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Imaging of the Gallbladder with Multi-energy CT

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Abstract

Purpose of Review The goal of this review article is to provide an overview of applications of multi-energy CT as they pertain to gallbladder imaging. We discuss benefits and shortcomings of MECT of various gallbladder pathology, with an emphasis on the imaging of gallstones and cholecystitis. It also touches on promising areas that warrant further investigation.

Recent Findings MECT has demonstrated improved sensitivity for cholelithiasis compared to conventional single-energy CT, with added value of MECT reconstructions, particularly virtual monoenergetic reconstructions, to detect isoattenuating gallstones. MECT iodine maps and virtual monoenergetic images potentially add value in evaluating other gallbladder pathologies, including detecting complications of acute cholecystitis, characterization of xanthogranulomatous cholecystitis and adenomyomatosis, and identifying and evaluating the extent of gallbladder carcinoma.

Summary MECT is emerging as a useful exam to evaluate the gallbladder, particularly in the setting of acute abdominal pain, and has the potential to eliminate the need for other imaging exams such as ultrasound.

Keywords Gallbladder · Dual-energy CT · Cholelithiasis · Adenomyosis · Gallbladder carcinoma · Xanthogranulomatous cholecystitis

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Introduction

Gallbladder disease is a common cause of abdominal pain; in fact, acute cholecystitis alone is the etiology in approximately 5% of patients presenting to the emergency room for abdominal pain [1]. Imaging plays a large role in the diagnosis of gallbladder disease as clinical symptoms may be vague and nonspecific [2]. The traditional modality of choice for initial evaluation of the gallbladder has historically been ultrasound. The primary reason is that ultrasound has a higher sensitivity than CT for diagnosing gallstones [3••], a common cause of abdominal pain even in the absence of active inflammation or cholecystitis. However, when one does not prospectively know the cause of the abdominal pain, CT is often the first and most appropriate exam. In addition, CT offers other benefits, including both the ability to assess for other causes of abdominal pain and more complete evaluation of gallbladder pathology, including assessing for complications of acute cholecystitis or extent of disease in gallbladder carcinoma. In addition, CT is less operator dependent compared to ultrasound. Despite these benefits, the main disadvantage of conventional CT in gallbladder evaluation is its decreased sensitivity compared to ultrasound in identifying cholelithiasis. Thus, in the acute setting, ultrasound is often ordered simultaneously or subsequently to "rule out" gallbladder pathologies.

Multi-energy CT (MECT) can overcome some of the shortcomings of conventional CT in gallbladder evaluation, with the potential to be a "one-stop shop" for evaluation of acute abdominal pain, including biliary colic. MECT was introduced conceptually as early as 1973, but has been used in mainstream clinical practice in the last decade, as clinical scanners capable of harnessing its true potential were built. An inherent limitation of conventional CT in that conventional X-ray attenuation has considerable overlap between different materials in the body (in other words, two different materials may have the same CT attenuation). By acquiring or detecting attenuation of the same region at two different X-ray energy levels (depending on the type of scanner used), MECT uses the change in attenuation of various materials at different energies to tell them apart. This attenuation change at different energies occurs due to each material's unique linear attenuation coefficient. Thus, MECT offers new ways of visualizing information from CT scans, such as creation of virtual monoenergetic reconstructions and material decomposition maps (including virtual noncontrast reconstructions and iodine quantification maps) [4••]. Commercially available scanners include dual-source dual-energy CT (Siemens Healthcare), rapid kV switching CT using a single x-ray source (GE Healthcare), and a dual-layer detector spectral CT (Philips Healthcare), as well as other options including sequential scanning with a single x-ray tube (Toshiba Medical Systems) and a twin beam single-source scanner (Siemens Healthcare). While a detailed discussion of the principles of multi-energy CT is beyond the scope of this article, the authors refer the reader to several excellent review articles discussing this subject [4••, 5••].

In this review article, we discuss the applications of MECT as they pertain to gallbladder imaging and provide an overview of proven benefits of the technology, with an emphasis on the imaging of gallstones and cholecystitis. This review also touches on promising areas that warrant further research and validation.

Cholelithiasis

Gallstones are a common entity in the United States, resulting in high health care costs. The presence of cholelithiasis is associated with the increased mortality rates from both cancer and cardiovascular disease in the US population [6]. Gallstones are composed of varying amounts of cholesterol, pigment, and calcium. While calcified stones are relatively easy to detect on conventional CT, cholesterol stones may be isoattenuating to surrounding bile and thus may be invisible on CT; a higher cholesterol content often makes the stone more difficult to detect on CT [7]. Published rates for sensitivity of conventional CT for gallstone detection range from 25 to 88% [8, 9]. In contrast, ultrasound has an accuracy of over 98% for gallstone detection, regardless of stone composition [10]. Even before MECT was in mainstream use, data had shown variable rates of gallstone detection on CT depending on the tube potential (kVp); Chan et al. showed sensitivity for gallstone detection of 81–86% when imaged at 140 kVp compared to 52–67% at lower kVp [8]. In some clinical settings, particularly in the emergency room setting in which CT and ultrasound are often ordered simultaneously to quickly identify the cause of unexplained abdominal pain, MECT provides incremental value in gallstone detection by its ability to visualize some isoattenuating calculi that are not seen on conventional CT. This could obviate the need for simultaneous ultrasound, thus potentially resulting in cost savings and decreased time to diagnosis.

There are multiple commercially available MECT image reconstructions that could be used to improve gallstone detection. Virtual monoenergetic reconstructions (also termed virtual monochromatic reconstructions) and virtual unenhanced reconstructions are most commonly used, but other postprocessing techniques discussed below also may add value.

MECT-derived virtual monoenergetic (VME) reconstructions simulate what the image would look like (and what the attenuation of tissues would be) if the image was created using a monoenergetic X-ray beam. These reconstructions may be created for a range of monoenergies, typically 40–190 or 200 keV depending on the type of spectral CT scanner. Different materials behave differently at low versus high monoenergies; for example, calcium and iodine have increased CT numbers at lower keV, while cholesterol has a lower CT number when imaged at a lower keV (Fig. 1). The different attenuation curves of cholesterol, calcium, and bile at various monoenergies can be exploited to differentiate them [11••].

Multiple studies have demonstrated the improved conspicuity of noncalcified gallstones on VME reconstructions. Uyeda et al. evaluated 51 dsDECT scans with noncalcified gallstones and compared tissue contrast between the stones and surrounding bile at 40 keV, 190 keV, and 70 keV (used as a surrogate for traditional 120 kVp images). They found maximal contrast between noncalcified gallstones and surrounding bile at 40 keV, and statistically significant higher stone–bile contrast at 40 keV compared to 70 and 190 keV [11••]. In another study performed on the single-source dual-energy CT (ssDECT) platform, scans from 24 patients with cholesterol stones were reviewed, and VME reconstructions ranging from 40 to 140 keV were evaluated. They found that the CT number difference between stones and surrounding bile was the greatest at 40 keV, while the CNR for gallstones was the greatest at 140 keV due to the decreased image noise at 140 keV [12••]. In a retrospective review of 217 patients with surgically confirmed gallstones who underwent ssDECT scans, there was improved visualization of stones at 40 keV VME reconstructions [13••].

Virtual unenhanced (VUE) reconstructions have also been assessed for their utility in gallstone detection, but have shown mixed results depending on the composition of

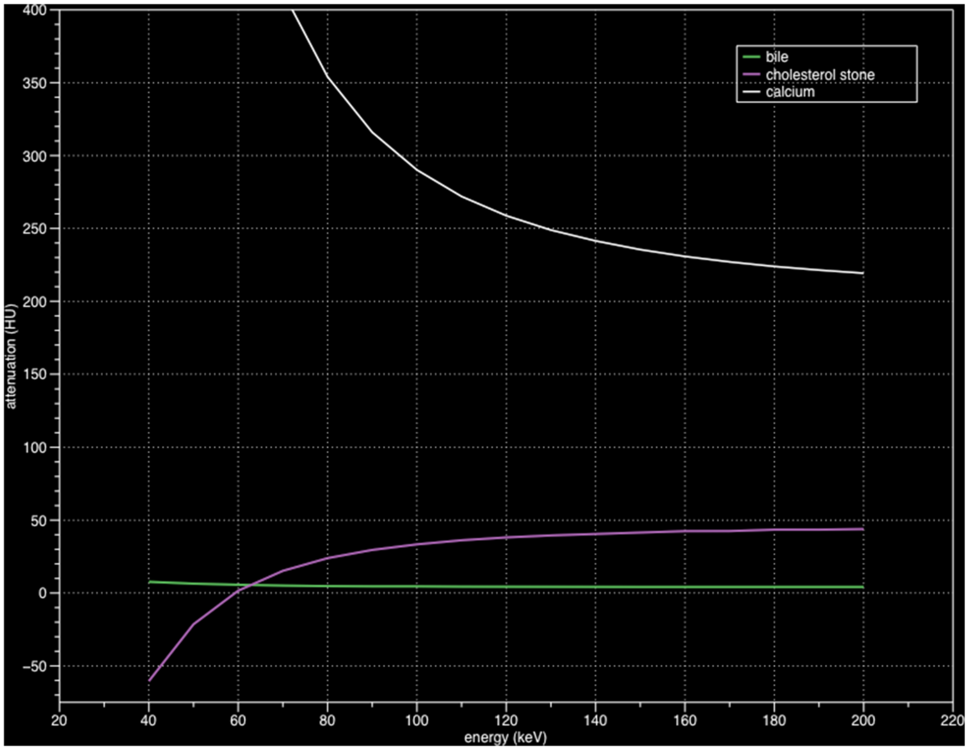


Fig. 1 Spectral plot from an SDCT with an isoattenuating gallstone with spectral curves for bile, a cholesterol gallstone, and bone. Note that near 70 keV (the equivalence point to 120 kVp conventional CT), the spectral curves for cholesterol (pink) and bile (green) overlap, illustrating how cholesterol is often indistinguishable from bile on conventional CT. The spectral curve for bile (green) across the monoenergetic spectrum shows an inversely proportional relationship- at lower keV, bile attenuation is higher. While the effective atomic number of calcium (white) is higher than bile, resulting in a much higher attenuation than bile at low keV, the spectral curve is also inversely proportional (spectral curve at 40 keV for calcium not included for scale). In contrast, the spectral curve for cholesterol is inverted, with a lower attenuation at lower keV and higher attenuation at higher keV. The greatest difference between attenuation of bile and cholesterol (i.e., where these two materials should be best discriminated) is at 40 keV

the stone. One study showed improved CNR of cholesterol gallstones on VUE reconstructions compared to true unenhanced images [14•]. However, it is important to note that while VUE reconstructions may improve visualization of isoattenuating or cholesterol gallstones, conspicuity of calcified gallstones and smaller gallstones is decreased [14•, 15]. This is because while VUE reconstructions are designed to remove iodine's contribution to the image, it also will remove the contribution of other materials with a higher atomic number closer to iodine, such as calcium and barium. Thus, a calcified gallstone that is highly attenuating on conventional images may actually be less attenuating on VUE reconstructions. As a result, VUE reconstructions may obscure stones that were visible on standard conventional images [15]. In the authors' opinion, VME reconstructions are the most helpful of the commercially available reconstructions to identify isoattenuating gallstones. An example of isoattenuating gallstones identified using both VME and VUE reconstructions derived from MECT is shown in Fig. 2.

Novel work on the dual-layer SDCT system have used the differential photoelectric and Compton properties of cholesterol and bile to perform a two-material decomposition using these two materials to identify isoattenuating gallstones (Fig. 2e) [16]. The isoattenuating gallstones may be identified and color coded using a preclinical custom postprocessing tool [17, 18].

Acute Cholecystitis

While cholecystitis may occasionally occur due to bile stasis or sludge, over 80% of patients with acute cholecystitis have gallstones [19]. Ultrasound is the traditional diagnostic modality of choice to evaluate the gallbladder due to its high sensitivity for cholelithiasis and its ability to assess for a sonographic Murphy sign [20]. However, in many patients with acute abdominal pain, CT is often the initial imaging test, as the etiology for the patient's pain is not clear. While traditional CT is not as sensitive as ultrasound for gallstone detection, recent work demonstrates improved sensitivity of CT compared to ultrasound (85% versus 68%, respectively) in evaluation of acute cholecystitis [21••], as CT may better detect additional

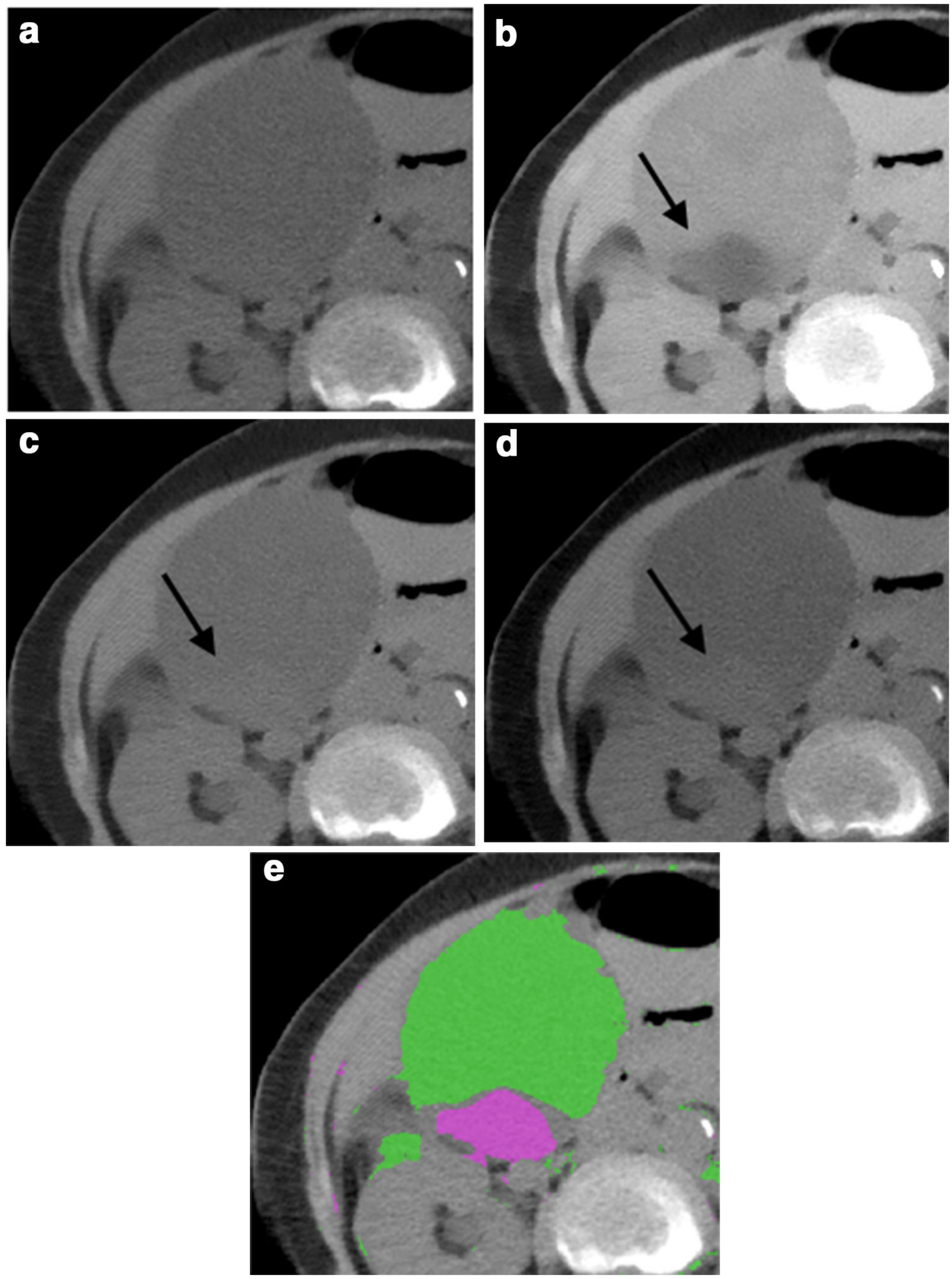
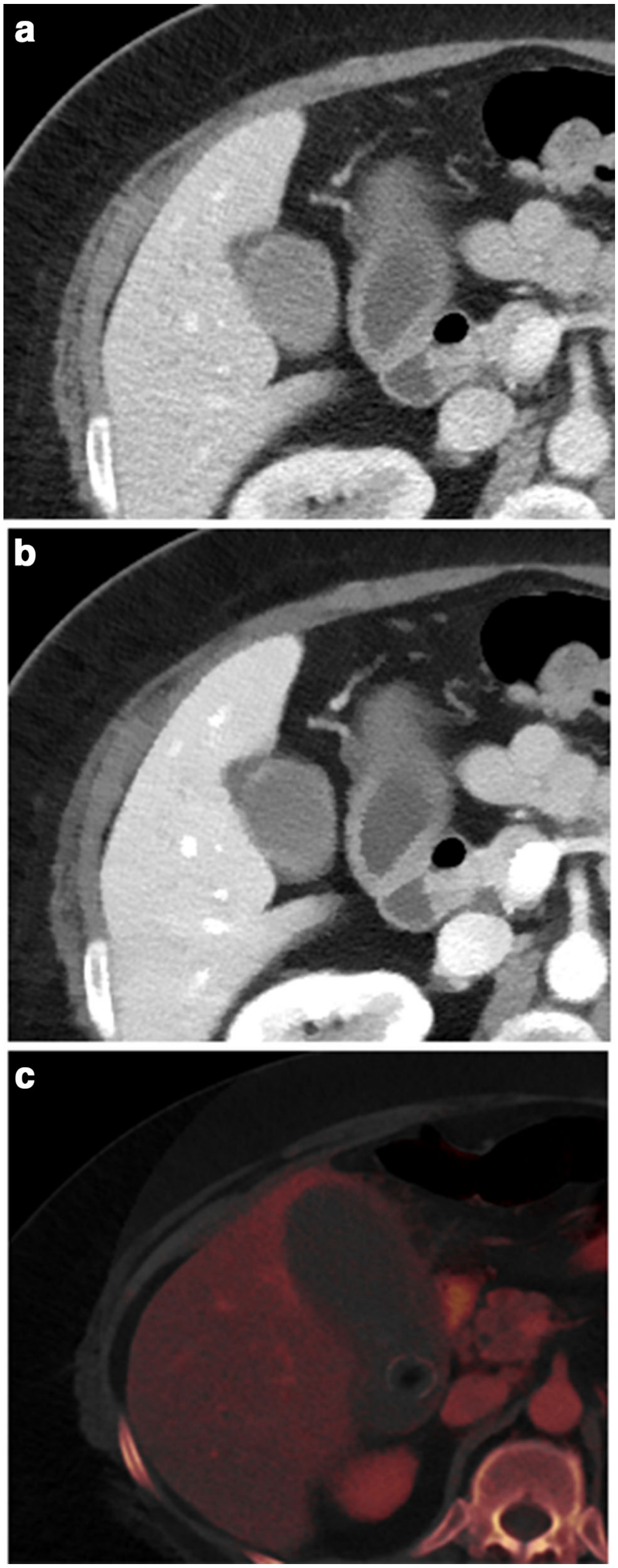


Fig. 2 Seventy-seven-year-old female with isoattenuating gallstones. On conventional images from an SDCT (**a**), the gallbladder appears distended but no definite stones are seen. However, virtual monoenergetic reconstructions (VME) demonstrate that there are several gallstones within the distended gallbladder (arrows), appearing hypoattenuating on 40 keV reconstructions (**b**) and hyperattenuating on 200 keV reconstructions (**c**). While virtual unenhanced (VUE) reconstructions have shown mixed results in identifying isoattenuating gallstones, in this case, the gallstones are only faintly visible on the VUE reconstructions (**d**). Lastly, novel preclinical postprocessing tools created on the SDCT platform (**e**) may be used to create a two-dimensional histogram based on the photoelectric and Compton properties of cholesterol and bile, which then may be color coded and displayed for rapid identification of isoattenuating gallstones (image courtesy Todd Soesbe, PhD, UT Southwestern Medical Center)

imaging findings of acute cholecystitis such as gallbladder wall thickening and hyperemia, pericholecystic fluid, hyperemia of the adjacent liver parenchyma, and gallbladder distention [3••]. In fact, if these findings are seen in the absence of gallstones on CT, an ultrasound is often recommended by the radiologist [20]. Thus, many patients being worked up for upper abdominal pain may receive two imaging tests, with resultant increase in expense and time to diagnosis [22].

MECT has the potential to be a "one-stop shop" for an imaging test for biliary colic for its ability to both more easily identify gallstones on CT and its improved conspicuity of ancillary findings of acute cholecystitis [23••]. Mural hyperemia may be seen using either iodine maps or low keV reconstructions (Fig. 3). Similarly, hypervascularity of the liver parenchyma adjacent to the inflamed gallbladder (CT equivalent of the "hot rim" sign) may be more easily detected using low keV reconstructions or iodine maps (Fig. 3c) [23••]. MECT reconstructions can also be used to improve conspicuity of complications of acute cholecystitis. Gallbladder perforation may be better identified using VME reconstructions and color-coded iodine overlays by increasing conspicuity of a nonenhancing defect in the gallbladder wall; pericholecystic

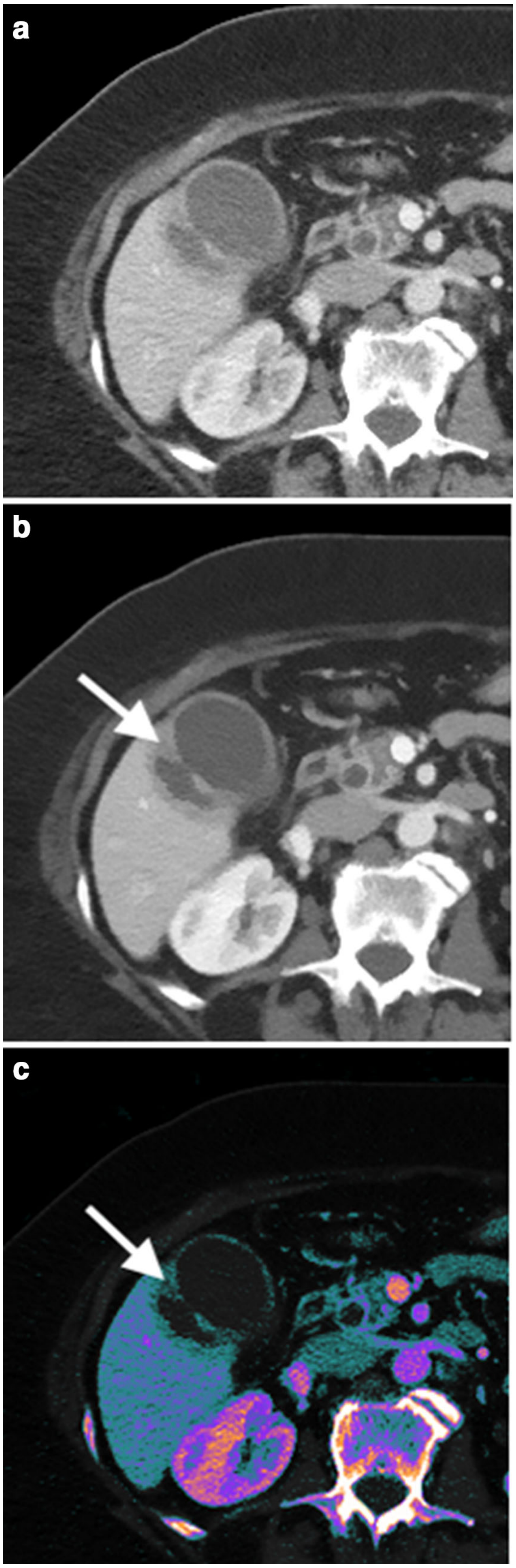


◀ **Fig. 3** Acute cholecystitis. Conventional CT image from a contrast-enhanced SDCT on a 33-year-old woman with right upper quadrant pain (**a**) demonstrating pericholecystic fat stranding, subtle gallbladder wall thickening, and gallstones (not shown). 50 keV VME reconstruction (**b**) shows improved visualization of the thickened gallbladder wall. Color-coded iodine overlay from a contrast-enhanced dsDECT (**c**) in a different patient with right upper quadrant pain demonstrates a distended gallbladder with the increased iodine uptake of the surrounding liver parenchyma secondary to hyperemia, a finding known as the dual-energy "hot rim" sign

abscesses (Fig. 4) similarly may be more easily detected. The potential for MECT to obviate the need for a concurrent ultrasound in the setting of biliary colic could prove to be cost effective in the emergency room setting.

Gallbladder Xanthogranulomatosis

Gallbladder xanthogranulomatous cholecystitis (XGC) is a subtype of chronic cholecystitis, which is characterized by focal or diffuse destructive inflammation and proliferative fibrosis. It is thought to be caused by intramural extravasation of bile from superficial mucosal ulcerations, resulting in a destructive inflammatory reaction. On histology, this disease is characterized by presence of multiple foci of intramural accumulation of lipid-laden macrophages. In XGC, marked wall thickening and dense local adhesions occur, which may mimic gallbladder carcinoma on imaging. In some cases, definitive diagnosis on imaging may be challenging and tissue diagnosis may be necessary. On imaging, a few characteristics are associated with XGC and can increase the diagnostic confidence when they are seen. First, hypoattenuating nodules can be seen within the thickened portion of the gallbladder wall [24]. While foci of mural hypoattenuation may be seen in the setting of adenomyomatosis as well, those in XGC correspond to areas of lipid deposition and may be detected by MR in some (but not all) cases [24]. Second, as XGC is primarily the disease of the gallbladder wall, an intact continuous mucosal lining is typically present and can manifest as diffuse or focal wall thickening in conjunction with the intramural hypoattenuating nodules [23••, 25, 26]. In contrast, gallbladder carcinoma, which is often confused with XGC, is a disease of the gallbladder epithelium and thus tend to disrupt the mucosal lining. These observations have been described in conventional CT. The incremental benefit of using MECT for these observations has not been validated. However, these observations theoretically may be easier seen or appreciated with iodine maps. As approximately 3/4 of cases of XGC have concurrent cholelithiasis [24], MECT reconstructions may aid in the detection of associated gallstones.



◀**Fig. 4** Eighty-year-old female with acute cholecystitis, presenting with right upper quadrant pain for 5 days. Conventional CT image from a contrast-enhanced SDCT as shown in (**a**) demonstrating mild gallbladder wall enhancement concerning for acute cholecystitis. A subtle defect is noted in the lateral wall of the gallbladder with an adjacent elliptical fluid collection concerning for focal perforation of the gallbladder wall and associated abscess. 50 keV VME reconstruction (**b**) and color-coded iodine overlay (**c**) better depict the gallbladder wall defect as a focal area of nonenhancement, and confirm the rim enhancement and lack of central enhancement of the adjacent abscess

Gallbladder Adenomyomatosis

Gallbladder adenomyomatosis refers to the proliferation and invagination of the gallbladder mucosa into the muscularis layer of the gallbladder wall, forming Rokitansky–

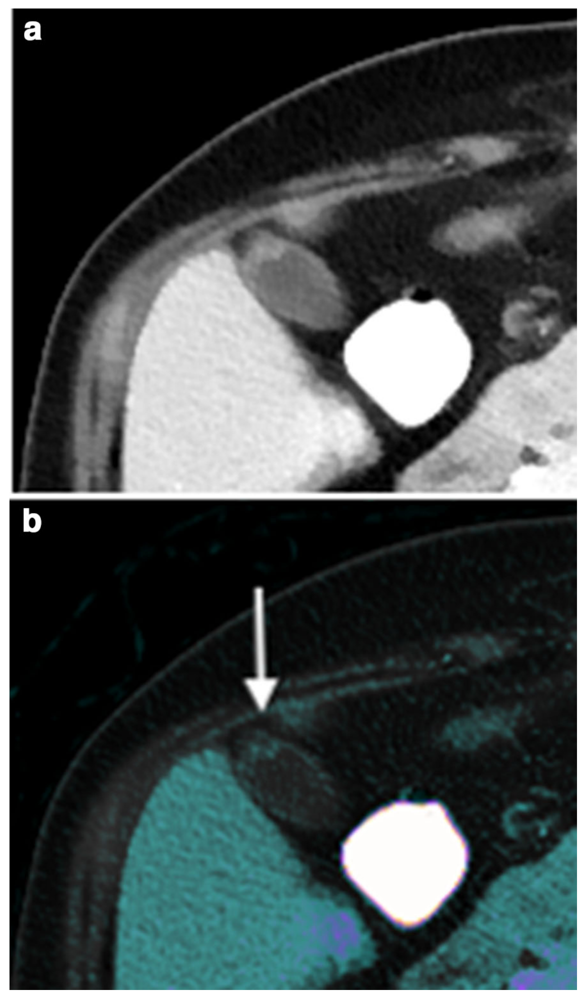


Fig. 5 Sixty-eight-year-old patient with gallbladder adenomyomatosis incidentally seen on a workup for urothelial carcinoma. Reconstructions from a contrast-enhanced SDCT demonstrate focal wall thickening at the gallbladder fundus, seen easily on the 50 keV VME reconstruction (**a**). Color-coded iodine overlay (**b**) demonstrating small foci within the wall with no detectable iodine signal (arrow) representing Rokitansky–Aschoff sinuses, characteristic of adenomyomatosis

Aschoff sinuses in which cholesterol crystals may precipitate. Adenomyomatosis is identified on up to 8% of cholecystectomy specimens and may be focal, diffuse, or segmental [19, 27]. Adenomyomatosis may be more definitively diagnosed on ultrasound by identifying the characteristic comet-tail artifact created by the cholesterol crystals [28•], or on MRI by the typical "pearl necklace" sign of T2 hyperintense spaces in the gallbladder wall (corresponding to the Rokitansky–Aschoff sinuses) [27]. On CT, adenomyomatosis may be difficult to distinguish from gallbladder carcinoma, particularly the diffuse and segmental forms. The fundal form of adenomyomatosis is most easily identified by CT, and manifests as focal hyperenhancement of the gallbladder fundus. This hyperenhancement may be more conspicuous on low VME or iodine overlay reconstructions (Fig. 5). Iodine overlay reconstructions can potentially help differentiate adenomyomatosis from carcinoma by demonstrating cystic areas without iodine uptake [23••] or fuzzy gray enhancing foci in the gallbladder wall, referred to as the "cotton ball sign" [29•].

Gallbladder Carcinoma

Gallbladder carcinoma, the most common malignant tumor of the biliary tract, is an aggressive disease with a very poor prognosis [30, 31]. On imaging, gallbladder carcinoma can present in a variety of ways- as a mass either within or replacing the gallbladder, focal or diffuse wall thickening, or an intraluminal polypoid lesion [32•]. There are many benign mimickers of gallbladder carcinoma, including adenomyomatosis, XGC, polyps, and cholecystitis. The utility of MECT has not been well studied. However, there are a few applications where MECT can potentially be helpful to distinguish between carcinoma and other causes of gallbladder wall thickening.

The features most suggestive of gallbladder carcinoma over the other entities is the presence of a thickened, enhancing gallbladder wall and invasion into the adjacent liver parenchyma, and MECT iodine maps and low VME reconstructions may improve visualization of these findings (Fig. 6). Gallstones are also commonly seen. The presence of wall thickening greater than 1 cm increases the likelihood of gallbladder carcinoma [23••]. In one study evaluating conventional CT of gallbladder carcinoma, top patterns associated with high odds ratio for diagnosis of gallbladder cancer include a thick enhancing inner layer of the gallbladder wall, enhancement of the inner layer above that of liver parenchyma, and a thin outer layer [33]. In contrast, the identification of nonenhancing foci of Rokitansky–Aschoff sinuses in a thickened gallbladder wall can differentiate between adenomyomatosis and carcinoma. The imaging appearance of gallbladder carcinoma and XGC can overlap significantly, but the presence of a continuous enhancing gallbladder mucosa and the identification of hypoattenuating foci (corresponding to xanthrogranulomas) within the gallbladder wall are more suggestive of XGC. The use of iodine quantitation maps to evaluate the gallbladder wall increases the enhancement to noise ratio, and thus could accentuate these observations in the setting of gallbladder carcinoma as it has for other types of malignancies [34–36]. However, additional studies are warranted. The diagnosis of gallbladder carcinoma is also confirmed by ancillary findings such as direct liver invasion by a gallbladder mass, liver and other distant organ metastases, and lymph node metastases.

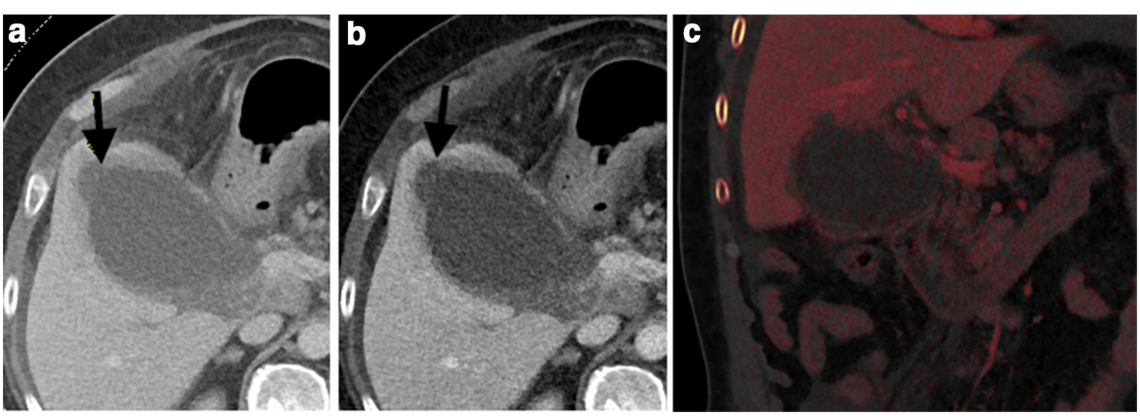


Fig. 6 Sixty-six-year-old male who had presented with abdominal pain and fever. Linear blended axial and coronal images (**a**) from dsDECT demonstrate a distended, thick-walled gallbladder with pericholecystic fat stranding. However, focal wall thickening at the gallbladder fundus, apparent invasion into the liver parenchyma (**a**, arrow), and adjacent periportal lymph nodes (not shown) raise concern for malignancy. This soft tissue extension into the adjacent liver is better appreciated on 50 keV VME reconstruction (**b**) and color-coded iodine overlay (**c**)

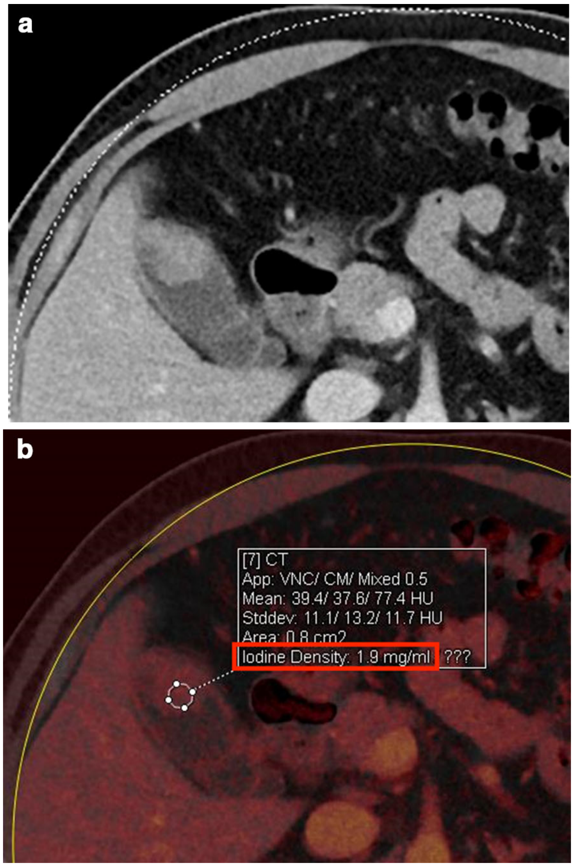


Fig. 7 Forty-eight-year-old male with a polypoid gallbladder lesion found after presentation with intermittent right lower quadrant pain. Linear blended image from a contrast-enhanced dsDECT (**a**) shows a hyperattenuating polypoid lesion in the fundus. Color-coded iodine overlay (**b**) with ROI drawn over the lesion clearly demonstrating postcontrast enhancement, thus increasing the suspicion for a polypoid gallbladder carcinoma. Cholecystectomy was performed with pathology showing invasive, moderately differentiated gallbladder adenocarcinoma

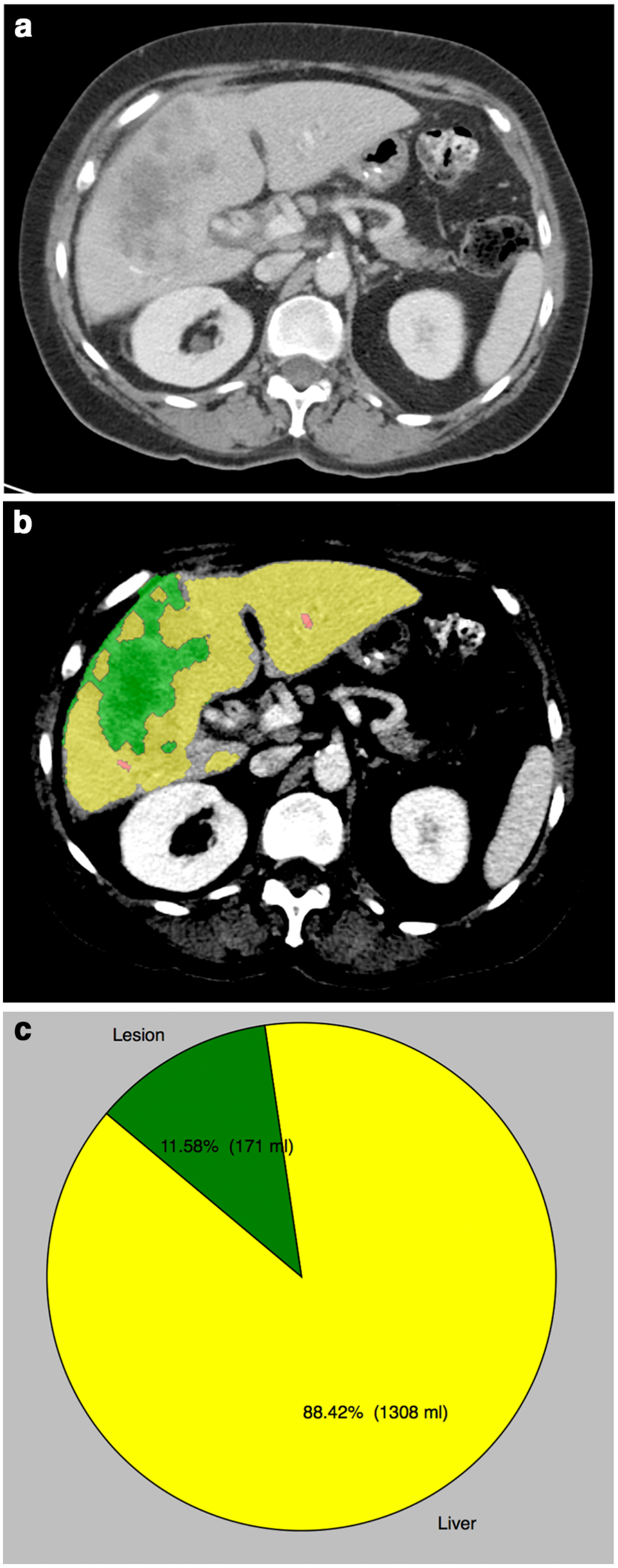
Fig. 8 Seventy-one-year-old female with gallbladder carcinoma and multiple hepatic metastases on a conventional SDCT image (**a**). Novel preclinical postprocessing tools created on the SDCT platform performed segmentation of hepatic tumors from normal liver parenchyma (**b**). Total volume of tumor over the liver volume can be calculated (**c**), facilitating quantitation of tumor burden in a patient (image courtesy Yin Xi, PhD, UT Southwestern Medical Center)

Only a minority (15–25%) of gallbladder carcinoma presents as intraluminal polypoid mass. Definitive characterization of an incidental polyp is challenging, particularly given that there are many benign types of gallbladder polyps including cholesterol and hyperplastic polyps, and other benign processes such as adherent biliary sludge that may also masquerade as true polyps. Malignant polyps tend to be larger and demonstrate hyperenhancement (Fig. 7). Studies have evaluated the use of contrast-enhanced ultrasound for evaluation of gallbladder polyps [37, 38•]. A similar observation was noted with conventional CT, in which the degree of enhancement was helpful in differentiating between benign and malignant polyps [39]. However, in the retrospective study where this relationship was assessed, the degree of enhancement was represented by CT attenuation on the portal venous phase, a practical choice as multiphase studies for elucidation of true enhancement are not frequently performed in the emergency room setting. MECT can evaluate for true enhancement by means of iodine quantitation maps even on a single-portal venous phase study, and thus increasing the diagnostic confidence in differentiation of enhancing polyps from other benign etiologies such as tumefactive sludge on a single-phase-contrasted CT exam.

An active area of research for MECT is its use in organ segmentation and lesion detection [40]. While there is a large overlap between attenuation of different tissues on conventional CT, the additional data available in MECT can potentially improve different tissue differentiation and segmentation performance. While little has been done that is specific to gallbladder cancer, there are a few studies investigating the use of MECT tumor burden calculation [41]. In our lab, we have demonstrated a prototype of automatic lesion detection tool based on spectral detector CT and machine learning is potentially capable of quantifying tumor burden in the liver as a percentage of the total liver volume in select cases (Fig. 8). If validated, tools such as these have the potential of replacing criteria-based methods such as RECIST in staging, restaging, and monitoring therapy response.

Conclusion

The gallbladder may be evaluated with multiple modalities depending on the pathology. MECT is emerging as a useful exam which can potentially eliminate the need for other imaging exams such as ultrasound in gallbladder evaluation. MECT has demonstrated improved sensitivity for cholelithiasis compared to conventional single-energy CT, with literature described above demonstrating the added value of MECT reconstructions in detection of isoattenuating gallstones. MECT iodine maps and virtual monoenergetic images are useful in evaluating other gallbladder pathologies, including detecting complications of acute cholecystitis, characterization of XGC and adenomyomatosis, and identifying and evaluating the extent of gallbladder carcinoma.



Compliance with Ethical Guidelines

Conflict of interest Both Yee Seng Ng and Lakshmi Ananthakrishnan declare that there is an institutional research agreement between UT Southwestern Medical Center and both Philips Healthcare and Siemens Healthcare, but neither of the authors has any personal conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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