Gadoxetate Disodium enhanced spectral dual-energy CT for evaluation of cholangiocarcinoma: Preliminary data

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HIGHLIGHTS

- Hepatic parenchyma showed an increase in attenuation measurement at the lower viewing energy.
- No significant difference was observed for measurement for single versus double dose of gadolinium.
- Visually the liver parenchyma did not enhance, limiting evaluation of cholangiocarcinoma.

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ABSTRACT

Purpose: Evaluate Gadoxetate Disodium enhanced dual-energy CT for visualization of perihilar cholangiocarcinoma by exploiting the hepatobiliary uptake of Gadoxetate Disodium and viewing images at the k-edge of gadolinium on the spectrum of simulated monoenergetic energies available with Dual Energy CT.

Material and methods: In this prospective, IRB-approved study in patients with suspected cholangiocarcinoma, subjects who underwent a clinically indicated Gadoxetate Disodium liver MRI were immediately scanned without further IV contrast administration using rapid kVp-switching dual energy CT (rsDECT). Initial Gadoxetate Disodium dose was the FDA approved clinical dose, 0.025 mmol/kg; after additional IRB/FDA approval, 10 subjects were scanned with 0.05 mmol/kg. Both 50 keV and 70 keV simulated monoenergetic images as well as gadolinium(-water) material density images were viewed qualitatively and measured quantitatively for gadolinium uptake in the hepatic parenchyma and any focal lesions identified.

Results: Of 18 subjects (mean age 55 years, 10M, 8F, weight 84 kg), eight were scanned with 0.025 mmol/kg (Group 1) and 10 with 0.05 mmol/kg Gadoxetate Disodium (Group 2). Five patients had cholangiocarcinoma (all in Group 1). On synthetic monoenergetic images using standard and double Gadoxetate Disodium dose, the liver parenchyma did not appear enhanced qualitatively. Comparison of mean hepatic parenchymal HU at 50 and 70 keV showed a measurable increase in attenuation at the lower viewing energy, which corresponded to the k-edge of gadolinium. No statistically significant difference was observed on quantitative gadolinium measurement of hepatic parenchyma for single versus double Gadoxetate Disodium dose using rsDECT gadolinium material density images. Of the five cholangiocarcinomas, the tumor to nontumoral hepatic tissue HU differences were 51.1 (32.2) (mean and std dev) and 49.0 (26.5) at 50 and 70 keV, respectively.

Conclusion: In this small pilot population, evaluation of potential hilar/perihilar cholangiocarcinoma using dual energy CT at both the single FDA-approved dose and double dose of gadolinium demonstrated observed differences in attenuation between the hepatic parenchyma and lesions. However, small sample size and heterogeneity of lesions warrants further investigation.

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1. Introduction

Cholangiocarcinoma is a neoplasm originating in the intra or extra-hepatic biliary epithelium. Despite a multimodality approach in the diagnosis and staging of cholangiocarcinoma, determining the extent of disease remains a challenge and the disease is often underestimated [1,4]. Conventional MDCT in conjunction with iodinated IV contrast is currently used to image patients with cholangiocarcinoma, and provides the advantage of a rapid exam of high resolution. Images are obtained during arterial and portal venous phase, as well as delayed phase scanning at 15 min. Cholangiocarcinomas typically show a higher attenuation compared to the surrounding hepatic parenchyma in the delayed phase, a finding that is attributed to abundant fibrous stroma [2].

MRI of the liver using extracellular gadolinium-based agents faces some of the same challenges as CT; however, MRI techniques benefit from inherent tissue contrast, which work to its advantage in evaluating tumors. More recently, the introduction of hepatobiliary agents such as Gadoxetate Disodium — Eovist™ (Bayer Healthcare NJ, USA) increases the contrast between tumoral tissue and normal surrounding hepatic parenchyma, improving visualization of hepatic lesions including cholangiocarcinomas [3]. The hepatobiliary phase is usually reached within 20 min after initiation of contrast injection in patients with normal hepatocyte function and last for at least 60 min [4]. In the hepatobiliary phase, tumors appear dark against brightly enhanced liver parenchyma, and in the case of cholangiocarcinomas might be better depicted this way rather than relying on delayed uptake in fibrotic tissues [4]. However, not all patients can undergo an MRI scan. In addition, patients might not be able to comply with breath holding requirements or tolerate the relatively longer scan times required for MRI compared to MDCT. With hepatobiliary phase imaging, an MRI scan typically lasts at least 30–45 min. To this end, an ideal imaging test for detection and staging of cholangiocarcinoma would be rapid and provide excellent hepatobiliary contrast enhancement.

Gadoxetate Disodium in combination with dual energy CT has the potential to fill this role well [5,6]. Gadolinium, as a chelated molecule, has been used as an MRI relaxation contrast agent for many years. Because of its electronic structure, it is also an effective x-ray contrast agent due to relatively high attenuation and advantageous k-edge in the diagnostic x-ray energy range: 50.2 keV compared to 33.17 keV for iodine (Figs. 1–2). We hypothesized that utilizing dual energy simulated monoenergetic images corresponding to the k-edge of gadolinium while employing a gadolinium-based hepatobiliary agent such as Gadoxetate Disodium would help better visualize hilar cholangiocarcinomas. The purpose of our project was to perform a qualitative and quantitative evaluation of Gadoxetate Disodium enhanced rapid kVp-switching dual energy CT (rsDECT) in visualizing perihilar cholangiocarcinomas.

2. Materials and methods

This prospective, HIPAA compliant study was approved by our IRB. All patients with suspected cholangiocarcinoma who were referred to the liver transplant clinic of our tertiary care medical center and who had a gadoxetate MRI ordered for clinical evaluation were eligible. Patients who had hepatobiliary surgery within the last 2 years, were less than 19 years of age, or were pregnant, were excluded from the study. We did not exclude patients who had percutaneous transhepatic drains in place. After full written informed consent was obtained, subjects underwent a clinically indicated Gadoxetate enhanced MRI scan of the liver per standard of care followed immediately by a research rsDECT scan of the upper abdomen, without additional IV contrast, within 1 h of the Gadoxetate administration. To expedite the process, subjects were transported in a wheelchair from the MRI scanner to the dual energy scanner located on a different floor in the same outpatient multidisciplinary clinic building. Demographics, time from injection to rsDECT acquisition, total bilirubin, serum Aspartate Amino Transferase (AST), serum Alanine Amino Transferase (ALT), serum creatinine and dose linear product (DLP) were recorded from the electronic medical record (Table 1).

MRI scan of the liver was performed on a Phillips 1.5T Achieva™ scanner (Philips Medical Systems, Best, The Netherlands). The Gadoxetate Disodium enhanced MRI scan protocol included 10–20 min delayed hepatobiliary images in addition to the other standard sequences. End point of the hepatobiliary phase was visualization of excreted contrast in the bile ducts. The rsDECT was performed on a GE HD750™ (GE Healthcare, Milwaukee, WI USA). After localization, a single acquisition through the liver was obtained in dual energy mode without administering any additional intravenous contrast agent (Table 2). Five mm thick simulated monoenergetic axial images were generated at 50 and 70 keV and gadolinium-(water) basis pair images were also generated at the same slice thickness. Initially, subjects were given the FDA-approved Gadoxetate dose of 0.025 mmol/kg. After the first 8 subjects were accrued, it was apparent that the standard clinical dose was suboptimal for visualization on rsDECT. After obtaining additional regulatory approvals including an Investigative New Drug (IND) letter from the FDA, as well as new approval from our institution’s IRB, all subsequent subjects were scanned with 0.05 mmol/kg Gadoxetate Disodium. Both groups were injected with Gadoxetate Disodium at a rate of 1 ml/s [7].

Qualitative evaluation: The IV Gadoxetate Disodium enhanced rsDECT images were reviewed in consensus by two radiologists.
FDA-approved Gadoxetate Disodium single dose: 0.025 mmol/kg

50 keV  70 keV  Water (Gadolinium)

Gadoxetate Disodium double dose: 0.05 mmol/kg

50 keV  70 keV  Water (Gadolinium)

Fig. 2. Qualitative evaluation — Shows no significant difference between the 50 keV, 70 keV and water(-gadolinium) images at single and double dose of Gadoxetate.

with greater than ten years’ experience in abdominal imaging, who understood that the patients were being evaluated clinically for potential cholangiocarcinoma but were blinded to the standard clinical MR images and any biopsy results. Images from the single (0.025 mmol/kg) and double (0.05 mmol/kg) dose of Gadoxetate Disodium at 50 keV (low energy corresponding to ‘k-edge’ of gadolinium), 70 keV (visually similar in practice to standard single energy CT obtained using a 120 kVp polychromatic beam), and gadolinium (-water) material density (MD) decomposition basis pair images, were evaluated for subjective hepatic parenchyma enhancement, intrahepatic biliary excretion of contrast, and detection of focal hepatic lesions. The above parameters were assessed with a consensus yes/no scoring system. For this qualitative evaluation, hepatic parenchymal enhancement was defined as appreciable enhancement more than the para-sinal muscles. Biliary excretion of contrast was defined as high density visualized within the intra- or extrahepatic bile ducts above the density of hepatic parenchyma. Similar to the way hypovascular and fibrotic cholangiocarcinomas tend to have a relatively low signal when compared to hepatic parenchyma on MRI scans using hepatobiliary agents, we surmised that cholangiocarcinomas would appear relatively hypodense when compared to hepatic parenchyma on rsDECT synthetic monoenergetic and gadolinium material density (MD) images. This criterion was used to qualitatively assess for any focal hepatic lesions.

Quantitative evaluation: Quantitative assessment of gadolinium uptake in Hounsfield units (HU) was measured within hepatic parenchyma as well as any focal lesions that were visualized at 50 and 70 keV using dedicated dual energy post processing software on a standard independent workstation (gemstone spectral imaging, GSI; advantage workstation, both GE Healthcare, Waukesha WS USA). For the parenchymal evaluation, four standardized ROIs (area of 295.2 mm² SD 8.05) were placed in the right anterior, right posterior, left medial and left lateral segments, and the mean was calculated for each patient as the individual attenuation for each energy level. ROIs of similar size were placed in the paraspinal muscles and subcutaneous fat on the same image to measure noise (standard deviation of the HU value of the ROI) for calculation of signal to noise and contrast to noise ratios. The ROIs were simultaneously populated to the same locations on all rsDECT images, viewed side by side on the GSI workstation. Quantitative rsDECT variables included mean attenuation of hepatic parenchyma and lesion at 50 and 70 keV, mean mg/cc gadolinium on gadolinium(-water) MD images, and standard deviation of attenuation of the muscle and fat at 50 and 70 keV.

Statistical Analysis: Quantitative variables are presented as mean ± standard deviation (SD), and qualitative variables are presented as frequencies and percentages. Due to the small sample
size of this study the analysis is largely descriptive in nature, however where applicable non-parametric approaches are used to assess differences. To examine the differences in quantitative variables at 50 keV and 70 keV for single and double doses of Gadoxetate Disodium, Kruskal–Wallis one-way ANOVA tests were performed to calculate if the differences in attenuation at different energy levels were statistically significant. Moreover, differences in hepatic parenchymal to lesion attenuation measurements at 50 and 70 keV energy levels for both dose levels were evaluated by estimating the mean within-group measurements and using the sign-test to assess statistical significance. All Data analysis was performed using commercially available statistical software (SAS v9.4). Statistical significance was defined as P-values less than 0.05.

3. Results

Demographics: A total of thirty-two patients were screened of which 18 met entry criteria, and were accrued into our study. Of these 18 patients, 7 (38.9%) were female, 3 (16.7%) were African American, with an average age of 54.9 years old (SD = 17.5 years, interquartile range: 42–69 years), and an average weight of 83.6 kg (SD = 20.9 kg, interquartile range: 65.8–99.8 kg). Eight subjects were scanned with 0.025 mmol/kg and ten with 0.05 mmol/kg dose of Gadoxetate. Nine had diffuse liver disease: sclerosing cholangitis (n = 7) and cirrhosis (n = 2). Eight subjects had focal liver lesions: cholangiocarcinoma (n = 5), Hepatocellular carcinoma (n = 1) and benign lesions (n = 2). One patient had cholecystitis. The final clinical diagnosis was based on biopsy or multidisciplinary consensus. Mean time to rsDECT scanning from injection in MRI was 36 min, (range 26–55 min). Mean scan time for both groups was 32 min (Table 1).

Qualitative Image Evaluation: Hepatic parenchymal enhancement was not appreciable in any of the subjects in either the single or double dose groups on the 50 kev, 70 keV and gadolinium (-water) basis pair images (Fig. 3). Only one subject demonstrated excretion of contrast into the bile ducts on all three types of images. The patient was scanned within 30 min of contrast administration. In 6 of the patients, hypodense lesions were detectable. Of these 5 were cholangiocarcinomas (all Group 1, 0.025 mmol/kg) and 1 was a HCC (Group 2, 0.05 mmol/kg). All cholangiocarcinomas were hilar or perihilar. In 5 other patients, contrast was seen excreted within the gallbladder, and in 13 of the patients, contrast was visibly excreted within the renal collecting systems.

Quantitative Image Evaluation: For the single Gadoxetate Disodium dose group (0.025 mmol/kg), the mean attenuation of hepatic parenchyma was 51.3 HU and 46.6 HU for 50 keV and 70 keV, respectively (Table 3). For the double dose group (0.05 mmol/kg) the mean attenuation of hepatic parenchyma was 53.2 HU and 52.2 HU for 50 keV and 70 keV respectively (Table 3). These differences were not statistically significant for either group.

In the single dose group, the mean attenuation difference between the hepatic parenchyma and focal lesions at 50 keV was 21.4 HU and at 70 keV was 18.8 HU (Table 4). Within the single dose group, the differences between 50 and 70 keV were not found to be significantly different (p = 0.7540). In the double dose group, the attenuation difference between hepatic parenchyma and lesion at 50 keV was 14.8 HU and at 70 keV was 9.2 HU (Table 4). There were observed differences in attenuation between the hepatic parenchyma and lesion for the single compared to double dose, however
Fig. 3. 79-year-old male with hilar cholangiocarcinoma shown on the hepatobiliary phase of the MRI scan at single dose of 0.025 mmol/kg performed on same day. On the qualitative analysis the hilar mass is barely visible. Quantitative measurement at 50 keV, the hepatic parenchyma measured 79 HU ± 24, and the cholangiocarcinoma measured 36.2 ± 17.8.

Table 3
Average of attenuation of liver, muscle and fat at 50 keV, 70 keV for single and double dose of Gadoxetate Disodium.

|                  | Liver - HU | Muscle - HU | Fat - HU |
|------------------|------------|-------------|----------|
| Gd single dose   | 0.025 mmol/kg (n = 8) | 51.3 ±32.8 | 47.6 ±38.2 | −141.5 ±39.95 |
| 50 keV           | 46.6 ±24.5 | 36.1 ±25    | −97.5 ±23.4 |
| 70 keV           | 4.7 (p = 0.29) | 11.5 (p = 0.21) | 44.1 (p = 0.01) |
| Gd double dose   | 0.05 mmol/kg (n = 10) | 53.2 ±39.2 | 54.1 ±42.8 | −144.8 ±43.1 |
| 50 keV           | 52.2 ±20.1 | 48.3 ±21.6  | −102.7 ±22.5 |
| 70 keV           | 1 (p = 0.71) | 5.8 (p = 0.17) | 42.1 (p < 0.01) |
| 50–70 keV        |            |             |          |

Table 4
Showing average of attenuation of liver parenchyma and lesions detected at 50 keV and 70 keV for single and double dose of Gadoxetate Disodium.

|                  | Liver - HU | Lesion - HU |
|------------------|------------|-------------|
| Gd single dose   | 0.025 mmol/kg (n = 5, all cholangiocarcinomas) | 51.1 ±32.2 | 29.7 ±34.3 | 21.4 (p = 0.063) |
| 50 keV           | 49.0 ±26.5 | 30.2 ±19.6  | 18.8 (p = 0.063) |
| Gd double dose   | 0.05 mmol/kg (n = 1, hepatocellular carcinoma) | 57.3 ±24.4 | 42.5 ±20.7 | 14.8 |
| 50 keV           | 48.1 ±23   | 38.9 ±13.4  | 9.2 |
| 70 keV           |            |             |          |

Small sample size and heterogeneity of lesions warrants further investigation.

The mean mg/cc gadolinium of the hepatic parenchyma in the single dose group was 0.65 mg/cc (±2.5) and for double dose was 0.38 mg/cc (±2.2) (Table 5). Gadolinium quantification of the hepatic parenchyma and lesions were also measured.

4. Discussion

To our knowledge, there have been no other studies in human subjects evaluating the use of Gadoxetate Disodium during abdominal dual energy CT. Our goal was to show that with rsDECT, we could combine imaging at the optimal k-edge of gadolinium with IV Gadoxetate Disodium administration to optimize cholangiocarcinoma evaluation. We did not intend to compare rsDECT to MRI for accuracy in detection and staging. In this small pilot study, using first the FDA-approved single and then a double dose of Gadoxetate, the qualitative evaluation did not demonstrate subjective enhancement of the hepatic parenchyma. There was a measurable increase in attenuation of the hepatic parenchyma at 50 keV compared to 70 keV, and measurable relative lower attenuation within lesions compared to the hepatic parenchyma. Quantification of gadolinium on the gadolinium (−water) MD images at both doses of Gadoxetate showed detectable levels of gadolinium but overall showed less detectable gadolinium for the double dose group than the single dose group. This might have been related to nonuniform scan delay in individual subjects although there was no difference in the mean scan delay between the two groups. Alternatively, since there was a trend towards higher HU at the lower keV suggesting some effect of parenchymal gadolinium on tissue contrast near the k edge, these preliminary findings might indicate that the quantitative gadolinium measurement is not robust with the present machine configuration, or that detection of the hepatobiliary phase with rsDECT, unlike MRI, does not plateau for 60 min.

Other factors besides scan delay, such as patient weight, underlying hepatic steatosis, and total bilirubin level which we did not control for in this pilot data might affect the qualitative and potentially the quantitative assessment of gadolinium using DECT on both synthetic monoenergetic and gadolinium MD images.

This pilot study is limited by the very small number of subjects, and although all were scanned for suspected cholangiocarcinoma clinically, only five were ultimately diagnosed with cholangiocarcinoma. Despite doubling the FDA approved Gadoxetate Disodium dose of 0.025 mmol/kg to 0.05 mmol/kg, we were not able to show a statistically significant increase in hepatic parenchymal attenuation or absolute contrast difference between cholangiocarcinomas and the hepatic parenchyma at these clinically acceptable dose levels. Quantitative assessment might have benefited from comparison with a baseline non-contrast rsDECT of the liver, which we did not acquire in efforts to limit radiation exposure to the subjects. The presence of hepatic parenchymal

Table 5
Gadolinium (−water) basis pair images showing gadolinium concentration at single and double dose of Gadoxetate Disodium.

| Gadolinium (−water) mg/cm³ | Liver mg/cm³ | Muscle mg/cm³ | Fat mg/cm³ |
|---------------------------|--------------|---------------|------------|
| Gadoxetate – Single dose (0.025 mmol/kg) (n = 8) | 0.65 ±2.5 | 0.44 ±2.5 | 3.76 ±2 |
| Gadoxetate – Double dose (0.05 mmol/kg) (n = 10) | 0.38 ±2.2 | 0.30 ±2.2 | 3.9 ±2 |
uptake of Gadoxetate in all subjects was confirmed on the hepato-biliary phase of the liver MRI obtained immediately prior to the rsDECT scan.

In summary, in this small pilot population, evaluation of hilar/perihilar cholangiocarcinoma using dual energy CT at both the single FDA-approved dose and double dose of gadolinium demonstrated measurable differences in attenuation of the hepatic parenchyma at routine viewing and lower energies, as well as between the hepatic parenchyma and lesions, but not at a statistically significant level, and qualitatively there was no detectable contrast enhancement in the hepato-biliary phase. However, the small sample size and heterogeneity of lesions may warrant further investigation. Multiple other factors such as patient weight, scan time, and total bilirubin levels potentially play a role in the degree of hepatic parenchymal enhancement. It is likely the doses of Gadoxetate that would be acceptable clinically will not provide adequate enhancement no matter the type of DECT acquisition. If strict timing parameters and patient physiologic conditions can be controlled or stratified in a larger population, it might help to understand whether the sensitivity of DECT for detection and quantification of gadolinium in the hepatic parenchyma could be sufficient enough to allow detection of lesions such as cholangiocarcinoma.

**Ethical approval**

IRB approved.

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**Author contribution**

Dr. John Thomas — PI and lead author.
Dr. David Bolus, Dr. Lincoln Berland, Dr. Michael Yester, Dr. Desiree Morgan all helped with the design of the study.

**Conflicts of interest statement**

No financial or personal disclosures to make.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request; IRB approval obtained.

**Guarantor**

Dr. John V. Thomas.

**Registration of Research Studies**

Clinical trials.gov — NCT01673802 “The Role of Gadoxetate (Eovist) Enhanced CT in Evaluating Cholangiocarcinoma”

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