UTILIZATION OF DUAL ENERGY COMPUTED TOMOGRAPHY BASED METAL ARTIFACT REDUCTION TO IMPROVE RADIATION TREATMENT PLANNING IN PATIENTS WITH IMPLANTED HIGH-Z MATERIALS

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UTILIZATION OF DUAL ENERGY COMPUTED TOMOGRAPHY BASED METAL ARTIFACT REDUCTION TO IMPROVED RADIATION TREATMENT PLANNING IN PATIENTS WITH IMPLANTED HIGH-Z MATERIALS

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ABSTRACT

High quality computed tomography (CT) scans are integral to the successful cancer radiation therapy treatment plan. Metal streak artifact in the CT image originates when a high density medical implant (dental, orthopedic, etc.) disproportionally attenuates the imaging beam and corrupts the imaging data. This impairs the physician’s task of identifying important boundaries between tumor and healthy issue. The ability of treatment planning software to accurately compute vital radiation dosimetry metrics is also compromised. Many methods have been explored to mitigate the complications of streak artifact; however, none have been found effective and efficient for routine clinical use. This work explores the hypothesis that dual energy computed tomography (DECT) with an accompanying Metal Artifact Reduction Algorithm (MARS) is a convenient solution that can effectively address the major radiation treatment planning related complications caused by metal streak artifact. This work is based on three principal specific aims: (1) verify that streak artifact is a meaningful problem for patients with high-Z implants to both delineation and dosimetric accuracy; (2) demonstrate that DECT reduces the deleterious effects of metal streak artifact in a phantom; and (3) demonstrate that DECT is a viable solution to metal streak artifact for a human patient with an implanted high-z material causing streak artifact. Institutional IRB approval was obtained for the work. Several phantom designs were utilized and patients being treated in the
University of Alabama at Birmingham (UAB) Department of Radiation Oncology were recruited for the study. A variety of metrics were used to assess the extent of streak artifact in the imaging data, as well as how successfully the artifact was allayed. The detriment of streak artifact to structure delineation and dosimetric accuracy were demonstrated in both phantom and patient imaging. DECT with MARS was successful in mitigating the effects of streak artifact to treatment planning in both phantom and patient imaging data. Dual energy CT with metal artifact reduction is useful in remedying the problems associated metal streak artifact in patients with high-z implanted devices, including both structure delineation and dosimetric inaccuracy. At present dual energy scans are being solely used clinically for diagnostic imaging; however, their potential value to radiation oncology is unmistakable.

Keywords

dual energy CT; spectral imaging; metal artifact; streak artifact; high-z artifact; treatment planning
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<tr>
<td>AAA</td>
<td>Anisotropic Analytical Algorithm</td>
</tr>
<tr>
<td>ABS</td>
<td>acrylonitrile butadiene styrene</td>
</tr>
<tr>
<td>ACO</td>
<td>artifact causing object</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>clinical target volume</td>
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<tr>
<td>DECT</td>
<td>dual energy computed tomography</td>
</tr>
<tr>
<td>DEI</td>
<td>dual energy index</td>
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<tr>
<td>FBP</td>
<td>filtered back projection</td>
</tr>
<tr>
<td>FFT</td>
<td>fast fourier transform</td>
</tr>
<tr>
<td>GE</td>
<td>General Electric</td>
</tr>
<tr>
<td>GMI</td>
<td>geographic miss index</td>
</tr>
<tr>
<td>Gy</td>
<td>gray</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield unit</td>
</tr>
<tr>
<td>IMRT</td>
<td>intensity modulated radiation therapy</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>kVp</td>
<td>peak kilovoltage</td>
</tr>
<tr>
<td>MARS</td>
<td>metal artifact reduction software</td>
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MVCT  megavoltage computed tomography
OAR  organ at risk
PACS  picture archiving and communication system
PMMA  polymethacrylate
PTV  planning target volume
ROI  region of interest
RSNA  Radiological Society of North America
RT  radiation therapy
SNR  signal to noise ratio
SRS  stereotactic radiosurgery
TAG  terbium aluminum garnet
UAB  University of Alabama at Birmingham
VMAT  volumetric modulated arc therapy
VOI  volume of interest
Z  atomic number
CHAPTER I
INTRODUCTION

Problem Statement, Significance, and Proposed Solution

Medical implants and other foreign bodies with high x-ray attenuation values produce imaging artifacts that manifest as streaks outwardly radiating from the object. Accordingly, the artifact is referred to as the high-z or metallic “streak” type. Implants of dense enough material are very common and represent a major obstacle to generating quality CT imaging data.  

Modern intensity modulated radiation therapy (IMRT) treatment planning relies heavily on CT imaging data at multiple stages of the process. Radiation oncologists require visualization of detailed anatomy to properly delineate the segmentation used for 3D reconstruction of both target volumes and Organs-At-Risk (OAR). Streak artifact often obscures the anatomical detail necessary for proper definition of region of interest (ROI) boundaries. Metallic implants also adulterate the accuracy of the linear attenuation profiles which form the basis for the CT data set and associated tissue density values. The inverse planning algorithms within treatment planning software packages utilize this CT data to determine the optimum beamlet weights and intensities for a desired dose distribution within a patient. Radiation prescription doses are based on large evidence-based studies that establish an optimum therapeutic ratio based upon a balance between the necessary dose for tumoricidal effect in a target volume and the maximum acceptable dose to OARs to
prevent undesirable complications. Underdose to the target volume associated with a tumor is associated with decreased locoregional control of disease. Overdose to an OAR is associated with increased adverse effects specific to particular type of tissue injury. For example, in lung or breast cancer therapy, as the percentage lung volume receiving $\geq 20$ gray (Gy) increases above 25-30%, the risk of radiation pneumonitis rapidly increases. In stereotactic radiosurgery (SRS) treatments to central nervous system (CNS) cancer, point doses to the brainstem greater than twelve gray are associated with symptoms ranging in severity from temporary nausea/vomiting to delayed cranial neuropathy. Both improper ROI delineation and CT data adulteration can lead to an undesirable effect upon the therapeutic ratio, and result in loss of disease control or radiation injury in healthy tissue.

Any implant with sufficiently high density can cause streak artifact. Implants commonly located near areas susceptible to tumors are: dental fillings, dental implants, spinal hardware, hip prostheses, cardiac pacemakers/defibrillators, stents, brachytherapy seeds, and fiducial markers. The most recent large survey (1988) revealed that an estimated 0.5 million pacemakers, 6.5 million orthopedic implants, and many more millions of dental implants were distributed among the US population. The numbers have increased significantly since then. Practitioners at the University of Washington reviewed all available treatment plans for oropharyngeal/oral cavity cancer over a two year period and noted artifact from dental amalgam in 73.6% of cases. In 95% of these cases, artifact was found to extend into or obscure portions of the Clinical Target Volume (CTV). Figures 1 and 2 demonstrate how easily relevant anatomical information can be obscured by artifacts.
The need for an effective strategy to manage streak artifact is underscored by cases such as that shown in Figure 3. After treatment, the patient returned with local tumor control.
failure. Retrospective analysis and alternative imaging revealed that streak artifact from
dental work had concealed nodal involvement of the patient’s carcinoma. It followed that
this particular area was not included in the Planning Target Volume (PTV) receiving the
full prescription and the obscured cancerous tissue was underdosed, resulting in
unfortunate loss of tumor control\textsuperscript{11}.

![Figure 3. Streak artifact from a dental implant obscuring right retropharyngeal nodal
space.\textsuperscript{11} Copyright Elsevier 2008. Reprinted with permission.]

Because such review is not undertaken for every patient with treatment failure and no
large studies have been done, it is impossible to say just how widespread treatment
failure attributable to streak artifact is. Given the frequency that streak artifact is
clinically observed and the degree of underdosing (up to 25%)\textsuperscript{2} that Monte Carlo analysis
has demonstrated to be possible for nearby target volumes, the expected prevalence of
streak-artifact-related treatment failure is very troubling.

Hence, an ideal approach to address the effects of high-z artifact to radiation treatment
planning would possess the following characteristics:
improves visibility in the region of the implanted device so that clinicians can properly identify and delineate the boundaries of both targets and OARs;

- reconstructs the CT image with unadulterated HU values;
- accurately relates the attenuation of the high-z object itself;
- can be implemented in clinical workflow with minimal additional effort to patient, clinician, physicist, or clinical staff;
- adds negligible additional radiation exposure to patient; and
- adds a minimum of additional cost to the treatment planning process.

This list presents a significant challenge, particularly given the severity of artifact in some cases. The classical “worst-case scenario” of high-z artifact occurs when patients with bilateral hip prostheses are imaged. Hip prostheses are manufactured in a variety of material combinations, but to adequately replicate all of the vital biomaterial properties of the hip, high-z substances are required. Figure 4 displays a CT image in which bilateral hip prostheses are obscuring occult colorectal carcinoma in an 85 year old man (confirmed at autopsy).
Figure 4. Bilateral hip prostheses obscuring appreciation of occult colorectal cancer in an 85 year old man.\textsuperscript{12} Copyright RSNA 2011. Reprinted with permission.

Study Design and Justification

This work investigates the feasibility of using dual energy CT-Based Metal Artifact Reduction (MARS) to confront the treatment planning complications associated with high-z objects in and about regions receiving radiation treatment. At the time of this work, there are three commercially available diagnostic dual energy CT systems, each with a slightly different design principle. This study evaluates the Discovery CT750HD (GE Healthcare). A myriad of other approaches have been designed to combat metal streak artifact in CT images, and a not-insignificant number have even applied to radiation oncology. Many of these techniques have been shown effective, but for varied reasons ranging from onerous computational demand to impracticality of integration into clinical workflow, have not been engaged for mainstream use.

Dual energy (or spectral) CT based MARS has several unique advantages over other streak artifact coping strategies. The first and most important, is that it is physics based. Multiple obtained spectra at different energies of essentially the same image space afford
the image reconstruction algorithm the luxury of exploiting the energy dependent
differential contributions of the two phenomena principally responsible for photon
attenuation, Compton scattering and the photoelectric effect. The second is that the
artifact reduction algorithm is already integrated into the clinical imaging workflow and
was indeed a design feature of the system. Finally, the technology at the root of the
approach was developed and is being supported and marketed by a major medical device
manufacturer. This results in a steady increase in availability of the technology, and
increased awareness of the technique logically follows.
CHAPTER II
BACKGROUND AND LITERATURE REVIEW

CT imaging has become a pillar of near every branch of modern medicine. Only a few decades ago the technology was considered a novelty and a luxury. It is now the standard of care for a wide variety of clinical indications. CT was the first imaging modality with the ability to non-invasively image the internal three-dimensional anatomy of the human body. It was a substantial improvement over traditional two-dimensional diagnostic x-ray imaging which is hindered by superposition any separate anatomical structures aligned along with the direction of the imaging axis.\textsuperscript{13}

Figure 5. Illustration of conventional x-ray (a) setup, and (b) sample resulting chest radiograph.\textsuperscript{14} Copyright 2009 by SPIE Press. Reprinted with permission.
The fundamental principle of CT is quite simple. One wishes to know the internal structure of an entity without physically invading it. A series of projections, essentially shadows, of the entity are acquired with a beam of photons of sufficient energy to pass through the object without being completely attenuated. The attenuation profile of the beam will be dependent on the path the photons traverse and will vary as the line profile along which the beam passes varies. As the number of projections obtained increases, so too does the capacity for discrimination of structural boundaries within the entity. One is then left with the mathematical task of recreating the internal structure from the array of beam projections that have been obtained. This is known as the “inverse problem”, and is covered in greater detail in a proceeding section.
Figure 6. Schematic illustration of the inverse problem posed by CT. Attenuation profiles, $p_\gamma(\xi)$, have been measured for a set of projection angulations, $\gamma_1$ and $\gamma_2$. The unknown geometry, or object with its associated spatial distribution of attenuation coefficients, has to be calculated from a set of attenuation profiles $[p_{\gamma_1}(\xi), p_{\gamma_2}(\xi), p_{\gamma_3}(\xi), \ldots]$.\textsuperscript{13} Copyright Springer 2008. Reprinted with permission.

History of Computed Tomography and its Use in Radiation Oncology

The dawn of the history of CT begins in 1895 with Wilhelm Röntgen’s study x-rays while experimenting with Lenard/Crookes tubes. Although others (including notables names such as Ivan Pulyui, Nikola Tesla, Fernando Sanford, and Heinrich Hertz)\textsuperscript{15-17} had discovered and studied the phenomenon as early as two decades previously, Röntgen’s correspondence to the Würzburg’s Physical-Medical Society journal, entitled “On a new kind of ray: A preliminary communication” was the first published work explicitly upon x-rays.\textsuperscript{18} He would later receive the 1901 Nobel Prize for his comprehensive elucidation of the topic. Also in 2004, the IUPAC named element 111, Roentgenium which had preliminarily been dubbed Unununium, after him in recognition of his work.\textsuperscript{19}
On April 20th, 1972, a previously unsung engineer employed with EMI Ltd, a company that some may recognize as the implausibly fortunate first-signers of the Beatles recording contract, and a consultant radiologist with Atkinson Morley’s Hospital delivered a lecture at the 32nd Congress of the British Institute of Radiology. The lecture was entitled, “Computerised Axial Tomography (A new means of demonstrating some of the soft tissue structures of the brain without the use of contrast media)”. The engineer, Godfrey Hounsfield, and the radiologist, Dr James Ambrose, had previously presented the results of some of their animal experiments to little interest.

Figure 8 shows an image from the first patient clinically imaged on the prototype EMI scanner, a patient with a suspected left (early convention seems to be viewing axial slices from a superior rather than inferior aspect of the subject) frontal lobe picture. The
surgeon who performed a resection soon after remarked that, “it looks exactly like the picture.”

Figure 8. Axial slice of the first patient imaged on the Atkinson Morley Hospital EMI prototype visualizing a left inferior frontal lobe tumor later confirmed to be a grade III astrocytoma by the surgeon performing resection.
As to be expected from the limited computing capability and the iterative algebraic reconstruction approach, images took a long time to process. Images from the prototype
scanner were taken from the hospital to EMI's headquarters via tape for overnight processing. Each axial image took approximately twenty minutes to generate with an ICL 1905 computer.\textsuperscript{21} Revolutions in computing and implementation of the filtered back projection (FBP) approach, and eventually fast-fourier transforms, quickly led to drastic reductions in reconstruction time and assuaged fears that mainframes would be required at hospitals wishing to utilize the new scanners.

The development of FBP as a solution to the “inverse problem” has an interesting and somewhat convoluted history. The definitive application of FBP to medical tomographic imaging was carried out by Allen Cormack in 1961 and later published in 1963.\textsuperscript{24}

In his original patent, Hounsfield notes:

“It has also been proposed to map the absorption coefficient of a two dimensional slice of a body from a knowledge of the line integral of the absorption coefficient along all lines intersecting the slice, by a process involving the application of Fourier inverting techniques. This proposal is described in a paper entitled “Representation of a Function by its Line Integrals, with some Radiological Applications” by A.M. Cormack (Journal of Applied Physics, Volume 14, Number 9, pages 2722 to 2727 and Number 10, pages 2908 to 2913). An experimental test was carried out on a special model, each line integral used in the evaluation being derived by letting a fine beam of gamma–rays of known intensity be incident on the slice and deriving a signal representing the integral along the line of the beam from the gamma–rays emerging from the body. The method described in this paper is capable in theory of yielding a unique principal solution, but is nevertheless complicated, has limited practical application and liable to error in the practically feasible forms.”\textsuperscript{25}

It is probable that Hounsfield did not immediately appreciate the significance of FBP and its close relationship to the Fourier transform. He likely was aware of the development of the modern Fast Fourier Transform (FFT) by J.W. Cooley and J.W Tukey which was published in 1965\textsuperscript{26}; however as he was working for a competitor of IBM, whose computers Cooley and Tukey had implemented FFT for, it is doubtful that he appreciated the extent to which it would revolutionize signal processing. It is also conceivable that
this passage was meant to negate the significance of Cormack’s work as part of a larger business strategy by EPI to minimize the vulnerability of the portfolio of the intellectual property they were in the process of establishing. EPI was implicitly aware of its inexperience within the medical industry and also knew that Hounsfield’s patents were vulnerable, particularly because of how apparent it became that Cormack’s methods would be necessary for mainstream implementation of the technology. Cormack’s work, as it turns out, was so indispensable that he would eventually share the 1979 Nobel Prize in medicine with Hounsfield.

Interestingly, the FBP problem had been solved several times previously. Although he did not publish his results, we know from discussion in a publication by Hermann Bockwinkel on the propagation of light in vibrating crystals that Hendrik Lorentz (shared 1902 Nobel Prize for his work in elucidation of the Zeeman effect) found a solution to the three-dimensional inverse problem via reconstruction with two-dimensional surface integrals. In 1917, Austrian mathematician Johann Radon published a detailed, comprehensive solution to what would become the tomographic inverse problem. Unfortunately for Radon, his work was published in German and rigorously esoteric, and its importance was not discovered until nearly fifty years after.

Review of Relevant X-Ray Attenuation Principles

There are a variety of types of interactions between an incident fluence of photons and media through which it passes. The relative prevalence of each of these interactions varies across the possible energy levels of the photon quanta. As such, only a few of the
interactions are important with regard to computed tomography and radiation treatments; they are listed below in Table 1.

Table 1. Most Important Photon Interactions with Atoms of the Absorber.\textsuperscript{31}

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Symbol for electronic attenuation coefficient (cross section)</th>
<th>Symbol for atomic attenuation coefficient (cross section)</th>
<th>Symbol for linear attenuation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson scattering</td>
<td>( e\sigma_{\text{Th}} )</td>
<td>( a\sigma_{\text{Th}} )</td>
<td>( \sigma_{\text{Th}} )</td>
</tr>
<tr>
<td>Rayleigh scattering</td>
<td>( e\sigma_{\text{c}} )</td>
<td>( a\sigma_{\text{c}} )</td>
<td>( \sigma_{\text{c}} )</td>
</tr>
<tr>
<td>Compton scattering</td>
<td>( e\sigma_{\text{c}} )</td>
<td>( a\sigma_{\text{c}} )</td>
<td>( \sigma_{\text{c}} )</td>
</tr>
<tr>
<td>Photoelectric effect</td>
<td>( e\tau )</td>
<td>( a\kappa_{\text{pp}} )</td>
<td>( \kappa_{\text{p}} )</td>
</tr>
<tr>
<td>Nuclear pair production</td>
<td>( e\kappa_{\text{tp}} )</td>
<td>( a\kappa_{\text{tp}} )</td>
<td>( \kappa_{\text{t}} )</td>
</tr>
<tr>
<td>Photodisintegration</td>
<td>( e\sigma_{\text{PN}} )</td>
<td>( a\sigma_{\text{PN}} )</td>
<td>( \sigma_{\text{PN}} )</td>
</tr>
</tbody>
</table>

Of these interactions, only four in particular are relevant to CT imaging and radiation treatment. At typical diagnostic imaging energies (40 kV – 140 kV), Compton scattering (Figure 10), photoelectric effect (Figure 11), and Rayleigh scattering occur are the three interactions that occur with meaningful probability. For near tissue density substances, Rayleigh scattering becomes inconsequential; however, when dealing with substances of higher z-values, such as metallic devices, the interaction becomes non-negligible. The final interaction of any material consequence is nuclear pair production, which only occurs at energies in the therapeutic range.

The differential cross-section for Compton scattering is derived from quantum electrodynamic theory and is given by the Klein-Nishima formula\textsuperscript{32}:
\[
\frac{d\sigma}{d\Omega} = \alpha^2 r_c^2 P(E_\gamma, \theta)^2 \left[ \frac{P(E_\gamma, \theta) + P(E_\gamma, \theta)^{-1} - 1 + \cos^2(\theta)}{2} \right]
\]

where:
- \(E_\gamma\) is the incident photon energy
- \(d\Omega\) is an infinitesimal solid angle element
- \(\alpha\) is the fine structure coefficient
- \(\theta\) is the scattering angle
- \(r_c\) is the reduced Compton wavelength of
- \(P(E_\gamma, \theta)\) is the energy and scattering angle dependent ratio of photon energy before and after collision

This can be simplified to \(^{31}\):

\[
\frac{\sigma_{c, KN}^V}{\rho} = \frac{ZN_A}{A} \sigma_{c, KN}^V
\]

where \(Z = \) atomic number, \(A = \) atomic mass, and

\(N_A = \) Avogadro's number, and \(\sigma_{c, KN}^V\) is the Klein-Nishina coefficient

In practice \(Z/A = 0.5\) for all low atomic number absorbers, but approaches 0.4 for higher atomic numbers. The \(Z/A\) for iodine is 0.417. Therefore, there is a small dependence of \(\sigma_{c, KN}^V / \rho\) on \(Z\).
Figure 10. Schematic (a) diagram and (b) vector representation of Compton Effect. An incident photon with energy $h\nu = 1$ MeV interacts with a stationary and free electron. A photon with energy $h\nu'$ is produced and scattered with a scattering angle $\theta = 60^\circ$. The difference between the incident photon energy $h\nu$ and the scattered photon energy $h\nu'$ is given as kinetic energy to the recoil electron. Copyright 2010 by Springer. Reprinted with permission.
The photoelectric mass attenuation coefficient is given by:

\[
\frac{\tau}{\rho} = \frac{N_A}{A} \alpha^4 (\varepsilon \sigma_{th}) Z^n \sqrt{\frac{32}{\varepsilon}}
\]

where:
- \( \varepsilon \) is the usual normalized photon energy, i.e., \( \varepsilon = \frac{hv}{(m_e c^2)} \)
- \( \alpha \) is the fine structure constant
- \( Z \) is the atomic number of the absorber.
- \( \varepsilon \sigma_{th} \) is the Thomson electronic cross section
- \( n \) is the photon energy dependent power for the \( Z \) dependence
  - ranging from \( n = 4 \) at relatively low photon energies to \( n = 4.6 \) at high photon energies.

Empirically, \( \frac{\tau}{\rho} \propto Z^3 / E^3 \) with the exception of discontinuity peaks around the absorption edge binding energies. These discontinuities correspond to a resonance phenomenon that occurs when a quanta of incident photons have energy levels very near to an L or K shell characteristic binding energy.
Rayleigh scattering is not frequently discussed in the context of medical imaging or therapy. The relationship between its mass attenuation, incident photon energy, and atomic number of scatter medium is given by:

\[
\frac{\sigma_{\mu}}{\rho} \propto \frac{Z}{(h\nu)^2}
\]

It only matters to imaging in the presence of a high-z material. For near-tissue-level densities, its interaction probability is negligible compared to the other attenuating factors. For higher density materials though, its mass attenuation contribution is within an appreciable difference of Compton scattering and photoelectric effect (Figure 12 and Figure 13).
Figure 12. Contribution of individual phenomena to overall mass attenuation for water (left) and stainless steel (right). Data courtesy of NIST XCOM.\textsuperscript{33}

With respect to therapeutic considerations, because of the nature of this photon-particle interaction, no energy is transferred during the interaction; therefore the energy transfer coefficient for Rayleigh scattering is always equal to zero and thus the process contributes does not towards dose deposition.
Figure 13. Mass attenuation coefficients for the main photon-matter interaction mechanisms for some materials in the diagnostic imaging range. Note the differential contributions of each mechanism across the range of energies for different substances. Data courtesy of XCOM Photon Cross Sections Database.
Pair production is the final photon-media interaction with any significance, but only so for therapeutic energies, and only about the nucleus. Another type of pair production can occur in the field of an orbital electron, and is often referred to as triplet production because of the ensuing ejection of the orbital electron. As the minimum mass-energy equivalence for an electron or positron is 0.511 MeV, the probability for their production at incident photon energies below 1.022 MeV is highly improbable. The process was first mathematically derived by Bethe and Heitler in 1934.\textsuperscript{34} A representation of it is displayed in Figure 14 below.

![Diagram of pair production](image)

Figure 14. Depiction of \textit{a priori} and \textit{ex post facto} nuclear pair production.\textsuperscript{31} Copyright 2010 by Springer. Reprinted with permission.

Basics of Computed Tomography Reconstruction

The most commonly used algorithm for reconstruction of CT images is FBP. All modern clinical CT systems implement some form of this process (Figure 15).\textsuperscript{13} To understand the concept of FBP, it is useful to have a basic idea of the flow of information from the acquisition of signal to its final reconstruction.
Simple backprojection was pioneered by Kuhl and Edwards in the 1960s for the original purpose of imaging with radioisotopes\cite{35}, but was quickly applied to transmission-based images.\cite{36,37} In it, line sampling projection data is obtained, and the attenuation value of each ray associated with its line sampling is backprojected onto an image matrix according to the path of the ray. Because the intersecting rays radiate in all directions from their point of convergence, the pixel whose attenuation is being modeled contributes to the attenuation value of all other pixels according to a $1/r$ dependence.\cite{38} This results in a characteristic blurring, which can be seen in Figure 16, one of Kuhl and Edwards’ original diagrams of the phenomenon.
Figure 16. (a) Reconstruction of a localized source of radioactivity, using back-projection. (b) Illustration of back-projection for a circular object. Note how profiles A, B, and D contribute a positive value to a cell outside the original object, thus producing the star artifact.\textsuperscript{39}

The use of a filter to alleviate the characteristic of the point spread function obtained in simple backprojection was first employed by Bracewell and Riddle for the purposes of radio astronomy\textsuperscript{40}, whereupon its utility for medical image reconstruction was quickly realized. In filtered backprojection, the line sampling data is Fourier transformed,
subjected to a high-pass filter which removes the contribution of other line samplings, inverse-Fourier transformed, and backprojected onto the line from which it was sampled.\textsuperscript{13}

Dual Energy Computed Tomography

The ink on Hounsfield’s first patent had scarcely time to dry before speculation on the possible benefits of using multiple energies arose.\textsuperscript{41-43} Hounsfield himself briefly touched upon the subject in one of his succeeding patents.\textsuperscript{44} However, the technology was still in its infancy and a large array of obstacles would have to be overcome before the notion could become a reality. Two separate scans were required at the time, complicating the use of contrast. Early scans lacked CT density value consistency, lengthy acquisition times meant unavoidable patient movement during scan, spatial resolution was limited, and contemporary post-processing capabilities were insufficient.\textsuperscript{45} It would not be until the mid-2000s that diagnostic CT would be mature enough for a resurgence in dual energy technology to become possible.

Broadly speaking, three elements are necessary for the successful execution of spectral CT imaging. The first is obviously the availability of x-rays of different energies. Although in practice using multiple sources is typically most viable, the polychromatic nature of Bremsstrahlung radiation makes one source a possible approach.

Figure 17 shows the spectra for the two peak tube potentials most commonly used in DECT. Energies too far outside of this range are usually not useful. Beams too far below
80 kVp are heavily attenuated by normal human tissue. Beams above 140 kVp result in poor soft tissue contrast.

Figure 17. Spectra of the Straton tube used in the dual source, dual energy CT at 140 and 80 kV peak tube potential. The peaks represent the characteristic lines of the tungsten anode and the continuous spectrum is a result of Bremsstrahlung. The mean photon energies are 53 and 71 keV, respectively. Copyright Springer 2011. Reprinted with permission.

The next requirement is a detector array capable of appropriately discriminating the spectrum associated with each energy level. All modern fan-beam CT’s use some type of solid-state scintillator detector. Each of the three clinically available dual energy technologies employs a different strategy in their detector array design for discrimination of the desired photon quanta.
The third requirement is an ample distinction in the attenuative properties of the substances or objects being resolved in the imaging study. This seems intuitive to the nature of all CT imaging, and indeed it is, but within the context of dual energy imaging it refers to utilizing the difference for optimum material based decomposition. Material-based decomposition is the process by which the relative contributions to an image of two substances (called basis materials) of arbitrary density are decomposed with respect to the differential contributions of Compton scattering and photoelectric absorption to their respective total attenuations. In theory, with the appropriate scan energies and material basis pairing, Rayleigh scattering could be used in place of one of the other phenomena, but the author was unable to find mention of this in the literature. Via the same concept, the entire image can be reconstructed at any energy level in between the levels of the high and low energy acquisition as a linear combination of the attenuation coefficients of the chosen basis materials. The premise was developed very quickly after the advent of CT by Alvarez et al in 1976.

The quality of the linear combination based reconstruction will depend on the magnitude of differences in Compton and photoelectric contributions to attenuation between the materials in the basis pair selected. The distinction between two substances is characterized by the dual energy index (DEI), which is expressed as:

$$DEI = \frac{H_x - H_y}{H_x + H_y + 2000}$$

where $H_x$ and $H_y$ are the CT values associated with each of the low and high energy tube potentials selected.

Currently there are three clinically available dual energy CT technologies, each marketed by a separate commercial vendor. Each mode of dual spectra acquisition has its own
blend of advantages and disadvantages. The three current types of dual energy scanning are:

- Dual source,
- Dual layer detector, and
- Rapid voltage switching.

The first clinical dual energy scanner was the SOMATOM Definition, introduced by Siemens. The SOMATOM Definition is a dual source scanner. There are two separate sources, each with its own detector that concurrently rotate and acquire spectra. The chief advantage to this technology is that the tube potential and current can be easily and independently altered for each source allowing for the highest versatility and range of difference of scan acquisition energies. Another advantage is existing dual energy reconstruction algorithms and material decomposition approaches have been previously developed and are relatively mature, as the dual source method is in principle equivalent to the method previously employed in years past of acquiring two separate and consecutive scans of an entity at different energies.

There are several disadvantages to the technique. The requirements in terms of hardware investment are considerably greater as two x-ray tubes and two detectors are required. Another drawback is that there is only so much space available within a gantry. This constraint hinders the size of the second detector, resulting in a smaller field of view for one of the acquired spectra. This means that only a portion of the axial slice is being imaged in temporal alignment. Recently, Siemens released an updated version of the unit, called the SOMATOM Flash, which has slightly improved the field of view of the second detector (Figure 18).
Another issue is that two separate filtered backprojections are required, which means a primary post-processing of data is impossible. This is because there are no equivalent projections for the temporally aligned field of view. Finally, there will necessarily be a great deal more noise in dual sourced images because of cross-scatter between the two beams and their respective detectors.

Philips’ offering is a specially adapted Brilliance 64 CT which uses a detector with two distinct scintillation layers optimized for interference with different photon energies (Figure 19).
This approach affords the best temporal resolution, offers a full field of view, and also is advantageous in only requiring a single tube. However, it suffers from both a lower dose efficiency and higher spectral overlap. Because it only has one source spectrum, it also is less effective at mitigating beam hardening artifacts associated with high density objects in the field of view.

The final dual energy CT modality is the fast kV switching method, utilized by General Electric (GE) in the Discovery CT750HD. They have proprietarily dubbed their technique as gemstone spectral imaging. In the fast kV switching technique, a single source rapidly alternates between emission of high and low energy x-ray fluences. In principle, this is the ideal method of acquiring a dual energy image sequence as each pair of projections is in both temporal and spatial alignment, and only one source-detector combination is required. However, this design faced several daunting challenges of
implementation. The first was a generator and tube capable of reliably switching between high and low peak tube voltages with minimal variance. However, because the tube potentials are monitored and recorded, it is in principle possible to correct for the variance during the image reconstruction process.

The second challenge was identifying a detector material with minimal afterglow and a short enough primary decay time that it could reliably parse the incoming quanta into their appropriately sourced spectrum. Primary decay refers to the amount of time required for a luminescent material to transition from its high to low energy state after being excited by incident radiation. This is typically on the order of nanoseconds in most inorganic scintillator materials, but can vary drastically based on the electronic band and crystal lattice structure. Some of the excitations are meta-stable and leave the material in a classically forbidden state. The resulting, much-slower decay results in delayed fluorescence or phosphorescence, or after-glow. Afterglow is quantified as the remaining fluorescence intensity proportion 3 ms after cessation of x-ray citation. When appropriate doped (normally with Tb or Pr), Gadolinium oxysulfide (Gd₂O₃S) or GOS ceramics have a primary decay time of 3-4 µs and an afterglow from 10⁻³ to 10⁻⁵ s. GE has christened the material as Gemstone.

A careful review of the patents coming from GE’s Advanced Ceramics Lab reveals that Gemstone is a terbium aluminum garnet (TAG) co-doped with lutetium and cerium, likely of one of the following stoichiometric proportions:
\[
\left(\text{Tb}_{1-x,y}\text{Lu}_x\text{Ce}_y\right)\text{Al}_z\text{O}_{12}
\]

where:

\[
\begin{bmatrix}
  x & y & a & z \\
  0   & 0.003 & 3.004 & 4.996 \\
  0.066 & 0.003 & 3.004 & 4.996 \\
  0.066 & 0.003 & 3.004 & 4.996 \\
  0.066 & 0.0065 & 3.004 & 4.996 \\
\end{bmatrix}
\]

Image Reconstruction with Fast Switching kVp Dual Energy CT

Chanda and Langan provide an excellent synopsis of the correction and reconstruction process. Once the projection acquisition is complete, several calibrations are necessary. This is due to limitations in the high and low energy switching of the tube. These imperfections make it difficult to determine a set tube voltage with the same spectral response as that actually acquired. The spectrum is then deconvolved into a linear superposition of known basis spectra, which is given by:

\[
S_p(E) = \sum_{k}^{N_k} \alpha_k S_k(E)
\]

where \( S_k(E) \) are the basis spectra of the known kVps, \( N_k \) is the number of basis spectra, and \( \alpha_k \) are the weights of the spectra. The normalized detector response is:

\[
R(d) = \frac{\sum_k \alpha_k G_k(d)}{\sum_d \sum_k \alpha_k G_k(d)}
\]

wherein:

\[
G_k(d) = \int_E S_k(E) E \left[ 1 - e^{-\nu_k(E)d} \right] e^{-\sum_k \nu_k(E) d \int_k(d)} dE
\]
where $\mu_d(E)$ is the linear attenuation coefficient of the detectors, $t_d$ is detector thickness, $\mu_b(E, d)$ and $I_b(d)$ are the linear attenuation coefficient and thickness of bowtie (a visualization of a bowtie filter is shown in Figure 20) material $b$ corresponding to the detector channel. $R(d)$ is known by measurement through a fast-switching air scan. $G_k(d)$ is determined from system geometry. All that is then left is to plug in $G_k(d)$ and $R(d)$ to solve for $\alpha$, using a least square fitting. This determines the calibration corrections for the basis spectra, which can now be spatially aligned in projection space and transmuted into a designated material basis pair projection. From here, the image can be reconstructed into a virtual monochromatic image anywhere in the given energy range using projection based material decomposition à la Alvarez 1976.
In terms of the two basis materials, the energy dependent attenuation in two kVp measurements can be expressed as:

\[
p_{\text{low}} = -\ln \left( \frac{I}{I_0} \right)_{\text{low}} = -\ln \left[ \frac{S_{\text{low}}(E) \exp \left\{ -[m_1 \mu_1(E) + m_2 \mu_2(E)] \right\} dE}{\int S_{\text{low}}(E) dE} \right]
\]

\[
p_{\text{high}} = -\ln \left( \frac{I}{I_0} \right)_{\text{high}} = -\ln \left[ \frac{S_{\text{high}}(E) \exp \left\{ -[m_1 \mu_1(E) + m_2 \mu_2(E)] \right\} dE}{\int S_{\text{high}}(E) dE} \right]
\]
where $\mu_1(E)$ and $\mu_2(E)$ represent the mass attenuation coefficients of each basis material, $m_1$ and $m_2$ are their respective effective densities, and $S_{low}(E)$ and $S_{high}(E)$ are empirical quantities dictated by the source spectrum, source filtration, and detector performance. From these, the projection space associated with any in-range energy can be reconstructed as if it had been obtained with that mono-energetic X-ray source.

$$p(E) = -\ln \left( \frac{I}{I_0} \right) = m_1\mu_1(E) + m_2\mu_2(E)$$

### High-Z Artifact

High-Z or metallic streak artifact arises based on the principle that low-energy x-rays are more intensely attenuated than high energy x-rays and that attenuation, $\alpha$, is more severe in high-z materials than low-z materials.

$$\alpha \propto \frac{Z^4}{E^3}$$

It should be evident from the $Z^4$ dependence in above relationship that beam hardening will be most severe for any materials in the body comprised of metal or ceramics (usually a metal oxide). Because the source spectrum is polychromatic in nature, the beam hardening leads to inconsistencies in the image projection space. These inconsistencies are manifest in the reconstructed images as white streaks outwardly radiating from the object, and in the case of multiple high-z objects, dark bridging between the objects. In practice, regions of sufficiently high attenuation are rendered as near-singularities in the attenuation profile of the projection space. The backprojection lines through that point
thus contain extremely high numerical values, which are assigned as high CT values in
the image reconstruction, which are displayed as the characteristic white streak lines.
The dual energy approach is well-suited to the streak artifact dilemma because the
relative contributions of the two physical processes, photoelectric and Compton effect, to
mass attenuation vary according to both energy level and Z number. A thorough
mathematical basis for the validity of the dual-energy based metal artifact reduction
process is excerpted from Ch. 9.6.3 of Buzug’s textbook\textsuperscript{13} and provided in Appendix A.
Partial volume effects which arise from large discontinuities between high and low
contrast regions also significantly contribute to the streak artifact observed around high-z
objects. Partial volume artifact can become an issue in situations where a structure
possesses a highly contrasted edge does not align with the edge of a detector element.
The intensity of the photon quanta that interacted with the edge will then necessarily be
averaged out over the width of the detector element. This leads blurring and reduced
contrast of the boundary in question. The likelihood of this happening is inversely
correlated with the resolution of the scanner, which is dictated by the detector element
size and density. Figure 21 shows an example of the classic version of this phenomenon
in an older scanner. If this edge happens to belong to a very high density object, it can
contribute to the radial streaking associated with metal artifact. Figures 22 and 23 further
illustrate how beam hardening and partial volume artifact coexist and persist even in
more modern scanners.
Figure 21. In this CT slice from an older, low-resolution scanner one can clearly see the blurred boundaries, particularly in zones of transition from very high to low contrast. This is a classic example of the partial volume effect.\textsuperscript{54} Copyright American Roentgen Ray Society 1978. Reprinted with verbal permission.

Figure 22. Example of the combination of partial volume and metal streak artifacts. a) Uncorrected 70 kVp reconstruction with lead insets. b) MARS corrected 70 kVp reconstruction. The actual inset width is 2.8 cm. These insets were actually hollow insets; the attenuation of lead is too high to visualize inside.
Figure 23. Metal artifacts in CT images of a jaw. a) presents the overview scan used to plan the axial slices. b–d) then show the axial reconstructions at different slice positions throughout the tooth area. Artifact from the dental amalgam is apparent. Copyright Springer 2008. Reprinted with permission.

Consequences of High-Z Artifact to Modern Radiation Therapy

The consequences of high-z artifact to radiation therapy have been well-studied in treatments with photons, electrons, and protons. The first and most obvious consequence
arises when a clinician is unable to visualize the true extent of gross disease, and leaves it out of the appropriate PTV. As intensity modulated treatments become an increasingly higher proportion of radiation therapies, the risk that inaccurate target delineation imparts to disease control probability increases as well. Highly modulated plans tend to have very steep dose gradients in the region surrounding designated target volumes. Indeed, steep gradients have become a planning goal, especially in stereotactic treatments. If the disease is not included in the target volume in one of these plans, it will likely be significantly underdosed.

The second consequence of high-z materials in the vicinity of treatment areas is the contribution of the inaccurate CT numbers in artifact regions to the calculated dose grid. All of the most updated versions of modern dose computation software employ algorithms that take into account the CT values in the scan. The CT values are converted to electron density (Anisotropic Analytical Algorithm), mass density (Acuros XB algorithm), or proton stopping power values depending on the type of plan or algorithm used. The default CT calibration curve used by Eclipse for conversion of CT values to electron density values is:

\[
\rho^{\text{e}} = 1.0 + 0.001 \times N_{CT} \quad -1000 \leq N_{CT} \leq 100 \\
\rho^{\text{e}} = 1.052 + 0.00048 \times N_{CT} \quad N_{CT} > 100
\]

where:

\[
\rho^{\text{e}} = \text{Electron density relative to electron density of water} \\
N_{CT} = \text{Dependence of the electron density from the electron density of water on CT number}
\]

If the CT values are inaccurate because of beam hardening, partial volume, or other effects the values to which they are converted in each plan type will also be. A third
consequence is the scatter of the therapeutic photons being delivered in the actual
treatment. The scatter can be appropriately modeled in the dose deposition algorithms,
but only provided the scattering cross sections used in the computation are accurate.
Again, without the correct CT values, this is impossible. Also, because scattering
direction is highly interface dependent, accurate discrimination of high-z structure
boundaries is necessary, even if the actual structure CT values are correct. Dose
perturbations and miscalculation in the vicinity of high-z objects have been
comprehensively modeled and studied.\textsuperscript{56-64} It has additionally been well-established that
the dose perturbations that arise from not correcting these errors can result in
unacceptable plan quality when the true dose distributions are elucidated in simulations
with artifact corrections.\textsuperscript{2, 65, 66}

Given the nature of the deleterious effects of streak artifact to radiation treatment
planning, dual energy computed tomography at first glance meets many of the
requirements for a clinically meaningful solution previously enumerated. We therefore
set out to verify its performance and suitability with regard to the problem of metallic
streak artifact in radiation treatment plans of patients with implanted high-z materials.
CHAPTER III
SPECIFIC AIMS

The applicability of a newly available dual energy CT scanner to the problems associated with metal streak artifact in radiation treatment planning was studied. It was hypothesized that the monoenergetic reconstruction from a spectral CT acquisition with metal artifact reduction sequencing would afford increased accuracy of rendered CT values in image arrays. It was further hypothesized that this in turn would result in increased visual quality of the scans, increased accuracy in volume rendering of contoured structures, increased structure boundary delineation accuracy, and finally increased accuracy of the dosimetric computations utilized in treatment planning computations. The research objectives in this work were arranged within the constraints of three distinct specific aims; each aim and the investigations and results pertaining to that aim are organized within its own section formatted as a preprint manuscript.

Aim 1: Verify that streak artifact caused by high-z implants is a meaningful obstacle to a) accurate delineation of regions of interest in the vicinity of high-z objects, and b) accurate computation of volumetric dose distributions in the vicinity of high-z objects

Aim 2: Demonstrate in a phantom that dual energy computed tomography can reduce the deleterious effects of streak artifact to a) accurate delineation of regions of interest in
the vicinity of high-z objects, and b) accurate computation of volumetric dose distributions in the vicinity of high-z objects.

Aim 3: Demonstrate in a patient that dual energy computed tomography can reduce the deleterious effects of streak artifact to a) accurate delineation of regions of interest in the vicinity of high-z objects, and b) accurate computation of volumetric dose distributions in the vicinity of high-z objects.
CHAPTER IV

IMPROVED STRUCTURE DELINEATION IN REGIONS AFFECTED BY HIGH-Z STREAK ARTIFACT WITH DUAL ENERGY COMPUTED TOMOGRAPHY

by

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Submitted to *Journal of Applied Clinical Medical Physics*

Format adapted for dissertation
Improved structure delineation in regions affected by high-z streak artifact with dual energy computed tomography

Abstract:

Purpose: In this study, we investigated the effects of high-z streak artifact on the accuracy of region of interest (ROI) discrimination and delineation in radiation treatment planning. We then test the hypothesis that using a dual energy computed tomography (DECT) scan can alleviate those effects.

Materials/Methods: We constructed two phantoms with an array of different types of objects frequently found in vivo known to cause high-z artifact when imaged with traditional CT. We imaged each of these phantoms with a GE Lightspeed treatment planning CT, with a Tomotherapy MVCT, and with a GE CT750HD dual energy scanner and then assessed how accurately a known-sized ROI could be segmented in each of the scans with both manual and auto-segmentation with the geographic miss index (GMI) metric.

Results: DECT scans facilitated more accurate segmentation of ROIs affected by streak artifact across nearly all artifact causing objects (ACO). Mean GMI was significantly reduced by using DECT in favor of the traditional CT scan (GMI_{lightspeed} = 18.08%, GMI_{DECT} = 4.56%; p<0.001).

Conclusion: In recent years, DECT scanners are becoming increasingly available as diagnostic radiology tools in hospitals. Our results indicate that DECT has the potential to be used to mitigate the deleterious effects of high-z streak on ROI delineation ability in radiation treatment planning scans.

Keywords: dual energy CT, high-z artifact, metal streak artifact, structure delineation

PACS numbers: 87.57.Q-, 87.57.nm, 87.56.-v, 87.55.-x
Introduction

An in vivo object with a high x-ray attenuation or a high-z value produce CT imaging artifact which radially streaks from the object. Medical implants are frequent culprits in the generation of this artifact due to their high densities. Radiation oncologists require visualization of detailed anatomy to properly delineate the segmentation used for 3D reconstruction of both target volumes and organs-at-risk (OAR). Streak artifact often obscures the anatomical detail necessary for proper definition of ROI boundaries. Failure to completely delineate a partially obscured target can result in its underdose which can in turn result in decreased locoregional control of disease. Overdose to an OAR is associated with increased adverse effects specific to particular type of tissue injury. For example, in lung or breast cancer therapy, as the percentage lung volume receiving $\geq 20$ gray (Gy) increases above 25-30%, the risk of radiation pneumonitis increases rapidly. In stereotactic radiosurgery (SRS) treatments to central nervous system (CNS) cancer, point doses to the brainstem greater than twelve gray are associated with symptoms ranging in severity from temporary nausea/vomiting to delayed cranial neuropathy. Both improper ROI delineation and CT data adulteration can lead to an undesirable effect upon the therapeutic ratio, and result in loss of disease control or radiation injury in healthy tissue.

The purpose of this work was first to examine the specific effects of several different types of high-z materials on visualizing and appropriately delineating regions of interest afflicted by their artifact, and then to test the hypothesis that dual energy computed tomography (DECT) was an effective solution for restoring proper contouring ability in ROIs detrimentally affected by high-z artifact.
Methods and Materials

Any object of density sufficiently higher than its surrounding media whether in a patient or water-resembling phantom can cause characteristic streak artifact due to its disproportionately high leverage on the average attenuation of all the line profiles that intersect it within the projection space being reconstructed by the filtered backprojection algorithm.

A series of phantoms were developed and tested for each of these ends. In the exploratory phase of the project, a pilot phantom was constructed as an investigatory proof of principle. A photograph of the pilot phantom is shown below (Figure 1). A table of the objects and artifact causing materials is also provided. Each artifact was situated near a polymethacrylate (PMMA) sphere (d = 0.625 in) in an axial plan with respect to the scan direction to observe the effect of the high-z material on visualizing a nearby region of interest. PMMA was chosen as the region of interest (ROI) material because the difference between it and water’s radiopacity is similar to that between tissue and many types of tumor.
Figure 24. Initial pilot phantom in an a) overhead oblique view and b) an overhead view. From left to right, high-z objects are: hip prosthesis, dental hardware, fiducial markers in epoxy bed, and implantable cardiac defibrillator.

Table 2 - Materials used in pilot phantom

<table>
<thead>
<tr>
<th>Object</th>
<th>Material</th>
<th>Density (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphere</td>
<td>PMMA</td>
<td>1.18</td>
</tr>
<tr>
<td>Hip prosthesis</td>
<td>Ti-6Al-4V</td>
<td>4.43</td>
</tr>
<tr>
<td>Dental hardware</td>
<td>Amalgam (Hg,Ag,Sn alloy)</td>
<td>13.48</td>
</tr>
<tr>
<td>Fiducial markers in epoxy bed</td>
<td>Gold</td>
<td>19.3</td>
</tr>
<tr>
<td>Implantable cardiac defibrillator</td>
<td>Titanium casing</td>
<td>4.43</td>
</tr>
</tbody>
</table>

The phantom was scanned in each of three CT scanners available to us at the time of study: a GE Lightspeed model used for treatment planning simulations in the UAB Department of Radiation Oncology, a TomoTherapy MVCT, and the GE CT750HD scanner. On the GE CT750HD, a monoenergetic reconstruction with and without a metal artifact reduction sequence (MARS) was obtained. A detailed discussion of the principles upon which the metal artifact reduction sequence is readily available in Buzug’s text on CT image reconstruction. V13 Views from various slices are shown below (Figure 2-5).
Figure 25. Coronal slice from all four obtained scan reconstructions: a) GE Lightspeed treatment planning CT, b) TomoTherapy MVCT, c) DECT w/o MARS, and d) DECT w/MARS. In an ideal reconstruction, the volume and boundaries of the ROI would not be compromised.
Figure 26. Axial slice through hip prosthesis and adjacent ROI for a) GE Lightspeed treatment planning CT, b) TomoTherapy MVCT, c) DECT w/o MARS, and d) DECT w/MARS.
Figure 27. Axial slice through dental fixture and adjacent ROI for a) GE Lightspeed treatment planning CT, b) TomoTherapy MVCT, c) DECT w/o MARS, and d) DECT w/MARS.
Following the scan from the pilot phantom, a more refined phantom was designed to investigate artifact effects of several additional materials in a more systematic fashion. The revised phantom is shown in Figure 6. The accompany table lists the materials tested in this phantom.
Figure 29. Second phantom design with additional materials being scanned on CT750HD. Materials detailed in

All scans were imported into the Eclipse v10 treatment planning system. Each ROI was then segmented, first manually in the window/level user found best visualized each ROI, and automatically with the CT ranger feature utilized in a cubic volume of interest (VOI)
with sides 0.3 inches larger than the actual diameter of each sphere. The upper and lower bounds of the CT ranger tool were set to three standard deviations above and below the mean CT value of the material. The user completing the manual segmentation task was instructed to contour the boundaries they could visualize and not “guess” based on their knowledge that the ROI was a sphere.

Table 3 - Artifact causing objects used in second phantom

<table>
<thead>
<tr>
<th>ROI # (L to R in Figure 29)</th>
<th>Object</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI 1</td>
<td>Aluminum rivet (adjacent)</td>
</tr>
<tr>
<td>ROI 2</td>
<td>Aluminum rivet (1cm away)</td>
</tr>
<tr>
<td>ROI 3</td>
<td>Gold fiducial cluster</td>
</tr>
<tr>
<td>ROI 4</td>
<td>Steel rivet (adjacent)</td>
</tr>
<tr>
<td>ROI 5</td>
<td>Steel rivet (1cm away)</td>
</tr>
<tr>
<td>ROI 6</td>
<td>Titanium encased ICD</td>
</tr>
<tr>
<td>ROI 7</td>
<td>Dental bridge hardware</td>
</tr>
<tr>
<td>ROI 8</td>
<td>Plastic coated applicator screw</td>
</tr>
<tr>
<td>ROI 9</td>
<td>Steel strut (axial positioning)</td>
</tr>
<tr>
<td>ROI 10</td>
<td>Steel strut (transverse positioning)</td>
</tr>
<tr>
<td>ROI 11</td>
<td>Steel strut (oblique positioning)</td>
</tr>
<tr>
<td>ROI 12</td>
<td>none</td>
</tr>
<tr>
<td>ROI 13</td>
<td>Titanium hip implant</td>
</tr>
</tbody>
</table>
The geographic miss index (GMI) was computed for each contour in each. The GMI is defined below:

\[ GMI_{\text{scan}} = \frac{|V_{\text{contour}} - V_{\text{theoretical}}|}{V_{\text{theoretical}}}, \]

where \( V_{\text{contour}} \) was the volume resulting from segmentation contours and \( V_{\text{theoretical}} \) the volume of the spheres based on manufacturer specifications. The Wilcoxon signed rank test was used for statistical comparison of distributions of GMI’s.

**Results and Discussion**

For the pilot phantom geographic miss index was highest in the MVCT scans, and lowest in the dual energy scan with MARS algorithm employed. Artifact caused significant distortion of target volume in all cases. For this limited data set, the type of artifact-causing object did not seem to affect the GMI. There was a substantial difference between GMI of manual segmentation versus auto-segmentation in two cases, but the difference was nearly zero in the rest.
Table 4. Mean geometric miss index for each type of scan and artifact causing object

<table>
<thead>
<tr>
<th>Effect</th>
<th>Automatic</th>
<th>Manual Segmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVCT_NoHighZ</td>
<td>43.7%</td>
<td>45.6%</td>
</tr>
<tr>
<td>MVCT_HighZ</td>
<td>38.9%</td>
<td>47.0%</td>
</tr>
<tr>
<td>GE_HighZ</td>
<td>30.6%</td>
<td>27.4%</td>
</tr>
<tr>
<td>DECT with MARS</td>
<td>22.2%</td>
<td>19.8%</td>
</tr>
<tr>
<td>DECT w/o MARS</td>
<td>28.9%</td>
<td>43.7%</td>
</tr>
<tr>
<td>Hip prosthesis</td>
<td>25.7%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Dental hardware</td>
<td>27.6%</td>
<td>30.7%</td>
</tr>
<tr>
<td>Au fiducials</td>
<td>24.4%</td>
<td>31.3%</td>
</tr>
<tr>
<td>ICD</td>
<td>23.8%</td>
<td>29.4%</td>
</tr>
</tbody>
</table>

For the second phantom, we did not use the MVCT scanner as our Tomotherapy unit had been decommissioned. We only employed auto-segmentation in the second phantom. Across the larger range of objects, the dual energy scans again improved GMI. Full results are shown below in Table 4 and plotted in Figure 7.
Table 5. Second phantom volume reconstruction performance statistics

<table>
<thead>
<tr>
<th>Artifact Causing Object</th>
<th>Automatic Segmentation Structure Volume (cc)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DECT w/o MARS (just spheres)</td>
<td>GE Scanne r (just spheres )</td>
<td>GE Scanne r (ACOs + spheres )</td>
<td>DECT w/o MARS (ACOs + sphere s)</td>
<td>DECT w/ MARS (ACOs +sphere s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROI 1 Aluminum rivet (adjacent)</td>
<td>2.10</td>
<td>2.17</td>
<td>2.05</td>
<td>2.09</td>
<td>2.12</td>
<td>2.11</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>ROI 2 Aluminum rivet (1cm away)</td>
<td>2.21</td>
<td>2.04</td>
<td>2.33</td>
<td>2.24</td>
<td>2.26</td>
<td>2.22</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>ROI 3 Gold fiducial cluster</td>
<td>2.08</td>
<td>2.37</td>
<td>1.96</td>
<td>2.04</td>
<td>2.17</td>
<td>2.12</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>ROI 4 Steel rivet (adjacent)</td>
<td>2.22</td>
<td>1.96</td>
<td>1.75</td>
<td>1.66</td>
<td>1.86</td>
<td>1.89</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>ROI 5 Steel rivet (1cm away)</td>
<td>2.21</td>
<td>2.13</td>
<td>1.97</td>
<td>1.85</td>
<td>2.20</td>
<td>2.07</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>ROI 6 Titanium encased ICD</td>
<td>2.11</td>
<td>2.18</td>
<td>1.32</td>
<td>1.58</td>
<td>2.00</td>
<td>1.84</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>ROI 7 Dental bridge hardware</td>
<td>2.13</td>
<td>2.38</td>
<td>1.91</td>
<td>2.08</td>
<td>2.19</td>
<td>2.14</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>ROI 8 Plastic coated applicator screw</td>
<td>2.11</td>
<td>2.28</td>
<td>1.98</td>
<td>2.18</td>
<td>2.18</td>
<td>2.15</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>ROI 9 Steel strut (axial positioning)</td>
<td>2.20</td>
<td>2.20</td>
<td>0.64</td>
<td>0.76</td>
<td>2.07</td>
<td>1.57</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>ROI 10 Steel strut (transverse positioning)</td>
<td>2.11</td>
<td>1.95</td>
<td>1.60</td>
<td>1.84</td>
<td>1.53</td>
<td>1.81</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>ROI 11 Steel strut (oblique positioning)</td>
<td>2.21</td>
<td>2.42</td>
<td>0.70</td>
<td>0.79</td>
<td>1.21</td>
<td>1.47</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>ROI 12 none</td>
<td>2.13</td>
<td>2.16</td>
<td>2.05</td>
<td>2.11</td>
<td>2.11</td>
<td>2.11</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>ROI 13 Titanium hip implant</td>
<td>2.13</td>
<td>1.97</td>
<td>2.05</td>
<td>1.90</td>
<td>2.09</td>
<td>2.03</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

Mean 2.15 2.17 1.72 1.78 2.00 1.96 0.21
Std. Dev. 0.0493 0.155 0.504 0.467 0.292
GMI of Mean Volume 2.64% 3.59% 18.08% 15.10% 4.56%
Figure 30. ROI volume reconstructions for second phantom a) without artifact causing objects and b) with artifact causing objects. The green line represents the theoretical ROI volume. The less affected the image set is by streak artifact, the closer to the theoretical volume the ROI reconstruction will be.
The second phantom contained substantially more artifact causing objects. Figure 7 shows each scan’s ROI volume reconstructions with and without the ACO present. For all but one ACO, dual energy CT w/ MARS performed substantially better at accurately reproducing the volume of the PMMA spheres. The distribution of GMI’s for DECT w/ MARS scans was significantly reduced compared to the distribution of GMI’s for traditional Lightspeed scan (median GMI_{Lightspeed} = 19.8%, median GMI_{DECT w/MARS} = 8.7%; p =0.007)

**Conclusion**

In this study, we have explored the significant effect high-z artifact can have upon the ability to delineate the proper boundaries of a region of interest. It is clear that streak artifact can pose a significant hindrance to accurate contouring and volume assessment of critical features within the vicinity of high-z objects, and in turn radiation treatment planning for affected patients. Clinicians should keep this in mind and employ strategies to minimize the effect of high-z artifact on the quality of their plans. Dual energy computed tomography may represent a sensible solution to this problem because of its ease of use and effective capability to mitigate streak artifact.

**References**


CHAPTER V

FAST-SWITCHING DUAL ENERGY COMPUTED TOMOGRAPHY MITIGATES
THE EFFECTS OF HIGH-Z STREAK ARTIFACT IN RADIATION TREATMENT
PLANNING

by

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Format adapted for dissertation
Fast-switching Dual Energy Computed Tomography

Mitigates the Effects of High-Z Streak Artifact in Radiation Treatment Planning

Summary:

We studied dual energy CT (DECT) as a tool to alleviate high-z streak artifact effects in patients with dense implants. The use of DECT treatment planning scans improved visualization of structural boundaries obscured by streak artifact in traditional scans. Using a DECT treatment planning scan in favor of a traditional scan also significantly improved the accuracy of dosimetry for plans with structures in the vicinity of high density objects.
Abstract:

Purpose: In this investigation, we tested the hypothesis that utilizing dual energy CT for treatment planning scans could reduce the negative effects of metallic streak artifact on both structure delineation and dosimetric accuracy.

Materials/Methods: We acquired scans of the Gammex 0467 CT calibration phantom with and without high-z insets on both a GE Lightspeed RT, which we currently use for radiation treatment planning, and a GE CT750HD dual energy CT. We assessed the accuracy of each scanner in reconstructing HU values of materials of known density in the vicinity of high-z materials. We then used a custom phantom to simulate treatment to a region between stainless steel bilateral hip prostheses. We used Gafchromic EBT2 dosimetric film to measure the dose delivered in the region between the prostheses and compared it to the dose calculated in plans using imaging data from the GE Lightspeed RT and the GE CT750HD dual energy scanner.

Results: DECT scans facilitated increased accuracy in reconstruction of Hounsfield unit (HU) values in and around high-z materials compared to traditional treatment planning scans. Mean dosimetric error was also reduced in the artifact-affected region near high-z objects by using DECT scans instead of traditional treatment planning scans.

Conclusion: In vivo high density materials pose a formidable challenge to accurate treatment planning because of the resultant high-z artifact. Dual energy CT reduces the image reconstruction and dosimetric inaccuracies associated with such artifact.
**Introduction**

Medical implants and other foreign bodies with high x-ray attenuation values produce imaging artifacts that manifest as streaks outwardly radiating from the object. Modern intensity modulated radiation therapy (IMRT) treatment planning necessitates accurate CT imaging data for both proper structure visualization and treatment dosimetry. Streak artifact often obscures the anatomical detail necessary for proper definition of region of interest (ROI) boundaries and also corrupts the accuracy of the linear attenuation profiles which form the basis for the CT data set and associated tissue density values. Inverse planning algorithms within treatment planning software packages utilize this CT data to determine the optimum beamlet weights and intensities for a desired dose distribution within a patient.

Both improper ROI delineation and CT data adulteration can lead to an undesirable effect upon the therapeutic ratio, and result in loss of disease control or radiation injury in healthy tissue. Any implant with sufficiently high density can cause streak artifact. Implants commonly implicated are: dental fillings, dental implants, spinal hardware, hip prostheses, cardiac pacemakers/defibrillators, stents, brachytherapy seeds, and fiducial markers.

Many methods for managing metal artifact have been explored and tested. As yet, none have proven worthy to be integrated into widespread routine clinical workflow. In this work, we study of the effects of high-z artifact, and the potential for dual energy (or spectral) computed tomography to mitigate them. We hypothesized that dual energy CT (DECT) can alleviate the inaccuracy in HU values caused by streak artifact in ROIs near high-z objects. We also hypothesized that an artifact-affected patient’s plan calculated
within the image space of a DECT scan will have a more accurate dose distribution than a plan calculated within a standard 120 kVp monoenergetic CT scan.

Currently there are three clinically available dual energy CT technologies, dual source, dual layer detector, and rapid peak tube voltage switching. Our study examines the fast kV switching technique, developed by General Electric (GE) and commercially deployed in the Discovery CT750HD. In the fast kV switching technique, a single source rapidly alternates between high and low energy x-ray fluence.

For a detailed discussion on the correction and reconstruction process for dual energy imaging, the reader is referred to Chanda and Langan, Alvarez et al., and Buzug. GE uses a proprietary metal artifact reduction sequence (MARS) to implement these principles in its scan reconstructions.

Methods and Materials

Improvement of HU value accuracy with dual energy computed tomography

The Gammex 0467 is a CT – electron density calibration phantom, with removable insets of known mass and electron densities. We obtained scans of the 0467 phantom in two configurations on the GE CT750HD dual energy scanner at alternating 70/140kVp energies and the GE Litespeed treatment planning CT at 120kVp. In the first configuration, no high-z objects were included. Scans of this configuration provided reference HU values for the ROIs whose HU values were being measured. In the second configuration,
Figure 31b), we symmetrically removed two of the Solid Water™ plugs on either side of the ROIs and replaced them with hollow lead cylinders, to simulate one of the worst possible scenarios for HU value inaccuracy.

As shown in Table 6, each of the two scans (with and without insets) was reconstructed at 70, 120, and 140 kVp.

Table 6. Gammex 0467 Phantom Scans

<table>
<thead>
<tr>
<th>No High-Z Insets</th>
<th>High-Z Insets</th>
</tr>
</thead>
<tbody>
<tr>
<td>70kVp w/o MARS</td>
<td>70kVp w/o MARS</td>
</tr>
<tr>
<td>70kVp with MARS</td>
<td>70kVp with MARS</td>
</tr>
<tr>
<td>120kVp w/o MARS</td>
<td>120kVp w/o MARS</td>
</tr>
<tr>
<td>140kVp w/o MARS</td>
<td>140kVp w/o MARS</td>
</tr>
<tr>
<td>140kVp with MARS</td>
<td>140kVp with MARS</td>
</tr>
</tbody>
</table>

Table 7. Material Properties of Gammex Phantom Insets.

<table>
<thead>
<tr>
<th>Rod Material</th>
<th>Electron Density (Rel. to H₂O)</th>
<th>Physical Density (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Water</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>B-200 Bone</td>
<td>1.10</td>
<td>1.15</td>
</tr>
<tr>
<td>Solid Water</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>Inner Bone</td>
<td>1.09</td>
<td>1.14</td>
</tr>
<tr>
<td>LN-300 Lung</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>Water</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Brain</td>
<td>1.04</td>
<td>1.05</td>
</tr>
<tr>
<td>CB2-30%</td>
<td>1.28</td>
<td>1.34</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>1.69</td>
<td>1.82</td>
</tr>
<tr>
<td>LN-450</td>
<td>0.44</td>
<td>0.45</td>
</tr>
<tr>
<td>Adipose</td>
<td>0.93</td>
<td>0.94</td>
</tr>
<tr>
<td>Liver</td>
<td>1.06</td>
<td>1.10</td>
</tr>
<tr>
<td>Breast</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>CB2-50%</td>
<td>1.47</td>
<td>1.56</td>
</tr>
<tr>
<td>Lead</td>
<td></td>
<td>11.34</td>
</tr>
<tr>
<td>Ti6Al4V</td>
<td>3.6</td>
<td>4.51</td>
</tr>
</tbody>
</table>
Figure 31. Gammex Phantom a) without and b) with insets.
Figure 32. 140 kVp scan of phantom a) no insets, b) with lead insets (top left and right) and titanium inset (bottom left), c) 140 kVp spectral monoenergetic reconstruction with MARS of phantom with same insets as (b).
After each scan was acquired, HU values in the cylindrical regions between the insets were compared using line profiles ( ) through the three insets, 2D areal histograms around the cylindrical ROIs ( )
Figure 42), and 28x28 pixel square histograms inside each ROI (Figure 43). The linear profiles were plotted against each other, and the square regions inside each ROI were statistically compared against reference values. The magnitude of differences between the mean HU values for each ROI in the reference scan
and the metal inset scans was also performed (Table 9.). Welch’s t-test was chosen because it is robust to the requirement of population variance equality. The test statistic was calculated using the following:

\[
t = \frac{\bar{X}_1 - \bar{X}_2}{s_{\bar{X}_1 - \bar{X}_2}}
\]

where

\[
s_{\bar{X}_1 - \bar{X}_2} = \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}
\]

The Welch-Satterthwaite equation was used to compute available degrees of freedom.

\[
d.f. = \frac{\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)^2}{\left(\frac{s_1^2}{n_1}\right)^2\left(n_1 - 1\right) + \left(\frac{s_2^2}{n_2}\right)^2\left(n_2 - 1\right)}
\]

**Improvement of Radiation Plan Dosimetry Accuracy with Dual Energy Computed Tomography**

A simple treatment plan was constructed and applied to each scan. The plan consisted of two 5cm x 10cm laterally opposed open fields with the beam axis centered...
on the lateral axis of the high-z insets (Figure 33). Each field was set to deliver 250 monitor units (MUs). We also generated a volumetric modulated arc therapy (VMAT) plan, with a 500 cGy prescription to the central ROI, and a standard normal tissue tolerance constraint.
Figure 33. Gammex phantom beam profile, two 5cm x 10cm laterally opposed open beams. Insets are same configuration as in Figure 2.

The plans were calculated first in Anisotropic Analytical Algorithm (AAA) 11.0.30 and then re-calculated in Acuros XB 11.0.31. Heterogeneity corrections were enabled. To fully utilize the potential of Acuros, a CT calibration curve was modified to extend through the range of stainless steel. We attempted to extend the curve such that lead could be included, however Acuros presently only allows densities up to 8.00 g/cm$^3$, which corresponds to ASI 304 stainless steel. Stainless steel and Ti6Al4V (grade 5 titanium alloy) are included in the default material density table. Because our lead insets were hollow, their attenuation could be represented by a lower density material whose attenuation corresponded to the weighted average of the thickness of air and lead along the diameter of the lead cylinder.
For each analysis, the gold standard reference was a scan acquired without metal insets where the inset contours from a rigidly registered scan with the insets were copied in. In this way, we had a scan with properly bounded metal structures, but no artifact.

In order to verify the results on film, a custom phantom was designed such that the insets from the Gammex phantom could still be used, but film could also be positioned inside to measure the dose delivered by plans (Figure 34). Acrylonitrile butadiene styrene (ABS) plastic was chosen as the material for the phantom due to its near-tissue mass and electron density. The phantom was designed such that the center could be removed to accommodate whatever shaped volume of interest was desired. We used the contours of a prostate gland from an RT-structure file to create a 3D printed replica of a prostate.
Table 8. Properties of ABS Relative to other Phantom Materials.\(^{74}\)

<table>
<thead>
<tr>
<th>Energy</th>
<th>Material</th>
<th>Effective Z</th>
<th>Electron Density Relative to Water</th>
<th>Physical Density (g/cm(^3))</th>
<th>Attenuation Coefficient ((\mu/\rho)) (x10(^{-2}) cm(^2)/g)</th>
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<tr>
<td>Co-60</td>
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<td>0.98</td>
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<td>2.9</td>
</tr>
</tbody>
</table>
Figure 34. Views of custom phantom for film dosimetry with a) no plugs and center intact, and b) with various tissue density plugs and center removed.

Figure 35. 3D printed prostate.
Figure 36. Custom phantom with 3D phantom embedded in center amidst Play-dough. Three 4x10 in² sheets of EBT2 Gafchromic™ were cut to fit the insets and the 3D printed prostate.

Figure 37. EBT2 Gafchromic film (left) and its modification (right) for use in custom phantom.

The same opposed 5 x 10cm beam profile used previously was used for the custom phantom as well (Figure 38).
Plans were calculated for each image set using AAA and Acuros. Each plan was delivered to the custom phantom on a TrueBeam STx (Varian) at 6 MeV to three configurations of the phantom:

- Solid Water insets (two 5 x 10 cm² laterally opposed beams, 250 MU each)
- steel insets (two 5 x 10 cm² laterally opposed beams, 400 MU each)
- titanium hollow cylinder insets (two 5 x 10 cm² laterally opposed beams, 400 MU each)

A new piece of film was used for each configuration of the phantom. The film was scanned with an Epson VX700 scanner and imported into the FilmQA Pro software package. A calibration curve of color intensity to dose exposure was generated from a previous irradiation sequence on the same type of film. Figure 39 shows the resultant curve as well as the model from which film-specific parameters were generated.
Calculated plans were compared to film plans. Isodose curve maps and isodose color maps were generated. Error between calculated and measured dose profiles was computed.

\[ X(D) = \frac{P2(D)}{D + E} \]

Figure 39. Color intensity to dose calibration curve used for dosimetric film analysis.
Figure 40. Mosaic for calibration of film, for conversion of component color values to series of dose exposures
Results and Discussion

The results are presented in two parts. The first part concerns the results associated with the impact of streak artifact on the accuracy of the HU values in uncorrected versus corrected images. The second concerns the effects on the predicted versus observed dosimetry.

HU value accuracy

The effect of the metal artifact reduction sequence in the spectral images on image quality is readily evident in Figure 32. The streak artifact is dramatically reduced, and the corrected image bears a much closer resemblance to the reference image. A comparison of a linear profile HU values through the region betwixt the two high-z insets is given in Figure 41. A surface contour shows the difference in a two-dimensional profile of the histogram values in Figure 42. HU values within each ROI, and according histograms, are shown in Figure 43. Table 9 lists of all the values associated with measurements alluded to by Figure 43.
Figure 41. Line profile of CT values of 140 kVp scan of phantom a) no insets, b) with steel insets (top left and right) and titanium inset (bottom left), c) spectral monoenergetic reconstruction with MARS.
Table 9. Gammex Phantom HU Value Comparison among Scans

<table>
<thead>
<tr>
<th>Scan with No Insets (Reference)</th>
<th>Traditional Reconstruction</th>
<th>140kV Monoenergetic Reconstruction w/ MARS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cortical Bone Water CB2-50%</td>
<td>Cortical Bone Water CB2-50%</td>
</tr>
<tr>
<td></td>
<td>CB2-30%</td>
<td>CB2-30%</td>
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<tr>
<td>Min</td>
<td>449</td>
<td>233</td>
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<tr>
<td></td>
<td>671</td>
<td>-52</td>
</tr>
<tr>
<td>Max</td>
<td>598</td>
<td>408</td>
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<tr>
<td></td>
<td>873</td>
<td>76</td>
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<tr>
<td>Mean</td>
<td>523.3</td>
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<td>Welch t-value</td>
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Statistical comparison with Reference HU values:

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<td>1.80</td>
<td>1068.22</td>
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Statistical comparison of traditional and MARS reconstruction

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<tr>
<td></td>
<td>29.16</td>
<td>1068.22</td>
<td>0.07</td>
</tr>
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</table>

With the exception of true water, both the traditional reconstruction and the spectral MARS reconstruction still had statistically different profiles of HU values from the reference scan within the three ROIs in between the metal insets (p<0.0001 for all comparisons). However, the DECT reconstruction’s distribution of HU values was far closer to the reference ground truth than the traditional reconstruction for all three ROIs ($\Delta CT_{Ref-Trad}^{ROI_1} = 492.48$, $\Delta CT_{Ref-Trad}^{ROI_2} = 143.3$, $\Delta CT_{Ref-Trad}^{ROI_3} = 508.4$; $\Delta CT_{Ref-MARS}^{ROI_1} = 71.6$, $\Delta CT_{Ref-MARS}^{ROI_2} = 33.9$, $\Delta CT_{Ref-MARS}^{ROI_3} = 88.6$; p < 0.0001 for all comparisons).
The reader can see that ROI boundaries are clearly appreciable in the corrected image (Figure 42c and Figure 43c). In the standard reconstruction, the boundaries of all three ROIs are invaded by streak, and the circular shape of the boundaries is distorted. There is still some streaking even in the corrected image, and the dark area of photon starvation in the very center of the metallic insets is still present, but markedly reduced from the standard reconstruction. However, they may also be due to the upper bound on the HU values placed in the reconstruction sequence. The true HU values of lead, steel, and titanium are all substantially higher than the 3071 upper limit allotted in the reconstruction. For any given scan calibrated such that the HU value of distilled water is 0, they can be calculated with the equation

\[
HU = \frac{\mu_x - \mu_{H_2O}}{\mu_{H_2O}} \times 1000
\]

where
- \(\mu_x\) is the linear attenuation of the material
- \(\mu_{H_2O}\) is the linear attenuation of water

At 140kV, 3071HU HU value corresponds to a linear attenuation of 0.626 cm\(^{-1}\), whereas the value for titanium is 0.810 cm\(^{-1}\), the value for stainless steel is 1.771 cm\(^{-1}\), and the value for lead is 27.103 cm\(^{-1}\).

Were the original sinogram reconstructed with an extended scale, the soft tissue resolution might be diminished, but HU values in severely beam-hardened/photon-starved region would be more accurate. This approach has been previously described\(^{75}\) and merits further study with the DECT artifact reduction approach.
Figure 42. Histogram of CT values in 2D region of 140 kVp scan of phantom a) no insets, b) with steel insets (top left and right) and titanium inset (bottom left), c) spectral monoenergetic reconstruction with MARS. Note that images are mirrored in this figure, because of ImageJ’s default image sequence ordering.
Figure 43. Histogram of CT values within 28x28 pixel squares inside each ROI for a) 140 kV scan with no insets, b) 140 kV scan with insets, and c) 140 kV scan with MARS.

Dosimetric Accuracy

We divided dosimetric analysis into two parts, that for the Gammex phantom and for the custom phantom. As previously described, each plan was computed with both the AAA
and Acuros XB dose computation algorithms. Isodose maps for all of the Gammex phantom plans are shown in Figure 44. The leftmost plans in the figure represent the ground truth reference plans (calculated with the insets registered such that no artifact was present in the image space). Qualitatively one can see that the plans constructed in the spectral MARS image sequences much more closely resemble the ground truth reference plans than those constructed in the standard image reconstruction sequences (middle).

Figure 44. Isodose color wash maps for Gammex phantom plans. Plans in the top row (a-c) were calculated with the AAA algorithm, plans in the bottom row (d-f) with the Acuros XB algorithm. Leftmost plans (a & d) represent the gold standard reference plans. The middle column plans (b & e) are the plans generated from standard scans. The right plans (c & f) were generated from spectral scans with MARS. Dose range shown is 200 cGy to plan max.
A DVH of all plans calculated in the Acuros XB algorithm was plotted and is shown in Figure 45. One can see in the plot that reference plan and DECT plan have nearly overlapping DVH’s for each structure. There is overdose to all of the structures of the plan generated in the uncorrected image sequence.

Figure 45. Comparative DVH of all Gammex phantom plans computed with Acuros XB algorithm.

A linear dose profile along the beam axis was measured across the same location in each of the plans. The results were plotted in Figure 46. One can see that the use of the DECT sequence renders the dose profile very close to that of the reference ground truth image for both the AAA and Acuros XB calculations.
Figure 46. Linear dose profile of phantom across beam axis.

The isodose curve map for the VMAT plan is shown in Figure 47. We noted that the isodose curve was not drastically different among these plans, and that using VMAT may be the best strategy when methods of reducing imaging artifact are unavailable. This would likely be particularly true if any of the arc’s control points where the beam profile projection overlapped with a high-z object were removed prior to optimization. Further study of this notion is worth consideration.
Figure 47. Isodose curve map for VMAT plan on a) phantom with no insets, b) phantom with virtually registered in high-z insets (reference plan), c) standard reconstruction of phantom with insets, and d) spectral CT with MARS reconstruction of phantom with insets.
Our next step was to actually deliver plans to our custom phantom, and verify simulated dosimetry results with film. The resultant film exposures are shown in Figure 48.
Figure 48. Film exposure from a) 2 x 250 MU 5x10cm² fields to phantom with solid water insets b) 2 x 400 MU 5x10cm² fields to phantom with hollow titanium cylinder insets, c) 2 x 400 MU 5x10cm² fields to phantom with steel insets
Figure 49 shows the relative error between the dose measured in the film exposure and the dose calculated from each particular image sequence. A three dimensional plot makes the relative error across the isodose map easier to visualize.

Figure 49. Error between calculated plan and measured film dose for a) ground truth reference plan, b) standard 120 kV reconstruction with AAA calculation, c) 140 kV spectral reconstruction with MARS and Acuros XB calculation

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Figure 50 displays this for the standard reconstruction computed with AAA and the DECT reconstruction computed with Acuros XB. The extremely high peaks
correspond to the holes in the film through which the insets pass. The difference between
the contours are quite evident, but perhaps most prominent are the two “saddle regions”
in between holes in the film. Here the relative error is a factor of 2-4x higher in the
traditional CT-based plan than the DECT-based plan.

Figure 50 shows a plot of the dose error of the traditional and DECT reconstructions
normalized to the gold standard plan. The error is lower for the dual energy with MARS plan.

![Figure 50](image)

Figure 50. Plot of the relative difference between calculated dose and film-measured dose
normalized to gold standard plan

A small but important consideration for the clinician considering utilizing dual energy CT
for their patients with high-Z implants is that most diagnostic scanners utilize a concave
table for patient comfort, and RT scanners use a flat bed. The different positioning may
present substantial scan registration challenges in patients whose treatment areas are in the thorax or abdomen, so a flat table should be used in such cases.
**Conclusion**

The use of fast-kVp switching dual energy CT for reducing metal streak artifact and its consequences to radiation treatment planning was studied with both treatment planning simulations and film dosimetry.

We found that fast kVp switching spectral CT significantly improved the accuracy of HU values in regions affected by metal artifact, and also improved the accuracy of the dosimetry in plans whose beams pass through high-z objects.

Our work demonstrates a considerable need to manage metal artifact in the vicinity of important structures within a radiation treatment plan, and that fast kVp switching dual energy CT with metal artifact reduction is viable and effective method for doing so.

**References**


5. Rinkel J, Dillon WP, Funk T, Gould R, Prevrhal S. Computed tomographic metal artifact reduction for the detection and quantitation of small features near large metallic


CHAPTER VI

DUAL ENERGY COMPUTED REDUCES METAL STREAK ARTIFACT IN PATIENTS WITH HIGH-Z IMPLANTS

by

EVAN M. THOMAS, RICHARD A. POPPLE, MATTHEW C. LARRISON, CHRISTOPHER D. WILLEY, JOHN B. FIVEASH

in preparation for *Journal of Medical Imaging and Radiation Oncology*

Format adapted for dissertation

(paper only partially complete – to be finished upon sufficient accrual of patients)
Dual energy computed tomography reduces metal streak artifact in patients with high-z implants

Running Head: DECT reduces streak artifact in patients

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Abstract

**Introduction:** Metal streak artifact from in vivo high-z objects can obscure important anatomical features and delineations critical to accurate radiation treatment planning. This study aims to test the hypothesis that dual energy computed tomography (DECT) can metal streak artifact.

**Methods:** Three patients with severe streak artifact in their treatment planning scans were sent to our diagnostic radiology department where they received an additional DECT scan. Each DECT scan was compared to the original treatment planning scan and scored by a team of eighteen observers who voted whether the image quality was worsened, unchanged, or improved.

**Results:** Observers voted in 85.2% of cases that DECT had improved image quality versus the traditional scan; in 13.0% of cases image quality was unchanged; and in 2.2% of cases image quality was worsened.

**Conclusions:** In cases where streak artifact intractably hampers radiation treatment planning, dual energy CT imaging should be considered as an adjunct measure.

**Five key words**
Dual energy CT; metal artifact; streak artifact; treatment planning; contouring
**Introduction**

Streak artifact from high-z materials often obscures the anatomical detail necessary for proper definition of region of interest (ROI) boundaries. Metallic implants also adulterate the accuracy of the linear attenuation profiles which form the basis for the CT data set and associated tissue density values.\(^2\),\(^3\)

A variety of methods for managing CT streak artifact have been developed and tested. However, most are too cumbersome or esoteric to be routine employable in day to day clinical workflow. In this work, we build on our previous study of the effects of high-z artifact, and the potential for dual energy (or spectral) computed tomography to mitigate them. We obtained IRB approval to study patients with implanted high-z materials and investigate whether dual energy CT could effectively alleviate the associated streak artifact in their CT scans. We hypothesized that dual energy CT would rectify image quality when streak artifact in traditional scans was severe enough to compromise the reader’s ability to discriminate relevant anatomy. We present the results here of using fast-switching DECT with MARS for three patients who appeared to our clinic with artifact obscuring some relevant aspect of their anatomy or disease.

**Methods**

We obtained Institutional Review Board (IRB) approval for our study to review dual energy CT for patients who presented to our clinic with metal streak artifact that affected any aspect of their treatment planning.

Three patients were referred to our diagnostic radiology department which maintains two CT750HD (General Electric) fast kVp switching dual energy scanners. High and low
peak tube energies were 140 kV and either 70 or 80 kV. Current was 625 mA. Image slice thickness was 0.625 mm. Monoenergetic image sequences were reconstructed with and without the metal artifact reconstruction sequence (MARS). Images were transferred via picture archiving and communication system (PACS) and imported into Eclipse (Varian) treatment planning software.

The first patient had spinal hardware from a laminectomy and fusion. The second patient had an intramedullary femur nail. The third patient had hemostatic clips remaining after an esophagopancreaticoduedenectomy.

The images were anonymized and independent radiologists were independently surveyed and asked to subjectively assess the quality of the sequences from the standard 120 kV reconstruction in comparison with the 140 kV monoenergetic reconstruction sequence with MARS. The observer assigned each comparison a score of (1), (2), or (3) indicating that the dual energy CT sequences 1) hindered visualization of relevant structure boundaries, 2) did not alter visualization of relevant structure boundaries, or 3) facilitated improved visualization of relevant structure boundaries. Fisher’s exact test was used to analyze a 3x3 contingency table of the results.

**Results**

Selections from an example sequence comparison are provided in Figure 51 for the patient with titanium spinal hardware.
One can see that the prominence of the streak artifact is not necessarily eliminated but greatly reduced. In many slices, visualization of previously obscured detail is restored.

Alternatively, a gif of the entire image sequence is available for viewing here:

GIF of spinal hardware CT sequence - standard and DECT

Error! Reference source not found. Table 10 shows the results of the survey. A significant majority of observers felt that the dual energy reconstructed sequences facilitated improved visualization of relevant structure boundaries across all three image sets (p = 0.0037).

where DECT imaging:
1) hindered visualization of relevant structure boundaries
2) did not alter visualization of relevant structure boundaries
3) facilitated improved visualization of relevant structure boundaries.

Table 10. Survey Results

<table>
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<th>Number of Observers Giving X Score</th>
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</tr>
<tr>
<td>Spinal hardware</td>
<td>0</td>
</tr>
<tr>
<td>Hemostatic clips</td>
<td>0</td>
</tr>
<tr>
<td>Intramedullary nail</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
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</tbody>
</table>

Discussion

The DECT images clearly aided in visualization of previously obscured structures, however their utility for radiation treatment planning was hindered by the concave table used in diagnostic radiology, which orients aspects of the patient differently than the flat tabletop used in treatment planning scanners. In situations where the relevant anatomy is rigid, a fusion can be achieved between scans taken on the concave and the flat bed without much difficulty. However, a flat tabletop is likely necessary for the proper fusion of the DECT to the treatment planning scan when the anatomy is not rigid.
Conclusion

In traditional CT scans where important anatomy or anatomical boundaries was obscured by streak artifact due to in vivo high-z materials, DECT was able to reduce the severity of the artifact and facilitate improved visualization and delineation ability according to a set of trained observers.

For institutions with the capability, acquiring DECT scans may be a useful supplement to traditional treatment planning scans for patients with high-z implants.

References


3. Hounsfield GN. Apparatus for examining a body by radiation such as X or gamma radiation. Google Patents; 1976.

CHAPTER VII

CONCLUSIONS

A comprehensive review of the history and principles of CT image acquisition and reconstruction was provided. The applicability of fast-switching kVp dual energy computed tomography to radiation treatment planning was investigated in a series of phantoms and in patients. Virtual monochromatic reconstructions at multiple energies were compared to standard reconstructions. Through these investigations, we determined that the use of fast-switching dual-energy CT imaging not only improves contouring ability in image regions afflicted by streak artifact (which is determined by the contrast between adjacent regions), but also dramatically improves the accuracy of the actual CT values in and around the artifact causing objects.

We also investigated the effect upon dosimetry of restoring the accuracy of CT values within images used to calculate the dose distribution of a radiation treatment plan in a commercial phantom. In a worst-case scenario type of plan, using dual energy CT image sequences improved the accuracy for plans computed with both the AAA and Acuros XB dose calculation algorithms. Film dosimetry was used to verify these results in a custom phantom designed for both CT - electron density calibration and dose verification.

Dual energy CT scans were then acquired for a cohort of patients with appreciable metal streak artifact in the vicinity of their treatment regions. The change in visual quality of the images between the standard reconstruction and the dual energy reconstruction were assessed by a group of independent radiologist observers. Observers overwhelming
agreed that the dual energy reconstructions improved their ability to discriminate relevant anatomical detail in the scans.

Dual energy imaging has long been posited as a solution to reducing metal streak artifact in CT images, however has only recently become available in a commercial format – currently principally to diagnostic radiologists. Modern hospital informatics allow the images to be easily transferred from one department to another, and now it is a trivial matter to obtain such an image series for patient. Many other solutions to metal streak artifact have been proposed. Of these, a great majority are successful in their task of correcting some of the artifact or restoring image integrity. However, nearly all of these solutions required third-party software, extra projection space sinogram manipulation, or a priori knowledge of the artifact causing objections in the scan.

Dual energy CT effectively circumvents all of these difficulties and is the first truly viable solution to metal streak artifact ready to be integrated into radiation treatment planning workflow. Some further work is necessary, such as generation and repeated validation of appropriate calibration curves for the new scanner at each available virtual monochromatic energy reconstruction that might be used.

We anticipate that this technology will eventually become a routine employed option for mitigation of metal streak artifact that compromises radiation treatment planning in patients with implanted high-z materials.
CHAPTER VIII

FUTURE WORK

The most important piece of future work required to facilitate use of DECT for treatment planning is the commissioning of a scanner for this process. Commissioning of the scanner such that it can be used at its full potential will require much more exhaustive CT to electron density calibration curves to be generated. Furthermore, additional validation of the dosimetry obtained from DECT scans in multiple treatment planning workstations is necessitated. Planning algorithms will need to be updated and/or modified to accommodate the presence of high-density materials in the optimization and calculation algorithms. Currently, Acuros XB does this, but only up to materials as dense as stainless steel, and no further.

Moreover, it would be useful to develop a quantitative artifact severity stratification of patient scenarios based upon the likely dosimetric error being incurred by their particular type and location of in vivo high-z material.

Finally, because dual energy scans can be reconstructed at any energy level at which linear superposition of the decomposed basis spectra is still valid, there are a tremendous number of permutations of acquisition and reconstruction energies. It is likely that some acquisition/reconstruction energy combinations are better suited to artifact reduction for particular density materials. An invaluable effort would be to determine which scan and reconstruction settings are optimal for each type of implant a patient may have.
REFERENCES


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APPENDIX A - MATHEMATICAL BASIS FOR DUAL-ENERGY BASED ARTIFACT REDUCTION

The following is excerpted with permission from Chapter 9.6.2 of T. M. Buzug, *Introduction to Computed Tomography: From Photon Statistics to Modern Cone-beam CT*. (Springer, 2008).

In the dual-energy approach, the energy dependence of the attenuation coefficient must be modeled as

\[ \mu(\xi, \eta, E) = k_{\text{absorption}}(\xi, \eta) \cdot \alpha_{\text{absorption}}(E) + k_{\text{scattering}}(\xi, \eta) \cdot \mu_{\text{scattering}}(E). \]  

(9.69)

Here, the spatial and energy dependence of the attenuation is factorized for the two main photon–matter interactions in the diagnostic energy window, i.e., photoelectric absorption and Compton scattering. The energy dependence of the photoelectric absorption is given by (2.32)

\[ \alpha_{\text{absorption}} \propto \frac{1}{(h\nu)^3}. \]  

(9.70)

The energy dependence of the Compton scattering is given by the Klein–Nishina equation (2.36), i.e.,

\[ \mu_{\text{Compton}} = n \cdot 2\pi r_e^2 \left[ \left( \frac{1 + \mathcal{E}}{\mathcal{E}^2} \right) \left( \frac{2 (1 + \mathcal{E})}{1 + 2\mathcal{E}^2} - \frac{\ln(1 + 2\mathcal{E})}{\mathcal{E}} \right) + \frac{\ln(1 + 2\mathcal{E})}{2\mathcal{E}} - \frac{1 + 3\mathcal{E}}{(1 + 2\mathcal{E})^2} \right], \]  

(9.71)

where \( \mathcal{E} = h\nu / m_e c^2 \) is the reduced energy of the incoming photon and \( n \) is the number of target atoms per unit volume. If (9.69) is substituted into (9.68), one obtains
where

\[ K_{\text{absorption}}(\xi) = \int_0^s k_{\text{absorption}}(\xi, \eta) \, d\eta \quad (9.73) \]

and

\[ K_{\text{scattering}}(\xi) = \int_0^s k_{\text{scattering}}(\xi, \eta) \, d\eta . \quad (9.74) \]

The integrals \( K_{\text{absorption}}(\xi) \) and \( K_{\text{scattering}}(\xi) \) can now be approximated by dual-energy measurements. That means, for instance, two different scans may be carried out at two different X-ray tube voltages. This leads to

\[
p_{1,\gamma}(\xi) = -\ln \left( \frac{1}{I_0} \int_0^{E_{\text{max}}} I_0(E) e^{-\alpha_{\text{absorption}}(E) K_{\text{absorption}}(\xi) - \mu_{\text{scattering}}(E) K_{\text{scattering}}(\xi)} \, dE \right) \quad (9.75)\]

and
where

\[ I_1 = \int_0^{E_{\text{max}}} I_1(E) \, dE \quad \text{and} \quad I_2 = \int_0^{E_{\text{max}}} I_2(E) \, dE . \]  

(9.77)

Obviously, two projection integrals, \( p_{1,\gamma}(\xi) \) and \( p_{2,\gamma}(\xi) \), are measured for two unknown variables \( K_{\text{absorption}}(\xi) \) and \( K_{\text{scattering}}(\xi) \). In this way, the integrals \( K_{\text{absorption}} \) and \( K_{\text{scattering}} \) can be estimated and, further, the distributions \( K_{\text{absorption}}(\xi, \eta) \) and \( K_{\text{scattering}}(\xi, \eta) \) can be obtained by inverting the integrals (9.73) and (9.74) using the reconstruction methods from Chap. 5. Knowing the distributions \( K_{\text{absorption}}(\xi, \eta) \) and \( K_{\text{scattering}}(\xi, \eta) \) in (9.69), artifact-free images can be reconstructed in an energy range that is correctly modeled with (9.70) and (9.71).
APPENDIX B - INSTITUTIONAL REVIEW BOARD APPROVAL

UAB
The University of Alabama at Birmingham
Institutional Review Board for Human Use

Form A: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federally Approved Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00000960 and it expires on August 29, 2016. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: FIVEASH, JOHN
Co-Investigator(s): 
Protocol Number: X110736802
Protocol Title: Utilization of Dual Energy CT for Treatment Planning Scans in Patients with Metal Artifact

The IRB reviewed and approved the above named project on 10/24/11. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.
IRB Approval Date: 10/24/11
Date IRB Approval Issued: 10/26/11

HIPAA Waiver Approved? Yes

签字：Lynn, M.D.
Acting Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:
The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review, research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
UAB IRB Approval of Waiver of Informed Consent and/or Waiver of Patient Authorization

✓ Approval of Waiver of Informed Consent to Participate in Research. The IRB reviewed the proposed research and granted the request for waiver of informed consent to participate in research, based on the following findings:
1. The research involves no more than minimal risk to the subjects.
2. The research cannot practically be carried out without the waiver.
3. The waiver will not adversely affect the rights and welfare of the subjects.
4. When appropriate, the subjects will be provided with additional pertinent information after participation.

Check one: [x] and Waiver of Authorization (below)
☐ or Waiver of Authorization (below)
☐ Waiver of Authorization not applicable

✓ Approval of Waiver of Patient Authorization to Use PHI in Research. The IRB reviewed the proposed research and granted the request for waiver of patient authorization to use PHI in research, based on the following findings:
1. The use/disclosure of PHI involves no more than minimal risk to the privacy of individuals
   i. There is an adequate plan to protect the identifiers from improper use and disclosure.
   ii. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
   iii. There is an assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The research cannot practically be conducted without the waiver or alteration.
3. The research cannot practically be conducted without access to and use of the PHI.

☐ Full Review

The IRB reviewed the proposed research at a convened meeting at which a majority of the IRB was present, including one member who is not affiliated with the IRB, or by one of the Vice-Chair or Designee.

Date of Meeting

Signature of Chair, Vice-Chair or Designee

☐ Expedited Review

The IRB used an expedited review procedure because the research involves no more than minimal risk to the privacy of the individuals who are the subject of the PHI for which use or disclosure is being sought. The review and approval of the waiver of authorization was carried out by the Chair of the IRB, or by one of the Vice-Chair of the IRB as designated by the Chair of the IRB.

Date

[Signature]

[Signature of Chair, Vice-Chair or Designee]

Rev. 12/08/2015
Investigator IRB Training By Project

Report Date: 10/27/2011

Protocol: X110726002 Link Number: APPROVED as of 10/25/2011

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