CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: CASE 5Y14

STUDY TITLE: Evaluation of Bone Metastases with Dual Energy CT

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Abstract

Computed tomography (CT) scans are routinely used in the evaluation of oncologic patients for initial diagnosis and subsequent disease staging. Detection of bone metastasis on standard CT, however, is limited in sensitivity, particularly in case of osteolytic intramedullary lesions [1]. Recent studies have shown the ability to detect bone marrow edema using CT with the use of a virtual non-calcium (VNC) dual energy CT (DECT) technique[2, 3]. Because bone marrow edema is similar in composition to intramedullary bone metastases (i.e. both are of soft tissue composition as opposed to calcium or fat), VNC DECT may also be helpful in the detection of bone marrow metastasis. Cancer patients obtaining a Positron Emission Tomography (PET) CT and a separate diagnostic CT scan as part of their routine clinical care will be enrolled into the study. The diagnostic CT scan will be performed on a DECT scanner and the images will be reconstructed as SECT images for routine clinical interpretation as well as VNC DECT images. The SECT images alone will be evaluated and scored, and then the VNC DECT images will be added to the SECT images for a second evaluation (consecutive reading session). Multiple readers blinded to the PET-CT findings for detection of bony metastatic disease will participate.

Primary Aims

1) Compare the accuracy of SECT with VNC DECT to standard SECT alone in the detection of metastatic bone lesions using PET-CT as the reference standard.

Hypothesis

The addition of VNC DECT to SECT will be more accurate in the detection of metastatic bone marrow lesions compared to SECT alone.

Introduction

Significance and Rationale

Bone is the most common site of metastatic disease.[4] Nearly 300,000 US adults are estimated to be living with metastatic bone disease.[5] Nearly two thirds of bone metastases occur in patients with breast, prostate, and lung cancer.[5] Bone metastases can present as predominantly sclerotic, lytic or mixed sclerotic and lytic lesions.

CT is the primary imaging modality utilized for the detection and staging of metastatic cancer because of its ability to evaluate a wide range of tissues in a short time and availability in many locations. The sensitivity of CT in detection of bone metastases is, however, limited with a recent meta-analysis reporting a pooled sensitivity of 73% compared to PET (pooled sensitivity 90%) and MRI (pooled sensitivity 90%)[1]. Detection of osteolytic lesions that are intra-medullary without cortical or soft tissue involvement is especially challenging on CT. These lesions most frequently occur in

patients with breast and lung cancer as well as patients with multiple myeloma and lymphoma. The primary difficulty of identifying intramedullary bone marrow lesions with conventional CT is the ability to visually discriminate the lesion which is of soft tissue composition through the trabecular bone which is composed of calcium. DECT with the use of a virtual non-calcium technique provides the ability to remove calcium and thereby the trabecular bone from the image and at least theoretically improve visualization of the underlying marrow elements composed of soft tissue and fat.

Although DECT has been available for several decades, it has not been widely used in clinical practice because of technical limitations and radiation dose concerns.[6] Recent second generation of DECT scanners from several vendors now have addressed many of the prior limitations allowing DECT scans to be performed with dose and image quality comparable to SECT scans.[7-9] Schenzle et al. showed that there is no significant difference in image noise for chest CT using DECT compared to SECT when performed with the same dose and the contrast to noise ratio can be doubled with optimized DECT protocols.[7] They concluded that CT can be routinely performed in dual energy mode without additional dose or compromises in image quality. Similarly, Purysko et al. showed that by adjusting the tube current (mA) at the scanner console to match the radiation output (CTDIvol) from a single energy CT (SECT), DECT of the abdomen can be performed without radiation dose penalty to patients. Using this technique in a cohort of patients undergoing single energy (SECT) and dual energy CT (DECT) in different occasions, DECT exams achieved similar image quality with similar or lower radiation dose compared to SECT. [10] The advantage of DECT is ability to separate tissues by material composition rather than simply by attenuation as in SECT. This is possible because change in attenuation of different materials between the two energies is related to the individual properties of the material (primarily its atomic number). As a general rule of thumb, as the difference in atomic numbers between the materials increases, the ability to separate the materials improves. DECT using this technique is currently being used in routine clinical practice in a number of applications such as multiphasic vascular, liver and kidney studies.[11, 12] For intramedullary bone, this same technique is modified to separate or "decompose" each voxel into fat, soft tissue (hematopoietic marrow), and calcium (trabecular bone). After the voxel is decomposed into those 3 materials, the calcium can be subtracted from the voxel creating a "virtual non-calcium" (VNC) image and removing the trabecular bone from the medullary space.[2]

Relevant literatures

There have been no studies to date showing the benefit of VNC DECT for the evaluation of bone metastases. Recent studies have, however, demonstrated the ability to visualize bone marrow edema with CT by using a VNC post processing technique of a DECT scan without increased radiation dose.[2, 3, 13] Pache et al. showed that VNC DECT can be used to identify bone marrow edema in the knee in a study of 21 patients with acute knee trauma.[2] The same group also showed that the detectability of the bone marrow edema is no different when using a dose equivalent to SECT and concluded that DECT can

provide additional information compared to SECT without additional radiation dose.[3] More recently, Bierry et al. showed that bone marrow edema in vertebral compression fractures can be accurately detected using VNC DECT.[13] Our hypothesis is that the same principle which allows visualization of bone marrow edema should also allow visualization of bone marrow metastases using a VNC technique with subtraction of trabecular bone. Preliminary work performed by one of the investigators (JP) has demonstrated the ability to identify bone marrow metastasis using a trabecular bone subtraction algorithm with SECT.

Methods

Data Collection

A subset of cancer patients being imaged with PET/CT for diagnosis and/or staging of disease at our institution also undergo a diagnostic CT scan as part of the clinical workup at the same time or within a short period of time. This subset of patients will be divided into 2 cohorts: patients with bone metastases on PET/CT and patients without bone metastases on PET/CT. 30 patients with bone metastases and 15 patients without bone metastases will be enrolled into the study. To be included in the study, the time between the diagnostic CT and PET/CT will be no more than 30 days with no intervening treatment to ensure that any differences found between the exams are related to imaging technique and not a change in disease. Minors (age < 18 years) will be excluded from the study. In order to maximize recruitment and generalizability of study results, all cancer types and both newly diagnosed and previously treated patients will be included. However, the vast majority of the patients that are imaged with PETCT and diagnostic CT are lymphoma patients.

All study patients will undergo a dose-matched DECT (140 kVp and 100 kVp) scan instead of a standard 120 kVp SECT for their diagnostic CT All scans will be performed on a single second-generation DECT scanner (Somatom Definition Flash, Siemens, Forchheim, Germany). A dual energy CT protocol using 140 kVp with Sn filter for the high energy beam (tube B) and 100 kVp for the low energy beam (tube A) will be performed with ~1.3 (tube A/tube B) ratio of tube currents. Multiplanar reformations will be done in 1mm – 3mm thick slices using a soft reconstruction kernel. To ensure that the radiation dose of the DECT will be no higher than the standard SECT protocols (Appendix 1), the CT dose index (CTDIvol) which measures the radiation output of the CT tube will be calculated for the SECT scan in each patient and the DECT tube currents will be adjusted to match this CTDvol. CT scans will be performed as routine diagnostic scans with administration of intravenous contrast and with or without oral contrast depending on the clinical indication. Established institutional guidelines will be followed for the administration of intravenous and oral contrast. (Appendix 2 and Appendix 3) . Linearly mixed images from the DECT will serve as the SECT equivalent images for clinical interpretation. These images are generated by combining the data from both energies (in other words, all the radiation dose will be used to generate these images). Post processed VNC DECT images will also be generated. 8 readers will evaluate the anonymized images in a single reading session. The SECT equivalent images will first

be interpreted alone; then the SECT equivalent images along with the VNC DECT images will be interpreted. The order of cases will be randomized and different for each reader. All of the following bony structures when visible will be evaluated: scapula, clavicle, thoracic vertebra, lumbar vertebra, ribs, sacrum, right and left pelvis (ilium, ischium and pubic bones) and right and left proximal femurs for the presence of metastatic lesions. For each location, the readers will mark the presence or absence of lesions, the number of lesions and their confidence in the presence of one or more lesions in that particular anatomic location. Confidence will be scored on a 0-100 scale allowing a direct correspondence to the degree of confidence from 0% to 100% for the presence of a lesion. The default score will be zero, i.e. no confidence in the presence of a lesion at a particular location. PETCT images will be evaluated by two readers in consensus to determine the presence of metastatic bone lesions in each anatomic location. The evaluating criteria will be the same as in routine clinical practice (i.e. all lesions must have visibly increased FDG uptake compared to the surrounding background ($SUVlesion/SUVbackground \geq 20\%$)).

Data Analysis
Each patient will be evaluated and scored at approximately 46 separate locations (12 pairs of ribs, 12 thoracic vertebra, 5 lumbar vertebra, sacrum, right and left hemipelvis, and right and left scapula). For each location, the readers will mark the presence or absence of lesions, the number of lesions and their confidence in the presence of one or more lesions in that particular anatomic location (using a 0-100 point confidence scale). Each location will be correlated with PETCT which will serve as the reference standard. Previous studies have shown PET to be the most accurate imaging technique to detect bone metastases and superior to nuclear medicine bone scintigraphy.[1] PET is still an imperfect gold standard. Unfortunately, only histopathology of each lesion would serve as a better gold standard which would not be feasible or ethical. Accuracy will be measured using nonparametric estimates of the area under the receiver operating characteristic (ROC) curve using methods for clustered data (i.e. multiple locations per patient) [14]. ROC area estimates will be constructed for each reader for both SECT alone and DECT as an adjunct to SECT. For each reader, the ROC areas of SECT and DECT plus SECT will be compared using a Wald test [14]; a significance level of 0.05 will be used.

ANOVA methods for multiple-reader ROC studies will be used to test the null hypothesis that the readers' mean ROC area with DECT as an adjunct to SECT is the same as the readers' mean ROC area with SECT alone [15]. A significance level of 0.05 will be used. A 95% confidence interval for the difference in ROC areas will be constructed.

Sample Size Considerations
Methods for determining sample size for multi-reader CAD studies was used [16]. The following assumptions were made for sample size calculation:
1. Based on previous work by Yang et al [1], we expect readers to have a high ROC area with SECT. Thus, we used an estimate of 0.90 as the ROC area with SECT.
2. We expect that DECT will increase readers' sensitivity by 0.10 or more, with little to no effect on specificity. Thus, we assumed that the ROC area with DECT will be 0.05 greater than with SECT alone.

Patients with metastatic disease will have, on average, 2 lesions [1],

The formula for determining sample size for MRMC studies [17] is:
$$\text{Power} = 1 - F(f_c; 1, df_1, \lambda) \hspace{3cm} [1]$$

where $F(f_c; 1, df_1, \lambda)$ is the distribution function of the test statistic F under the alternative hypothesis and $f_c = F^{-1}(1-\alpha; 1, df_1)$, where df_1 is (J-1) and

$$\lambda = [J ((\mu_{QT}-\mu_{HH})+0.05)^2] / [2\{\sigma_b^2(1-r_b) + \sigma_\varepsilon^2[(1-r_1)+(J-1)(r_2-r_3)]\}]$$

is the noncentrality parameter of the noncentral F distribution, J is the total number of readers in the study, σ_b^2 is the variability between readers, r_b is the correlation between accuracies when the same readers evaluate subjects using different tests, σ_ε^2 is the variability due to different subject samples, r_1 is the correlation between accuracies when the same subjects are evaluated by the same reader using different tests, r_2 is the correlation between accuracies when the same subjects are evaluated by different readers using the same tests, and r_3 is the correlation between accuracies when the same subjects are evaluated by different readers using different tests. We used estimates of σ_b^2, r_b, r_1, r_2, and r_3 from prior studies [16]. Note that σ_ε^2 is a function of the *effective* sample size, which we estimate as: # patients x 46 locations / design effect, where the design effect is $1+(s-1)r$ [16], where s=46 locations and r is the correlation between locations which we assume to be 0.5 for locations with mets and 0.2 for locations without mets [16].

From equation 1, we estimate that a study with 8 readers and 30 patients with bone metastases and 15 patients without metastatic disease will provide 84% power to detect a difference in ROC area of 0.05 or larger.

Informed Consent

A waiver of informed consent is being requested as participation in this study involves no more than minimal risk to the patient. DECT is FDA approved and used in routine clinical practice at many centers including the Cleveland Clinic for other purposes such as vascular imaging. Patients participating in this study will not receive additional CT scans or radiation. Dose and image quality of the scans will be equivalent to standard SECT scans. All the imaging studies that will be evaluated as part of this protocol will be obtained as a part of the routine clinical care of the patient. Eligible patients will be provided an information sheet (Appendix 4) explaining the study prior to their CT scans and participation in the study will be voluntary. Since all patients will undergo PETCT which will serve as the truth for the presence or absence of bone marrow metastasis, DECT will never by definition reveal lesions not detected by PETCT and any advantage of DECT over SECT in the detection of bone metastases will not directly benefit patients in the study.

To increase recruitment of patients with bone metastases, we would like to add an additional procedure as an amendment to the protocol. Patients of study co-investigators or licensed independent practitioners working with the co-investigators, with known bone

metastases who will be getting a routine clinical CT scan, will be asked to participate in the study by the ordering clinician. Patients will be provided with the patient information sheet (Appendix 4). If they volunteer to participate in the study, the clinical CT scan will be performed using a dual energy technique as stated in the protocol. In these patients, follow-up CT scans performed as part of routine clinical care will be used to confirm the presence or absence of any additional lesions detected using the dual energy CT technique. As before, enrolled patients will not receive any additional CT scans or any additional radiation exposure by participating in this study.

Confidentiality Assurances

Images will be anonymized and all patient identifiers will be removed. A subset of the deidentified images will be sent to Siemens Healthcare in Germany for dual energy reconstruction (please see HIPAA deidentification application, Appendix 5). The images will be sent either electronically using secure file exchange server and/or physically on DVD. The reconstructed images will be sent back to CCF for analysis. All patient information will be kept in a spreadsheet on a password-protected folder on the CCF network. Only authorized study staff will have access to this spreadsheet.

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Adult Abdominal Imaging CT Protocols
Revised: March 10, 2014

PREP

NPO x 4 hours before scan with IV contrast. Check with referring MD and CCF policy for special situations regarding medications (i.e. Diabetic patients on Insulin).

CONTRAST

Intravenous: (also see separate policy regarding renal function and IV contrast)

Standard -	Omnipaque 300 – low osmolar nonionic contrast material
	Omnipaque 350 – used for dedicated CTA studies. Not to be used for CT urography.
Options -	Omnipaque 240 – used for central line injections

Oral:

Water - all patients get 1 cup as they get on scan table
Water-soluble - 900 ml Omnipaque solution (50 omnipaque 240 + 850 ml water)
VoLumen (Low density Barium product) - 900 -1350 ml slowly over 1 hr

Emergency Department
- All patients who are to receive positive oral contrast especially recently post-operative patients should receive water-soluble oral contrast. These patients can be scanned within 20-30 minutes of when they start drinking.
- Trauma and flank pain protocol patients receive no oral contrast
- Additional indications when ED CT scans can be performed without oral contrast are published in a separate memorandum.

Miscellaneous:
Rectal, bowel stoma – use water soluble enteric contrast as above.
Bladder, neobladder - mix 25 ml **sterile Omnipaque 240** in 250 ml **sterile 1/2 NSS**
Peritoneal dialysate - CT Peritoneography. This is now being managed by pharmacy and Imaging Institute nursing. Must be prepared administered under sterile conditions. **Please refer to dedicated SOP.**

Note: NO positive oral contrast agent is to be given for CTA studies – Pre or Post stent, Renal studies, Liver imaging, Pancreatic imaging, Acute flank pain exams, Acute trauma patients, CT Urograms, CT Cystograms or GI bleeding studies. Water or VoLumen can be used.

2014.03 BH, EQ

APPENDIX 2

Cleveland Clinic
Imaging Institute

Guidelines for Administration of IV Contrast for CT and MR Exams, Based on eGFR

Target Group:		Original Date of Issue:	Version
Cleveland Clinic health system		12/05/2007	2
Approved by:	**Date Last Approved/Reviewed:**	**Prepared by:**	**Effective Date**
SOSC	02/07/2014	Brian Herts (STAFF)	02/07/2014

Purpose

These guidelines are provided to assist the referring physician and radiologist in preparing patients before CT and MR examinations to reduce certain risks associated with intravenous contrast administration. Specifically, the goals are to prevent or minimize the occurrence of contrast-induced acute kidney injury (CI-AKI) from iodinated contrast media and nephrogenic systemic fibrosis (NSF) from gadolinium-based agents. Risks of CI-AKI and NSF are higher for patients with chronic kidney disease especially when there are other co-morbid conditions. Because estimated or measured glomerular filtration rate (GFR) serves as a better indicator of chronic kidney disease than serum creatinine alone, these recommendations are based on estimated GFR. A calculated estimated GFR (eGFR) from serum creatinine should be available from the Cleveland Clinic laboratory for all outpatients. If the eGFR is not available, if only a serum or whole-blood creatinine is available (the latter from point of care testing,) then use the GFR calculator on the kidney.org website (www.kidney.org/professionals/kdoqi/gfr_calculator.cfm) to estimate the patient's GFR. This website will contain the most up-to-date recommendations for estimating the GFR. Since there is no best predictor of GFR for inpatients, the website can also be used to estimate GFR for those inpatients who do not have a diagnosis of AKI only if they have a stable creatinine.

In general, the risk of CI-AKI is less with IV than with intra-arterial (IA) administration of contrast and is estimated to be less than 4% (Barrett BJ et al.) and CI-AKI is extremely uncommon with outpatients whose eGFR is greater than 45 ml/min/1.73m^2 (Weisbord SD et al.)

Hydration with isotonic IV fluid is the single best method to reduce the risk of CIN, and prolonged IV fluid administration (12 hours pre and post) is more protective than a single bolus of fluid. Oral hydration (preferentially to include salt and water) will have some protective effects, but the data is insufficient to determine how much protection this affords.

As always, the risks, benefits and alternatives should be carefully considered before proceeding with any radiological examination. Alternative imaging exams such as MR and CT without contrast, Ultrasound or nuclear medicine studies (such as V/Q scan to replace CT for pulmonary embolism) also should be considered before proceeding with any contrast-enhanced examination.

Guidelines

This document provides guidelines for selective screening of patients for chronic kidney disease, to identify those patients at an increased risk for contrast-induced nephropathy (CIN) from iodinated contrast media and nephrogenic systemic fibrosis (NSF) from gadolinium-based agents.

Screening for Chronic Kidney Disease

Before CT and MR examinations, in those outpatients with stable renal function and risk factors for chronic kidney disease (CKD) or contrast-induced nephropathy (see below), a creatinine or GFR within the last 2 months is

2/11/16 version 3

APPENDIX 3

Cleveland Clinic
Imaging Institute

Dispensing Oral Contrast for CT Exams SOP

Target Group:		Original Date of Issue:	Version
Cleveland Clinic – health system		Not Set	1
Approved by:	Date Last Approved/Reviewed:	Prepared by:	Effective Date
SOSC	08/15/2013	Tracy Painter (CLINICAL MANAGER II)	08/15/2013

Printed copies are for reference only. Please refer to the electronic copy for the latest version.

Purpose

To define the process for dispensing oral contrast for patients undergoing CT examinations.

Policy Implementation Procedure

ADULTS

Water Soluble Contrast Agents (Dilute Omnipaque™ 240 or other agent)
1. The Technologist/Nurse will check the order/protocol in EPIC / SyngoWorkFlow to verify the need for and type of oral contrast for the CT exam.
2. Once verified, the Technologist/Nurse will mix the contrast with the appropriate amount of water.
   a. **The ordered amount of contrast solution is the amount that must be given to the patient or the patient's representative.
3. Once mixed the Contrast Solution Bottle must be labeled as follows:
   a. Patient's Name
   b. Patient's MRN
   c. Omnipaque 240 and water, shake before giving to patient
   d. Amount of Contrast the Patient is Requested to Drink
   e. Expiration Date & Time
4. Timing of scan relative to water-soluble oral contrast (adult patients):
   a. Emergency Department patients can be scanned 20-30 minutes after the time they started drinking contrasat.
   b. All other patients can be scanned as early as 30 minutes after the start of enteric contrast; if there are concerns for distal small bowel and colonic disease then waiting 40-50 minutes is optimal.
   c. Patients CT scans should not be delayed because of a failure to tolerate the po contrast. Volumes consumed should be appropriately recorded in the technologist note.

Barium Contrast Agents (e.g. VoLumen™ and Readi-Cat®)
- VoLumen is indicated for CT Enterography studies assessing patients for inflammatory bowel disease or obscure GI bleeding. Readi-Cat can be used as

2/11/16 version 3

APPENDIX 4
RESEARCH STUDY EXPLANATION FOR PATIENTS
Evaluation of bone metastasis with dual energy CT

The Cleveland Clinic Imaging Institute is conducting a research study to determine if a dual energy CT can find cancer in bones better than a single energy CT.   You are being asked to participate in this research because your physician has ordered a diagnostic CT. Currently both dual and single energy CTs are used to obtain diagnostic CTs. If you agree to participate in this research, you will undergo your diagnostic CT using the dual energy CT. Dual energy CT uses two x-ray beams at different strengths to create the images instead of using a single x-ray beam as is done in single energy CT.

Participation in the research will not result in additional scans or radiation to you. The scanner will look the same and feel the same as a standard CT (see picture below). The scan will take the same time as a single energy CT scan. The clinical findings from the dual energy CT will be reported to your physician and recorded in your medical record. Your care will not change as a result of participating in this study.

For research purposes, the dual energy CT will also create an additional set of images that will be used for further analysis. This analysis will have no impact on your clinical care. Your scan and medical information will be kept in a confidential manner by the research team. You will experience no direct benefit but knowledge gained from the study will increase our understanding and may benefit future patients.

Your participation is voluntary and your decision will not impact your CT appointment or current clinical care. If you have questions about the research, please tell the radiation technologist and they will have a member of the research team meet with you.

Please indicate your decision of whether to participate or not participate in the research to the radiation technologist.

Naveen Subhas MD
Principal Investigator

APPENDIX 5

HIPAA De-Identification Application

> DO NOT COMPLETE IF INFORMED CONSENT WILL BE OBTAINED
> OR WAIVER OF CONSENT IS RESTRICTED TO INTERNAL USE

IRB # : _____   PI Name : Naveen Subhas

Title: Evaluation of bone metastases with dual energy CT

Research that involves the disclosure of protected health information (PHI)* to a third party without a signed informed consent from the subject must remove all direct patient identifiers. To be compliant with HIPAA, the following subject identifiers must be removed from all disclosures to third parties:

- Names (individual, employer, relatives, etc.)
- Address (street, city, county, zip code – initial 3 digits if geographic unit contains fewer than 20,000 people, or any other geographical codes)
- Telephone/Fax Numbers
- Social Security Numbers
- Dates (except for calendar years)
    - Birth Date
    - Admission Date
    - Discharge Date
    - Date of Death
    - Ages >89 and all elements of dates indicative of such age (except that such age and elements may be aggregated into a category "Age>90"
- E-mail Addresses/URLs/IP addresses
- Medical Record Numbers
- Health Plan Beneficiary Numbers
- Account Numbers
- Certificate/License Numbers
- Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
- Device Identifiers and Serial Numbers
- Biometric Identifiers (e.g. finger or voice prints or full face photographic images)

I certify that the protected health information (PHI)* to be disclosed outside CCHS for the research study referenced above does not include any of the identifiers listed above.

Principal Investigator Signature: _____ Date: _____

_____

* PHI: individually identifiable health information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health condition of an individual.