American College of Radiology

Annual Progress Report: 2007 Formula Grant

Reporting Period

July 1, 2009 – June 30, 2010

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.

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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 Activation and Enrollment

The study activated on July 7, 2009, as of the end of the reporting period, June 30, 2010, 505 subjects had been enrolled in the study, distributed among the sites as shown in Table 1 below. Table 2 indicates cumulative accrual. The trial is designed to accrue for 24 months, July 2009-July 2011. It is anticipated that analysis of the primary study endpoint will be completed by December 2011, but as a one year follow up is necessary for analysis of the secondary aims, this analysis will be incomplete at the end of the funding period. Additional funding has been sought to allow complete data collection for the one year follow up aims.

Early accrual lagged behind expectations due to slower implementation at sites and study design issues that were addressed through an amendment to the protocol, as detailed below. As a result, accrual rates have accelerated and are now comparable with the original projections despite continued challenges at one site (University of Pittsburgh). The site investigator is working diligently to increase coordinator staffing, while the protocol team is considering alternatives including extending the enrollment period or decreasing the sample size. In addition, one strategy employed to offset accrual difficulties has been to use alternative funding from the ACRIN (American College of Radiology Imaging Network) Fund for Imaging Innovation to enable a site outside of PA to participate in the trial (Wake Forest University, NC).

Trial Monitoring and Reporting As this trial's design calls for a 1:2 randomization ratio (traditional care to coronary CTA), the statistical team monitors this metric (see Table 3) as well

as forms submission, eligibility, protocol deviations, and follow up rates on a monthly basis, reporting any issues to the protocol team on their monthly teleconferences.

The statistical team also provided quarterly reports to the ACRIN PA Data and Safety Monitoring Board detailing patient demographics, accrual, adverse events, and, when triggered, adjudication results for all major cardiac events. All recommendations by the Board were forwarded to the ACRIN PA Network Chair and protocol investigators for further discussion and action.

The progress of the trial was reviewed by the ACRIN Cardiovascular Committee on a quarterly basis via a verbal report by the protocol investigator on a teleconference.

Participating sites transmitted CT angiography images to the ACRIN Core Lab for quality control and archival. The ACRIN imaging analyst, in conjunction with the trial biostatistician, provided monthly radiation dose reports to the study principal investigator. He reviewed contrast series' dose as well as total radiation dose, providing feedback to the site PIs in an effort to decrease radiation dose without sacrificing image quality.

During the reporting period, the ACRIN Regulatory Department implemented the monitoring and auditing plan for the trial. Monitoring is now completed at the University of Pennsylvania and Penn-Presbyterian.

Protocol Amendments

The protocol was amended twice (March, 2010 and June, 2010) during the reporting period. The ACR IRB approved both amendments and local site IRB approval is completed for the March 2010 amendment and in progress for the June, 2010 amendment.

Revisions included the following:

- Opening of some timing issues with the trial's design (e.g., approximating blood draw times at the Hospital of the University of Pennsylvania and Penn-Presbyterian)
- Adding a description of medical monitor and adjudication committee roles
- Clarifying procedures in cases when historical data is discovered to conflict with patient self-report of medical history in the ED environment
- Adding a site outside of Pennsylvania
- Explanation of timing guidelines for 30-day and 1-year follow-up processes (including minimum contact attempts)
- Clarification of which follow-up responses at 30 days will trigger medical record review
- Addition of off-study criteria related to creatinine clearance and D-dimer lab results obtained prior to CT coronary angiography,
- Implementing a process for pre-contract CT acquisition of high calcium score that might keep a participant from completing the contrast-enhanced study imaging
- Allowance of a CT coronary angiography as soon as it is available, in addition to recommending CTs be completed within about 90 minutes after labs have been confirmed for eligibility
- Reduction in the Informed Consent Form contents

- Addition of an appendix listing cardiac diagnosis definitions for the trial
- Addition of an adjudication committee

Data Collection

Initial data collection was conducted using a comprehensive set of CRF's developed specifically for this trial. These forms are now fully electronic, enabling direct data entry at the site using web-based screens and internal validation logic.

Table 1: Accrual by Institution

Institution	Date Site Opened	Total Accrual
Penn Presbyterian Med Ctr	07/15/2009	72
Pennsylvania State/Hershey Med Ctr	12/01/2009	106
U Pennsylvania School of Med	07/07/2009	289
U Pittsburgh Med Ctr	01/18/2010	20
Wake Forest University	04/26/2010	18
Total (5 institutions):		**505**

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.

Table 2: Cumulative Accrual over Time (24 months)

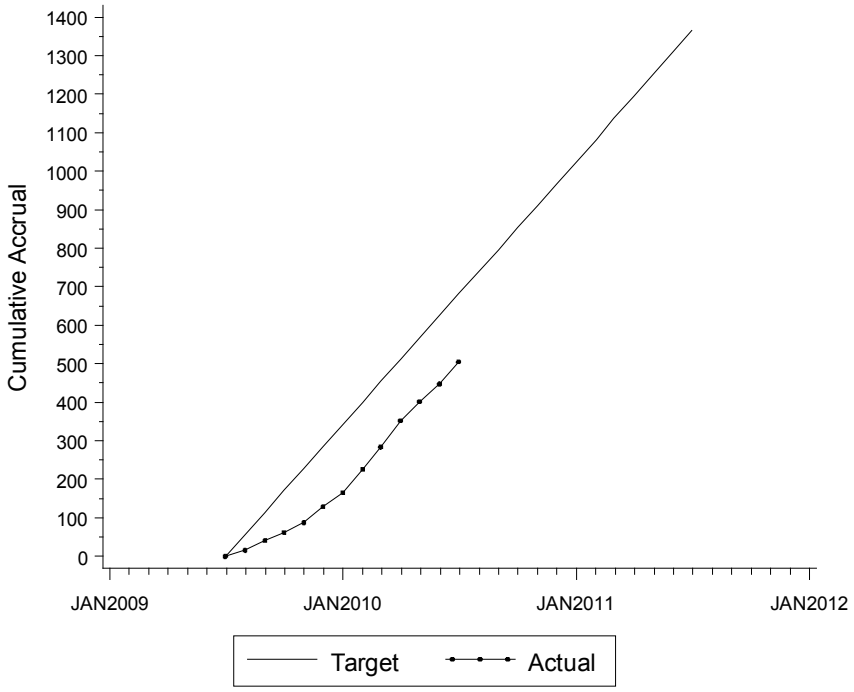

Table 3: Accrual by Study Arm

	Frequency	Percent
Traditional Care	167	33.07
CT Coronary Angiogram	338	66.93

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.

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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 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

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

PHASE 2 - 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

Phase 1 data for this reporting period:
I. IMAGING DOSE FROM RECONSTRUCTION

Several open source tools for the cone-beam CT image reconstruction were studied. The feasibility of applying the CT reconstruction methods to the imaging dose reconstruction was investigated with the preliminary tests of two software tools. These two toolboxes are jSNARK and Image Reconstruction Toolbox.

jSNARK - is programming system for the reconstruction of 2D and 3D images from their projections. http://dig.cs.gc.cuny.edu/~swr/jsnark is an open source programming system designed to help researchers to develop and evaluate different image reconstruction algorithms with the cone-beam projection data. jSNARK provides a framework in which many modes of data (different geometrical arrangements of X-ray source and detectors, different X-ray spectra, etc.) can be processed with many of the published reconstruction algorithms (ART, block ART, back projection and Radermacher's weighted back projection, Katsevich's algorithm, etc.). They were specifically designed to help with the problem of reconstructing cross-sections of the X-ray absorption coefficient distribution inside the body from X-ray projections. jSNARK is capable of generating mathematically described phantoms that realistically represent various cross-sections of the human body, together with mathematically simulated projection data of these cross-sections reflecting the characteristics (including noise) of various possible tomography devices. It is capable of 2D, 3D, and 4D reconstructions (the extra dimension of time), and statistical evaluation of the performance the reconstruction algorithms.

Image Reconstruction Toolbox (IRT) http://www.eecs.umich.edu/~fessler/code/ is a collection of open source algorithms for image reconstruction (and related imaging problems) developed at University of Michigan using MATLAB language. Taking advantage of extensive developmental functions from MATLAB, this toolbox provides interactive environment for algorithm development, data visualization, data analysis, and numerical calculation. IRT is also useful for to users wishing to gain an intuitive understanding of image reconstruction by playing with the software. The toolbox can use preset phantom objects to generate projection data that can be back-projected. The adjustable settings include a selection of filters, change in number of viewing angles, data bins, and reconstruction field of view. It is capable of performing image filtering operations, plus image windowing controls, and visualizing the projection data and sinograms. The code is written in MATLAB which will be helpful for us to develop the dose reconstruction algorithms based on this toolbox.

As a result of the evaluation of jSNARK and IRT we found that these software toolboxes can help us to understand, evaluate, and develop different image reconstruction algorithms and investigate the correlations and differences between image reconstruction and dose reconstruction.

II. IMAGING DOSE FROM MEASUREMENT

An ion chamber and radiochromic films were used for the measurements of imaging dose from kilovoltage cone-beam CT (kV CBCT) imaging. The ion chamber was a 0.6cm^3 PTW 30010 Farmer chamber (PTW, Freiburg, Germany) with nominal photon energy range from 30kV to 50MV. It was calibrated by an Accredited Dosimetry Calibration Laboratory, which is directly traceable to the National Institute of Standards and Technology (NIST), for the energies of 100kV and 120kV. The ion chamber served as an absolute dosimetry tool in our study based on the AAPM Task Group report 61 "AAPM protocol for 40-300kV x-ray beam dosimetry in radiotherapy and radiobiology". The radiochromic films used in this study were Gafchromic® XR-QA2 films (International Specialty Products, Wayne, NJ). The radiochromic films were calibrated by the ion chamber measurements. The Gafchromic film dosimetry in kV energies, usage of the films, and the uncertainty analysis were summarized from the related studies. Based on the literature review a basic dose-response calibration was carried out and some preliminary results were derived.

II.1. Summary of radiochromic film dosimetry for kilovoltage x-ray beams

With commercial products becoming more readily available, radiochromic film is used extensively for kV beam dosimetry. The widely investigated film models in research articles are Gafchromic® XR-QA (including the upgraded version XR-QA2) and XR-RV2 (including the upgraded version XR-RV3) films although some other Gafchromic films (e.g., XR-CT2) are also capable of kV dosimetry with high sensitivity. Gafchromic® XR-QA2 is sensitive to dose range of 0.1cGy to 20cGy with imaging detail at greater than 5000dpi. Gafchromic® XR-RV3 is specially formatted for skin dose measurement with wide dose range of 0.01Gy to 30Gy and high resolution greater than 5000dpi. Compared to ionization chambers, semiconductors, thermoluminescent detectors, and radiographic films, radiochromic films have the advantage such as ease of handling due to its insensitivity to visible light and self-developing characteristics, full 2D dosimetry, high sensitivity in diagnostic energy range, and high spatial resolution. These features made the radiochromic films suitable for the IGRT dosimetry, especially for the kV CBCT imaging dose measurements. Studies have shown that radiochromic films were successfully used for kV photon beam dosimetry during CBCT image acquisition. The structures of all types of Gafchromic films can be found from the manufacture's website. AAPM Task Group 55 made a comprehensive presentation regarding to radiochromic film dosimetry, mainly with some older types of films for MV beams and relatively higher dose range. While many concerns in this Task Group report remain same for the kV energy film dosimetry, more specified features for the film models which are designed for low energy photon beam dose measurements can be found in the later literature. The procedures and concerns of kV dosimetry of radiochromic films are summarized as following.

II.1.1 radiochromic film exposure and dose response relation

The relationship between absorbed dose and radiochromic film response should be calibrated with a large uniform radiation field before dosimetric application. This relationship is presented as a curve, which is often known as calibration curve. A reference dose measurement is needed to create this relation. For the kV beams several instruments were reported in publications, which include, but are not limited to, various ion chambers, FLUKE TNT-12000 x-ray test device (Fluke Biomedical, Everett, WA), Unfors Xi (Unfors Instruments, Billdal, Sweden) multipurpose solid-state kV and dose meter. In our study, a calibrated Farmer chamber was used to derive the calibration curve. Film sensitivity to wide range of absorbed dose should be characterized and optimal conditions for imaging dose measurement using this specific film should be determined. Different models of curve fitting for dose-response relationship were proposed by different studies, but no model was used in general. Radiochromic film dose response may be affected by many factors, so the calibration should be done under same (or as close as possible) conditions of use.

II.1.2 Post-exposure growth and ultraviolet light sensitivity

The typical behavior of post-exposure growth of Gafchromic film is that the optical density of the film increases significantly in the first minutes, but the rate of optical absorption diminishes rapidly with time. This is because the active component in Gafchromic film is a radiation sensitive monomer and the initial polymerization reaction takes place within a few milliseconds post-exposure, but several radiation chemical effects require longer time to reach chemical completion. Many studies suggested that the rate of change of film response decreases continuously and rapidly with time after exposure, becoming very slow after about 24 hours. So it is recommended to read the films at least 24 h after the exposure and try to use consistent time intervals for calibration and measurements. A short exposure of the films to ultraviolet light or visible room light during the measurements will not have a significant impact on the radiation dosimetry, but the impact of long term exposure should be avoided or carefully evaluated.

II.1.3 Energy dependence and dose-rate dependence

The sensitivity of radiochromic film response varies with different energies of beam. For example, the sensitivity of Gafchromic® XR-QA film is significantly higher for the radiation beams with energies in the range of 80-140 kVp. Gafchromic XR type T films showed nearly constant response for the photon energies greater than 300keV, but varied significantly in the range of 0-300keV. The variation of the film response should be examined with multiple energies of beams and film response calibration should be done for every energy beams that is intended for use. In contrast, the film response is almost dose-rate independent.

II.1.4 Polarization effects

The measured optical density of radiochromic film may change substantially due to the polarization of the analyzing light. Studies have shown that almost all Gafchromic films have the polarization effects more or less depending on the absorbed dose, scanning system, etc. For the application, film orientation and alignment should be consistent with the ones used for calibration.

II.1.5 Film uniformity and image processing
Film uniformity should be evaluated using a large flat radiation field to incorporate it into the measurement uncertainty. Some image processing techniques can be used to reduce the impact caused by non-uniform response of film and scanning system.

II.1.6 Scanning system
Several different scanning systems were compared for dosimetric properties of Gafchromic films. Recent studies have shown increasing interest in using flatbed document scanner for radiochromic film scanning and have had great success with such scanners. A good document scanner offers many advantages such as high resolution, high precision, good stability, and low cost. By using a color flatbed document scanner, different color channels (red, green, or blue) can be selected for the readout, and different scanning modes (i.e. reflective scan and transmission scan) can be chosen. The scanner used in our study is an EPSON Expression 10000XL (Seiko Epson Corporation, Suwa, Nagano, Japan) scanner. Each scanner has a unique response and several properties of a scanner should be characterized before its use, which includes spatial uniformity, repeatability of scanner response, characteristics of light sources and light detectors, spatial resolution, and positional accuracy.

II.1.7 Uncertainty analysis
Any dose calibration system or measurement system should by accompanied by the uncertainty analysis for the measurement accuracy. A comprehensive list of all uncertainty sources of radiochromic film measurement was given in the literature. A rigorous method to account for the uncertainties from different sources is desired. The combination of uncertainties can be achieved by a relatively simple estimation using the Gaussian propagation of errors and assuming the absence of cross-correlation terms, or by a complete classification and analysis of all sources of uncertainties in radiochromic film dosimetry.

II.2. Gafchromic® XR-QA2 film calibration with ion chamber for kV CBCT imaging
According to the procedures described above, we did a preliminary study on the dose response calibration with our Gafchromic® XR-QA2 films. Measurements were performed on two kV CBCT imaging devices mounted to Elekta Synergy accelerators. 120kVp beam with half value layer of 6.96mm aluminum was used for calibration. The ion chamber mentioned above was used for absolute dosimetry. The film and chamber were put in radiation fields of same settings (100SSD, in air, small field used for head and neck imaging) respectively to correlate the measured air kerma from ion chamber with the response of radiochromic film. Output of imaging system was controlled by adjusting the mAs settings. Figure 1 shows the correlation between measured air kerma and machine output (mAs).

Radiochromic films were cut into 2X3cm^2 pieces and exposed to different levels of outputs. The lower 2X1 cm^2 part was used for labeling and handling (Figure 2). The region inside the blue square in Figure 2 was used to read out the pixel values, both in reflective mode and in transmission mode. Films were scanned before and 24 hours after the irradiation. Three pieces of films which didn't undergo any irradiations were also scanned at the same time together with the other films and they were used as the controlled films. The pixel value changes in the irradiated films were corrected by the changes in the controlled films, and the corrected values were used as the film response to the kV radiation. Gaussian curve fitting was used for the analysis of pixel

values inside the ROI (blue square) to eliminate the abnormally behaving pixels. Mean pixel value and standard deviation inside the ROI were calculated for dose response curve and uncertainty analysis.

Figures 3 and 4 show the dose calibration curves in reflective scanning mode and transmission scanning mode, respectively, for the given beam quality of 120 kVp energy. Measured points are fitted with polynomial functions (order 4). Besides the dose response calibration, the impacts of different color channel readouts, different scanning modes, different regions in scanner used, and long time post-exposure readout variations were also investigated.

A method based on the polynomial chaos was sought in this study for uncertainty analysis. This is described in the next section.

III. POLYNOMIAL CHAOS FOR UNCERTAINTY ANALYSIS IN RADIOCHROMIC FILM DOSIMETRY

Radiochromic film is a dosimeter of choice in applications requiring high spatial resolution, two dimensional measurements. Because there are a variety of uncertainties in film measurement such as temperature, humidity and exposure to all kinds of radiation, a rigorous mathematical method to evaluate these uncertainties is desired. The polynomial chaos expansion method is an attractive technique for uncertainty quantification due to its strong mathematical basis and ability to produce functional representations of stochastic variability. When tailoring the orthogonal polynomial bases to match the forms of the input uncertainties, excellent convergence properties can be achieved for general probabilistic analysis problems. For instance, the stochastic nature of dose deposition and optical photons detection can be described by Poisson random variables in the model and the dose variation within region of interest can be described by Gaussian random variables. The corresponding stochastic processes are characterized by Hermite and Charlier polynomial expansions. This method takes into account input uncertainties via the parameters of the problems and propagates the uncertainty distributions in terms of probability density functions. In this work we represent every uncertain parameter as a Gaussian or Poisson random variable in the model, and solve the stochastic differential equation by using the polynomial chaos expansion method. In the end the desired uncertain quantities are given by their means and standard deviations, or even higher moments.

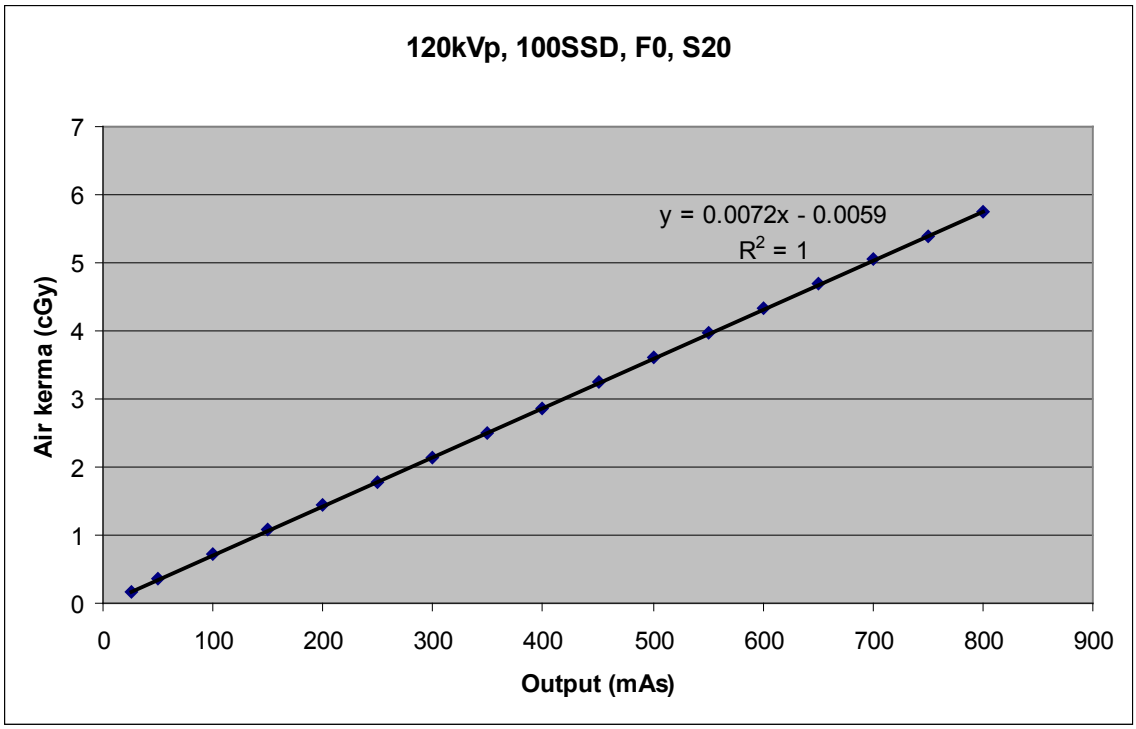

Figure 1. Correlation between measured air kerma (cGy) and machine output (mAs) with 120kVp beams and small field size measured at 100SSD.

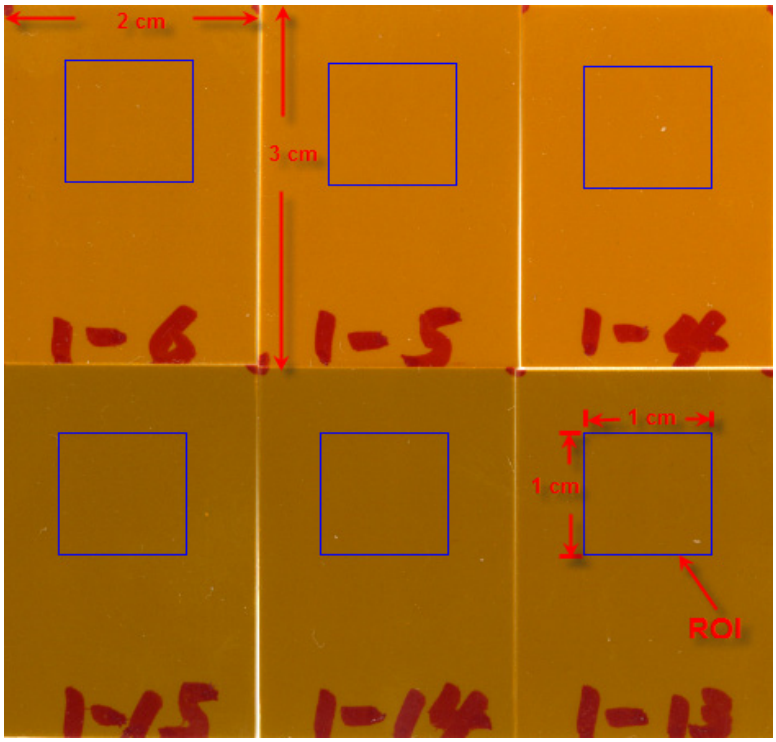

Figure 2. Films scanned with reflective mode 24 hours after the irradiation. Six pieces of films were exposed to different output levels. The dimension of each piece of the film is $2X3cm^2$. Blue square indicates the region of interest (ROI) for pixel value analysis.

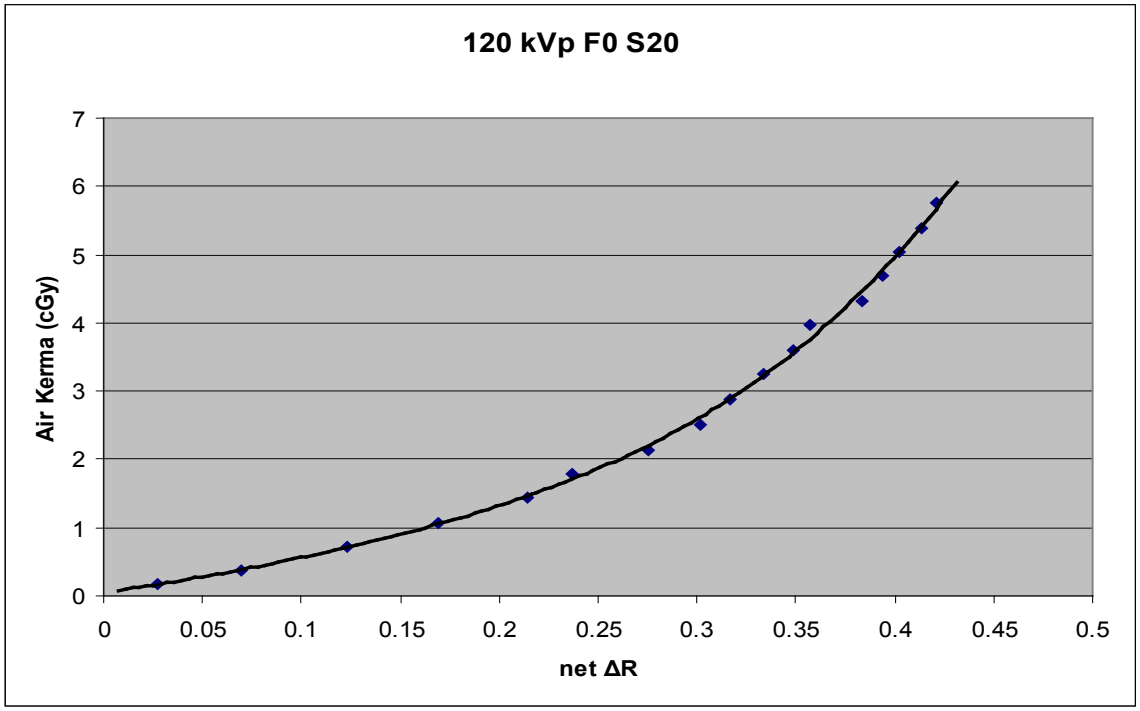

Figure 3. Dose response calibration curve for reflective scanning mode. X axis is the film response represented by net pixel value change and Y axis is the corresponding air kerma.

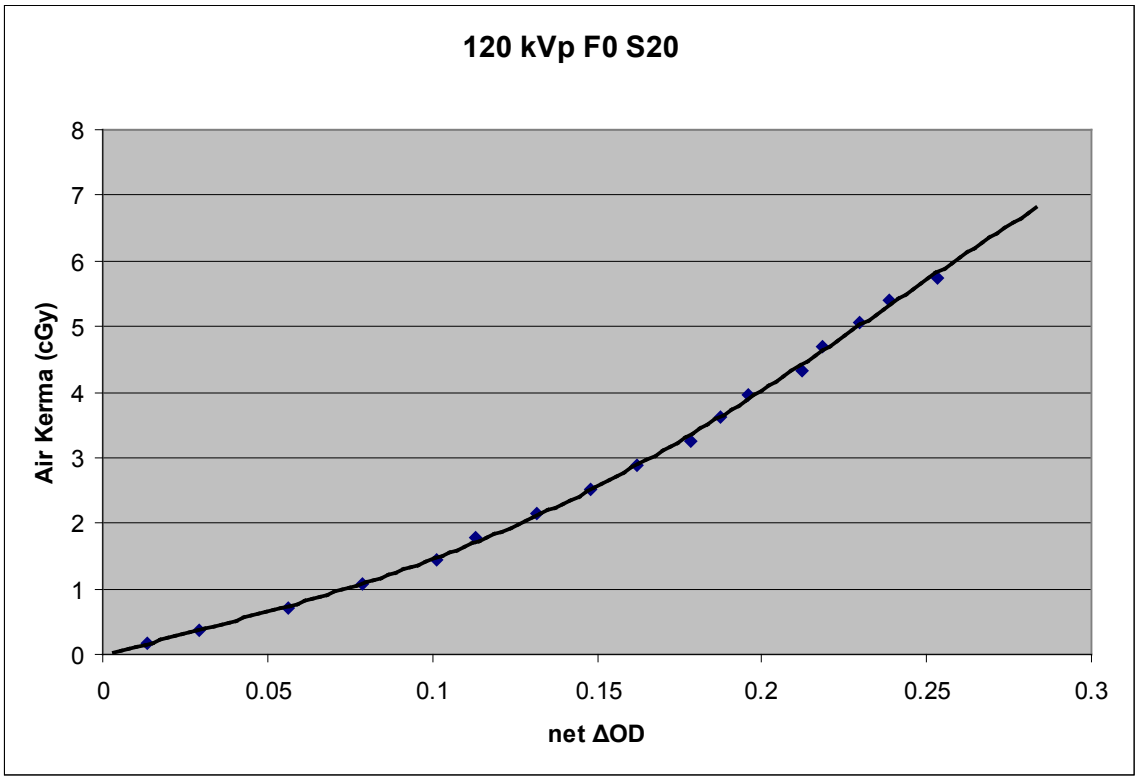

Figure 4. Dose response calibration curve for transmission scanning mode. X axis is the film response represented by net optical density change and Y axis is the corresponding air kerma.