Applications of dual energy CT for improving staging and monitoring of therapy response in patients with osseous metastases from castrate-resistant prostate cancer

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Protocol Title:

Pilot study to assess feasibility of using dual energy CT to improve staging and monitoring of therapy response in patients with osseous metastases from castrate-resistant prostate cancer.

Short Title:

Dual energy CT for improving staging and monitoring of therapy response in patients with castrate-resistant prostate cancer.

Purpose of the Study:

To evaluate the capabilities of dual energy CT as a more precise and accurate tool for staging and monitoring of therapy response in patients with osseous metastases from castrate-resistant prostate cancer.

Our working hypothesis is that, by providing quantitative material-specific information of tissue composition, dual energy CT may yield more accurate and precise quantitative information for the staging and monitoring of therapy response in patients with osseous metastases from castrate-resistant prostate cancer. State of the art dual-energy MDCT technology, which is available and routinely utilized at Duke University, relies on simultaneous acquisition of two CT datasets at different energy levels, ***without*** increasing patient radiation exposure. The dual energy datasets can be used to calculate conventional CT images, similar to a routine single energy CT acquisition, or they can be further processed to extract material-specific information. The latter datasets have proven to be beneficial in multiple clinical scenarios (2-4).

Patients with osseous metastases from prostate cancer provide a common clinical and diagnostic challenge. Not uncommonly, subclinical metastatic lesions may only become detectable at imaging in response to therapy due to increased bone deposition during the first three months of post therapy. Commonly used imaging tests (such as CT or bone scan) are unable to reliably differentiate this phenomenon (also referred to as “flare”) from progressive metastatic osseous disease. This diagnostic challenge may have profound negative effects on patient management as it will require multiple additional imaging follow-up studies before an accurate assessment of tumor response can be formulated with appropriate management (Prostate Cancer Clinical Trials Working Group 3 [PCWG3]).

We postulate that dual energy CT may provide additional critical information in this clinical scenario. Specifically, by providing material-specific quantitative information on iodine concentration within tissues, dual energy CT may be able to distinguish between iodine uptake within viable metastatic osseous disease and lack of thereof within treatment-related reactive sclerotic lesions. This differentiation may not be possible using conventional attenuation measurements with single-energy CT due to the challenging anatomical environment within the

vertebral body where sclerotic metastatic tissue coexists with the complex structural anatomy of the fine trabecular bone.

Background & Significance:

Prostate cancer (PCA) is the most frequently diagnosed cancer in North America. It is the fourth most common cause of cancer death overall and the third most common cause of cancer death in men. In this cancer, bone represents a preferential site of metastases, and patients with advanced disease have a very high incidence of bone metastases. Autopsy data from prostate cancer patients indicate an incidence of secondary bone lesions as high as 65–75%, preceded only by multiple myeloma. These bone metastases are typically osteosclerotic (i.e. with increased osteoblastic activity), and likely to produce a significant impact on patients' functional status and quality of life, not only related to pain, but also to the relevant risk of skeletal-related events that can negatively impact physical well-being and activities of daily living.

Castrate-resistant PCA presents a spectrum of disease ranging from rising prostate-specific antigen (PSA) levels in the absence of metastases or symptoms and despite androgen-deprivation therapy, to metastases and significant debilitation from cancer symptoms. Castrate-resistant PCA is usually suspected in patients with new symptoms on androgen deprivation therapy, with a rising PSA, or with new evidence of disease on bone scans or CT scans.

Novel hormonal agents such as abiraterone acetate and enzalutamide improved survival significantly for patients with metastatic castration-resistant prostate cancer. Nevertheless, median survival is limited to 35 months after initiation of therapy. Therefore, it is beneficial to have a more accurate diagnostic measure to assess time to progression, either for patients to receive optimal therapy regimes or for studies to have a more accurate time to progression measure (5, 6). For this reason, the PCWG3 defined criteria for progression of the disease. The most challenging task is the assessment of bone metastases in the early phase of therapy due to common onset of a flare phenomenon. The flare phenomenon refers to the increase in radiotracer uptake at previously diagnosed or new previously undetected lesions soon after initiating therapy. Increased uptake is transient, but variable, lasting between three and six months. It is thought that the increase is a response to bone deposition and repair at treated sites. This increase in signal makes the distinction between progression of bone lesions or increased metastatic spread and successful treatment considerably difficult. In CT scans these lesions would appear osteosclerotic and thus could not be distinguished between therapy response and progression. For this reason, the PCWG3 defined progression as "appearance of at least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule). If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented." This implicates that progression needs to be dated back and diagnosis of progression is delayed by three months typically.

This highlights the critical need to precisely and accurately determine between flare and progressive disease after onset of therapy.

State of the art dual-energy CT enables simultaneous acquisition of two CT datasets at different energy levels ***without*** exposing patients to additional radiation dose. These datasets can be used to reconstruct regular CT images of identical image quality compared to conventional single-energy CT or facilitate further processing of dual-energy material-specific density images. Preliminary evidence suggest that material density images may improve detection of lithic metastatic lesions, such as in patients with multiple myeloma (7).However, the diagnostic accuracy of material density analysis in patients with sclerotic osseous metastases (such as patients with PCA) remains to be investigated. This is a particularly challenging task due to bone mineral deposition within primarily osteosclerotic metastatic lesions, remodeling of bone due to therapy response, and the complex structural anatomy of the trabecular bone within the vertebral bodies.

Our working hypothesis is that, by providing quantitative material-specific information of tissue composition, dual energy CT may yield more accurate and precise quantitative information for the staging and monitoring of therapy response in patients with osseous metastases from castrate-resistant prostate cancer.

Purpose of this study

Primary Objective:

Demonstrate the feasibility of using dual energy CT to improve staging and monitoring of therapy response in patients with osseous metastases from castrate-resistant prostate cancer, compared to regular single energy CT and technetium bone scans.

Secondary Objectives:

Analyze the feasibility to detect bone metastasis at baseline more accurately.

Analyze iodine uptake of soft tissue metastasis more accurately and monitor its change during therapy.

Correlate whether iodine quantification is a viable biomarker for early detection (small size) of lymph node metastases.

Exploratory Objective:

Determine whether dual energy CT is able to have prognostic capabilities in terms of therapy response and overall survival.

Design & Procedures:

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

Inclusion Criteria:
1. Oncology patients with castrate-resistant prostate cancer planned for therapy with abiraterone acetate or enzalutamide and prednisolone undergoing clinically indicated MDCT of the chest, abdomen and pelvis
2. > 18 years old
3. Serum creatinine < 2.0
4. BMI < 35kg/m^2
5. Sign informed consent

Exclusion Criteria:
History of anaphylactoid reaction to iodinated contrast material

All MDCT examinations will be performed using a third-generation dual-source dual-energy MDCT platform (Somatom Definition FORCE, Siemens Healthcare, Forchheim, Germany). Each patient will receive an unenhanced dual energy scan followed by a contrast-enhanced dual energy scan as part of clinical routine work up (Table 1). The preliminary unenhanced dual energy scan, which is currently *not* part of our routine clinical protocol, will provide necessary information for the baseline material density quantitative analysis of the bone marrow. For the contrast-enhanced scan, each patient will be scanned in a caudocranial direction during the hepatic venous phase 60-70 seconds after the start of contrast medium injection. No change in the contrast material injection protocol will be performed for this this study.

Patients will be examined with a dual-energy protocol at baseline (i.e., before starting therapy), and during the first and second follow up scans in order to differentiate between patients with partial remission, stable, or progressive disease.

Table 1. Details of the dual-energy CT scan protocols.

		kVp	**Pitch**	**Effective mAs**	**mAs / rotation**	**Relative $CTDI_{vol}$ (%)**	**Relative DLP (%)***
1st scan	Tubes 1 + 2	120	1	200	200	100	100
	Tube 1	100	1				
	Tube 2	150	1				
2nd scan	Tubes 1 + 2	120	1	200	200	100	100
	Tube 1	100	1				
	Tube 2	150	1				

Images will be reconstructed following conventional protocols and will include 5.0 and 0.6 mm slice thickness using filtered back projection (FBP) and commercially available iterative reconstruction (advanced modeled iterative reconstruction algorithm [ADMIRE]).

In addition, we will collect relevant clinical and demographic patient's information, such as prostate cancer related parameters, medical record number, age, gender, and body weight, height and body mass index. We will also collect information regarding the CT parameters, radiation dose and image quality.

For part of this investigation we will use commercially available dual-energy CT postprocessing software (SyngoVia VB10, Siemens Helathcare, Forchheim, Germany). At the same time, we will also be working in collaboration with Siemens Healthcare as part of study Pro00078046. Selected and fully anonymized image datasets in dicom format or raw-projection format will be shared with Siemens scientists for the purpose of developing postprocessing software which will be used in the study. While existing dual-energy CT software can be used to separately analize the pre and postcontrast phases, we will work in collaborations with Siemens to elaborate strategies and potentially dedicated prototype software which will register the image datasets and perform advanced dual-energy CT postprocessing.

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

Selection of Subjects:

1. Subject Recruitment and Compensation:

Consent Process:

One hundred and fifty eligible participants will be contacted via mail by their attending oncologist (Dr. A. Armstrong) prior to their clinically indicated CT scan. The study coordinator will consent eligible participants according to the inclusion criteria provided in the Design & Procedure section. If necessary, the participants will have no less than 24 hours to consider their participation. Consenting will take place in a private room. The prospective participant may have family or a friend present during the consent process, if they wish. At least an hour will be slotted for the consent process, but we will not prevent the subject from asking questions beyond that time. If the subject wishes to consider the study overnight or longer, an additional appointment will be made for the subject to continue the consent process. From the time of initial contact until the participant completes the study they will have complete freedom to access the coordinator by phone, email or in person. Each patient is given the possibility to refrain from the study after the baseline scan or the first follow up examination without any disadvantage regarding clinical treatment or imaging.

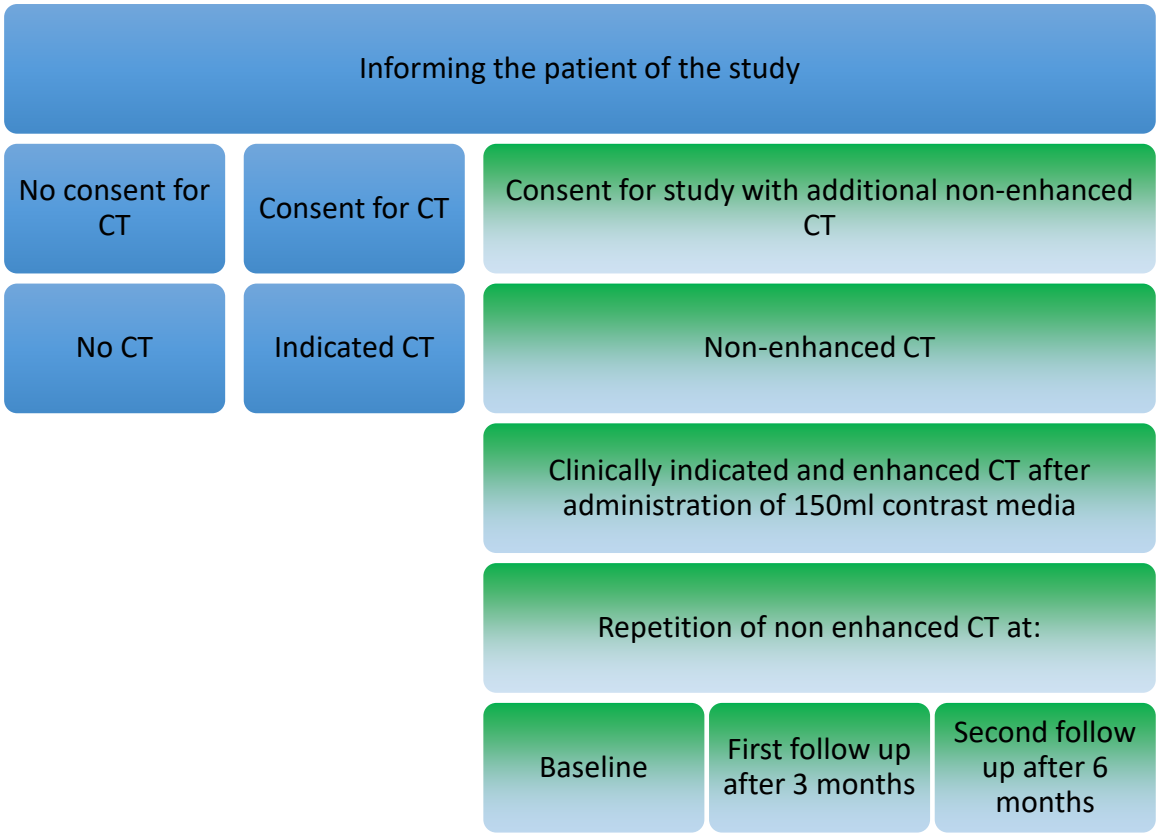
There will be no financial compensation for participation to this study.

Subject's Capacity to Give Legally Effective Consent:

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

2. Study Interventions:

The diagnostic scan will be preceded by a not clinically indicated non enhanced dual energy scan. The overall radiation dose to the patient for the first and second acquisition will be twice the radiation dose of a conventional CT of the chest, abdomen and pelvis.



3. Risk/Benefit Assessment:

The contrast-enhanced CT scan of the chest, abdomen and pelvis will be performed according to the clinical indication of castration-resistant prostate cancer, as determined by the referring oncologist.

This initial diagnostic scan will be preceded by an unenhanced dual energy scan, which is currently *not* part of our routine clinical protocol. This preliminary scan will provide the necessary information for the baseline material density quantitative analysis of the bone marrow. A second acquisition following intravenous contrast medium administration will be performed thereafter. Our protocol will result in a twofold increase in overall radiation dose to the patient compared to a routine conventional CT of the chest, abdomen and pelvis. This protocol will be repeated at baseline, first and second follow up resulting in three

additional CT scans in total and a cumulative additional radiation exposure of approximately 30mSv. This increase in radiation dose is not outside the standard of care as multiphasic MDCT examinations which include pre-, post-contrast imaging are routinely performed, even in young patients without cancer, for the work-up of indeterminate liver, renal, or adrenal lesions, as well as in patients with unexplained hematuria. Of note, many of these multiphasic CT protocols at our institution include dual-energy CT as the standard of care. Considering the demographic of PCA, we anticipate that most of our patients will consist of older age males with decreased life-expectancy. As such, the clinical implications of the marginal increase in radiation dose with our dual-energy CT protocol are favored to be negligible. Furthermore, some patients might even benefit from additional unenhanced CT scans because some secondary findings can be distinguished more precisely when additional unenhanced CT information is available.

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

4. Costs to the Subject:

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

5. Data Analysis & Statistical Considerations:

All image data will be processed using either commercially available software (SyngoVia VB10) or software prototypes developed for dual-energy CT postprocessing. All study data will be analyzed at Duke University. However, to further develop software prototypes which will be needed for image registration and advanced dual-energy CT postprocessing, we will work in collaboration with Siemens scientists as part of project with duke id Pro00078046. This will require we share with Siemens sample datasets, which will include DICOM image series or raw-projection datasets. In all cases, we will only share fully anonymized data.

To ensure consistency and reproducibility of the data, quantitative measurements of iodine uptake will be performed on a dedicated secondary workstation unit (Core2 x6800; Intel, Santa Clara, Ca) equipped with a previously validated custom Matlab-based software (Matlab, Ver. 2009a, Math-Works, Natick, Ma). Qualitative analysis of post-processed datasets will be performed on an offline workstation equipped with Osirix (Pixmeo SARL, Bernex, Switzerland). Statistical analysis will be performed in collaboration with the department of biomedical statistics. Multi-parametric regression analysis will identify whether dual energy based, calcium corrected iodine maps a valuable biomarker for monitoring and staging of

metastatic bone disease in prostate cancer. For the specific objectives of this study we intend to perform the following analyses.

To demonstrate the feasibility to monitor metastatic bone disease in castration resistant prostate cancer more accurately than regular single energy CT, single phase dual energy CT and technetium bone scans a quantitative analysis of iodine uptake will be performed. ROC statistics will be calculated to find optimal threshold of this biomarker. Qualitative analysis will be done by multiple readers in blinded fashion to determine sensitivity and specificity for distinction between disease progression at first follow-up three month after initiation of therapy. Findings will be correlated with technetium based bone scans.

To analyze the feasibility to detect bone metastasis at baseline more accurately, unenhanced bone marrow imaging will be calculated and additional dual energy based, calcium corrected iodine maps will be used to determine a threshold for detection of vital bone metastasis in order to calculate color coded bone maps for risk of presence of bone metastases. Qualitative analysis will be done by multiple readers in blinded fashion to determine sensitivity and specificity.

To analyze iodine uptake of soft tissue metastasis more accurately and monitor its change during therapy, a ROI based analysis will be performed for suspect metastatic lesions at three time points to see effects of therapy and to distinguish between partial remission, stable disease and progressive disease. A blinded multi reader assessment of iodine maps will be performed to calculate sensitivity and specificity for qualitative analysis of dual energy based examination compared to single-energy CT.

As an exploratory objective we want to determine whether dual energy CT has prognostic capabilities when assessing bone marrow metastases and soft tissue metastasis in terms of therapy response and overall survival. This exploratory objective will require long term follow up and access to patient data exceeding the time period of the baseline and first two follow up CT examinations. Caplan Mayer curves will be drawn and correlated with findings of bone marrow analysis.

Another exploratory objective is to correlate whether adjusted iodine quantification is a viable biomarker for early detection of lymph node metastases, which are too small to fulfill RECIST criteria of a metastasis at baseline but will become evident on follow up. A ROI analysis will be performed to assess whether adjusted iodine uptake might be a viable biomarker for early detection of lymph node metastases.

6. Data & Safety Monitoring:

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

7. Privacy, Data Storage & Confidentiality:

Every effort will be made to ensure subjects' confidentiality. All images containing subject PHI will remain on PACS and on the radiology department server. PHI recorded with data will be kept in a file on a password-protected computer. Any images used in publications or presentations will have all PHI removed. No identifiable PHI will be released outside of DUHS. There will be signed informed consents that will have some PHI on them that will need to be kept for at least six years along with the Regulatory Binder with an enrollment log in it.

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