American College of Radiology

Annual Progress Report: 2011 Formula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Formula Grant Overview

The American College of Radiology received $1,777,126 in formula funds for the grant award period January 1, 2012 through December 31, 2015. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

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

Anticipated Duration of Project

1/1/2012 – 12/31/2015

Project Overview

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

Aim 1: Evaluation of Candidate Pathways of Therapeutic Intervention in Anal Cancer: RTOG 9811 is a Phase III trial of patients with carcinoma of the anal canal. Using data and samples from this trial, this project will correlate expression of ERCC1, p53, p16 and PTEN via AQUA® technology, protein co-expression of EGFR and Ki-67 and amplification of EGFR with clinical outcome factors.

Aim 2: Validating cytoplasmic Hu antigen R (HuR) expression as a marker for gemcitabine (Gem) response in pancreatic cancer patients: RTOG 9704 is a Phase III trial of patients with
resected pancreatic cancer. Using this trial’s data and samples, this project will evaluate HuR cytoplasmic expression as an independent predictor of response to Gemcitabine treatment. This project will also evaluate correlations between deoxycytidine kinase (dCK) and HuR expression.

**Aim 3: Correlation of Soft Tissue Sarcoma Tissue Biomarker Expression Patterns with Treatment Response and Outcomes:** RTOG 9514 is a Phase II Study of Neoadjuvant Chemo and Radiation Therapy in the Management of High-Risk, High-Grade, Soft Tissue Sarcomas of the Extremities and Body Wall. Using this trial’s data and samples, expression patterns for “candidate” tumor biomarkers will be defined and subsequently correlated with clinically relevant outcomes.

**Aim 4: Markers and Potential Therapeutic Targets for Improving Tumor Response in Head & Neck (H&N) Cancer:** This project will use data from two Phase III trials for locally advanced H&N cancer: RTOG 0129 and 0522. A separate grant, using specimens/data from non-RTOG trials, will develop candidate DNA methylation and mi-RNA biomarkers of response to treatment and prioritize them for clinical validation. This Aim 4 project will validate and refine the selected signatures of therapeutic response, using the above mentioned RTOG trials.

**Aim 5: Correlating Pathologic Variables with Outcomes in Patients with Non-Urothelial Muscle Invasive Bladder Cancer After Bladder Preserving Trimodality Therapy:** The final project utilizes multiple RTOG bladder sparing trials, focusing specifically on those patients with variant histologies. This project will focus on correlating central pathologic review data for these patients with long-term outcomes.

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**Other Participating Researchers**

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**Expected Research Outcomes and Benefits**

**Aim 1: Evaluation of Candidate Pathways of Therapeutic Intervention in Anal Cancer:** Identification of designated pathways and accurate measurement of designated proteins using standardized and quantitative technologies will enable improved patient selection for treatment and provide possible targets for therapeutic interventions.

**Aim 2: Validating cytoplasmic Hu antigen R (HuR) expression as a marker for gemcitabine**
(Gem) response in pancreatic cancer patients: A strong relationship between HuR and survival after Gem treatment may provide a foundation to develop strategies for tailoring or intensifying Gem-based therapeutic regimens, including the potential to direct clinical trial eligibility.

**Aim 3: Correlation of Soft Tissue Sarcoma Tissue Biomarker Expression Patterns with Treatment Response and Outcomes:** This project may aid in prognostication and guide trial design for this relatively rare tumor, where a limited number of potential patients makes every clinical trial extremely valuable as a way to improve the treatment of this disease.

**Aim 4: Markers and Potential Therapeutic Targets for Improving Tumor Response in Head & Neck Cancer:** This project may serve to streamline cancer therapy by logical selection of tumor-specific treatment. Such individualization of therapy may result in increased efficacy and reduced overall treatment toxicity.

**Aim 5: Correlating Pathologic Variables with Outcomes in Patients with Non-Urothelial Muscle Invasive Bladder Cancer After Bladder Preserving Trimodality Therapy:** This project may provide information for use in the design of future RTOG and other trials that utilize trimodality therapy in the treatment of muscle-invasive bladder cancer patients with variant histologies.

**Summary of Research Completed**

**Aim 1:** Statistical analyses were done, an abstract of the results was submitted to the 2014 ASTRO Annual Meeting and are summarized below.

Recently, there have been several studies published on the prognostic significance of human papillomavirus (HPV) status and outcome in patients with squamous oropharyngeal cancers, with improved outcome in patients with HPV-positive versus HPV-negative tumors. However, the impact of HPV pathway activation on prognosis in patients with anal cancer has not been well studied. The purpose of this analysis was to measure expression of p16 (surrogate for HPV) and p53 expression status in pre-treatment tumor biopsies of anal cancer patients enrolled on RTOG 98-11, a phase III trial comparing chemoradiotherapy of 5FU/mitomycin/RT (Arm 1) vs. chemoradiotherapy of 5FU/cisplatin/RT (Arm 2), and to correlate expression with clinical outcome.

P16 and p53 expression were measured using fluorescence immunohistochemistry and automated quantitative image analysis. P16 was measured in the tumor and expressed as a ratio of tumor to normal epithelial controls. P53 tumor expression was normalized by calculation of nuclear to cytoplasmic (n/c) staining ratios. Expression of each marker was analyzed using X-tile cut-points defining high vs. low expression status, based on outcome. Cox proportional hazards models were used to explore associations between tumor marker status and clinical endpoints: overall and disease-free survival (OS, DFS), loco-regional and colostomy failure (LRF, CF), and distant metastases (DM). The hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) comparing groups as specified in the results are reported for these endpoints.

Two-hundred and eighty-two pre-treatment tumors were analyzed from RTOG 98-11. Of
evaluated specimens, 155 (n=78, Arm 1; n=77, Arm 2) were eligible and analyzable. There were no significant differences in baseline characteristics or outcomes between analyzable and unanalyzable patients. Median follow-up was 6.3 years. Patients whose tumor had high p16/low p53 status (n=126, 81%) were more likely to be female, have better performance status, and have smaller tumors. Four-year OS for patients with high p16/low p53 vs. other (n=29, 19%) was 88% (95% CI 80-92%) vs. 60% (95% CI 39-75%), log rank p-value <0.0001. On multivariate analysis, high p16/low p53 status was associated with better OS [HR 0.26 (0.14, 0.49), p<0.0001], better DFS [HR 0.47 (0.27, 0.82), p=0.0075], and lower risk of LRF [HR 0.46 (0.21, 0.99), p=0.049].

In this biomarker analysis, high p16/low p53 tumor status was associated with better clinical outcomes in this subset of patients with anal cancer treated with CRT on RTOG 98-11. Further exploration of the optimal diagnostic cut-point should be further evaluated. Differential treatment strategies could be considered for patients with these distinct tumor subtypes.

**Aim 2:** Completed in a previous period.

**Aim 3:** No progress to report for this period.

**Aim 4:** No progress to report for this period.

**Aim 5:** Statistical analyses were done, an abstract of the results was presented at the 2014 ASCO GU Annual Meeting and are summarized below.

Bladder preserving combined-modality therapy for muscle-invasive bladder cancer (MIBC) includes transurethral resection and concurrent chemo-RT given in two phases. After the induction phase with chemotherapy and radiation (chemo-RT) to 40 Gy the tumor response is assessed by cystoscopic biopsies and urine cytology. Early salvage cystectomy is promptly offered in case of persistent disease, otherwise patients proceed to consolidation chemo-RT to 64 Gy. The two most recent RTOG protocols 9906 and 0233 allowed patients with near-complete response (Ta or Tis) after induction chemo-RT and completed consolidation with a total RT dose of at least 60 Gy. Bladder recurrence, salvage cystectomy rates and disease-specific survival were estimated by the cumulative incidence method, and bladder-intact survival and overall survival by the Kaplan-Meier method.

A pooled analysis was performed on 119 eligible patients with MIBC enrolled on RTOG trials 9906 and 0233, who were classified as having a complete (T0) or near-complete (Ta or Tis) response after induction chemo-RT and completed consolidation with a total RT dose of at least 60 Gy. Bladder recurrence, salvage cystectomy rates and disease-specific survival were estimated by the cumulative incidence method, and bladder-intact survival and overall survival by the Kaplan-Meier method.

Among 119 eligible patients, 101 (85%) achieved T0 and 18 (15%) achieved Ta or Tis after induction chemo-RT and proceeded to consolidation. After a median follow-up of 5.9 years, 36/101 (36%) T0 patients vs. 5/18 (28%) Ta or Tis patients experienced bladder recurrence (p=0.52). Fourteen patients among complete responders eventually required late salvage cystectomy for tumor recurrence, in comparison to one patient among near-complete responders (p=0.47). Disease-specific, bladder-intact and overall survivals were not significantly different between T0 and Ta/Tis cases.
There is no apparent difference in the bladder recurrence and salvage cystectomy rates between complete and near-complete responders as judged at the time of cystoscopic evaluation after induction phase of bladder preserving CMT. It is appropriate to recommend that patients with Ta or Tis after induction chemo-RT continue with bladder-sparing therapy.

**Research Project 2: Project Title and Purpose**

*Development and Evaluation of Novel Methods for Cancer Clinical Trial Interim Monitoring* – Clinical trials provide first line scientific evidence necessary to advance treatment for cancer. With the increasing number of new treatment options being tested, there is a need for improvements in trial design and monitoring in order to a) terminate a trial in a timely manner when the therapy is ineffective, b) plan activities that take place during the trial efficiently (for example, interim safety and efficacy analyses), and c) derive and apply trial stopping rules and statistical power estimates that realistically reflect the interim data structure. To address these needs, we propose a series of methodological projects aimed at addressing current questions in clinical trial monitoring. These projects encompass a range of challenges in clinical trial conduct that apply broadly to cancer research as well as clinical research in general.

**Anticipated Duration of Project**

7/1/2012 – 12/31/2015

**Project Overview**

Three specific investigations are proposed as follows:

*Aim 1: Comparison of futility monitoring methods using oncology trials:* Futility monitoring is an important component in the conduct of clinical trials. An optimal rule would allow timely stopping if the new therapy is harmful or is unlikely to ultimately prove effective. Commonly used methods for futility monitoring include conditional power (CP) boundaries, repeated confidence intervals (RCI, adjusted for multiple looks), testing to reject the alternative hypothesis, and the recently proposed linear inefficacy boundary (LIB20). We will evaluate and compare the performances of these methods, using event histories from completed clinical trials of the Radiation Therapy Oncology Group (RTOG) and other cooperative groups.

*Aim 2: Prediction of landmark event times in oncology trials:* In clinical trials with planned interim analysis, it can be valuable for logistical reasons to predict the times of landmark events such as the 50th and 100th event. Parametric (for example, Exponential, Weibull) models and nonparametric methods have been proposed for this purpose and these work well in simulation studies. However, the performance of these approaches has not been fully evaluated in real clinical trials. For this analysis, we will apply these prediction models to data from RTOG oncology trials with time to event as an outcome. These methods when applied to ongoing clinical trials will be useful tools for planning interim analyses and Data Safety Monitoring Board (DSMB) meetings.

*Aim 3: Repeated confidence intervals and prediction intervals under fractional Brownian motion*
for stochastically curtailed tests: The repeated confidence interval (RCI) approach is an important method for sequential monitoring of clinical trials. Stochastically curtailed tests (SCT) also known as conditional power is another common approach. These methods are based on Brownian motion (BM) assumption, which is a special case of fractional Brownian motion (FBM). However, it is possible that the interim statistic is an aggregated process of many different processes. Therefore, the future path will depend on both the past and current interim statistics. For these cases FBM is a good sensitivity measure to see if the observed processes deviate from BM and adjust the design accordingly. For this project we will derive RCIs based on SCTs under FBM and investigate the impact on sample size and design characteristics.

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Barry Davis, MD, PhD; Dejian Lai, PhD – employed by the University of Texas

Expected Research Outcomes and Benefits

Clinical trials are a critical step in the search for effective therapies of cancer as all reliable treatment options arise through this process. However, the process can be slower than desired if, for example, a futility monitoring method is unable to stop a trial when interim results are showing inefficacy of the new regimen; or, due to lack of accurate and precise method of predicting event times, DSMB meetings and trial closeout cannot be planned and scheduled efficiently. Clinical trials are process intensive, and most importantly require the greatly valued contribution of patient participants, who are seeking the best possible option for their personal situation, while at the same time contributing to research. A more efficient treatment evaluation strategy and logistic planning could improve both knowledge acquisition and patient care. Lastly, common assumptions for interim analysis tools need to be verified during actual trial conduct and adjusted if the conditions are not satisfied to guarantee enough statistical power to detect the expected treatment effect of the new therapy. We propose three areas of research that have immediate practical implications for cancer clinical trials. Comparing and selecting the optimal futility boundary will lessen patients’ exposure to inactive treatment, improve resource utilization, and accelerate dissemination of important clinical information. Decisions regarding whether to continue or terminate a trial will be made more timely and efficiently if interim analyses and DSMB meetings take place at the accurately predicted event times. And finally, results on impact of deviations from design assumptions will inform investigators the importance of assessing these conditions and provide necessary tools for realistic clinical trial design and
monitoring.

Summary of Research Completed

**Aim 1: Comparison of futility monitoring methods using oncology trials**
During the past year, we have had further discussions with three other cooperative groups funded by National Cancer Institute (NCI) concerning potential trials to be included in this analysis for aim 1. From the National Surgical Adjuvant Breast and Bowel Project (NSABP), we examined eight large trials for breast cancer (N=5) and colon cancer (N=3). We conducted interim analyses for 20 comparisons/trials from the Mayo Clinic using tested SAS programs. From CALGB, we collected interim results from a total of fourteen trials with survival outcomes. While compiling data for a total of about 70 comparisons/trials, we did further analyses of Radiation Therapy Oncology Group (RTOG) and NSABP studies (~28 trials/comparisons), and the savings on sample sizes, information time and trial duration (when these trials were stopped according the protocol’s stopping rules) are summarized in tables 1, 2, 3. These show that the LIB20 method yields more savings on sample sizes and time.

**Aim 2: Prediction of landmark event times in oncology trials**
From the preliminary results of 3 prediction approaches, it is clear that the exponential and Weibull models predicted poorly for the landmark dates, particularly for the prediction of time to reach the 206th and 303rd death. From 07/01/2013 to 06/30/2014, we primarily focused on developing a Weibull cure-mixture model, which could accommodate the cure probability from treatments. We also applied this Weibull cure-mixture model to the RTOG 0129. The description of Weibull cure-mixture model and the prediction results from Weibull cure-mixture models is described below.

The mixture cure model assumes that the study subjects are a mixture of susceptible (uncured) individuals, that may experience the event of interest, and non-susceptible (cured) individuals, that will never experience event. Let U be the latent indicator of whether an individual is susceptible (U = 1) or non-susceptible (U = 0) to the event of interest and T is a non-negative random variable denoting the time to event time of interest, defined only among the susceptible subjects (U=1). The mixture cure model is given by $S(t|x, z)=\pi(z) * S(t|U=1, x) + 1- \pi(z)$, where $S(t|x,z)$ is the unconditional survival function of T for the entire study population, and $S(t|U=1, x)$ is the survival function for susceptible subjects given a covariate vector x. $\pi(z) = P(U=1|z)$ is the probability of being susceptible given a covariate vector z, which may share some common covariates as x. The survival function of cured subjects can be set to 1 for all finite survival time t, because cured subjects will never experience the event of interest. Of note, when $t \rightarrow \infty$, $S(t|x, z) \rightarrow 1- \pi(z)$, and when $\pi(z)=1$ for all $z_i$ (i.e., when there is no cured fraction), the mixture cure model reduces to the standard survival model. We assume cure probability can be modelled by the binary logistic regression. Among the uncured subjects, the time to event follows two-parameter Weibull survival model with $S(t) = \exp(-\beta t^\alpha)$, where $\alpha$ is shape parameter, and $\beta$ is scale parameter. We further assume that the survival function and cure probability varies with treatment groups. For simplicity, we do not consider any other covariates in the either the logistic regression model or Weibull survival model. Results of the predictions are shown in figures 1 and 2 below. For the prediction of 206th death, the Weibull mixture cure prediction model underpredicts the time to reach 206th death, but it performed better than standard Weibull prediction.
model. For the prediction of 303rd death, the Weibull cure-mixture prediction model substantially outperformed the standard Weibull prediction model.

**Aim 3: Repeated confidence intervals and prediction intervals under fractional Brownian motion for stochastically curtailed tests**

Based on the results of Davis and Hardy (1992), Zhang (2011) and Zhang, Lai, Davis (2012), we finished R programming for the computation of stopping boundaries under fractional Brownian motion and stochastic curtailment. For a total of ten interim analyses, we present ratios of RCI when the Hurst parameter is not equal to 0.5 in table 4. Same values from well-known designs such as those of Pocock and O’Brien-Fleming are also compared with respect to repeated confidence intervals.

The impact of the different number of interim analyses and type I and type II error rates are also studied in table 5. We can see these RCIs are more conservative than the Pocock and OBF designs and the Hurst parameter impact RCI width when it deviates from 0.5. We have chosen to use the Beta Blocker Heart Attack Trial (BHAT) as an example to illustrate how to apply these design methods.

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Table 3. Trial time saved, 3 looks.

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Table 4. Ratios of RCI width for different designs with ten interim analyses

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* Ratios are to that of a fixed design.
Table 5. Ratios of sample sizes for different number of interim analyses, alpha=0.1

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* The ratios are between sample sizes of designs using RCIs based on SCTs, Pocock and OBF design types and a fixed sample size design with type II errors of 0.2 and 0.1.

Figure 1: Prediction of 206th death using nonparametric, standard Weibull and Weibull cure-mixture models
Research Project 3: Project Title and Purpose

*Biological Modeling of Tumor Control and Normal Tissue Complication for NSCLC Treated with SABR* – Hypo-fractionated stereotactic ablative radiation therapy (SABR) is currently being used to treat early stage non-small cell lung cancer patients. The responses of tumor and nearby critical structures to SABR may be quite different from that of the conventional radiation therapy (RT) for which dose and radiobiological parameters for tumor control and toxicities of critical organs have been accumulated over the past two decades. Such parameters are still sparse and far from consensus for SABR treatment for lung cancer. The purpose of this study is to establish clinically useful nomogram for dose tolerance parameters and model the biological parameters for tumor control and normal tissue complication based on institutional data for hypo-fractionated lung SABR.

Anticipated Duration of Project

1/1/2012 – 12/31/2015
Project Overview

Three specific sub-projects are proposed as follows:

Aim 1: Establish a web-based software system to manage and evaluate patient clinical data, dose delivery and treatment outcomes for NSCLC patients treated with hypofractionated stereotactic ablative radiation therapy across institutions: The core of the system software used in this project is a database that will store patient data. It will allow for a systemic integration of data for each patient as well as for all patients. As for the former, data of various provenances as Digital Imaging and Communications in Medicine—Radiation Therapy (DICOM RT) files or treatment outcomes will be available for each patient. This software system provides data-mining capability since it can seek emergent properties as derived from the entire content of the database. Each patient is quantum of information in a space of all treatment outcomes. Treatment outcomes of all accrued patients will be mapped back to their treatment plans.

Aim 2: Establishment of correlation between the dosimetric characteristics of treatment plans obtained with various dose computation algorithms and treatment outcome: Various dose engines exhibit different accuracy of calculation. The database will store all dose distributions resulted from these different dose engines and identify the most accurate dose distributions, which in turn will be equated with dose delivered during treatment. Software system will allow for turn-on key calculation of these dosimetric parameters that can be correlated to individual patient treatment outcomes. Moreover, the dosimetric parameters of all accrued patients with their treatment outcomes will be analyzed as a population-based data. This analysis will be implemented as one of the functionalities of the software system.

Aim 3: Establishment of correlation between biological characteristics inherent to treatment plans and treatment outcomes: Biologically-based characteristics of each treatment plan as is the case for their dosimetric characteristics are fixed after the plan is approved and the course of radiation treatment completed. Based upon the dosimetric data and treatment outcomes, biological parameters for tumor control and normal tissue complication will be derived. From these parameters and treatment outcomes, a clinically useful nomogram for dose tolerance parameters will be developed.

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Expected Research Outcomes and Benefits

The proposed methodology utilizes the current state-of-the-art medical informatics approach to investigate the combination and consolidation of patient data and outcome results. This type of study explores emergent features, which can only be derived from a consolidated approach to data, i.e., the sought results and conclusions would not be obtained looking and evaluating all data components separately. It combines data from various sources and stores data under unique patient key in database. Clinically-driven data mining will expose patterns of dose distributions and resulting treatment outcome and will connect it with biological modeling of the treatment parameters. This will help establish a clinically useful nomogram for dose tolerance parameters and model biological parameters for tumor control and normal tissue complications. This knowledge cannot be acquired otherwise since the discovery of the correlation calls for a consolidated approach as described in this project. Data as saved in an electronic patient record (ePR) for this SABR-based database is always accessible and can be retrieved and processed in the future if new developments warrant. The quality of the results clearly will depend on the number of patients accrued in the system. We have treated over 700 non-small cell lung cancer (NSCLC) patients with SABR during the past 10 years. This along with a busy SABR program in our clinic guarantees dependable influx of patients for such processing. The nomogram to be developed in this project is expected to provide personalized adaptive management of NSCLC patients. The database will also allow for quantification of efficacy of SABR.

Summary of Research Completed

We have prepared a poster abstract of results from this grant for the American Society for Radiation Oncology (ASTRO) 56th Annual Meeting at the Moscone Center in San Francisco, CA. The abstract is titled “A free multi-model program for comparing linear-quadratic and non-linear quadratic models in TCP prediction of SABR-treated NSCLC” with authors Kang J, Zhang Y, Clump DA, Flickinger JC, Li X, Huq M. Saiful.

In the previous reporting period (July 1, 2012-June 30, 2013), the Principal Investigator used the Radiation Oncology Data Miner software provided by Charles Mayo, Ph.D., (Mayo Clinic, Rochester, Minnesota) to predict tumor control probability (TCP) and normal tissue complication probability (NTCP) on a 28 patient dataset. At that time, we were not able to compare our predictions to treatment outcomes; however, during this project period, we were able to analyze this data. During this project period July 1, 2013-June 30, 2014, we developed in-house code written in MATLAB (Mathworks, Inc.) whose output is TCP and NTCP for early stage NSCLC. The input is an individual patient’s DVH treatment plan (Fig. 1).

The impetus for developing our in-house code is that there has been extensive debate over the appropriateness of the linear quadratic (LQ) model for calculating Biologically Effective Dose (BED) for hypofractionated doses (typically >~17 Gy/dose) as discussed in two separate “point-counterpoint” articles by Brenner and Marks in 2008 (Semin Radiat Oncol) and Kirkpatrick and Brenner in 2009 (Medical Physics). This debate stretches back to at least 1995 in a letter to the editor by Marks in the Red Journal.
Our in-house code is a novel, easily-modified pipeline (Fig. 2) built in the “de facto” radiotherapy MATLAB that predicts tumor control probability (TCP) and normal tissue complication probability (NTCP) for an LQ and non-LQ models. Currently the code supports BED calculations using the Linear Quadratic model (Fowler 1976), the Universal Survival Curve (Parks 2008) and the Linear-Quadratic Linear model (Astrahan 2008).

The details of our MATLAB based-system that interfaces with DVH files from our treatment planning system (TPS) are as follows. Using initial parameters from the literature, we calculate BEDs for the linear-quadratic (LQ), linear-quadratic-linear (LQ-L), and universal survival curve (USC) formulations. For the LQ model, we use $BED_{LQ} = n_f d \left(1 + \frac{d}{\alpha/\beta}\right)$ where $\alpha/\beta = 10$, number of fractions $n_f = 4$, and dose-per-fraction $d = 12$ Gy. For LQ-L, we used $BED_{LQL} = nd_T \left(1 + \frac{d_T}{\alpha/\beta}\right) + n(d - d_T) \left(1 + \frac{2d_T}{\alpha/\beta}\right)$ where the LQ-L threshold dose $d_T = 11$ Gy. For USC, we used $BED_{USC} = \frac{1}{\alpha D_0} \left(D - d_q\right)$ for the high dose fractions (threshold $D_T = 6.12$ Gy) where $\alpha = 0.33$ Gy$^{-1}$, $D_0 = 1.25$ Gy and $D_q = 1.8$ Gy. We then calculated corresponding EUDs for the three BED formulations and use them in Niemierko’s TCP model, $TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{1+\gamma_{50}}}$ where we used $\gamma_{50} = 1.2$ and $TCD_{50} = 65.2$ Gy for 12 month local control in NSCLC.

We piloted our model with 41 patients with early-stage central NSCLC treated with SABR consisting of 48 Gy over 4 fractions. Their treatments were planned using our TPS and their DVHs were exported into MATLAB and processed as described previously. Using the gross tumor volume DVH, the average TCP among 41 patients calculated using LQ is 83.1±6.5%, LQ-L is 80.9±7.4%, and USC is 79.1±6.0% where the ranges represent 95% confidence intervals. The true 12-month local control rate for this cohort is 88.6% (Fig. 3).

In summary, our software system takes DVH files as inputs to determine TCPs based on different assumptions for LQ/non-LQ cell killing in SABR-treated early-stage central NSCLC. Using a small pilot dataset, we see that our local control estimates are within a reasonable range of actual probability. We plan to increase our data set size, incorporate parameter optimization, and validate our model on a different fraction schedule consisting of peripherally-treated 30 Gy x 3 NSCLC patients.

Here are the milestones completed during this past reporting year, 7/1/2013-6/30/2014:

**Aim 1: System development and data collection**
- Patient enrollment for treatment with different prescription dose. (Also for Aim 2)
  - Status – completed (we have 12Gy x 4 and 30Gy x 3 data)

**Aim 2: Development of relationship between dose parameters and treatment outcomes**
- Conduct analyses of LQ vs. non-LQ for BED calculations and submit abstract for presentation and national meeting
  - Status – abstract was submitted and accepted at the American Society for Radiation Oncology (ASTRO) annual meeting in September 2014.
- Conduct more analyses of dose parameters obtained from the various dose calculation algorithms, such as pencil beam convolution algorithm and anisotropic analytical algorithm, different dose scheme, and from different treatment modalities.
  - Status – in progress

**Aim 3: correlate radiobiological characteristics in treatment planning to outcomes**

- Compare linear quadratic (LQ) and non-LQ models to calculate tumor control probability (TCP) for NSCLC and correlate with treatment outcomes
  - 12 Gy x4 schedule status – completed
  - 30 Gy x3 schedule status – in progress

- Compare linear quadratic (LQ) and non-LQ models to normal tissue complication probability (NTCP) for organs at risk (OAR) and correlate with treatment outcomes
  - 12 Gy x4 schedule status – in progress
  - 30 Gy x3 schedule status – in progress

![Graphs showing continuous and differential DVH](image)

**Fig. 1**: representative patient showing continuous DVH (left) and differential DVH (right). The differential DVH is essentially a derivative of the continuous DVH.
Fig. 2: Pipeline to convert dose volume histogram to tumor control probability and normal tissue complication probability. In our system, we can (1) input dose volume histograms (DVH) from multiple patients; (2) retrieve initial parameters from published data; (3) calculate biologically effective doses (BED) and equivalent uniform dose (EUD) for LQ/non-LQ models; and (4) calculate NTCP/TCP based on each model.
Research Project 4: Project Title and Purpose

Quantitative Uncertainty Investigations for Clinical Trial Protocols – There are many factors that can confound the interpretation of results from cancer clinical trials that use radiation for therapy. Focus on such factors increases when a study gives an unexpected result that is counterintuitive. This was the case for a recent Radiation Therapy Oncology Group (RTOG) protocol, #0617 for Non-Small Cell Lung Cancer (NSCLC) where a lower dose arm gave significantly improved survival. The research proposed here examines radiation dose uncertainties that are either intentionally included in the protocol design process to improve accrual, or are unanticipated. Uncertainties for the RTOG 0617 protocol will be carefully analyzed to identify and quantify potential uncertainties.

Anticipated Duration of Project

7/1/2012 – 12/31/2015

Project Overview

Three specific investigations comprise this project:

Specific Aim 1.0 Quantitative uncertainty investigation: Evaluate uncertainties for the radiotherapy processes
Specific Aim 1.1 Structure delineation
Target definition is a major source of errors in radiation treatment. The variability in delineation

![Fig. 3: True tumor control rate compared with tumor control probability (TCP) calculated by LQ, LQ-L and USC.](image)
of targets and critical normal structures has been shown to be highly variable. These variations, in turn, have been shown to have significant impact on dosimetric and radiobiological outcome. These variations will be quantified and their impact on treatment outcome will be simulated. Special attention will be paid to the process of image fusion, and the impact of this technique on accurate target delineation.

Specific Aim 1.2 Radiotherapy treatment planning
At least two components of treatment planning can produce major uncertainties for the radiotherapy process. First, variations can be introduced when the dose prescription is adapted for use in a clinical trial that is multi-institutional. Second, dose calculation, and plan optimization processes can introduce uncertainties. This sub aim will identify and model uncertainties associated with the treatment planning process.

Specific Aim 1.3 Radiotherapy delivery
Significant variations in the dose delivery step of the process have been reported to have discernable impact on treatment outcome. Examples are uncertainties in the equipment dose calibration and the possibility of delayed or deleted treatments. These variations will be quantified and simulated for inclusion in outcome predictions.

Specific Aim 1.4 TCP/NTCP and outcome model uncertainty
Techniques for modeling of Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) remain crude. Thus, differences between the outcome modeling methods used to analyze the data is another major variation. The various models emphasize different aspects of the input data. These uncertainties will be quantified as part of this research.

Specific Aim 2.0 Propagation of uncertainties to outcome
Strategies will be developed to combine the uncertainties derived from the investigations of specific aim 1 to the eventual outcome.

Specific Aim 3.0 Application of modeling to the RTOG 0617 protocol
The model for uncertainty propagation will be applied to the example of the unexpected results for the RTOG 0617 protocol.

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Adam Dicker, MD, PhD; Yan Yu, PhD – employed by Jefferson Medical College
Expected Research Outcomes and Benefits

Evidence-based medicine has become the foundation of radiation oncology development. There are different levels of evidence upon which radiation therapy practice is based. The quality of the evidence depends significantly upon any variance for the individual chain of steps for the different techniques upon which the evidence is based. Radiation therapy consists of a large number of such stepwise processes, each of which poses variance/uncertainty that impact upon the final outcome, such as survival or quality of life.

In this project, we will identify and investigate the uncertainties associated with radiotherapy processes. These uncertainties will be propagated to affect the outcome predictions, using appropriate mathematical algorithms. We will collaborate with experts in the fields of computational/mathematical modeling.

The preliminary results from RTOG #0617 protocol comparing high-dose (74 Gy) with standard-dose (60 Gy) radiotherapy for treatment of non-small cell lung cancer were unexpected in that survival for the low-dose arm was significantly improved. This difference was not accompanied with any identifiable difference in radiation toxicity. This unexpected result might be explained by the propagation of uncertainties that could, in effect, decrease the stated prescribed dose differences. Investigation of this unexpected result will serve as an example of the use of the modeling techniques developed in this research project. This investigation is critically important for informing the design of subsequent similar trials. We plan to study uncertainties associated with all the processes of the trial, and quantify these uncertainties and their impact upon the outcome.

Summary of Research Completed

Specific Aim 1.1 Structure delineation

While investigating the uncertainties in structure delineation, the team also attempted to validate a quality assurance tool for cardiac structure delineation. The efforts yielded a publication level paper and several abstracts. The abstracts are as follows.

Abstract 1: Variation of cardiac contours using different heart definitions for NSCLC patients enrolled on RTOG 0617

Purpose: In lung cancer radiation therapy, excess heart dose has been shown to impact overall survival. Precise heart contouring is crucial to accurate assessment of heart dose. However, heart contouring is a challenge due to motion, heart to blood vessel transition, and distinguishing pericardium from heart. Thus, it is important to investigate how heart contours drawn using different definitions can affect dosimetric evaluation.

In the NSCLC trial RTOG 0617, 74Gy was not superior to 60Gy. Dosimetry for various normal tissues is of intense interest and, with respect to heart dosimetry, may have affected the trial’s outcome. In this secondary analysis, we investigated the difference between submitted heart contours and recontours by radiation oncologists using a single atlas developed following the
Materials/Methods: Treatment plans for 478 cases submitted by 200+ institutions were evaluated. Following completion of the trial, 5 experienced thoracic radiation oncologists collectively contoured the pericardium for each case, guided by a common atlas. The recontoured volumes were inclusive of the pericardium. Geometric and dosimetric comparisons of these recontours with the original heart contours were performed.

Results: The volume (mean 883.7 ± 218.8 ml) of new heart contours was on average 46.1% larger than original heart contours (mean 646.2 ± 219.0 ml). The average Dice coefficient between the contours was 0.81 ± 0.10; the average Hausdorff distance was 38.8 ± 14.5 mm. Heart V_{5Gy}, V_{10Gy} - V_{65Gy}, mean, maximum dose were calculated. The new contours had higher normalized volume V_x than the original at any selected dose level (Table 1).

Conclusions: The results show that original heart contours had lower volumes and doses with respect to those drawn using the heart atlas and underscore the importance of using a heart atlas prospectively to improve quality assurance of RT delivery. This dataset will be used to develop heart DVH constraints for subsequent NRG Oncology lung cancer protocols.

Abstract 2: Inter Observer Variability In Esophageal Contours For Patients With Non-small Cell Lung Cancer Treated With Definitive Chemoradiotherapy: RTOG 0617 Experience.

Purpose: RTOG 0617 study randomized more than 544 patients with locally advanced non-small cell lung cancer (NSCLC) to receive standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab. 74 Gy was not superior to 60 Gy in terms of overall survival and local-regional control. Factors predictive of less favorable overall survival in multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume >5 Gy. The authors believe that excess esophageal dose may be a vital component influencing the overall outcome in the high-dose arm. The purpose of this analysis was to determine the inter-observer variability and its impact on esophageal doses.

Materials and Methods: CT scans of randomly selected 35 patients accrued in RTOG 0617 clinical trial were loaded into MIM without any structures and dose. The esophagus was delineated by an experienced thoracic radiation oncologist independent of submitted contours. The external circumference of the esophageal wall was contoured for the new esophageal volumes. Geometric and dosimetric comparisons were performed between the original submitted esophageal contours and new contours. The two esophageal volumes sets were compared using Dice coefficients. Mean, maximum radiation dose and the specific radiation doses to different esophageal volumes \[V_{35Gy}(\%), V_{50Gy}(\%), V_{60Gy}(\%), \text{ and } V_{70Gy}(\%\)] were also calculated.

Results: The original submitted esophageal volumes ranged between 15.9 and 72.6 cc with average volume of 36.4 ± 14.7. The newly contoured esophageal volumes ranged between 26.03 and 83.48 cc with average volume of 43 ± 15 cc. The Dice coefficients ranged between 0.36 and 0.84 with a median value of 0.75. The average Dice coefficient was 0.72 ± 0.11. The original submitted esophageal volumes were significantly different when compared with the newly esophageal volumes (P = 0.016). Most of the difference was based on the length of the esophagus contoured. These differences in volumes led to differences in the esophageal doses, with the relative differences ranging between: 0 and 25% for \(V_{35Gy}\); 0 and 22% for \(V_{50Gy}\); 0 and 22% for \(V_{60Gy}\); 0 and 18% for \(V_{70Gy}\); 0 and 46% for mean dose and 0 to 15% for maximum dose.

Conclusion: A high inter-observer variability in contouring esophageal volumes was observed; these differences led to different esophageal dosimetric parameters. Further work including
multiple observers and a larger group of patients is planned. We will also use esophageal dose-volume and fractionation characteristics to compare and validate predictors of radiation esophagitis.

Abstract 3: A New Quality Assurance Tool For Radiotherapy Structure Delineation: Atlas-based Automatic Segmentation (ABAS) Of Cardiac Structures For Non-small Cell Lung Cancer From RTOG 0617

Purpose: To evaluate the feasibility of the ABAS for the automatic delineation of cardiac structures (pericardium, atria, ventricles) when compared with the manually contoured cardiac structures. Furthermore, we explored using the ABAS contouring as a quality assurance (QA) tool.

Methods and Materials: In order to quantify the interobserver variation of contouring, four experienced thoracic radiation oncologists independently delineated the cardiac structures (pericardium, atria and ventricles) for each of the same 17 patients, blinded to submitted contours from institutions, following a consistent guideline. For each patient, an overlap and a merge of the contours by the four experts were generated. The mean and max width between the overlap and merge contours were calculated.

The ABAS library is constructed using a total of 100 such recontoured cases, 20 from each oncologist, using commercially available software (MIMvista Corp., Cleveland, OH). The atlas template voxel size was 3×3×3mm3. The ABAS library was then used to generate contours for 469 cases. To quantify the precision of the automatically delineated cardiac structures using ABAS, they were compared with the manually delineated structures from experts. The discrepancies between the manual and automatic contouring were evaluated for 469 cases, and the Dice Similarity Coefficient (DSC), Jaccard Index (JI) and Housdorff Distance (HD) between the two types of contouring were calculated for geometrical comparisons. The fractional volume dose factors, (VD’s, D= 5, 15, 25, 35, 45, 55 Gy) were calculated for pericardium, for dosimetric comparison. To test the feasibility of using the ABAS for quality assurance, we used 373 patient cases with heart contours that resulted in a discrepancy of more than 5% in mean heart dose. DSC between the test and ABAS contours were calculated. We tested the sensitivity of three different thresholds of DSC for picking out these discrepant contours.

Results: For interobserver variations, the mean width is 4.5±1.0 mm for pericardium, 7.5±0.9 mm for atria, 5.7±1.5 mm for ventricles. The max width is 21.3±5.0 mm for pericardium, 27.5±4.2 mm for atria, 27.0±7.7 mm for ventricles.

The geometrical study results were shown in Table 2. There is minimal difference between different VD’s for automatically and manually delineated pericardium contours. Using threshold value of 0.86, 0.87 and 0.88, the rate with which we can pick out discrepant contours is 0.85, 0.90 and 0.93, respectively.

Conclusions: ABAS demonstrates great potential to accurately delineate the cardiac structures automatically, and it is feasible to be used for cost-effective QA for clinical trials.

Specific Aim 1.2 Radiotherapy treatment planning

Abstract 4: Treatment Plan Quality Assurance for RTOG 0621 with Knowledge Engineering

Purpose: To report on the treatment plan quality of cases submitted for RTOG 0621. To use the knowledge-guided treatment planning tool to predict the best achievable plans for organs-at-risk (OARs) sparing. We hypothesized that this tool will aid in improving radiation plan quality for
cooperative group trials.

Methods: The dosimetric data from 80 cases submitted for RTOG 0621, a phase II post-prostatectomy adjuvant radiation trial, were evaluated against the criteria specified in the protocol. The knowledge-guided treatment planning tool was used to predict best achievable plans and to evaluate whether we can improve the plan quality indices. This tool was developed from the evidence-based approach by learning from a database of 88 high-quality prior prostate IMRT plans. The anatomical features of the PTVs and OARs and their spatial relationships on OARs dose sparing variation were modeled by the multiple regression method. The DVHs were analyzed and tested against the protocol criteria. For cases failing the criteria we implemented the knowledge-guided treatment planning tool on their dicom data and obtained the best achievable DVHs’ ranges which was checked against the criteria.

Results: Of the 80 submitted cases (10 cases used 3DCRT technique and 70 used IMRT), 72 cases (90%) met per protocol/variation acceptable criteria for target coverage, 66 cases (83%) for OAR sparing. We used the knowledge-guided treatment planning tool to predict the best achievable OARs dosimetric values. For the 14 cases that failed OAR criteria, 72% improved to per protocol, 14% improved to variation acceptable and 14% still deviation unacceptable. All dosimetric values improved except in one 3D and one IMRT cases for bladder V50Gy criterion. In summary, of the 14 cases having deviation unacceptable, 12 of them were improved to variation acceptable or better.

Conclusion: We reported good dosimetric plan quality for cases submitted for RTOG 0621. The knowledge-guided treatment planning tool can be used to guide improvement of treatment plans in future clinical trials.

Specific Aim 1.4 TCP/NTCP and outcome model uncertainty

The team has calculated the equivalent uniform dose (EUD) of the target volumes for all patients. The team is still investigating a good way to study the outcome model uncertainty.
Table 1. Different dose parameters for original and new contours

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<th>$V_{30\text{Gy}}$ (%)</th>
<th>$V_{45\text{Gy}}$ (%)</th>
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Table 2: Geometrical Comparison Results for Cardiac Structures

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<td>Ventrical</td>
<td>0.83±0.08</td>
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Research Project 5: Project Title and Purpose

Arterial Stiffness and Wave Reflections as Determinants of Regression of Left Ventricular Hypertrophy and Fibrosis Assessed with Cardiac MRI After Aortic Valve Replacement for Severe Aortic Stenosis – This project will evaluate the importance of arterial stiffness and wave reflections as determinants of persistent left ventricular (LV) hypertrophy and fibrosis (assessed using cardiac magnetic resonance imaging [MRI]) after correction of severe stenosis (tightness) of the aortic valve. We aim to test the hypothesis that stiff arteries and increased wave reflections impede pumping of blood by the LV after aortic valve replacement and prevent adequate regression (improvement) of hypertrophy and fibrosis of the myocardium despite correction of aortic valve stenosis. Proof of hypothesis would identify potentially treatable abnormalities identifiable on imaging for future targeted therapy. This project also will assess the value of a novel cardiac MRI sequence to characterize myocardial fibrosis without the use of gadolinium.
Anticipated Duration of Project

1/1/2012 – 12/31/2015

Project Overview

Previous C.U.R.E. funding established a network of academic medical centers in Pennsylvania (ACRIN PA) with the broad goal of advancing the role of imaging in the detection and/or treatment of disease by conducting early stage imaging clinical trials. This project seeks to continue the work of that network. This multi-institutional project will prospectively evaluate potential determinants of the regression (improvement) of left ventricular hypertrophy and fibrosis assessed by cardiac MRI before and after aortic valve replacement (AVR) for severe aortic stenosis. We will enroll 80 eligible participants with severe aortic stenosis who are scheduled to undergo AVR. A gadolinium-enhanced cardiac MRI scan, along with arterial pulse wave recordings and novel non-contrast myocardial tissue characterization sequences (T1rho mapping), will be performed immediately prior to AVR and repeated 6 months after AVR. These data will be used to assess left ventricular mass (LVM), left ventricular myocardial fibrosis, arterial stiffness, and wave reflections. We will test the hypotheses that arterial stiffness and arterial wave reflections are associated with a less pronounced reduction of LVM and fibrosis and with a greater degree of residual fibrosis and hypertrophy despite correction of aortic stenosis via AVR. Importantly, we also will assess the value of T1rho imaging in detecting the degree of myocardial fibrosis at baseline and degree of reduction after AVR, using post-gadolinium T1-mapping as a reference method.

Principal Investigator

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Other Participating Researchers

Scott R. Akers, MD, PhD; Julio A. Chirinos, MD, Walter Witschey, PhD – employed by the Hospital of the University of Pennsylvania

Expected Research Outcomes and Benefits

We expect to demonstrate that arterial stiffness and wave reflections are important determinants of residual left ventricular hypertrophy and fibrosis (adverse prognostic markers assessed with cardiac MRI) after aortic valve replacement. This would identify a novel, potentially treatable mechanism that could be targeted with therapy in future trials and can be assessed by cardiac imaging studies.
We expect to validate T1rho, a novel MRI imaging method that does not require gadolinium contrast, as a technique for the assessment of myocardial fibrosis. This would allow for myocardial fibrosis (an important abnormality that needs to be assessed in several cardiac conditions) to be imaged without the use of gadolinium contrast, which is contraindicated in many patients who have advanced kidney impairment.

**Summary of Research Completed**

**Site Qualification and Study Accrual**

All four participating sites completed qualification and activated on the study during the reporting period. Study enrollment totals 14 subjects as of June 30, 2014 (Table 1 below). Recruitment has proven to be challenging on this study at three of the four sites due to MRI scheduling constraints, competing studies, lower than anticipated volume of aortic valve replacements, and a lack of interest on the part of subjects. However, we are actively implementing strategies to enhance enrollment, including enrolling a cardiothoracic surgeon in the study team at the Penn site. In addition, a fifth site, Lancaster General Hospital, was invited to participate to help boost recruitment; activation is expected this month.

**Technical Challenges**

There were technical challenges to the MRI component of ACRIN 4008 and on the whole, we have overcome those during the past year. The paragraphs below summarize the challenges we faced and the steps to find a solution. The two main challenges we faced were (1) inconsistent software or hardware at different sites and (2) custom sequences.

Inconsistent MRI hardware and software is a common problem with all multi-site MRI studies. Although the study protocol was written to ensure consistency by specifying a single scanner manufacturer (Siemens) with a uniform field strength (1.5T), there were differences in hardware and software. The main issue we faced was to resolve protocol deviations related to differences in hardware or software at two of the five sites (UPMC and LGH) as illustrated in Table 2 below.

The second challenge relates to the custom MRI sequences required to obtain endpoints in the trial. Each of the sequences outlined in Table 3 below required negotiation of research agreements which extended the timeline to activation.

Most of these problems were resolved in January after the study physicist, Walter Witschey, PhD, provided on-site expertise to ensure protocol consistency. The remaining problems are that T1rho and MOLLI are not currently available for VB19 software and DENSE is not compatible with Esprit scanners. As a result, there are protocol deviations at LGH and UPMC which will require additional programming to ensure compatibility.
Table 1: Accrual by Institution

<table>
<thead>
<tr>
<th>Institution</th>
<th>Date Site Opened</th>
<th>Total Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennsylvania State/Hershey Med Ctr</td>
<td>10/24/2013</td>
<td>1</td>
</tr>
<tr>
<td>U Pennsylvania School of Med</td>
<td>07/31/2013</td>
<td>1</td>
</tr>
<tr>
<td>U Pittsburgh Med Ctr</td>
<td>11/04/2013</td>
<td>12</td>
</tr>
<tr>
<td>Veteran Affairs Med Ctr– Phila.</td>
<td>08/05/2013</td>
<td>0</td>
</tr>
<tr>
<td>Total (4 institutions):</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

Table 2: Scanner hardware and software at site in ACRIN 4008

<table>
<thead>
<tr>
<th>Site</th>
<th>Scanner</th>
<th>Field</th>
<th>Software</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philly VA</td>
<td>Avanto</td>
<td>1.5</td>
<td>VB17</td>
</tr>
<tr>
<td>U Penn</td>
<td>Avanto</td>
<td>1.5</td>
<td>VB17</td>
</tr>
<tr>
<td>LGH</td>
<td>Avanto</td>
<td>1.5</td>
<td>VB19</td>
</tr>
<tr>
<td>UPMC</td>
<td>Esprit</td>
<td>1.5</td>
<td>VB17</td>
</tr>
<tr>
<td>Penn State-Hershey</td>
<td>Avanto</td>
<td>1.5</td>
<td>VB17</td>
</tr>
</tbody>
</table>

Table 3: Custom pulse sequences in ACRIN 4008

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Entity</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>DENSE</td>
<td>Siemens</td>
<td>WIP</td>
</tr>
<tr>
<td>MOLLI</td>
<td>Siemens</td>
<td>WIP</td>
</tr>
<tr>
<td>T1rho</td>
<td>Penn</td>
<td>C2P</td>
</tr>
</tbody>
</table>

* WIP = works-in-progress, C2P = customer-2-peer