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Feasibility of Discriminating Uric-Acid from Non-Uric-Acid Renal Stones Using Serially Acquired Low- and High-energy CT Scans on a Single-Source CT Scanner

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Abstract

Objective—To demonstrate the feasibility of differentiating uric acid (UA) and non-uric-acid (NUA) renal stones using two consecutive, spatially-registered low- and high-energy scans acquired on a conventional CT system.

Materials and Methods—A total of 34 patients undergoing clinically indicated dual-source, dual-energy CT exams to differentiate UA and NUA kidney stones were enrolled in this IRB-approved study. Immediately after clinically-indicated dual-source, dual-energy CT and written informed consent, two consecutive scans (one at 80 kV and one at 140 kV) were performed on a conventional CT scanner over the region limited to stones identified on the dual-source scan. After 3D deformable registration of the 80 and 140 kV images, UA and non-UA stones were identified using commercial software. Sensitivity, specificity, and accuracy of stone classification were calculated using the dual-source results as the reference standard.

Results—A total of 469 stones were identified in dual-source exams (26 UA and 443 NUA). Average in-plane stone diameter was 4.4 ± 2.5 mm (range 2.0 to 18.9 mm). Overall sensitivity, specificity, and accuracy for identifying UA stones were 73%, 90%, and 89%, respectively. The sensitivity, specificity, and accuracy were 95%, 97%, and 97% for stones ≥ 3 mm (n = 341, 19 UA and 322 NUA).

Conclusions—Accurate differentiation of UA and NUA renal stones is feasible using two consecutively-acquired and spatially-registered conventional CT scans.

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Introduction

CT is the preferred imaging technique for renal stone detection in many institutes due to its high sensitivity, specificity, and ability to detect radiolucent stones [1–3]. CT images provide reliable information not only about the presence or absence of renal stones, but also about the location and size of each stone. CT has also been used to identify the elemental composition of renal stones in order to guide patient management. For example, certain types of stones can be treated non-invasively (e.g., uric acid [UA] stones can be treated with urinary alkalinization). Stone composition can also be used to predict the efficacy of noninvasive extracorporeal shock wave lithotripsy [4].

Previous research attempted to use CT number from non-contrast single-energy CT to differentiate stone composition [5–7]. However, the overlap of CT numbers in different stone types limited its application to routine clinical practice [8, 9]. Recently, dual-energy CT has been introduced into clinical practice and its application in stone composition has been investigated. In dual-energy CT, the CT number ratio is calculated using the CT numbers of a given material at two different beam energies. Stones with different mineral compositions have different CT number ratios. Therefore, stone composition can be differentiated by setting threshold CT number ratios. Several *in vitro* and *in vivo* studies have reported accurate differentiation of UA stones from non-UA (NUA) stones using dual-energy CT [10–15] and have assessed further differentiation among NUA stones [16–20].

In most of these studies, the dual-energy data were acquired using dual-source CT scanners. Unlike conventional CT scanners that have one X-ray source and one detector array, dual-source CT scanners have two X-ray sources and two opposing detector arrays, which are mounted approximately orthogonal to one another [21, 22]. Dual-energy CT data are acquired on a dual-source scanner by simultaneously acquiring data with each source/detector pair, where one X-ray source uses a low tube potential setting and the other a high tube potential setting.

Techniques for acquiring dual-energy CT data have also been investigated using CT systems having only a single X-ray source. These include the use of fast kV switching, in which the tube potential is rapidly switched between low- and high-tube potential values during data acquisition, and dual-layer detectors, in which lower-energy photons are absorbed predominantly in the innermost detector layer and high-energy photons are absorbed in the outermost detector layer, after having passed through an attenuating filter [19, 23, 24]. Like dual-source CT, these techniques require special hardware and software that is available on a limited number of high-end scanner models. To have a wider clinic impact, a dual-energy technique that can be used on any CT scanner is required.

Dual-energy CT was originally implemented using two separate scans of the same patient anatomy using two different tube potentials (beam energies) [25, 26]. The major limitation of this approach was the long time interval between the two scans, which made the data analysis extremely vulnerable to patient motion. Over the past several decades, scan and interscan delay times became dramatically shorter. Thus, for relatively stationary organs, such as the kidneys, ureter, and bladder, the use of two separate scans to perform dual-

energy CT may be feasible. However, even in relatively stationary organs, misregistration can occur, as demonstrated in a recent study that found an average distance between the locations of the same kidney stone in two separate scans of 2.7 mm along the z-axis and 4.3 mm along in the axial plane [27].

We hypothesize that use of commercially-available 3D deformable registration techniques [28, 29] can register the data from two separate scans with sufficient accuracy to allow accurate stone differentiation analysis using dual-energy CT techniques. The purpose of this study, therefore, was to determine the accuracy with which two consecutively-acquired conventional CT scans (one acquired using a low tube potential and the other acquired with a high tube potential) can differentiate UA renal stones from NUA renal stones, using a clinically indicated dual-source, dual-energy CT exam as the reference standard.

Materials and Methods

Study Design

The accuracy with which dual-source dual-energy CT scanning can differentiate UA from NUA renal stones is very close to 100% [10–15]. Based on this, and to avoid limiting patient enrollment to only those scheduled for surgical stone retrieval or having to wait for spontaneous stone passage, this study used a clinically indicated dual-source, dual-energy stone composition scan as the reference standard.

Patient Enrollment

This prospective, HIPAA-compliant patient study was approved by our Institutional Review Board. We recruited subjects from patients undergoing clinically indicated dual-source, dual-energy CT scanning for the purposes of stone detection and differentiation of UA from NUA renal stones. If stones were found on the clinically indicated dual-source, dual-energy CT exam, a study coordinator was contacted and the patient was invited to participate in the study, with the two consecutive conventional scans occurring on the same day as the clinical dual-source exam. Written informed consent was obtained for patients agreeing to participate. For female patients of childbearing potential, a urine pregnancy test was performed, and only patients with negative results were enrolled. Subjects were then scanned on a conventional CT scanner scanner at our institute on the same day (usually within 1 hour) as their clinical dual-source, dual-energy exams.

CT Scans

Scans were performed on two scanners at our institute, a dual-source Siemens Definition Flash scanner, and a conventional (single-source) Siemens Definition AS+ scanner (Siemens Healthcare, Forchheim, Germany). The clinically indicated dual-source, dual-energy CT exam was performed on the Definition Flash scanner and followed our clinical scan protocol. The tube potentials were selected based upon patient size: 80 kV and 140 kV for patients with lateral measurement at top of the liver smaller than 35 cm, and 100 kV and 140 kV for patients larger than 35 cm, for better penetration with 100 kV. In both scenarios, a tin filter was added to the 140 kV beam (Sn140 kV) to improve energy separation and material differentiation [30]. Automatic exposure control (CareDose 4D) was turned on, and

the quality reference mAs values were 460/178 for the 80/140 kV beams and 240/185 for the 100/140 kV beams. The volume CT dose index (CTDI_{vol}) for a standard-sized patient (lateral size of 35–40 cm) was approximately 18 mGy. Images were reconstructed with a medium-smooth dual-energy kernel (D30) at 1 mm image thickness and 0.8 mm increment for both low- and high-energy data sets. A mixed-image data set was also generated as a linear combination of low- and high-energy images, with a weighting factor of 0.5 for each image set [31]. The mixed images used all available photons from both low- and high-energy scans so that image noise was lower than either the low- or high-energy images alone. The mixed images were used for stone detection and size measurement, similar to a routine single-energy renal stone CT scan, and had image quality and radiation dose similar to a typical single-energy scan [31].

The two consecutive conventional CT scans (i.e. the single-source, dual-energy CT exams) were performed on a Definition AS+ scanner. An 80 kV scan was performed first, with the scan region limited to the few centimeters cranial and caudal to the stones identified in the dual-source, dual-energy exam. A 140 kV CT scan was performed over the same scan region after the 80 kV scan and a 4-second time delay to allow the tube potential to change and the patient table to be moved back to the same starting position [32]. Both the 80 kV and 140 kV scans were completed in a single breath-hold. Automatic exposure control (CareDose 4D, Siemens Healthcare) was turned on, and the quality reference mAs values were 340 and 80 for the 80 kV and 140 kV beams, respectively, with total CTDI_{vol} of approximately 15 mGy, similar to that of the dual-source, dual-energy CT exam. These CTDI_{vol} values were also similar to our routine single-energy stone exams, and similar to that reported in the literature using dual-energy CT to differentiate stone compositions [10, 13, 16, 17, 33].

The major differences between the two scanning approaches were simultaneous (dual-source) versus non-simultaneous (conventional single-source) acquisition of the low- and high-kV data and the use of tin filtration on the 140 kV beam of the dual-source scanner, which facilitated the use of 100 kV on the dual-source scanner with larger patients. For all conventional scan data, images were reconstructed separately for the 80 and 140 kV scans, with reconstruction parameters selected to be the same as those used in dual-source, dual-energy exams: a medium smooth kernel (D30), 1 mm slice thickness, and 0.8 mm increment. The starting and ending location and reconstruction field of view were identical for the 80 kV and 140 kV scans.

Dual-Energy Processing

Stone composition differentiation from the dual-source, dual-energy exams was performed as part of the patients' clinical care. Commercial software (Syngo VA 44, Dual-Energy Application, Siemens Healthcare) was used to differentiate UA from NUA renal stones. The CT number ratio was calculated voxel by voxel for each stone and compared with a preset threshold (1.13 for 100/Sn140kV and 1.21 for 80/Sn140kV). If the CT number ratio was below the threshold, the voxel was colored red to indicate UA; above the threshold, the voxel was colored blue to indicate NUA. A 'range' parameter is used in the commercial dual-energy CT application to control the number of nearby voxels that are included when

determining the composition at a given voxel, which aims to reduce the influence of image noise on stone composition. We selected a value of 3 for the dual-source, dual-energy exams; in several years of clinical use and several research publications, this value has provided reliable results.

Similar dual-energy processing was performed on the conventional single-source images using prototype software (Syngo VA 44, Dual-Energy Application, Siemens Healthcare). The software is similar to that used for the dual-source exams, but with a built in 3D deformable registration algorithm. The CT number ratio threshold was set to 1.15, the default value suggested by the manufacturer. The range parameter was set to 3, as it was for the dual-source, dual-energy exams. A built-in 3D deformable registration algorithm was automatically performed to register the 80 and 140 kV images after data were loaded into the dual-energy application. Registration was performed prior to the classification of stones as UA or NUA. Mixed images were generated as the linear combination of 80 kV and 140 kV images after the 80 kV images were registered to the coordinate system of the 140 kV images. Mixed images generated with and without the use of 3D deformable image registration were compared to visually evaluate the ability of the registration process to accurately register stones in the two separate scans.

Data Analysis

A genitourinary radiologist reviewed the color-coded images of stone composition for both dual-source, dual-energy and single-source, dual-energy CT exams. Results from dual-source, dual-energy CT scans were considered the reference standard because this method has been previously shown to be very accurate [10–15]. For stones with mixed color, the fraction of each component was estimated by examining the axial images. Stones with 50% or more pixels labeled with red were considered to be UA stones, otherwise they were considered to be NUA stones. This approach mimics the decision criteria used in our clinical practice. The sensitivity, specificity, accuracy, and positive and negative predictive values for correctly identifying UA stones were calculated for the conventional, single-source, dual-energy data using the results of the dual-source, dual-energy clinically indicated scan as the reference standard. The size of each stone was characterized by its widest diameter in the axial plane, as measured by the evaluating radiologist ([initials blinded for review]). Stones with widest diameter ≥ 2 mm were included in the data analysis. Because small stones were more prone to motion and registration errors, accuracy was also calculated for stones ≥ 3 mm.

Results

A total of 34 patients were enrolled in this prospective study and were scanned using both dual-source and single-source dual-energy CT techniques. One patient was excluded from the data analysis because the first scan (80 kV) did not include the upper poles of the kidneys and missed the stones. The remaining 33 patients (15 male, 18 female) had a mean age of 58 ± 13 years (range 28 to 83 years). Among these 33 patients, 20 patients had only NUA stones, 4 patients had only UA stones, and the other 9 patients had UA and NUA stones. The average CTDI_{vol} and DLP were 13.7 mGy (range from 6.3 to 22.7 mGy) and

454 mGy·cm (range from 134 to 1038 mGy·cm) for dual-source, dual-energy exams; and 16.2 mGy (range from 7.5 to 29.3 mGy) and 333 mGy·cm (range from 71 to 960 mGy·cm) for single-source, dual-energy exams.

An example of 80 kV and 140 kV images from the same patient undergoing single-source, dual-energy CT is shown in Figure 1, where the kidney stones appear at different locations in the 80 and 140 kV images due to patient motion (Fig. 1a and b). The mixed images generated from these scans, without use of registration techniques, resulted in relatively blurrier stones having decreased brightness and located at positions of the stone in both the 80 and 140 kV images (Fig. 1c). This is due to the fact that stones were at different locations of the 80 and 140 kV images. However, 3D deformable image registration brought the two data sets into alignment. The mixed images showed only stone locations that were present in the 140 kV images, the blurring was reduced, and the stone brightness increased (Fig. 1d).

After image registration, CT number ratio calculation and stone composition labeling was performed. Sample color-coded images (Fig. 2 and 3) show stone composition characterizations from single-source exams that were in agreement with those from the corresponding dual-source exams. In a different case, an NUA stone was incorrectly characterized as a UA stone in the single-source exam (Fig. 4).

A total of 469 renal stones were detected on the dual-source, dual-energy CT. Among these stones, 341 were ≥ 3 mm, as measured along the longest axis on the axial images from dual-source exams. Average stone size was 4.4 ± 2.5 mm (range 2.0 to 18.9 mm). Among the 341 stones with size ≥ 3 mm, 19 were identified as UA and 322 NUA by the dual-source exams. Among the 19 UA stones, 18 were correctly identified as UA stones in single-source exams. Among the 322 NUA stones, 312 were correctly identified as NUA stones in single-source exams. The corresponding sensitivity and specificity were 94.7% and 96.9%, and positive and negative predictive values were 64.3% and 99.7%, respectively for detecting UA stones. Accuracy for identifying UA stones was 96.8% for stones ≥ 3 mm.

When considering all of the 469 renal stones at all sizes, 26 UA and 443 NUA stones were identified by the dual-source, dual-energy CT. Single-source, dual-energy scans correctly identified 19 of the 26 UA and 399 of the 443 NUA stones. Sensitivity and specificity for identifying UA stones were 73.1% and 90.1%, respectively, and positive and negative predictive values were 30.1% and 98.3%. The accuracy for identifying UA stones was 89.1% for all stone sizes.

Discussion

To reliably analyze renal stone composition using dual-energy CT, the low- and high-energy images ideally should be obtained simultaneously (e.g., with dual-source or dual-layer detector techniques) or near simultaneously (e.g., with the kV switching technique). Although present on certain high-end scanners, these features are not available on the majority of CT scanners currently installed in clinical practice. To perform dual-energy CT on a single-source scanner without special hardware, we performed two consecutive scans at different tube potentials. Respiratory motion or unintended patient motion during the time

interval between the two scans could change the relative locations of stones in the low- and high-energy images and degrade the accuracy of stone composition analysis. The 3D deformable registration technique applied in this study addressed this motion issue by mapping the two image sets onto the same coordinate system.

In general, smaller stones were more challenging to classify. Patient motion and residual registration errors made this task even more challenging for single-source, dual-energy CT, in which data were acquired in separate scans. This was demonstrated by the observation that most misclassified stones were <3 mm. Consistent with our findings, the majority of published studies about stone composition analysis either focused only on relatively large stones or demonstrated that performance was better in larger stones (e.g., >3 mm) [10, 15, 16, 27].

In the application of dual-energy scans to the determination of stone composition, 'CT number ratio threshold' and 'range' are two important parameters whose specific values potentially affect the results. For the single-source dual-energy exam performed in this study, the default value of 1.15 suggested by the manufacturer was selected for the CT number ratio threshold. On the basis of our clinical experience with dual-source dual-energy exams, a value of 3 was selected as the 'range' parameter for both types of exam. However, these values are not guaranteed to generate the highest differentiation capability from the single-source dual-energy exams. This study focused on the feasibility of dual-energy CT using two consecutively acquired scans on a single-source CT scanner. Another study is warranted to investigate the effect of changing the CT number ratio threshold and range values on stone composition differentiation, and to determine the optimal values of these parameters.

This study had several limitations. First, no ex vivo analysis of patient stones was available, mainly because not all of the patients who participated in this study had their stones removed or passed the stones spontaneously and saved them for analysis. Therefore, we used stone composition determined with dual-source, dual-energy CT as the reference standard. The accuracy of dual-source, dual-energy CT has been validated by multiple groups, particularly with stones larger than 3 mm [10–15]. A second limitation of this feasibility study was a relatively small patient cohort, a total of 34 patients was included for this feasibility study. However, the relatively large number of identified stones (N=469), and analysis of the data on a per-stone basis, minimize the impact of the small cohort size on the conclusions of this study. The promising results obtained here suggest that studies correlating the accuracy of single-source, dual-energy CT against ex vivo stone analysis could be performed to determine *in vivo* accuracy in a larger patient cohort.

In conclusion, we have demonstrated that accurate differentiation of UA and NUA renal stones is feasible using two consecutively-acquired and spatially-registered scans obtained on a conventional single-source CT scanner. The accuracy was 97% for stones 3 mm or larger and 89% for all stones. This may allow dual-energy differentiation of stone composition to be performed on most conventional CT scanners, making the method much more widely available to help in the diagnosis and management of renal stones.

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Fig. 1.

Use of 3D deformable image registration to improve single-source dual-energy images. Sample 80 kV (a) and 140 kV (b) images show mismatched stone locations due to patient motion. A mixed image (c) directly generated from these images shows blurred stones with degraded brightness. After performing 3D deformable image registration, the generated mixed image (d) shows the same stone locations as in the 140 kV image, with reduced blurring and increased brightness. All images are displayed with window width and window center of [770, 220].

Fig. 2. Identification of uric-acid stones in a 68-year-old male. Both (a) dual-source CT and (b) single-source CT detected two uric-acid stones in the upper pole of the left kidney.

Fig. 3. Identification of non-uric-acid stones in a 53-year-old female. Both **(a)** dual-source CT and **(b)** single-source CT detected four non-uric-acid stones in the right kidney.

Fig. 4. Divergent findings in a 68-year-old male. Dual-source CT **(a)** detected a non-uric-acid stone in the right kidney, but single-source CT **(b)** identified a uric-acid stone.