

Protocol Title:

Patient- and Task-specific Radiation Dose Optimization for Pediatric Abdominopelvic CT Applications

NCT03429712

Purpose of the Study:

To implement a recently validated single-energy dual-source multi-detector computed tomography (DSSE) dose split technique in a cohort of pediatric patients to determine, without increase in patient radiation dose, the optimal patient-specific and task-specific radiation dose levels for pediatric abdominal CT applications.

Our working hypothesis is that by using a DSSE dose split technique, we will be able to compare reader diagnostic accuracy for detection of disease across a broad range of different radiation dose levels, without the need of multiple CT acquisitions or artificial noise insertion tools.

We postulate that our research will have important clinical implications. By generating datasets at different (including sub-mSv) radiation dose levels from a single DSSE acquisition within the same patient, the dose split technique will minimize the impact of important confounding variables for the assessment of dose reduction strategies, including inter-patient or inter-scan variability. This will enable more accurate and precise optimization of CT radiation dose according to patient size, diagnostic task, and reconstruction algorithm. It will also accelerate the development and validation of novel reconstruction or noise reduction algorithms, facilitating determination of minimally acceptable dose levels for a wide range of diagnostic tasks.

Background & Significance:

Radiation dose reduction has been a primary driver of technology development and research in multi-detector computed tomography (MDCT). The basic tradeoff of dose reduction is that a reduction in the radiation exposure is unavoidably associated with a reduction of image quality. The most common example of image quality degradation is the increase in image noise ('mottle') in the CT images which can compromise diagnosis. By decreasing the statistical noise associated with low photon count projection data (low dose), iterative reconstruction (IR) methods offer the potential for substantial radiation dose reductions, while providing diagnostic-quality images. Although previous studies have indicated the potential for a radiation dose reduction of up to 75% using IR methods for routine abdominal applications, there is significant variability in the literature regarding the specific recommendations for dose reduction. This observation highlights the critical need to precisely and accurately determine to what degree the radiation dose can be decreased using IR methods without compromising diagnostic image quality. This unmet need is a significant barrier to the effective clinical implementation of IR methods.

Although many factors may have contributed to this large inter-study heterogeneity — including technical differences among rapidly evolving IR methods and important differences in study design and clinical tasks — we postulate that the lack of data from large clinical trials has been one of the primary sources of variability. Previous studies from both phantom and clinical studies have shown a substantial discrepancy in the recommended minimum dose level required to maintain adequate diagnostic performance. This observation may be partially explained by the limitations of traditional surrogate markers of image quality (such as noise magnitude and contrast-to-noise ratio), which cannot capture the nonlinear changes in noise (i.e., noise texture) and image quality using IR methods. This is further compounded by the inherent difficulty in translating data from phantom experiments to the complex human system.

Newer generation dual-source MDCT platforms enable the reconstruction of image datasets at different radiation dose levels from a single CT acquisition. Recent studies have shown that, when both radiation tubes are operated at the same tube potential and tube current (i.e., dual-source single-energy [DSSE] acquisition mode), half-dose and full-dose images can be reconstructed from the same CT acquisition using the projection data of only one tube or both tubes, respectively. Of note, because each x-ray tube in a dual-source CT system has its own generator, it is technically possible to set up individual adjustments of the output (and thus radiation dose) of each radiation tube during a DSSE acquisition. The separate reconstruction of the projection data of each tube independently or the combination of both tubes expands the number of different radiation exposure datasets that can be reconstructed from a single DSSE acquisition within the same patient, thus providing a powerful methodology for assessing the potential radiation dose reduction using IRs.

This strategy overcomes some of the major limitations of previous studies comparing different radiation exposure levels from separate study cohorts (an approach that is confounded by potentially large inter-patient variability) or the utilization of artificial noise insertion tools to simulate reduced-dose CT datasets. Furthermore, compared to multiple single-energy CT acquisitions at different radiation dose levels, a variable dose split DSSE protocol eliminates the need for multiple intravenous contrast material injections and avoids potential variability due to misregistration among different datasets secondary to patient motion or differences in contrast material timing.

Design & Procedures:

This is a prospective Health Insurance Portability and Accountability Act-compliant study for which we are asking for Authorization from the Institutional Review Board.

A non-inferiority statistical analysis was performed for comparing the reconstruction algorithms SAFIRE-3 at 50% and 37.5% radiation exposure against the reference FBP at 100% using the readers' score of overall image

quality as the primary outcome measure. The reader-to-reader and patient-to-patient variability were estimated from actual data [1]. The power analysis results – shown in Figure 1 – demonstrate that with 4 readers a power of more than 80% to test for non-inferiority is achieved with approximately 50 patients. We will select 100 total consecutive pediatric patients undergoing clinically-indicated MDCT of the abdomen and/or pelvis as part of their clinical care. One half (N = 50) of patients will have an indication of *acute* abdominal/pelvic pain/abnormality and the other one half (N = 50) will have an *oncologic* abnormality with indication for imaging of the abdomen and pelvis. Patients will be considered ineligible if they have any contraindication to iodinated contrast material, such as a previous history of anaphylactoid reaction or renal failure (serum creatinine level > 2.0 mg/dL [177 µmol/L]). Women of childbearing potential or refusing urine pregnancy *test* or with a positive test result will be also excluded.

All MDCT examinations will be performed using a second-generation or third-generation dual-source MDCT platform (Somatom Definition FLASH or Somatom Definition FORCE, Siemens Healthcare, Forchheim, Germany), which are equipped with a research-only acquisition mode DSSE dose split software. This software allows the system to be operated in DSSE mode and the effective tube current time product to be adjusted by the user for each tube independently. Each patient will be scanned using a DSSE dose split technique before or after intravenous contrast medium administration during the arterial and/or venous phases matching the medical indication. Patient radiation dose exposure as well as image quality will be comparable to a standard of care MDCT examination, as indicated in our recently published research indicating the experience in 21 patients [1]. The tube output (CTDI_{vol}) for each DSSE acquisition will be selected to match the typical tube output of a conventional MDCT acquisition for a specific CT protocol and patient size. Examples of typical tube output parameters for DSSE acquisitions in pediatric patients are provided below and are based on Duke standard of care protocols for pediatric patients:

		kVp	Pitch	Effective mAs	mAs / rotation	Relative CTDI _{vol} (%)	Relative DLP (%)
Pediatric abdomen and pelvis	Tubes 1 + 2	120	1.2	200	200	100	100
	Tube 1	120	1.2		160	80	80
	Tube 2	120	1.2		40	20	20

State of the art radiation protection features will remain in place, like automatic exposure control of the tube current, which adapts the x-ray tube current according to the patient body habitus relative to a quality reference value. In pediatric examinations additional bowtie filters will be utilized.

By using the project CT data of each x-ray tube independently (A or B) or in combination (A+B), we will reconstruct multiple radiation dose levels for the same patient and same phase of contrast enhancement, ranging from 20% up to 100% dose. The 100% dose dataset will be sent to PACS routinely without delay and used for routine clinical interpretation of the CT examinations.

Images will be reconstructed at 5.0 and 0.6 mm slice thickness using a conventional FBP and two commercially available IR methods: sinogram-affirmed iterative reconstruction (SAFIRE) and advanced modeled iterative reconstruction algorithm (ADMIRE). The SAFIRE and ADMIRE algorithms allow the user to select a strength parameter between one and five that controls how aggressively the algorithm reduces noise. Images will be reconstructed using different strengths, including a strength of three (the recommended setting for abdominal imaging applications according to the manufacture), four, and five.

In addition, we will collect relevant clinical and demographic patient's information, such as indication for the exam, medical record number, age, gender, and body weight, height, and body mass index. We will also collect information regarding the CT parameters, radiation dose, and image quality. The latter assessment will be performed based on both qualitative (by means of readers and model observer studies) and quantitative metrics of image quality (such as contrast, noise, contrast-to-noise ratio, and spatial resolution).

All raw and reconstructed CT datasets will be stored on a dedicated and password-protected server in the Department of Radiology. The image reconstruction process will take place within the radiology department on a radiology owned and maintained workstation.

Selection of Subjects:

Fifty patients with acute abdominal/pelvic pain/abnormality and fifty patients with an oncologic abnormality undergoing clinically-indicated MDCT of the abdomen and/or pelvis as part of their clinical care will be eligible for inclusion in the study.

Subject Recruitment and Compensation:

Consent Process:

Subjects will be selected through a prospective review of the CT schedule for the Radiology Department. Prior approval from the subject's physician will be obtained prior to enrollment into the study, and the study will be introduced to the potential subject by a caregiver familiar to them per the Policy Statement Regarding Recruitment 10/22/2007.

The study coordinator will consent the eligible participant or legal guardian in the case of a minor according to the inclusion criteria provided in the Design & Procedure section. If necessary, the participants will have no less than 24 hours to consider their participation. Consenting will take place in a private room. The prospective participant may have family or a friend present during the consent process, if they wish. At least an hour will be slotted for the consent process, but we will not prevent the subject from asking questions beyond that time. If the subject wishes to consider the study overnight or longer, an additional appointment will be made for the subject to continue the consent process. From

the time of initial contact until the participant completes the study they will have complete freedom to access the coordinator by phone, email, or in person.

There will be no financial compensation for participation to this study.

Subject's Capacity to Give Legally Effective Consent:

Subjects without capacity to give consent will not be recruited in this study.

Study Interventions:

All patients will undergo a clinically-indicated MDCT examination using a DSSE dose split technique. Patient radiation dose exposure as well as image quality will be comparable to a standard of care MDCT examination.

Risk/Benefit Assessment:

The only identifiable risk for this study is the unlikely but not impossible loss of confidentiality. We have taken all the precaution to minimize this risk. Identifiable PHI will remain with their respective CT exam on a radiology department server and on PACS. HIPAA trained Duke personnel will have access to these exams, and only HIPAA trained Duke personnel will be involved in the study. For each exam, a date, exam protocol type, patient name, and patient ID number will be recorded. Files containing these ID numbers and the dates of the exams will be kept by one of the investigators on a password-protected computer.

Costs to the Subject:

There will be no cost to the patients entered in the study.

Data Analysis & Statistical Considerations:

The two patient cohorts (those with acute abdominal/pelvic pain/abnormality and oncologic process) will be evaluated in concert utilizing the following methodology.

To ensure consistency and reproducibility of the data, measurements of noise and image quality will be performed on a dedicated secondary workstation unit (Core2 x6800; Intel, Santa Clara, Ca) equipped with a previously validated custom Matlab-based software (Matlab, Ver. 2009a, Math-Works, Natick, Ma). Patient anterior abdominal subcutaneous fat will be used for noise assessments and different abdominal organs and vascular structures will be used. To ensure consistency and reproducibility of the data, all measurements will be repeated ten times on three consecutive images along the z-axis.

Four separate image quality figures of merit (FOM) will be measured from the images of each subject. These FOMs will include the contrast-to-noise ratio (CNR), the Rose model signal-to-noise ratio (SNR), the nonprewhitening matched filter detectability index (d'NPW), and the nonprewhitening matched filter with eye filter detectability index (d'NPWe). Each of these metrics will be analyzed using a repeated measures linear model where the repeat

measurements are across the different dose levels and different reconstruction algorithms. The predictors in linear model will be (a) the radiation dose (b) reconstruction algorithms. We will also examine if there is an interaction between dose and reconstruction algorithm. The estimated effects from the linear model will be used to identify the optimal dose and reconstruction combination.

Also, the noise power spectrum (NPS) and task-transfer function (TTF) will be reported for each reconstruction algorithm. The NPS and TTF are both components of the d' FOM.

Observer data analysis will be performed. Subjective image quality will be assessed in a blinded and randomized fashion by at least 4 independent radiologists. To minimize the effect of recall bias from the interpretation of multiple data sets within the same patient, data sets will be presented to readers over multiple sessions separated by a 2-4 week interval. All patient identifiers will be removed from images. Readers will rank image quality on a 100-point scale. Image quality attributes will be evaluated, including the following: 1) sharpness (defined as the discreteness of the margin of liver and splanchnic vasculature); 2) noise (defined as the amount of graininess or mottle of the image); 3) artifacts (including beam hardening or streaks due to metal or high-density materials such as residual barium within the colonic lumen); and 4) overall image quality (regarded as the reader's desire to use a certain image appearance to confidently detect the presence or absence of intraabdominal or intrapelvic abnormality). Standardized criteria will be presented to readers in a training session just prior to image evaluation session. Readers will be asked to detect the abnormality(s) within the abdomen or pelvis and rate their confidence in detection on a 100-point scale. With interpretation of multiple studies reconstructed at multiple dose intervals over a defined time interval, reader fatigue will also be assessed on the basis of lesion detection ability and/or subjective assessment of self-reported reader fatigue.

Data & Safety Monitoring:

Each CT dataset included in our study will have patient data associated with it on PACS and on the radiology department server. From each dataset, the necessary image reconstructions will be made on a workstation within the radiology department by a Duke radiologist. Qualitative scoring of the reconstructed images will take place in the radiology department by Duke radiologists. For each exam, a date, exam protocol type, patient name, and patient ID number will be recorded. PHI will be kept on a password-protected computer and will be deleted from the data after publication, thus leaving no link to identifiable PHI.

Privacy, Data Storage & Confidentiality:

Every effort will be made to ensure subjects' confidentiality. All images containing subject PHI will remain on PACS and on the radiology department server. PHI recorded with data will be kept in a file on a password-protected

computer. Any images used in publications or presentations will have all PHI removed. No identifiable PHI will be released outside of DUHS. There will be signed informed consents that will have some PHI on them that will need to be kept for at least six years along with the Regulatory Binder with an enrollment log in it.

References:

1. Bellini D, Ramirez-Giraldo JC, Bibbey A, et al. Dual-Source Single-Energy Multidetector CT Used to Obtain Multiple Radiation Exposure Levels within the Same Patient: Phantom Development and Clinical Validation. *Radiology* 2017; 283:526-537.

Figure 1:

