Multimodality Imaging, including Dual-Energy CT, in the Evaluation of Gallbladder Disease

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Imaging of the gallbladder has a key role in the examination of patients with abdominal pain—especially pain localized to the right upper quadrant. Pathologic conditions that affect the gallbladder include cholelithiasis and associated complications such as acute and chronic cholecystitis, choledocholithiasis, gallstone pancreatitis, and cancer. Modalities used to image the gallbladder include ultrasonography (US), computed tomography (CT), magnetic resonance (MR) imaging, and nuclear scintigraphy. US is the primary imaging modality used to evaluate entities suspected of being gallbladder disease, as it is both sensitive and specific for demonstrating gallstones, biliary duct dilatation, and inflammatory features. However, CT is often the first imaging examination performed in patients who present to the emergency department with acute abdominal pain. Because the CT appearance of gallstones is variable, depending on the composition of the stone, pattern of calcification, and presence of gas, gallstones and other gallbladder conditions can be difficult to detect at conventional multidetector CT, with which data are acquired by using a single x-ray energy spectrum. Dual-energy CT, with which one takes advantage of the material-dependent x-ray absorption behavior of concurrently acquired high- and low-kilovolt-peak data, can add value by increasing the conspicuity of noncalcified gallstones and improving the detection of acute cholecystitis and gallbladder malignancy. In addition, MR cholangiopancreatography can be helpful for assessing choledocholithiasis and complicated biliary duct disease.

Introduction

Imaging of the gallbladder has an essential role in the examination of patients who present with abdominal pain, especially pain localized to the right upper quadrant. Bile is produced in the liver and stored in the gallbladder. Bile in the gallbladder can become supersaturated with cholesterol and lead to crystal formation and subsequent gallstone formation. Gallbladder disease is common, and gallstone disease is the leading cause of inpatient admissions for gastrointestinal problems (1), with more than 700,000 cholecystectomies performed annually in the United States (2). Pathologic conditions that affect the gallbladder include cholelithiasis, choledocholithiasis, acute cholecystitis, adenomyomatosis, xanthogranulomatous cholecystitis (XGC), and carcinoma. Associated complications of gallstone disease include gallstone pancreatitis, obstructive jaundice, gallstone ileus, and Mirizzi syndrome.
Because gallstones vary in composition, calcification pattern, and gas content, many of them are difficult to detect with conventional multidetector CT, with which data are acquired at a single energy spectrum of between 80 and 140 kVp—most commonly 120 kVp.

Dual-energy CT iodine-selective postprocessing techniques can be used to create virtual nonenhanced CT images, from which the iodine content is subtracted. The iodine content can be displayed as a pure iodine map or an iodine overlay map on which the iodine content is superimposed, in color, on top of the gray-scale virtual nonenhanced images.

Noncalcified gallstones may be difficult to distinguish from surrounding bile at conventional single-energy CT performed at 120 kVp, as these entities often have similar Hounsfield unit values because their attenuation is similar at the mean energy value (typically around 70 keV) of this x-ray spectrum.

Dual-energy CT findings that are suggestive of acute cholecystitis include increased iodine content in the pericholecystic hepatic parenchyma compared with that in the hepatic parenchyma elsewhere, secondary to hepatic arterial hyperemia.

Dual-energy CT iodine overlay images have the potential to facilitate improved detection and characterization of gallbladder carcinoma. With the iodine content highlighted, carcinoma can be visualized more easily because compared with benign entities such as XGC and adenomyomatosis, carcinoma will demonstrate increased uptake of iodine.

Modalities commonly used to image the gallbladder include ultrasonography (US), multidetector computed tomography (CT), magnetic resonance (MR) cholangiopancreatography, and hepatobiliary nuclear scintigraphy. In addition, dual-energy CT is a rapidly emerging imaging technique with demonstrated utility for a broad range of clinical applications across multiple organ systems and pathologic conditions (3–6). In this article, we review the pathophysiology and characteristic imaging features of gallstones and other gallbladder conditions, with a focus on potential dual-energy CT postprocessing applications to enhance the detection of benign and malignant gallbladder disease.

Imaging Armamentarium

The normal gallbladder is not typically visualized at conventional abdominal radiography, and only 10%–15% of gallstones are adequately calcified to be detected with conventional radiography. Thus, conventional radiography is a poor examination for screening gallbladder disease (7).

US is the preferred and most commonly used imaging modality for initial assessment of the gallbladder and bile ducts. In addition to being sensitive and specific for the detection of gallstone disease and gallbladder inflammation, US does not involve the use of ionizing radiation and is inexpensive, portable, and readily available, making it an excellent initial imaging modal-

ity. In the nonemergent setting, imaging ideally should be performed with the patient having fasted for at least 6 hours to achieve maximal gallbladder distention. Patients who present with acute abdominal pain can be imaged while in the fasting or nonfasting state. When evaluating the gallbladder, attention should be directed to the wall and contents of the gallbladder, the degree of distention, and the status of the extrahepatic and intrahepatic biliary ducts (8).

Although traditionally it has been believed that multidetector CT is less sensitive for the detection of acute gallbladder disease, it is frequently performed in patients who present with acute abdominal pain. In a retrospective study involving 57 patients who underwent both CT and US within 48 hours of each other for evaluation of right upper quadrant pain, Harvey et al (9) found CT to be substantially less sensitive (39%) than US (83%) for the detection of acute biliary disease. However, CT and US were found to have similar specificity: 93% and 95%, respectively.

Because gallstones vary in composition, calcification pattern, and gas content, many of them are difficult to detect with conventional multidetector CT, with which data are acquired at a single energy spectrum of between 80 and 140 kVp—most commonly 120 kVp. However, recent technologic advances in dual-energy CT have enabled the concurrent acquisition of data with use of two different x-ray energy spectra—at high–kilovolt-peak (typically 140 kVp) and low–kilovolt-peak (typically 80–100 kVp) values. Typically, a weighted average of the high– and low–kilovolt-peak imaging data is obtained to create “mixed,” or “blended,” images that are comparable to traditional 120-kVp contrast material–enhanced CT images. Several dual-energy CT postprocessing techniques can then be used to differentiate or quantify materials with sufficiently different x-ray absorption behaviors as a function of x-ray energy (3). Although there are many potential dual-energy CT postprocessing techniques, this article is focused on applications that are relevant to gallbladder imaging.

Dual-energy CT iodine-selective postprocessing techniques can be used to create virtual nonenhanced CT images, from which the iodine content is subtracted. The iodine content can be displayed as a pure iodine map or an iodine overlay map on which the iodine content is superimposed, in color, on top of the gray-scale virtual nonenhanced images (Fig 1). The iodine maps can be used to directly quantify the amount of iodine and determine the degree of enhancement, even from a single contrast-enhanced CT image acquisition.

By using the relative x-ray absorption of each voxel at high and low kilovolt peaks, virtual monochromatic images can be created. Virtual
choledocholithiasis, suspected Mirizzi syndrome, and suspected acute cholecystitis with equivocal US findings, and differentiation of gallbladder carcinoma from benign entities such as XGC and adenomyomatosis. Compared with CT, MR imaging does not involve the use of ionizing radiation and facilitates improved stone conspicuity. MR cholangiopancreatography techniques enable one to take advantage of the high signal intensity of static fluids in the biliary tract on heavily T2-weighted images. Patients fast for 3–6 hours before the examination to reduce fluid secretions within the stomach and duodenum, reduce bowel peristalsis, and promote gallbladder distention.

Standard protocols typically include the following MR imaging sequences: (a) axial and coronal T2-weighted breath-hold steady-state fast spin-echo, (b) axial in-phase and out-phase T1-weighted breath-hold gradient-echo, (c) axial T2-weighted respiratory-triggered fat-saturated, (d) axial nonenhanced and gadolinium-enhanced dynamic T1-weighted three-dimensional breath-hold fat-suppressed gradient-echo, and (e) oblique T2-weighted steady-state fast spin-echo two- and three-dimensional fat-saturated MR cholangiopancreatography with maximum intensity projection (11). Functional MR cholangiography can be performed with T1-weighted fat-saturated images after the administration of contrast agents that are excreted in bile, including gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Monroe...
Township, NJ) and gadoxetate disodium (Eovist/Primovist; Bayer Healthcare Pharmaceuticals, Whippany, NJ) (12,13).

Hepatobiliary nuclear scintigraphy involves the injection of 5 mCi (185 MBq) of a technetium 99m iminodiacetic acid derivative. In an examination of the normal (nondiseased) anatomy, hepatic parenchymal uptake is observed within 5 minutes after the injection, the bile ducts are visualized within 10 minutes, and the gallbladder is seen within 15 minutes. The radiotracer should be followed to the small bowel to ensure that the common bile duct (CBD) is patent (14).

**Normal Appearance of the Gallbladder**

The gallbladder is a hollow viscus in the right upper quadrant between hepatic segments IV and V that serves as a repository for bile produced in the liver. The gallbladder is composed of a neck, body, and fundus and can hold 30–50 mL of bile when it is filled. The normal gallbladder measures up to 10 cm in the sagittal dimension and 2–3 cm in the transverse dimension, with a wall thickness of less than 3 mm. The gallbladder connects to the extrahepatic bile duct via the cystic duct. Although not typically seen at US or CT, the cystic duct is routinely seen at MR cholangiopancreatography and frequently demonstrates an undulating course that is due to spiraling Heister valves (15). The anatomy of the biliary tree, cystic duct, common hepatic duct, and CBD are well visualized with MR imaging (Fig 2).

**Gallbladder Disease and Associated Complications**

**Cholelithiasis**

More than 20 million adults in the United States are estimated to have gallstones, with women being more commonly affected than men (16). The prevalence of gallstones increases with age (16). Despite a 10%–15% prevalence of gallstones, most patients who have them are asymptomatic throughout their lives. Biliary colic is the most frequent manifesting symptom and is typically caused by transient obstruction of the cystic duct. However, complications such as gallstone pancreatitis (Fig 3a), obstructive jaundice, gallstone ileus (Fig 3b), and Mirizzi syndrome (Fig 3c and 3d) can occur.

Bile stones form owing to the supersaturation of bile components such as cholesterol, which is probably related to defects in biliary lipid metabolism. Biliary dysmotility, obesity, metabolic syndrome, rapid weight loss, estrogen use, and certain diseases such as cirrhosis and Crohn disease have been shown to be risk factors for gallstone formation (2). The majority (80%) of gallstones are composed mainly of cholesterol, whereas the remaining 20% are pigmented stones composed mainly of calcium bilirubinate (17).

US has high sensitivity (>95%) and accuracy (>95%) for the detection of gallstones (18–20), which appear as echogenic foci demonstrating posterior acoustic shadowing. Gallstones usually produce “clean” shadowing without reverberation artifact, as most of the sound waves are absorbed or reflected by the stones. Gallstones occasionally demonstrate “dirty” shadowing and reverberation artifact if they contain nitrogen gas within fissures. Gallstones are characteristically mobile and change location when the patient is imaged while in supine and decubitus positions. The “wall-echo-shadow” sign refers to the US appearance of a contracted gallbladder filled with stones, which creates a dense shadow that precludes the visualization of deeper structures (17).

The CT appearance of gallstones can vary (Fig 4). Calcified gallstones are readily detected at CT, but noncalcified gallstones are often difficult to visualize because they are isoattenuating to the surrounding bile. When gallstones degenerate, they may contain nitrogen (8), which can collect in central fissures in a star-shaped pattern and create the so-called Mercedes-Benz sign (Fig 4c). This finding should not be mistaken for emphysematous cholecystitis.

Dual-energy CT postprocessing techniques can be applied to improve the detection of gallstones. In a study performed by Kim et al (21), high-quality virtual nonenhanced CT images were found to be acceptable replacements for true nonenhanced CT images for the detection of gallstones. However, the virtual images had limited utility in the detection of gallstones smaller than 9 mm and relatively radiolucent gallstones with attenuations of 78 HU.
or lower. Investigators in another study (22) found that virtual nonenhanced CT images, as compared with true nonenhanced images, actually enabled better visualization of noncalcified gallstones.

We have found virtual monochromatic imaging to be helpful in improving the conspicuity of gallstones that are isoattenuating to bile on conventional 120-kVp CT images (23). Noncalcified gallstones may be difficult to distinguish from surrounding bile at conventional single-energy CT performed at 120 kVp, as these entities often have similar Hounsfield unit values because their attenuation is similar at the mean energy value (typically around 70 keV) of this x-ray spectrum. To overcome these limitations of conventional CT, dual-energy CT acquisition with virtual monochromatic imaging postprocessing at low (eg, 40-keV) and high (eg, 190-keV) monoenergetic levels can be performed to greatly improve the image contrast between cholesterol-containing gallstones and surrounding bile.

Gallstones that are isoattenuating to bile at conventional CT or 70-keV dual-energy CT become more conspicuous on higher- and lower-kiloelectron-volt virtual monochromatic images because cholesterol-containing gallstones have an

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Figure 3. Complications of cholelithiasis. (a) Coronal contrast-enhanced CT image in a 58-year-old man shows peripancreatic inflammatory changes (straight arrows) and fluid (curved arrow) due to acute pancreatitis caused by a punctate calcified gallstone at the ampulla (arrowhead), consistent with gallstone pancreatitis. (b) Coronal CT image enhanced with intravenous and oral contrast media in a 32-year-old woman shows a distended stomach and multiple dilated loops of small bowel, with oral contrast material (arrowhead) in a gallbladder-duodenal fistula and a 4.0-cm noncalcified gallstone (arrow) in the distal ileum, consistent with gallstone ileus. (c) Axial T2-weighted fat-saturated MR image in a 57-year-old man who presented with nausea, vomiting, malaise, and weight loss shows dilatation of the intrahepatic bile ducts (arrows). (d) Coronal MR cholangiopancreatographic image in the patient in c shows intrahepatic biliary duct dilatation (curved arrows), with obstruction just distal to the confluence of the hepatic ducts, secondary to external compression by two stones (straight arrows) in the cystic duct or gallbladder neck. Findings in c and d are consistent with Mirizzi syndrome.
energy-dependent x-ray attenuation curve that is distinctively different from that of bile (24). Noncalcified cholesterol-containing gallstones appear to have lower attenuation than bile on low-energy 40-keV images, but they appear hyperattenuating on high-energy 190-keV images (Fig 5). Compared with high–kiloelectron-volt images, low–kiloelectron-volt images are more valuable in the detection of gallstones because the contrast between noncalcified stones and surrounding bile is maximal at low–kiloelectron-volt virtual monochromatic imaging energy levels. In one study, 100% of noncalcified gallstones demonstrated a greater than 20-HU difference in attenuation compared with the surrounding bile; 75% of gallstones, a greater than 44-HU difference; and 50% of gallstones, a greater than 60-HU difference at low–kiloelectron-volt virtual monochromatic imaging levels (23).

MR imaging has high sensitivity and specificity for the detection of gallstones. Gallstones are best seen with T2-weighted and MR cholangiopancreatography sequences, with all stones appearing as signal voids surrounded by bright bile on heavily T2-weighted images (Fig 6). MR imaging can help in differentiating between cholesterol-containing and pigmented stones because cholesterol stones are typically T1 hypointense and pigmented stones are typically T1 hyperintense (25,26).

**Choledocholithiasis**

One potential complication of gallstones is choledocholithiasis. Approximately 10%-20% of patients who undergo cholecystectomy are found to have choledocholithiasis (27). Given the high prevalence of laparoscopic cholecystectomy and that residual stones can result in substantial morbidity, preoperative identification and treatment of CBD stones are critical for the management of gallstones. The detection of bile duct stones aids in the selection of patients who may benefit from preoperative endoscopic retrograde cholangiopancreatography and can help determine the appropriate treatment approach (27).

Stones smaller than 5 mm can be clinically silent, or they may cause transient pain. However, they usually ultimately pass into the duodenum via the ampulla of Vater (8). Stones larger than...
5 mm frequently do not pass and can obstruct the CBD, resulting in abdominal pain, cholangitis, and pancreatitis (8). Choledocholithiasis is easier to detect when there is concomitant biliary duct dilatation (8,28). However, a normal CBD diameter does not reliably indicate the absence of bile duct stones, as up to one-half of patients with choledocholithiasis will be found to have nondilated ducts at imaging (12,28). Thus, it is important to closely inspect the bile ducts for possible stones—even in the absence of biliary duct dilatation (12,28).

US findings of choledocholithiasis include echogenic foci that may demonstrate posterior acoustic shadowing within a fluid-filled bile duct. The distal CBD is often difficult to evaluate owing to obscuration by adjacent bowel gas, which contributes to the limited sensitivity (18%–63%) of US for the detection of CBD stones (29–31). Although there is a higher likelihood of choledocholithiasis in the setting of biliary dilatation (28), the degree of CBD dilatation seen at US has not been shown to be sufficient for identifying patients who are at substantial risk of developing CBD stones (32).

The visibility of choledocholithiasis at CT varies according to the composition of the stones. Stones that are calcified or higher in attenuation than the surrounding bile are more easily detected than are isodensity stones (Fig 7a). Stones whose content is almost purely cholesterol may appear lower in attenuation than surrounding bile; however, this scenario is rare. Multidetector CT has a reported sensitivity of 69%–87% and specificity of 83%–92% for the detection of choledocholithiasis (33).
Because the use of dual-energy CT with virtual monochromatic imaging can facilitate increased conspicuity of noncalcified gallstones, it is logical to deduce that virtual monochromatic imaging can also be used to increase the visualization of stones in the biliary ducts. This benefit also is possible because cholesterol-filled gallstones have an energy-dependent x-ray attenuation curve that is distinctively different from that of bile (23,24). In our experience, a bile duct stone that is isodense to bile at conventional CT or 70-keV dual-energy CT appears with lower attenuation than bile at low-energy 40-keV imaging and with higher attenuation than bile at high-energy 190-keV imaging, similar to stones in the gallbladder.

Compared with US and CT, MR cholangiopancreatography has the highest sensitivity (89%–95%) and specificity (95%–100%) for the detection of choledocholithiasis (34–36). CBD stones appear as low-signal-intensity foci surrounded by bright bile on T2-weighted MR images and demonstrate no enhancement (8) (Fig 7b and 7c). Biliary inflammation coexisting with choledocholithiasis manifests as periductal edema, biliary wall thickening, and enhancement after contrast material administration (12).

**Acute Cholecystitis**

Acute cholecystitis is the most common acute complication of cholelithiasis and accounts for 3%–9% of hospital admissions for acute abdominal pain (37). Eighty percent to 95% of cases of acute cholecystitis are the result of a stone obstructing the cystic duct or gallbladder neck. Acute acalculous cholecystitis accounts for the remaining 5%–20% of cases (8) and is not related to a stone; rather, it is caused by bile stasis, gallbladder ischemia due to diminished cystic artery blood flow, or systemic infection. Nearly all patients suspected of having acute cholecystitis require diagnostic imaging, as clinical findings and laboratory test results cannot sufficiently confirm or exclude cholecystitis (37). In fact, in more than one-third of patients suspected of having cholecystitis, another cause of pain, such as pancreatitis, right lower lobe pneumonia, pyelonephritis, nephrolithiasis, or hepatitis, is identified at imaging (38).

US is preferred for initial examination of patients highly suspected of having cholecystitis, but it may have limitations related to patient body habitus. The US findings of noncomplicated acute cholecystitis (Fig 8a) include gallstones that are often impacted in the cystic duct or gallbladder neck, greater than 3-mm wall thickening, pericholecystic fluid, increased mural blood flow, gallbladder distention (>4–5 cm in the transverse plane and >10 cm in the sagittal plane, with convex walls), and the Murphy sign (8,39,40). The Murphy sign represents localized pain, with maximal tenderness elicited with transducer probe pressure on the gallbladder. It must be noted that the presence of any of these findings in isolation is not specific for acute cholecystitis, and, thus, the overall clinical picture must be considered when interpreting imaging findings.

**Gallbladder wall thickening** can be seen in association with other gallbladder diseases such as chronic cholecystitis and gallbladder malignancy, and extracholecystic conditions such as hypoalbuminemia, third spacing of fluid due to kidney or heart failure, hepatitis, and pancreatitis (41). Gallbladder distention may be seen in the setting of prolonged fasting, parenteral nutrition, and cholestatic (eg, narcotic) drug use (42). In addition, although investigators in early studies (43) have found the US Murphy sign in combination with gallstones to have high positive predictive value for the diagnosis of acute cholecystitis (92%), this sign is operator dependent and can be absent in the setting of analgesic use or gangrenous cholecystitis (42).
The CT findings of acute cholecystitis are similar to the US findings and include gallbladder distention, fluid and fat stranding surrounding the gallbladder, wall thickening, and gallstones (Fig 8b and 8c) (44). Because multidetector CT is more limited in the detection of gallstones and cannot be used to evaluate focal right upper quadrant tenderness, conventional wisdom indicates that CT is inferior to US in the diagnosis of acute cholecystitis. However, CT is often the first imaging examination performed in patients with pain that is not characteristic of acute cholecystitis. Although the negative predictive value of CT is inferior to that of US, it is still relatively high (89%) (9); thus, negative CT findings can favor the absence of cholecystitis (9).

Dual-energy CT postprocessing iodine overlay images can be helpful in the evaluation of acute cholecystitis. Dual-energy CT findings that are suggestive of acute cholecystitis (Fig 8d) include increased iodine content in the pericholecystic hepatic parenchyma compared with that in the hepatic parenchyma elsewhere, secondary to hepatic arterial hyperemia. This finding is known as the dual-energy CT hot rim sign (45), which is analogous to the “hot rim” sign seen at hepatobiliary scintigraphy and MR imaging (46). In addition, increased iodine uptake in the gallbladder wall—that is, the dual-energy CT hot gallbladder sign—may be seen (46). These dual-energy CT findings of acute cholecystitis parallel the findings seen at MR imaging, which include increased transient pericholecystic hepatic parenchymal enhancement on arterial phase images and increased gallbladder wall enhancement, which have sensitivities of 62% and 92%, respectively, for the diagnosis of acute cholecystitis. Both of these findings have been found to have high specificity (92%) for the diagnosis of acute cholecystitis (45).

MR imaging can be helpful for diagnosing acute cholecystitis in cases of equivocal US or
CT findings (Fig 9). In such cases, MR imaging may depict stones in the gallbladder neck or cystic duct, which are seen as filling defects on MR cholangiopancreatographic and T2-weighted images, and associated gallbladder wall abnormalities, including wall thickening with increased T2 signal intensity (46).

Another examination that should be considered in cases with equivocal US or CT findings of acute cholecystitis is hepatobiliary scintigraphy. Hepatobiliary scintigraphy with technetium 99m–labeled iminodiacetic acid analogs (ie, HIDA scanning) has higher sensitivity and specificity for the detection of acute cholecystitis than does US. HIDA scanning has sensitivities ranging from 91% to 92% compared with US, which has sensitivities ranging from 26% to 73%. HIDA scanning has a specificity of 71%–79% compared with US, which has a specificity of 58%–80% (47–49).

If there is no visualization of the gallbladder despite tracer activity in the CBD and small bowel 60 minutes after the agent is administered, then imaging should be performed for an additional 30 minutes after administration of morphine, which contracts the sphincter of Oddi, redirecting bile toward the cystic duct. The diagnosis of acute cholecystitis is made when there is no visualization of the gallbladder 30 minutes after morphine-induced augmentation (Fig 10) or a total of 4 hours after tracer administration if the patient is unable to receive morphine owing to an allergy.

Imaging has an important role in the detection of complications related to acute cholecystitis, which include emphysematous cholecystitis, gangrenous cholecystitis, hemorrhagic cholecystitis, pericholecystic abscess, and gallbladder perforation. Gangrenous cholecystitis is the most common complication of acute cholecystitis and often necessitates emergent surgery. Intramural hemorrhage and microabscesses, as well as intraluminal purulent debris and sloughed membranes, are characteristic of gangrenous cholecystitis (25) (Fig 11a).

Perforated cholecystitis is most commonly seen in association with gangrenous cholecystitis. Perforation most commonly occurs at the gallbladder fundus, where the blood supply to the gallbladder via the cystic duct is most distal. Imaging findings include discontinuity of the gallbladder wall, pericholecystic fluid and inflammatory change, and an extraluminal position of the gallstones (Fig 11b) (44).

Emphysematous cholecystitis is caused by gas-forming bacterial infection and develops in less than 1% of patients with acute cholecystitis (8). Emphysematous cholecystitis is more common in men and diabetic patients (25,44). The diagnosis is made when intraluminal or intramural air is present, and it can be easily determined with CT (Fig 11c). On US images, intraluminal gas appears as dirty acoustic shadowing.

**Xanthogranulomatous Cholecystitis**

XGC is an uncommon form of chronic cholecystitis with which focal or diffuse destructive inflammation of the gallbladder occurs. The disease is typically seen in women 60–70 years of age (25). XGC is characterized by the intramural accumulation of lipid-laden foamy macrophages, which results in scarring and marked proliferative fibrosis. Pathophysiologically, XGC is believed to be caused by the intramural extravasation of bile from superficial mucosal ulcerations, which results in a destructive inflammatory response as histiocytes ingest chemically irritating cholesterol crystals (50,51).

XGC appears as diffuse or focal gallbladder thickening, hypoattenuating intramural nodules (ie, xanthogranulomas), heterogeneous enhancement of the wall, and infiltration into the pericholecystic fat and adjacent liver (25) (Fig 12). The CT findings of XGC and gallbladder carcinoma overlap substantially (52). The most reliable CT findings that distinguish XGC from gallbladder carcinoma are intramural hypoattenuating nodules in a thickened gallbladder wall that occupy
more than 60% of the wall, and continuous linear enhancement of the gallbladder mucosa (25,52). Xanthogranulomas have markedly elevated signal intensity on T2-weighted MR images.

**Gallbladder Adenomyomatosis**

Adenomyomatosis is a benign hyperplastic cholecystosis that is estimated to occur in up to 8% of patients who undergo cholecystectomy (8). Ninety percent of patients with adenomyomatosis have concurrent cholelithiasis (25,53). Adenomyomatosis is characterized by hyperplasia of the gallbladder mucosa, with invagination into a hypertrophic muscular layer leading to the formation of intramural diverticula known as Rokitansky-Aschoff sinuses (RAS). Adenomyomatosis may be focal, segmental, or diffuse (8). The focal type is the most common, and it usually occurs at the gallbladder fundus, forming a nodule referred to as an adenomyoma. The segmental type is that of circumferential wall thickening, which causes a stricture that divides the gallbladder lumen into interconnected compartments. Segmental adenomyomatosis has been associated with a higher frequency of gallbladder carcinoma (54). The diffuse type involves thickening of the entire gallbladder (53,55,56).

The US findings of adenomyomatosis include focal, segmental, or diffuse gallbladder wall thickening with small anechoic cystic spaces, which represent RAS. Embedded within the RAS are small echogenic foci, representing crystals or stones, that characteristically demonstrate V-shaped reverberation or comet-tail artifacts. A twinkling artifact may be present at color Doppler US (8,55).

Detection of adenomyomatosis can be challenging with CT, as RAS are often small. In addition, it can be difficult to distinguish the focal or diffuse wall thickening of adenomyomatosis from that of gallbladder carcinoma (57). There is the potential for dual-energy CT to aid in this differentiation. On dual-energy iodine overlay CT images, iodine does not appear in the bile-filled RAS (Fig 13a). In contrast, with gallbladder carcinoma, the masslike lesion or wall thickening demonstrates increased iodine content (Fig 13c).

MR cholangiopancreatography is very useful for distinguishing adenomyomatosis from gallbladder carcinoma, as it can depict the fluid-filled RAS. The RAS appear as small intramural foci of low signal intensity on T1-weighted images and with markedly high signal intensity, equivalent to that of bile, on T2-weighted images (25,58). The RAS may show a characteristic curvilinear arrangement, which appears as the “pearl necklace” sign on T2-weighted images.
(Fig 14). This sign has been shown to be 62% sensitive and 92% specific for the detection of adenomyomatosis (59).

**Gallbladder Carcinoma**

Gallbladder carcinoma is the most common biliary tract malignancy worldwide, with an incidence of 2.5 cases per 100,000 individuals annually (25). Patients with gallbladder carcinoma can present with right upper quadrant pain, jaundice, and weight loss, or the malignancy may be incidentally diagnosed after cholecystectomy performed to treat gallstones or cholecystitis. The typically vague clinical manifestations of gallbladder carcinoma contribute to advanced disease having developed by the time of presentation. In addition, the thin muscular layer of the gallbladder and continuity of the gallbladder wall with adjacent liver parenchyma promote the early spread of gallbladder carcinoma into the hepatic parenchyma and through the lymphatic and vascular systems (25).

The prognosis depends on the stage of disease. The 5-year survival rate is 50% among patients with stage I disease (tumor confined to the gallbladder) and 2%-4% among those with stage IV disease (tumor invading the main portal vein or hepatic artery or invading at least two extrahepatic organs) (60). Females are more commonly affected than are males. Cholelithiasis is a well-established risk factor that is believed to be secondary to chronic inflammation of the gallbladder that results in mucosal dysplasia and consequent evolution to carcinoma. Other risk factors include cigarette smoking, postmenopausal status, and increased age, with an average age at presentation of 65 years (60). Porcelain gallbladder, characterized by diffuse calcification of the gallbladder wall, also has been associated with gallbladder carcinoma (61), although at a much lower incidence than previously estimated—5%-7% in recent studies (62,63). In addition, a common anomalous junction of the pancreaticobiliary duct, also known as a long common pancreatic-biliary channel, has been associated with a higher prevalence of gallbladder carcinoma. This junction is believed to be secondary to the reflux of pancreatic fluid into the biliary system, which leads to chronic inflammation and metaplasia within the gallbladder (25,51,60,64).

The three major imaging findings of gallbladder carcinoma are (a) irregular focal or diffuse gallbladder wall thickening (Fig 15a), (b) an intraluminal polypoid mass (Fig 15b), and (c) a mass obscuring the gallbladder wall or completely replacing the gallbladder. Gallbladder carcinoma most commonly appears as a large solid mass in

![Figure 11. Complications of acute cholecystitis. (a) US image shows a gallbladder containing weblike internal echoes (straight arrow), which represent sloughed membranes and debris; a thickened wall; and pericholecystic fluid (curved arrow)—findings consistent with gangrenous cholecystitis. (b) Axial T2-weighted MR image shows a discontinuous posterior gallbladder wall (arrows), with extraluminal gallstones (arrowhead)—findings consistent with perforated cholecystitis. (c) Axial contrast-enhanced CT image shows gas (arrows) within the gallbladder, wall thickening, and pericholecystic fluid (arrowhead), consistent with emphysematous cholecystitis.](image)

![Figure 12. Xanthogranulomatous cholecystitis. Coronal contrast-enhanced CT image shows multiple hypoattenuating intramural nodules (arrows), or xanthogranulomas.](image)
the gallbladder fossa that extends into the liver and adjacent organs. There is usually obscuration of the gallbladder, and there may be gallstones in the mass. At MR imaging, the mass has intermediate signal intensity on T1-weighted images, is heterogeneously hyperintense on T2-weighted images, and demonstrates early and persistent enhancement after gadolinium-based contrast material administration (25). Focal or diffuse gallbladder wall thickening of greater than 1 cm at CT or MR imaging and asymmetric gallbladder wall thickening are highly suggestive of carcinoma. Additional imaging features that favor a diagnosis of malignancy include associated lymphadenopathy, extension of soft tissue into the adjacent liver, and hematogenous metastasis (51). PET/CT has a role in the detection of unsuspected metastases, which can alter staging and treatment (51,65). Gallbladder carcinoma demonstrates intense accumulation of fluorine 18 fluorodeoxyglucose (FDG) PET/CT images in the same patient show an FDG-avid gallbladder mass (arrowhead in d) with extensive lymphadenopathy (arrows in e). Biopsy results confirmed the diagnosis of metastatic gallbladder carcinoma.

**Figure 13.** Dual-energy CT differentiation between adenomyomatosis and gallbladder carcinoma. (a) Axial iodine overlay dual-energy CT image shows no iodine content within a masslike lesion (arrow) at the gallbladder fundus, supporting the suspicion of adenomyomatosis. (b) Axial mixed dual-energy CT image in a different patient shows a soft-tissue mass (arrow) extending from the gallbladder into the liver. (c) Axial iodine overlay dual-energy CT image in the patient in b shows increased iodine uptake (arrow) within the mass, which is of concern for carcinoma. (d, e) Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT images in the same patient show an FDG-avid gallbladder mass (arrowhead in d) with extensive lymphadenopathy (arrows in e). Biopsy results confirmed the diagnosis of metastatic gallbladder carcinoma.

**Figure 14.** Adenomyomatosis. Axial T2-weighted MR image shows multiple hyperintense foci in a curvilinear arrangement (circle), producing the pearl necklace sign that is characteristic of adenomyomatosis, in the gallbladder wall.
wall thickening is the most diagnostically challenging manifestation of gallbladder carcinoma. **Dual-energy CT iodine overlay** images have the potential to facilitate improved detection and characterization of gallbladder carcinoma. 

*With the iodine content highlighted, carcinoma can be visualized more easily (Fig 13c) because compared with benign entities such as XGC and adenomyomatosis (Fig 13a), carcinoma will demonstrate increased uptake of iodine (66). Smooth continuous enhancement of the gallbladder mucosa on dual-energy CT iodine overlay images is suggestive of XGC rather than carcinoma.*

**Conclusion**

Gallbladder imaging has a pivotal role in the examination of patients who present with acute abdominal pain, particularly when the pain is localized to the right upper quadrant. It is important to be familiar with the imaging appearances of various gallbladder diseases, including gallstones, infection, and malignancy, and the limitations of each imaging modality. Recent and ongoing improvements in dual-energy CT and associated postprocessing techniques can facilitate increased conspicuity of noncalcified gallstones with virtual monochromatic imaging, improved detection of acute cholecystitis at CT with iodine maps, and the detection of iodine uptake in gallbladder carcinoma.

**References**

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