Gallbladder Carcinoma: Multimodality imaging pearls and pitfalls

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LEARNING OBJECTIVES

1. To describe the pathogenesis, clinical features, patterns of spread and differential diagnosis of gallbladder carcinoma.

2. To illustrate key imaging features and highlight potential interpretative pitfalls.

3. To review the role of different imaging techniques in staging and management.
Background

Introduction

Gallbladder carcinoma is the commonest biliary tract tumour. The incidence of gallbladder cancer is 1.2 cases 100,000 persons in the United States [1] and it typically presents with non-specific symptoms. Diagnosis at a curative stage remains problematic. Recent advances in imaging technology have improved non-invasive staging. The ideal treatment for gallbladder carcinoma is curative surgical resection; therefore, accurate pre-operative evaluation of gallbladder tumours is essential. Techniques, such as ultrasonography, CT and MRI are able to detect abnormalities of the gallbladder but cannot always reliably differentiate between malignancy and other benign disease processes. PET-CT has a valuable role in detecting occult metastatic disease in patients who are potentially suitable for radical treatment. Knowledge of characteristic imaging features aids diagnosis and helps guide optimal treatment.

Pathogenesis

Gallbladder carcinoma is three times more common in women and more frequently affects caucasians [2]. The frequency of diagnosis increases with age. Higher prevalence has been reported from New Mexico, Bolivia, Chile, Israel, and northern Japan [3]. Ethnic groups with an increased prevalence of cholelithiasis have a greater risk of developing gallbladder carcinoma [4,5]. Acute cholecystitis is most often caused by gallstones [6] and develops in 1-3% of patients with symptomatic gallstones [7]. Adenocarcinoma (well to moderately differentiated) is the commonest form of gallbladder carcinoma.

Risk factors include: female sex, increasing age, post-menopausal status, smoking, ethnic origin, increased body mass, cholelithiasis, porcelain gallbladder, chronic biliary infection (e.g. Salmonella typhi), primary sclerosing cholangitis, exposure to chemicals used in the rubber, automobile, wood finishing, and metal fabricating industries and congenital anomalies of the biliary tree [8-15].

Pathogenesis is not fully understood but chronic irritation and inflammation of the gallbladder can lead to mucosal dysplasia and subsequent carcinoma [12]. Porcelain gallbladder is an uncommon condition in which there is diffuse calcification of the gallbladder wall, and 10%-25% of patients with this condition develop gallbladder carcinoma (Fig 1) [14]. Several congenital anatomical anomalies such as cystic dilatation of the biliary tree, choledochal cysts [15,16], anomalous junction of the pancreaticobiliary ducts (with or without a coexistent choledochal cyst) [17-20], and low insertion of the
cystic duct [21] are associated with a higher prevalence of gallbladder carcinoma, compared with that in the general population.

**Clinical Features**

Early-stage gallbladder carcinoma is typically diagnosed incidentally because of inflammatory symptoms related to co-existent cholelithiasis or cholecystitis [22]. However, the majority of patients with gallbladder malignancy present with advanced disease. Clinical presentation is non-specific and the diagnosis is usually unsuspected. Symptoms may include abdominal pain, weight loss, fever, and jaundice. Jaundice occurs more frequently as a result of malignant obstruction of the biliary tree rather than hepatic metastases or co-existent choledocholithiasis [23]. Gallbladder carcinoma is incidentally diagnosed during histopathological analysis after cholecystectomy for benign disease in approximately 2% of patients [24].
IMAGING FINDINGS

Gallbladder carcinoma may appear as a mass completely occupying or replacing the gallbladder lumen (Fig 2), focal or diffuse asymmetric gallbladder wall thickening (Fig 3), or an intraluminal polypoid lesion (Fig 4) [22].

Role of Imaging Techniques

Plain Radiography: Abdominal radiographs may be the initial examination and may demonstrate calcified gallstones or a porcelain gallbladder (Fig 1). In rare cases, calcification precipitating in mucus within the neoplastic glandular tissue may also be visible on radiographs. Abnormal collections of gas in the right upper quadrant may be visible on radiographs when the tumour has invaded adjacent bowel and a fistula has formed, gas may also be present in the biliary tree. Contrast studies such as barium enema and upper gastrointestinal series may demonstrate the findings of adjacent bowel invasion.

Ultrasoundography (US): US is often the first-line investigation in suspected gallbladder disease. It has a relatively high sensitivity for detection of advanced gallbladder malignancy, but is limited for diagnosis of earlier tumours and unreliable for staging. Gallbladder carcinoma presents as a polypoid lesion in 15-25% (Fig 5) [25, 26]. Tumours are usually > 1 cm in diameter and may have a thickened implantation base [25]. Movement of a polypoid mass occurring with a change in patient position is usually due to a "pseudotumour" caused by biliary sludge or clot [27]. Carcinomas that completely replace the gallbladder have irregular margins and heterogeneous echotexture at US (Fig 6). Heterogeneous echotexture reflects varying degrees of tumour necrosis. Echogenic foci and acoustic shadowing associated with the tumour may be related to co-existing gallstones (Fig 7), gallbladder wall calcification or tumoral calcification [28]. Direct extension to the liver and biliary tree is seen as a tumour inseparable from the adjacent liver [22]. This is a common associated finding with large, advanced carcinomas. Subtle areas of focal wall thickening may reflect an early tumour. However, these may be difficult to detect, since they may cause only minor elevation of the mucosa when viewed sonographically. Pronounced wall thickening (> 1.0 cm) with associated mural irregularity or marked asymmetry should raise concern for malignancy (Fig 8) or complicated cholecystitis.

Computed Tomography (CT): CT is widely used for further characterization and staging of potentially malignant gallbladder lesions. CT is commonly performed pre and post
intravenous contrast with arterial and portal venous imaging. Multiplanar and 3D volume-rendered reconstruction images can be generated which are useful for surgical planning [29]. Gallbladder carcinoma is usually hypodense on unenhanced CT, and ~40% of lesions show hypervascular foci of enhancement =/> liver after contrast (Fig 9) [30,31].

Contrast-enhanced CT can be helpful in distinguishing complicated cholecystitis from gallbladder carcinoma. A hypodense band around the gallbladder on CT is reported to be highly suggestive of Xanthogranulomatous cholecystitis [32]. On contrast-enhanced CT, diffuse symmetrical wall thickening suggests a non-neoplastic process, whereas asymmetrical, irregular, or extensive thickening, which may have marked enhancement during the arterial phase that persists or becomes isodense to the liver during the portal venous phase, should raise suspicion of gallbladder carcinoma (Fig 10) [31,33]. It may also demonstrate a hypoattenuating or isoattenuating mass in the gallbladder fossa and soft-tissue invasion of the liver (Fig 4). The tumour may contain low attenuation areas reflecting necrosis, enhancement reflects viable tumour [34]. The low attenuation areas within the tumour mass or thickened gallbladder wall may appear nodular [35]. Demonstration of associated lymphadenopathy, soft-tissue extension into the liver, and evidence of haematogenous metastases favours the diagnosis of gallbladder carcinoma (Fig 11). Biliary obstruction at the level of the porta hepatis and lymph node metastasis are frequent associated findings (Fig 12). The location and characterization of calcification within the gallbladder or tumour is well defined with CT [22].

Extension of the primary tumour into the liver or hepato-duodenal ligament is well depicted by CT. Findings of tumour invasion into the hepato-duodenal ligament include well-defined nodular masses caused by discrete lymph nodes; matted masses due to confluent adenopathy; mixed, well-defined, and confluent masses in various locations along the hepato-duodenal ligament; and infiltrating, enhancing areas of soft-tissue attenuation obscuring the portal vein margins [36].

Magnetic Resonance Imaging (MRI): Although MR imaging is not typically employed as a primary imaging modality for the gallbladder it is used widely for further characterization of potentially malignant gallbladder lesions and staging. It may be useful in cases of focal or diffuse mural thickening to distinguish gallbladder carcinoma from adenomyomatosis and chronic cholecystitis. On MR, gallbladder carcinoma is usually hypo to iso-intense on T1-weighted and moderately hyper-intense on T2-weighted sequences (Fig 3, 13) [22]. Ill-defined early enhancement is typical appearance on dynamic gadolinium-enhanced imaging [37]. Intense irregular, peripheral enhancement during the early arterial phase in larger tumours (Fig 14). Contrast may be retained in fibrous stromal components of gallbladder carcinoma during the portal venous and delayed phases (Fig 15), aiding differentiation from large central hepatocellular carcinomas, which typically show contrast washout [33].
On MR, tumour extension has the same signal intensity as the primary lesion [38]. Biliary dilatation is a common finding. Infiltrative tumour growth with spread along the cystic duct to the extra-hepatic bile duct, lymph node enlargement, and intraductal spread of tumour results in biliary dilatation and obstruction.

Positron Emission Tomography - Computed Tomography (PET-CT): Fluorine-18 FDG (fluorodeoxyglucose) PET-CT is a well established imaging technique in oncological imaging that provides information about metabolic activity in lesions [39]. PET-CT is usually performed 1 hour after administration of FDG. FDG avid uptake in the region of the gallbladder is suspicious but not specific for primary malignancy (Fig 16) [40,41]. PET-CT is highly sensitive in detecting distant metastases from gallbladder cancer and is superior to contrast enhanced CT. Distant metastases are associated with poor survival of only few months, regardless of the therapy. The majority of patients with distant metastases do not qualify for curative resection. PET-CT helps identify occult metastases (Fig 17) not detected by contrast enhanced CT. In patients with unsuspected gallbladder cancer detected following laparoscopic cholecystectomy iatrogenic dissemination of gallbladder carcinoma in the peritoneal cavity and port sites (Fig 18) can occur. PET-CT frequently results in a change of oncological management of patients [41,42]. There may be a role for dual-time imaging as uptake on delayed PET is reported to be more sensitive for detection of gallbladder carcinoma [43]. False-negative PET-CT may occur in the setting of small lesions due to the reduced sensitivity of PET for detection of sub-centimetre tumours. Gallbladder carcinoma may arise as a nidus in pre-existing background chronic cholecystitis, which can obscure or delay the diagnosis of cancer. FDG PET-CT is limited in this setting because benign inflammatory and infective processes also accumulate FDG and may result in false-positive interpretation (Fig 19).

Evaluation of Tumour Extension: Direct cholangiography by ERCP, percutaneous transhepatic cholangiography, or intra-operative cholangiography may be performed in patients with biliary involvement when the diagnosis of gallbladder carcinoma is unsuspected or when therapeutic management of biliary obstruction is necessary. Cholangiography may demonstrate malignant strictures or obstruction involving the extra-hepatic bile ducts, confluence of the right and left hepatic ducts, and right lobe intrahepatic ducts [44]. Associated findings from cholangiography include intraluminal gallbladder filling defects that may represent tumour or stones, a mass displacing and invading the gallbladder, and intraductal filling defects that may represent tumour or coexistent choledocholithiasis.

Pattern of spread: Lymphatic spread is common in gallbladder carcinoma (present in 50% of patients at diagnosis). Positive lymph nodes are more likely to be greater than 10 mm in antero-posterior dimension and have ring like or heterogeneous contrast material enhancement [45]. The masses produced by lymph node metastasis around the distal common bile duct and pancreatic head may mimic a pancreatic head carcinoma [27].
Lymphatic metastases progress from the gallbladder fossa through the hepato-duodenal ligament to nodal stations near the head of the pancreas.

Three pathways of lymphatic drainage have been suggested: the cholecysto-retropancreatic pathway, the cholecysto-celiac pathway, and the cholecysto-mesenteric pathway [46]. The cystic and pericholedochal lymph nodes are the most commonly involved at surgery [47] and are a critical pathway to involvement of the coeliac, superior mesenteric, and para-aortic lymph nodes. The node of the foramen of Winslow, the superior pancreate-duodenal node, and the posterior pancreate-duodenal nodes are the most common nodes demonstrated by CT (Fig 11) [48].

Haematogenous metastases are most commonly seen in the liver [449]. Pulmonary, skeletal, cardiac, pancreatic, renal, adrenal, and cerebral metastases occur less frequently. Haematogenous metastases to the liver are well depicted by CT and MR imaging.

Radiological Differential Diagnosis: Gallbladder carcinoma manifesting as diffuse gallbladder wall thickening has a differential diagnosis that includes the more common inflammatory and non-inflammatory causes of wall thickening. These conditions include heart failure, cirrhosis, hepatitis, hypoalbuminemia, renal failure, and cholecystitis [50]. Occasionally, a pericholecystic abscess, gallbladder necrosis, or fistula formation to adjacent bowel can complicate acute cholecystitis. The findings in these cases may simulate those of an aggressive neoplastic process. Gallbladder carcinoma should be suspected when there are features of a focal mass, lymphadenopathy, hepatic metastases, and biliary obstruction at the level of the porta hepatitis.

Xanthogranulomatous cholecystitis (Fig 20,21) is a pseudo-tumoral inflammatory condition of the gallbladder that radiologically simulates gallbladder carcinoma. The CT features of xanthogranulomatous cholecystitis and gallbladder carcinoma overlap substantially and these entities cannot be reliably differentiated. Both diseases may demonstrate gallbladder wall thickening, infiltration of the surrounding fat, hepatic involvement, and lymphadenopathy.

Adenomyomatosis is a common tumour like lesion of the gallbladder with no malignant potential. It may involve the gallbladder in a focal, segmental, or diffuse form. At US, adenomyomatosis is characterized by focal or diffuse gallbladder wall thickening and anechoic or echogenic foci in the gallbladder wall (Fig 22). These echogenic foci may produce a ring-down reverberation artefact. Rokitansky-Aschoff sinuses are best visualized with MR imaging performed with breath-hold technique and T2-weighted pulse sequences; therefore, MR imaging can be useful for distinguishing this benign entity from gallbladder carcinoma. Occasionally adenomyomatosis can cause false positive FDG uptake at PET-CT (Fig 23)
The differential diagnosis for tumours which manifest as an intra-luminal polypoid mass includes adenomatous, hyperplastic, and cholesterol polyps; carcinoid tumour; metastatic melanoma and a haematoma within the gallbladder. The differential diagnosis for a mass replacing the gallbladder fossa includes hepatocellular carcinoma, cholangiocarcinoma, and metastatic disease to the gallbladder fossa.

The differential diagnosis of a polypoid gallbladder lesion includes adenomatous or hyperplastic cholesterol polyps as well as uncommon tumors such as carcinoid or metastases such as melanoma.
Images for this section:

Fig. 0: Porcelain gallbladder.

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**Fig. 0:** Mass occupying the gallbladder lumen.

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Fig. 0: Eccentric gallbladder wall thickening on T1W MRI.

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Fig. 0: Gallbladder mass infiltrating the liver.

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Fig. 0: Gallbladder polyp.

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**Fig. 0:** Irregular margins and heterogenous echotexture at US.

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**Fig. 0:** Co-existent gallstones.

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Fig. 0: Pronounced wall thickening and hypervascularity.

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Fig. 0: Avidly enhancing gallbladder polyp.
**Fig. 0:** Asymmetrical, irregular wall thickening that becomes isodense to the liver during the portal venous phase.

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Fig. 0: Portocaval and peripancreatic lymphadenopathy.

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**Fig. 0:** Intrahepatic duct dilatation due to obstruction at the level of the porta hepatis.

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Fig. 0: Eccentric gallbladder wall thickening on T2W MRI.

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**Fig. 0:** Early T1W post gadolinium.

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Fig. 0: Delayed T1W post gadolinium.

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**Fig. 0:** FDG avid uptake in the region of the gallbladder is suspicious for primary malignancy.

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**Fig. 0:** PET-CT identify occult retroperitoneal metastases not detected by contrast enhanced CT.

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**Fig. 0:** Iatrogenic dissemination of gallbladder carcinoma in the peritoneal cavity and port sites detected following laparoscopic cholecystectomy.

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**Fig. 0:** Benign inflammatory and infective processes also accumulate FDG and may result in false-positive interpretation. In this case, PET-CT demonstrates focal cholecystitis.

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Fig. 0: Xanthogranulomatous cholecystitis may demonstrate gallbladder wall thickening, infiltration of the surrounding fat, hepatic involvement, and lymphadenopathy.

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**Fig. 0:** Xanthogranulomatous cholecystitis: PET-CT demonstrates avid FDG uptake thus giving a false positive result for gallbladder carcinoma.

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Fig. 0: Adenomyomatosis, at US, is characterized by focal or diffuse gallbladder wall thickening and anechoic or echogenic foci in the gallbladder wall. These echogenic foci may produce a ring-down reverberation artefact.

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Fig. 0: Adenomyomatosis can cause false positive FDG uptake at PET-CT.

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Conclusion

The clinical and radiological detection of gallbladder carcinoma at a curative stage remains problematic. It is imperative for radiologists to closely scrutinize the gallbladder, particularly in patients who are at increased risk of developing gallbladder carcinoma, for subtle morphologic abnormalities that may indicate cancer. Multi-modality imaging plays a central role in evaluation and staging of gallbladder carcinoma. Understanding the spectrum of radiological appearances and patterns of disease spread is essential to enable accurate staging and guide optimal patient management.
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