health care providers to promote culturally congruent patient care. Guided by this model, we partnered with the nationally recognized recruitment firm ePharmaSolutions to develop the program for physicians and clinical research associates (CRAs) who have primary contact with cancer patients. ePharmaSolutions is an organization headquartered in Philadelphia, PA that develops technology solutions in order to streamline and accelerate site selection/activation, study training, and patient enrollment. The firm has partnered with more than 190,000 researchers from 107 companies, and has facilitated study start up and enrollment for the top 20 pharmaceutical companies in the world (www.epharmasolutions.com). In addition, eight subject matter experts were utilized to develop the program, including nurse and physician investigators, clinical research associates, and patient advocates. The training program instructed health professionals in the barriers, myths, beliefs, and norms within the Latino and African American culture that may impede clinical trial enrollment and provide strategies for overcoming these barriers. It consisted of a module on theoretical models surrounding cultural competency, a module covering the facts and myths surrounding recruitment of African American and Hispanic/Latino populations, an interactive module covering culturally-targeted communication strategies related to recruitment, and finally an interactive module discussing barriers to recruitment and brainstorming strategies to overcome these barriers. The 4-hour in-person training program took place at the June 2011 RTOG semi-annual meeting in Philadelphia, PA. It was recorded on video which will be posted on the RTOG website to provide access to RTOG clinical

research associates and investigators who were not present at the in-person training. The Cultural Competency Recruitment Training Program also incorporated the distribution of culturally appropriate recruitment and education materials. These materials included information on where to find Spanish translated consent forms for RTOG clinical trials of disease sites that have a high incidence in Latino populations, as well as NCI developed culturally appropriate general informational pamphlets regarding clinical trials for Latino and African American populations.

The CCA is a 26-item instrument designed to measure cultural diversity experience, awareness and sensitivity, and competence behaviors. Internal consistency reliability for the CCA has ranged from .80 to .89, and construct, content, and face validity and test-retest reliability have been established. In one study, the CAS subscale reliability was .76, and the CCB subscale reliability was .93. For this study, the CCA was modified for use by clinical research associates and physician investigators as it relates to their interactions with Latino and African American cancer patients considering radiation therapy clinical trials. Instead of referring to clinical practice in general, the tool was adapted to apply specifically to the research setting. The revised tool was evaluated for face and content validity by subject matter experts. A quasi experimental single group pretest posttest design will be utilized for the survey portion of this study. Those present at the in-person training were asked by the program leader at the training session to fill out a paper version of the CCA tool prior to the commencement of training, and then will be sent a reminder to complete a web-based version of the 3 months post training CCA tool in September 2011. In addition to the tool, participants were asked to fill out demographic information including their RTOG site, gender, whether they are a CRA or physician investigator, years of work experience and whether or not they have completed any prior cultural competency training related to their role in radiation clinical trials other than the training provided. Of the 79 participants in the training program, 57 chose to participate in the survey study. A web-based portion of the baseline and 3 month post survey will be made available on the RTOG website for those completing the video-assisted training who wish to participate in the study.

Recruitment for this study is still ongoing. Video-assisted training is expected to provide at least 100-150 additional participants to power our statistical analyses.

Research Project 5: Project Title and Purpose

Emerging Imaging Technology Clinical Trials in PA: Reproducibility and Responsiveness of MRI Measures of Body Composition and Lipid Metabolism in Women with Gestational Diabetes The purpose of the multi-site Pennsylvania study is to evaluate the reproducibility and responsiveness of MRI measures of maternal body composition and lipid metabolism in the assessment of gestational diabetes. The MRI measures to be evaluated are associated with problems and diseases related to processing of blood sugar and obesity.

Summary of Research Completed

This project was deleted. No health research grant funds were spent on this project.

Research Project 6: Project Title and Purpose

Remote Review of Quality of Radiation Treatment for Lung Cancer: A Pilot Project - Definitive radiotherapy is the standard therapeutic approach for inoperable lung cancer. However, this treatment can potentially result in fatal treatment complications. The purpose of this pilot project is to develop methods of collecting clinical data directly from distinct electronic medical record systems at a variety of radiotherapy facilities to assess quality of treatment delivery in lung cancer. The clinical data will be standardized and aggregated in a central database from which queries will be performed to retrieve critical data. The methods developed will assure secure transfer, review, and analysis in compliance with regulatory requirements. The overall goal will be to scale this approach for automated collection of quality of care data across multiple institutions to analyze and improve radiation treatment delivery for lung cancer patients.

Anticipated Duration of Project

1/1/2009 – 12/31/2012

Project Overview

The hypothesis: Despite significant barriers to full interoperability, it will be possible to demonstrate remote secure access to Radiation Oncology Electronic Medical Records, to remotely retrieve clinically significant quality of care data on lung cancer patients, to remotely aggregate these at a central secure super server, and conduct initial analyses of these quality data to evaluate quality of Radiation Oncology delivered.

Specific Aims include demonstrating the feasibility of collecting and aggregating in a central database established quality parameters for workup and radiation treatment of lung cancer from multiple institutions with different Electronic Medical Records (EMR) systems, validating the de-identification engine and confirming secure HIPAA compliant internet-based data transfer and software interoperability, performing data extractions on the aggregated data and analyzing quality parameters, and demonstrating compliance with the larger connectivity goals of the NCI Ca-BIG in clinical Radiation Oncology.

The investigators will develop a core data set description to implement parallel processes and systems for radiation oncology facilities using the two different EMR systems. To facilitate the study and re-use of these data, the repository will follow and model the principles of the cancer Biomedical Informatics Grid (caBIG) and its related technologies, including the consistent definition and translation of data elements to NCI-defined ontologies and taxonomies. Where ontologies and taxonomies are undefined by caBIG (e.g., for radiotherapy delivery data), the researchers will cooperate with the vendors and standards bodies to define structure and vocabulary that will facilitate research against the unified database.

In the current project, another process will be required wherein a data upload from each vendor system to a super-server will result in an aggregate of combined datasets. A requirement of this process will be that data from each vendor's dataset will be mapped and/or converted to standard caBIG-compliant data elements. In addition, software tools will be required to assure data quality

and integrity, to provide data quality reports back to each of the vendors, and to provide outcome and analysis reports to Quality Research in Radiation Oncology (QRRO).

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Expected Research Outcomes and Benefits

At the present time, only 3% of all patients with a diagnosis of malignancy are enrolled into clinical trials. The therapeutic outcome data for the remaining 97% of patients is usually not collected and is rarely put to rigorous data analysis to identify predictors of outcome. One approach to overcome this obstacle is to aggregate and query data from multiple treatment sites so a more robust analysis on the larger patient population can be performed. We propose in this project to develop an approach to standardize and aggregate data at a remote site on lung cancer patients at multiple institutions receiving radiation treatment. The radiotherapeutic management of lung cancer is a rapidly evolving field with newly validated quality measures that correlate with likelihood of cure as well as toxicity. This approach could then be used to identify new measures of treatment outcome and quality of radiation treatment delivery. The ability to analyze larger, aggregated data on lung cancer patients would allow for identification of critical treatment parameters that would not be apparent on analysis of smaller subsets of patients. This will allow comprehensive assessment of quality of care during treatment and for recent time periods. Patients will benefit from a more timely quality of care assessment system. The long-term goal of this project would be to improve the baseline standard of radiotherapeutic treatment of lung cancer patients.

Summary of Research Completed

As stated in the Strategic Research Plan the Specific Aims were:

> Specific Aim #1: To demonstrate the feasibility of collecting and aggregating in a central database established quality parameters for workup and radiation treatment of lung cancer from multiple institutions (approximately 20) with two different widely used Radiation Treatment Electronic Medical Records (EMR) systems.

Specific Aim #2: To validate the de-identification engine and confirm secure HIPAA compliant internet-based data transfer and software interoperability.

Specific Aim #3: To perform data extractions on the aggregated data set interrogating patient demographic, tumor specific, and radiotherapeutic treatment parameters from any lung cancer patient receiving or having received radiation treatment at a participating institution and to analyze the data to establish baselines for quality parameters.

Specific Aim #4: To demonstrate that this method of remote access and aggregation will be compliant with (and the first example of) the larger connectivity goals of the NCI Ca-BIG in clinical Radiation Oncology.

Due to changes in standards for remote access, Aim #4 will be revised as follows: To demonstrate that this method of remote access and aggregation will be compliant with existing standards according to appropriate Integrating the Healthcare Enterprise (IHE) Technical Frameworks.

There was no activity on this project during the reporting period.

Research Project 7: Project Title and Purpose

Quantitative Imaging Biomarker Tools – The purpose of this study is to evaluate, develop, unify, and evaluate standards-based tools that are used to collect, record, and analyze quantitative imaging data in order to discover imaging biomarkers for more accurate analysis of image results collected in clinical trials. The critical barriers being addressed by our study are that at present, the assessment of cancer treatment response based on image assessment is cumbersome, with poor tools for measuring and capturing vital image metadata required for this assessment. Our outcome will bridge these barriers and advance the field by improving the efficiency of response assessment evaluation on images.

Anticipated Duration of Project

10/15/2010 – 12/31/2012

Project Overview

Our objective is to develop and unify standards-based tools for collecting, recording, and analyzing quantitative imaging data for discovering and using imaging biomarkers for more accurate analysis of image results collected in clinical trials. The hypothesis is that by unifying the currently fragmented set of tools for quantitative image analysis, the evaluations researchers conduct will be more efficient and accurate. We will accomplish our objectives by pursuing the following specific research aims:

- Compile and refine tools enabling automated extraction of quantitative imaging biomarkers.
- Develop a standards-based software platform to unify quantitative imaging tools for efficient image evaluation and data interoperability.
- Assess our platform in a study requiring evaluation of quantitative imaging data.

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Expected Research Outcomes and Benefits

Our ultimate goal by developing these tools is to facilitate assessment of treatment response and clinical decision-making in cancer. Our unified tools will enable cancer researchers to validate and standardize methodologies and to share imaging data and related imaging meta-data for quantitative measurements of responses to cancer therapies. Our work will enable oncologists to make better treatment choices for their cancer patients – a potential benefit to over 1.4 million patients with new cancers annually.

Summary of Research Completed

Aim 1: Analyze and refine tools to determine if enabling automated extraction of quantitative imaging biomarkers will improve the efficiency of the analysis of imaging data.

We began with an assessment of the major quantitative imaging tools available and in use in the ACRIN core laboratory. In addition to identifying which tools provide open programming interfaces, this assessment included an inventory of all quantitative software applications including the vendor, version, operating system, imaging applications, current ACRIN uses (by application and ACRIN trial), DICOM compatibility, type of layer/annotation management, and type of Region of Interest (ROI) export. We then conducted a detailed gap analysis. This analysis was performed by working with core laboratory imaging analysts and radiologists to identify what features are used and what features are missing in terms of tools and workflow for each of the following reader scenarios – RECIST assessments, PET assessments, and DCE-MRI assessments.

Two instances of ePAD were installed and tested on separate reader workstations – one using Osirix, one using ClearCanvas. Both Osirix and ClearCanvas are open-source advanced DICOM-compliant image viewers. DICOM (Digital Imaging and Communications in Medicine) is a standard for handling, storing, printing, and transmitting medical imaging. The DICOM standard was developed

by the National Electrical Manufacturers Association (NEMA) and has been nearly universally accepted by the medical imaging equipment vendors and healthcare IT organizations.

We chose to first focus on improving the efficiency and analysis of RECIST assessments. Using the current version of ePAD, code was written to support unambiguous identification of target lesions and automated tracking (matching) of images across various time points. This functionality is in the testing/validation stage.

Aim 2: Develop a standards-based software platform to unify quantitative imaging tools for efficient image evaluation and data interoperability.

In tandem to extending functionality of the ePAD tool, as discussed in Aim 1 above, we are working on developing a web-based platform. The platform will store all image data according to the caBIG Annotation and Image Markup (AIM) standards to maximize interoperability. AIM is a "standard" means of capturing descriptive information added to the image in the clinical environment. The first few months of the project period were devoted to assessing and then implementing the appropriate infrastructure and firewall updates required for deployment of a web-based platform. We set up and tested project-specific DICOM servers populated with test cases. Together, the ACRIN and Stanford team installed and tested ePAD with the DICOM servers at ACRIN. ePAD was successfully configured to interface with both the ClearCanvas and dcm4chee servers. The dcm4chee server is an open source DICOM- and HL7-compliant image manager/archive which provides many robust and scalable services and can be accessed by the Stanford team via a web interface.

Work is currently under way to define the user requirements and technical specifications for the planned XML database and query interface to support queries and extraction of AIM data. In connection with this, we are currently communicating with the Northwestern AIM team regarding implementation/development of AIM on ClearCanvas.

Aim 3: We will assess our platform in a study requiring evaluation of quantitative imaging data.

A pilot reader study is underway using the current version of the Osirex-ePAD tool. The pilot reader study consists of 20 CT cases (with 4 imaging time points) and three readers. The pilot study compares the accuracy of image review with and without the ePAD tool with a minimum 30-day washout period between the reviews. The first reader has finished both reviews. The second reader has finished the first review (with iPAD) and is currently in the washout period. We are currently looking to identify the third reader. In addition to serving as the pilot study for a later reader study with the updated ePAD tool (Aim 1), the pilot reader study is being used to further assess and define user requirements for extending the functionality of the current workflow and analysis tools.