American College of Radiology

Annual Progress Report: 2007 Formula Grant

Reporting Period

July 1, 2010 – June 30, 2011

Formula Grant Overview

The American College of Radiology received $2,433,581 in formula funds for the grant award period January 1, 2008 through December 31, 2011. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Emerging Imaging Technology Clinical Trials in PA: Coronary CT for Rapid Discharge of Low Risk Patients with Potential Acute Coronary Syndrome - The purpose of this multi-center study in four academic medical centers in Pennsylvania is to evaluate the safety of using coronary CTA (computerized tomography angiography) for rapid disposition of low risk patients who present with chest pain to emergency departments and to further evaluate the effect of a coronary CTA strategy on cost and efficiency of care, as well as on emergency department and inpatient resource utilization.

Anticipated Duration of Project

1/1/2008 - 12/31/2011

Project Overview

A multi-institutional clinical trial is proposed to evaluate prospectively the safety of using coronary CTA for rapid disposition of low risk patients who present to the Emergency Department (ED) with chest pain. Patients will be enrolled at four or more centers throughout Pennsylvania. Each will receive a coronary CTA shortly after ED presentation, along with a single measurement of cardiac enzymes and clinical evaluation for evidence of coronary disease. The trial seeks to evaluate the effect of a coronary CTA strategy on patient outcomes, safety, cost and efficiency of care, as well as on ED inpatient resources.

Principal Investigator

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Other Participating Researchers

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Expected Research Outcomes and Benefits

Coronary CT will allow rapid triage of low and intermediate risk patients presenting to Pennsylvania EDs with chest pain. The majority of patients (>75%) will be eligible for immediate discharge without the need for extended observation and testing. Patients discharged after a negative coronary CT will have a lower rate of adverse events, repeat ED visits and hospital admissions.

A coronary CT based strategy for low to intermediate risk acute coronary syndrome (ACS) evaluation will result in decreased short-term and long-term cost of care for Pennsylvanians, as well as improved utilization of ED and hospital resources. This will result in decreased health care expenditures and improved access to ED and hospital resources for all Pennsylvanians.

Summary of Research Completed

Study Aims
Specific study aims are outlined below for the trial entitled: ACRIN PA 4005: Randomized Controlled Study of a Rapid "Rule Out" Strategy Using CT Coronary Angiogram Versus Traditional Care for Low- to Intermediate-Risk Emergency Department Patients with Potential Acute Coronary Syndromes.

Study Objectives/Specific Aims
In this study, eligible participants with potential ACS will be randomized to traditional "rule out" care (Group A) or a rapid "rule out" strategy comprising CT coronary angiography (Group B).

Primary Aim

3.1.1 To estimate the rate of major cardiac events (AMI or cardiac death) within 30 days in participants in Group B, who were found not to have significant coronary artery disease. "Significant" coronary artery disease is defined as greater than or equal to 50% stenosis of the left main, left anterior descending (LAD), left circumflex, right coronary artery (RCA), or their first order branches.

Secondary Aims

3.2.1 To estimate and compare the rates of significant coronary artery disease detected within the index visit and subsequent workup, in participants across the two study groups.

3.2.2 To compare hospital length of stay across the two study groups. Hospital length is defined as the time interval from the triage time in the Emergency Department to discharge from the hospital.

3.2.3 To compare health care utilization and cost of care in the two study groups during the index hospitalization.

3.2.4 To compare cardiac health care utilization and cost of care in the two study arms during 1 year post randomization. Health care utilization components will include cardiac-related lab tests, diagnostic (imaging) tests, interventions, repeat ED visits for cardiac related problems, and repeat hospitalizations for cardiac pain.

3.2.5 To compare the two study groups in terms of the respective rates of major cardiac events (cardiac death, AMI, and revascularization) within 1 year post randomization, experienced by participants who were not found to have significant coronary disease at the index visit.

Reporting Period Milestone: 7/1/10-6/30/11 Complete enrollment and continue follow up
Accrual continues to be strong on this study and by June 30, 85.2% of the targeted 1365 subjects were enrolled (see Figure 1 below). Extrapolating from existing trends, it is anticipated that accrual will not be completed by the July, 2011 goal, but should be complete by late October/early November. Frequent site calls and biweekly accrual updates are among the efforts used to increase the rate of accrual in the traditionally slow summer months.

The study's primary aim (outlined above) is driven by the 30 day follow up rate which presently stands at 94% for the reporting period. The analysis of the primary aim will be completed and submitted to the Commonwealth on time (February 28, 2012). As noted in last year's report, the one year follow up necessary for analysis of the secondary aims will be incomplete at the end of the funding period. Additional funding has been secured from the ACRIN Foundation to allow complete data collection of the one year follow up time point and the subsequent analysis.

Data Queries
As the trial nears completion, the statistical and data management team are focusing on the data "clean-up", querying the sites for any incomplete data. More than 500 queries have been written based on the nearly 20,000 forms submitted for the study.

Monitoring and Auditing
Site monitoring has been completed at all sites; all five sites received a score of acceptable or acceptable with follow up. Site audits are presently in progress.

Radiation Dose Reporting
One monitoring component calls for the co-Principal Investigator to review radiation doses as reported on the image tags and provide assistance, as needed, to the sites to help ensure the lowest dose while still providing high, diagnostic image quality.

Figures 2 illustrates the dose distribution overall and Figure 3 highlights that the overall average study dose has continued to decrease over time.

Figure 1: Accrual by Institution

Institution	Date Site Opened	Total Accrual
Penn Presbyterian Med Ctr	07/15/2009	127
Pennsylvania State/Hershey Med Ctr	12/01/2009	192
U Pennsylvania School of Med	07/07/2009	687
U Pittsburgh Med Ctr	01/18/2010	42
Wake Forest University	04/26/2010	116
Total (5 institutions):		1164

Note: The four Pennsylvania sites are supported by the C.U.R.E. grant. Wake Forest University in North Carolina is supported by the ACRIN Fund for Imaging Innovation; C.U.R.E. guidelines preclude substantial expenditures outside of the Commonwealth of Pennsylvania.

Figure 2: Radiation Dose Histogram

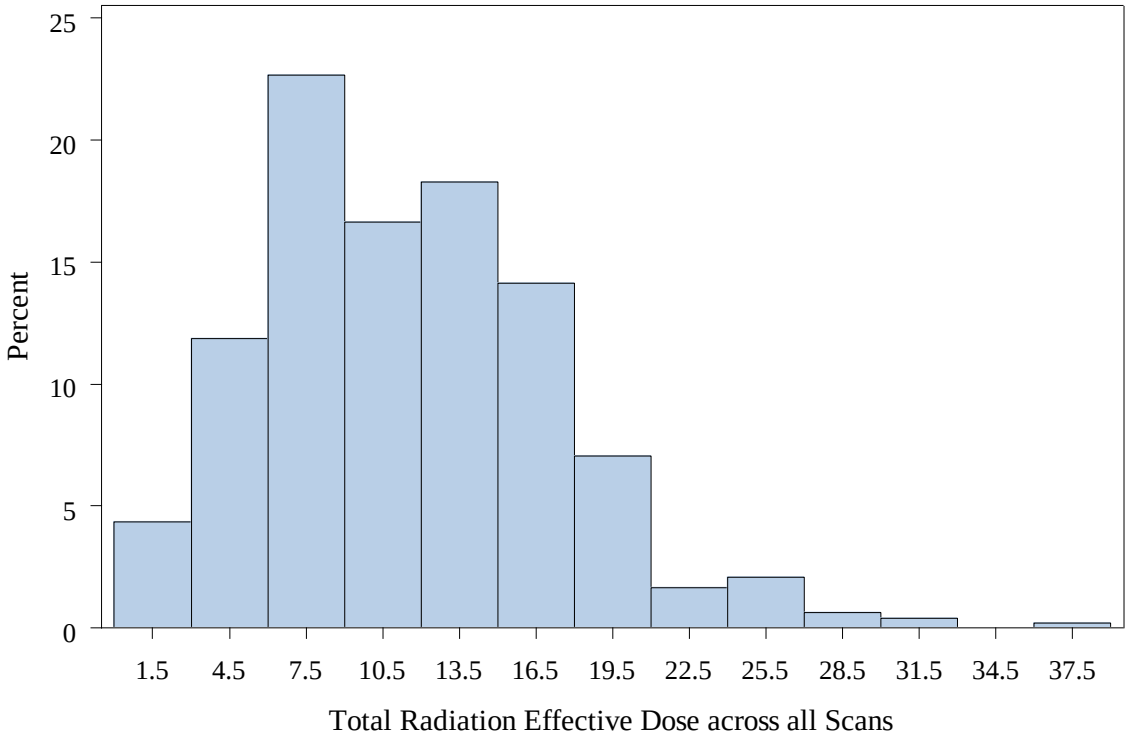
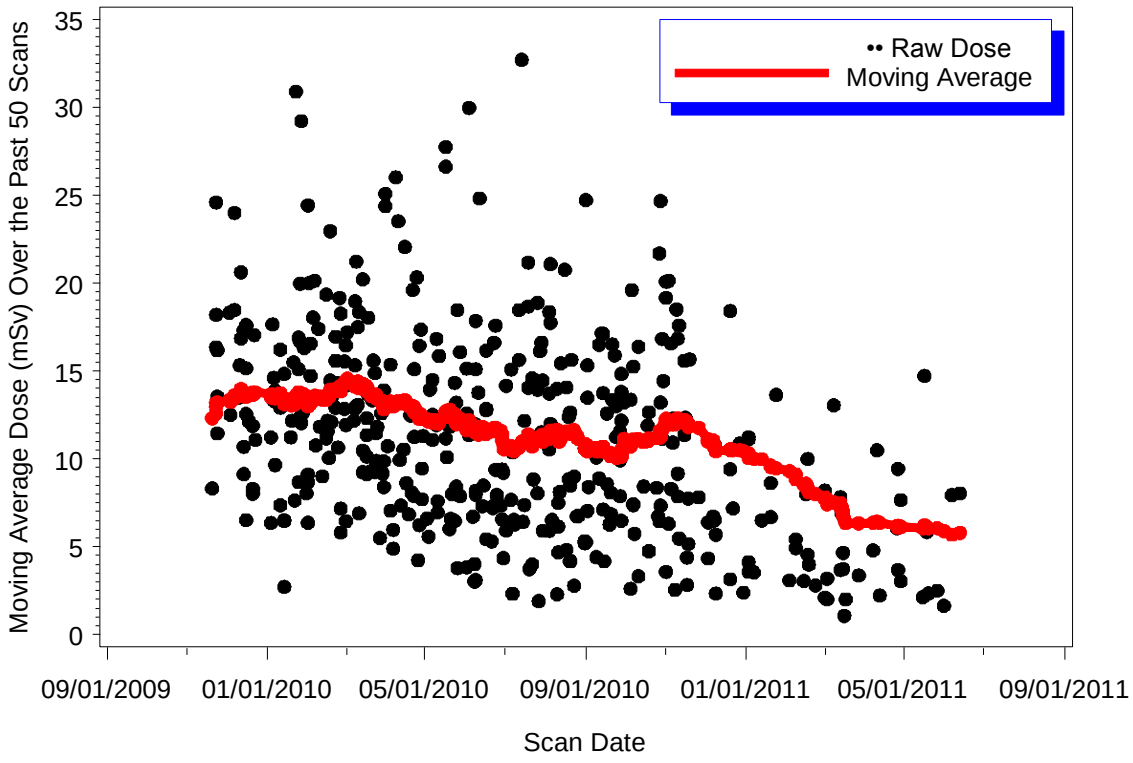


Figure 3: Radiation Dose Over Time

A moving average of dose (mSv) is computed from the prior 50 scans. The average begins once 50 scans are available. The raw dose is plotted as dots.



Research Project 2: Project Title and Purpose

Controlling Patient Dose Resulting from the Use of Frequent Image Guidance in RTOG Protocols - The use of Image Guided Radiation Therapy (IGRT) in clinical trails can increase the dose prescribed in cooperative group protocols. Additionally, the imaging can increase the dose to healthy sensitive structures that are positioned near the target region. The purpose of this study is to quantify the radiation dose the patient receives to various parts of the body as a result of the frequent use of image guidance and to devise techniques that will limit the imaging dose the patient receives.

Anticipated Duration of Project

1/1/2008 - 12/31/2011

Project Overview

Image Guided Radiation Therapy (IGRT) makes it possible to check and correct a patient's position each day of treatment. Potentially, this development could allow a decrease in the margin traditionally placed around the target region to provide for daily setup uncertainties. Taking full advantage of this new development is complicated by the fact that IGRT changes the dose distribution the patient receives. This situation is particularly troublesome when designing cooperative group studies that use IGRT. At least for some IGRT techniques, the prescribed dose can be significantly changed when the imaging dose is added. In addition, the dose delivered outside the target region might result in second malignancies or other long-term complications for patients with an otherwise good prognosis. A major problem is that the large number of different approaches being used for IGRT creates considerable variation in the dose delivered for each system. Thus, the first aim of this work is to characterize the dose distribution for all available approaches. These measurements will include a determination of the dose difference that occurs when the technique used for the same IGRT system is changed. The second aim of this research is to devise methods that will allow clinics to take advantage of the new IGRT techniques while limiting the imaging dose delivered to the patient.

In order to achieve the first aim, measurements will be gathered from approximately six Radiation Therapy Oncology Group (RTOG) institutions. The institutions will be selected to guarantee that each IGRT technology (there are currently six different approaches in clinical use) is included in the study. Phantom measurements will be carried out to characterize the dose distribution. This information will be used to determine the relative doses and dose distributions for each technology, and this might allow some technologies to be used more frequently than others. The second aim will be addressed with a patient study. The purpose of this study will be to determine the relationship between the imaging frequency and the ability to reduce margins. The hypothesis for this part of the research is that the imaging frequency can be reduced while maintaining the ability to reduce margins to spare radiation-sensitive healthy tissues. A secondary hypothesis is that the imaging technique (amount of anatomy included in the image, imaging energy, mAs or monitor units) can be modified to decrease patient dose. Both of these hypotheses will be addressed with the patient study.

Principal Investigator

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Geoffrey Ibbott, PhD – employed by Radiological Research Center, Texas
Fang-Fang Yin, PhD – employed by Duke University
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Larry Kestin, MD – employed by William Beaumont Hospital
Laura Dawson, MD – employed by Princess Margaret Hospital
Jeff M. Michalski, MD – employed by Washington University

Expected Research Outcomes and Benefits

Integrated in-the-treatment-room image guidance promises to be an important advancement in Radiation Oncology. However, the added dose delivered to the patient can be problematic and must be properly managed when this technology is used as part of a clinical trial. Thus far, there are no standards or guidelines for the use of image guidance as a radiation therapy tool. This research will establish such guidelines. The benefit for patients enrolling in clinical trials, and for patients in general who are being treated with radiation that is guided by frequent imaging, is twofold: First, the dose of radiation prescribed for their treatment can be more accurately achieved. This will be accomplished by monitoring the dose due to imaging so that corrective actions can be adopted if certain levels are exceeded. Second, the dose delivered outside of the target region where no known or potential disease exists, can be reduced. Limiting the dose to non-target tissues will reduce the complications resulting from the treatment. This will be accomplished through a series of measures that include restricting the field size used for imaging and limiting the number of x-rays used to produce the image or images.

Summary of Research Completed

Aim #1: To determine the absolute dose and dose distribution for different in-room image guidance systems used for radiation therapy treatments.

Progress:
Introduction
Determination of the dose resulting from the use of image guided radiation therapy (IGRT) is strongly dependent on the availability of dosimeters capable of accurate measurement. Radiochromic film has many advantages for this application. The development of this dosimeter has surged as the availability of radiographic film is decreasing rapidly. Our effort over the past year has concentrated heavily on new developments for radiochromic film. Our contribution to this development process is summarized below.

I. Film exposure and air kerma measurement
GafChromic XR-QA2 radiochromic film is a newly upgraded model from GafChromic XR-QA. This model of film is specially designed for the low dose measurement for low energy (kilovoltage) photon beams with high sensitivity and dose measurement range of 0.2-50cGy. Reference dosimetry calibrations with various x-ray techniques were reported for XR-QA model and also for some other similar models. In this study we generated the dose calibration curve for XR-QA2 film using a calibrated Farmer-type ion chamber and a flat-bed document scanner, Epson Expression 10000. Reference dosimetry was performed for a 120kVp photon beam (the energy frequently used in our Cone-Beam Computed Tomographic (CBCT) imaging protocol). A Farmer-type ion chamber was sent to a National Institute of Standards and Technology (NIST) traceable ADCL facility for calibration at this energy, and this calibration was used for absolute air kerma measurement. Films were cut to 2x3 cm^2 pieces and irradiated by X-ray Volume Imager (XVI) CBCT system mounted on Elekta linear accelerator. Fifteen dose points ranging

from 0-9cGy were used to generate the calibration curve. For each dose point, three pieces of films were exposed.

II. Film scanning and film response calculation

Films were scanned before and 24 hour after the irradiation. Both reflection and transmission scanning modes were used to study the possibility and performance of using transmission mode for reference dosimetry. Each scan was repeated three times to include scanning reproducibility in the uncertainty analysis. A relatively large ROI ($1x1cm^2$) was used to account for scanner non-uniformity and film non-uniformity. Scanned values from red color channel were used. Film response was calculated as reflectance (pixel value) change in reflection mode or optical density change in transmission mode, with correction from the controlled (unexposed) films. Several different fitting functions were tested and the one with best fitting quality was used to generate the dose calibration curve.

III. Uncertainty analysis

Uncertainty of dose calibration included experimental uncertainty and curve fitting uncertainty. Experimental uncertainty covered most uncertainties from experiment including scan reproducibility, film and scanner non-uniformity, etc., and it was mainly characterized by the standard deviation of pixel values inside the ROI. Fitting uncertainty represented the goodness of the curve fitting. Figures 1 and 2 show the dose calibration curves and uncertainty level for reflection and transmission scanning modes, respectively.

IV. Impact of scanning spatial resolution on the calibration uncertainty

Low scanning spatial resolution (dot per inch or DPI) introduces less noise and thus produces lower standard deviation of pixel values inside the ROI. This means the experimental uncertainty in the film calibration changes with spatial resolution and a single uncertainty level is not adequate to be applied to all kind of different scanning procedures, especially different scanning spatial resolutions. To investigate the impact of spatial resolution on the calibration uncertainty, we scanned the films at six different resolution levels, 50, 96, 150, 200, 300, and 400 DPIs, and calculated the uncertainty for each. Figure 3 shows the change of calibration uncertainty with DPI at 4.32cGy dose point for both reflection and transmission scanning modes.

V. Characteristics of the new gafchromic XEQ2 films

The film was calibrated free in air to air kerma levels between 0 and 9 cGy using 120 kVp photon beams produced by the XVI imager. Films were scanned using transmission and reflection scanning modes with the Epson Expression 10000 XL flat-bed document scanner. The impact of film size, region of interest of the analysis, scan uniformity, scan resolution, scan orientation and scanning films on alternate sides on the analysis process were investigated. Post irradiation growths reflectance and irradiation angular dependence of the film were tested at different air kerma levels.

V.1 An Impact of film size and region of interest on image analysis

Figure 1 shows the percentage variation of the reflectance of each film piece from the reflectance of the largest film piece (10 cm x 11 cm) analyzed using the largest ROI (8.0 cm x 8.0 cm) when films were analyzed using different ROI(s). It should be noted that films were analyzed using ROI(s) appropriate to their sizes (for example, film piece 1 cm x 2 cm was only analyzed using

0.7cm x 0.7cm ROI, whilst film piece 10.0 cm x 11.0 cm was analyzed using all ROI(s)). The largest film piece of 10 cm x 11 cm is used as a reference size; as it is expected to give the average response of the film and takes into account any non uniformity in the film. The net reflectance of film pieces of different sizes (ranging from 1cm x 2cm to 10 cm x11 cm) changed only slightly (< 3%) when analyzed using different region of interests (ranging from 0.7 cm x 0. 7 cm to 8cm x8 cm). The change in net reflectance of each film pieces when analyzed using different ROI(s) was less than 1%. The variations did not show a clear trend and were within the total uncertainty of the reflectance.

A Film piece of 10 cm x 10 cm exposed free in air to air kerma of 2.67 cGy was scanned using reflection mode using six different region of interest (0.7 cm x 0.7 cm, 1cm x 1cm, 2cm x 2cm, 4cm x 4cm, 6cm x 6 cm and 8 cm x 8 cm). Figure 2 shows the reflectance change as a function of ROI. The reflectance changes were almost the same and the variations were within their uncertainties. The reflectance changed by less than 1 % when the region of interest was changed from 0.7 cm x 0.7cm to 8 cm x 8 cm, indicating that the size of the region of interest does not have any significant effect on the value of the reflectance. It also indicates the good uniformity of the film. Similar result was observed for film pieces of smaller sizes s indicated above. Hence, it was decided to use a film piece of 2 cm x 3 cm and region of interest of 1 cm x 1cm for all the calibration measurements and other investigations.

V.2 Scanner Uniformity

Scanner uniformity along in the central area of the scanner was investigated. Figure 3 shows the variation in reflectance with distance away from the center of the scanner (along the center line of the scanner) for two films (one exposed to 1.3 cGy and the other exposed to 9.0 cGy). A maximum variation of 3.7% and 1.8 % were observed in the reflectance of the films exposed to 1.3 cGy and 9.0 cGy respectively. These variations were in fact within the relative uncertainty of the reflectance of the two films. Figure 4 shows the percentage variation of the reflectance at different positions (center of the scanner as a reference position) inside the scanner. A maximum change of 3.2 % and 1.3 % were observed in the reflectance of the films exposed to 1.3 cGy and 9.0 cGy respectively and these variations were within the relative uncertainty of the reflectance.

V.3 Scanning Orientation

Figure 5 shows the variation of the relative difference in reflectance and optical density of portrait and landscape scanning orientations with air kerma for both reflection and transmission scanning modes. The relative difference was higher for transmission mode at all air kerma points. For both scanning mode, the relative difference was higher at low doses, being 15% and 9% at 0.18 cGy for transmission and reflection scanning modes respectively. However, at doses commonly used in CBCT procedures, the relative difference was ~ 2 % for both scanning modes.

<u>Aim #2: To determine if the procedure used for image guidance can be modified, without compromising the advantages of this new technology, to control and possibly limit the extra dose the patient receives.</u>

<u>Progress</u>: There was no progress on this aim during the reporting period.

<u>Grafts and Tables for:</u>

III. Uncertainty analysis

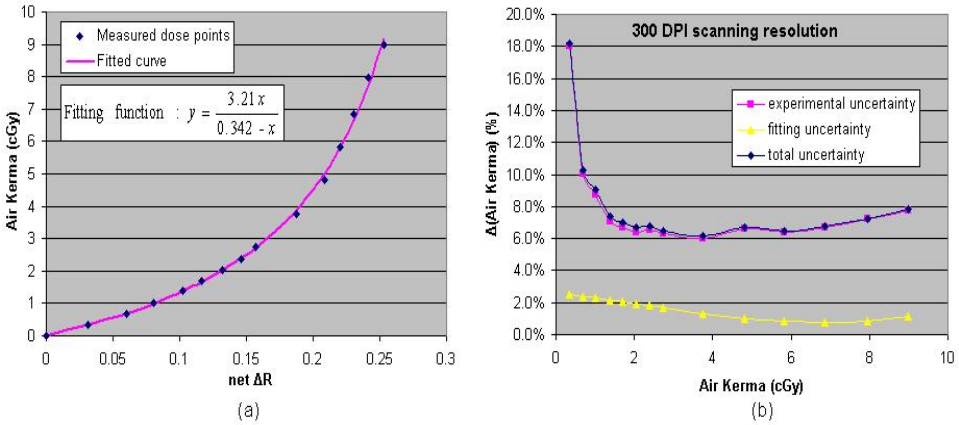


Figure III-1. Dose calibration curve and uncertainty analysis with reflection mode. (a) Dose calibration curve. X axis is net pixel value change. Y axis is air kerma. (b) Uncertainty in dose calibration with 300DPI scanning spatial resolution.

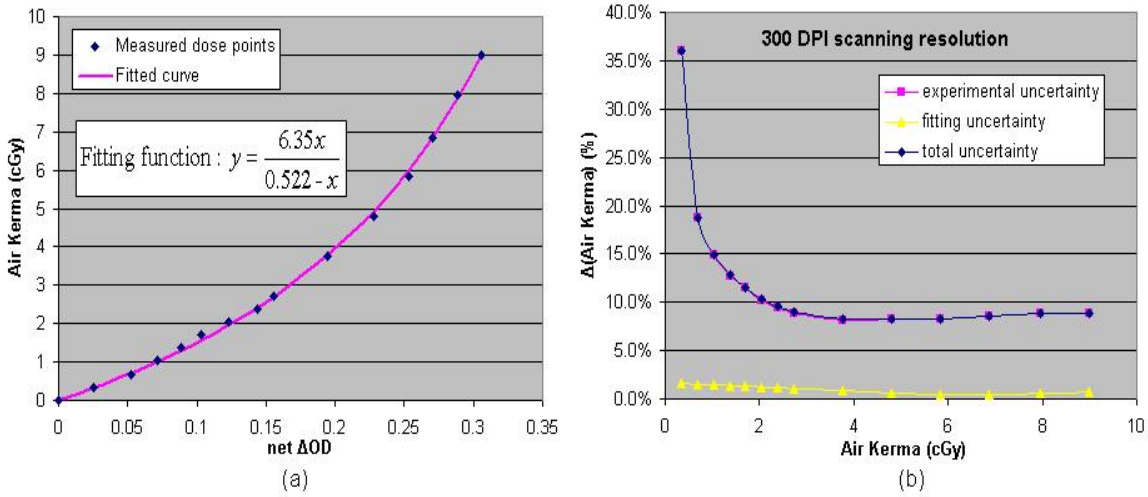


Figure III-2. Dose calibration curve and uncertainty analysis with transmission mode. (a) Dose calibration curve. X axis is net optical density change. Y axis is air kerma. (b) Uncertainty in dose calibration with 300DPI scanning spatial resolution.

IV. Impact of scanning spatial resolution on the calibration uncertainty

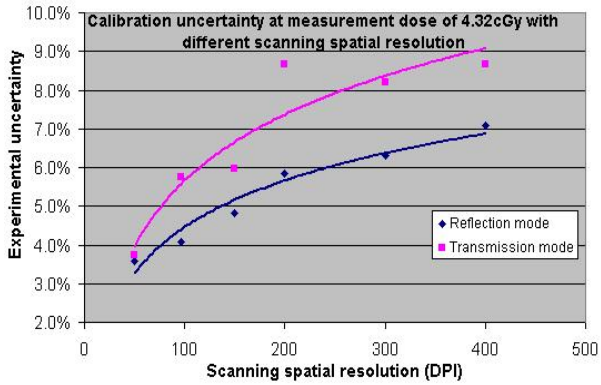


Figure IV-1 Calibration uncertainty at measurement dose of 4.32cGy with different scanning spatial resolutions.

V. Characteristics of the new gafchromic XRQ2 films

V.1 Impact of film size and region of interest on image analysis

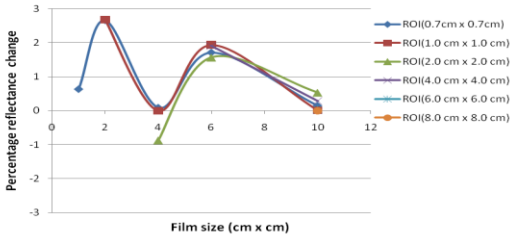


Figure 1. percentage change in reflectance of each film piece from reflectance of largest film piece analyzed using largest ROI as a function of film size for different ROI.

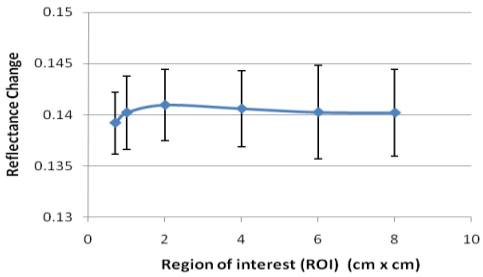


Figure 2. Reflectance change as a function of ROI for a film piece of 10 cm x 10 cm.

V.2 Scanner Uniformity

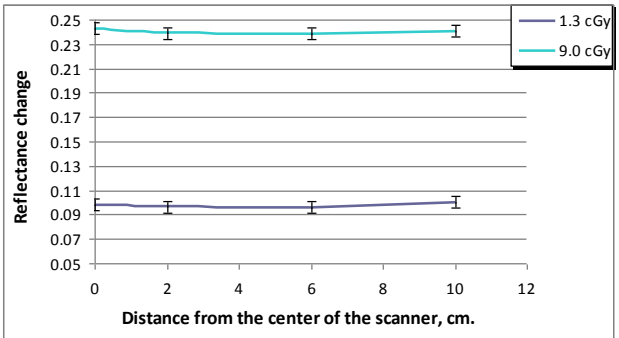
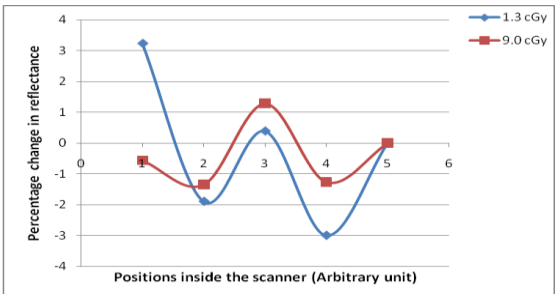


Figure 3. Variation of Reflectance change with distance from the center of the scanner



Figture 4. Percentage change in reflectance at different positions inside the scanner (position 1 (left top corner), position 2 (left bottom corner), position 3 (right top corner), position 4 (right bottom corner) and position 5 (center of the scanner)

V.3 Scanning Orientation

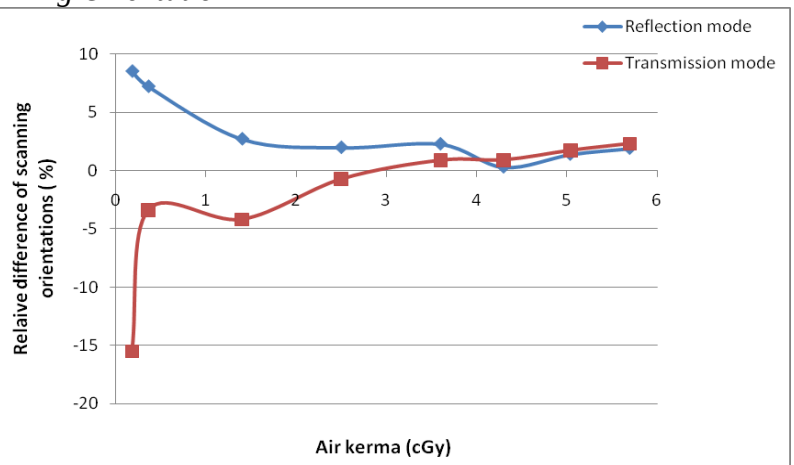


Figure 5. Variation of relative difference in reflectance and optical density of portrait and landscape scanning orientations with air kerma