




Approach to Biliary Malignancies

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Abstract

Biliary malignancies arise from anywhere along the biliary tract and broadly encompass gallbladder cancer and cholangiocarcinoma. Surgical resection with curative intent remains the mainstay treatment for biliary tract malignancies, but despite advances in treatment and management over the years, prognosis remains poor. The majority of patients present with nonspecific clinical symptoms and are diagnosed at late-stage disease when surgical resection is no longer an option. In the minority of patients presenting with early-stage disease, it is particularly important to determine accurate radiological staging and take a multidisciplinary approach to determine patients suitable for curative surgical resection. A range of imaging modalities is often used in combination, each providing complementary information to characterize and stage disease. Gallbladder cancer and cholangiocarcinoma are distinct entities and the approach to each of these will be discussed separately.

Keywords

- ▶ biliary tract malignancy
- ▶ cholangiocarcinoma
- ▶ gallbladder cancer

Introduction

Gallbladder cancer arises from epithelium of the gallbladder or cystic duct. Adenocarcinomas comprise 90% of tumors and the rest are mostly adenosquamous or squamous cell carcinomas.¹ Prevalence is higher in parts of Southeast Asia and South America in comparison to the West; elderly females are more commonly affected and female to male predominance is at a ratio of 3:1.² Cholelithiasis and chronic cholecystitis are the main risk factors leading to gallbladder cancer due to repeated irritation and inflammation of gallbladder mucosa, causing to dysplasia and subsequently carcinoma. Other well-known risk factors include polyps greater than 1cm, inflammatory bowel disease, primary sclerosing cholangitis (PSC), porcelain gallbladder, choledochal cysts, and an anomalous pancreaticobiliary duct junction.³

Clinical presentation is largely nonspecific. Some patients are asymptomatic with gallbladder cancer detected incidentally at routine cholecystectomy for presumed benign gallbladder disease in 1 to 3% of cases, or imaged incidentally for other suspected pathology.⁴ Even still, in

symptomatic cases, presentation may commonly overlap with features suggestive of benign biliary disease such as jaundice, right upper quadrant pain, pruritis, and fever. Such symptoms can easily be clinically attributed to gallstones or cholecystitis, so investigation for gallbladder cancer requires a high index of clinical suspicion with a thorough clinical assessment including evaluation of risk factors, adequate laboratory, and imaging workup to arrive at a diagnosis.⁵

The absence of a submucosal layer around the gallbladder and the anatomical location of the gallbladder are significant contributory factors for the tendency of early, aggressive local invasion into adjacent structures such as the liver and biliary tree.⁶ Three main patterns of disease spread have been described. The most common is direct hepatic invasion into segments 4 and 5, found in 69% of patients, or of neighboring organs, through intraperitoneal spread resulting in omental, peritoneal deposits and ascites and through subperitoneal spread resulting in involvement of the hepatoduodenal and gastrohepatic ligaments and spread to the pancreas, duodenum, mesentery, and stomach. The propensity for early locoregional spread means

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patients often already have lymph node and distant metastases at first presentation.^{7,8} Curative surgical resection rates are low, between 10 and 30%, and may not be an option in the presence of vascular invasion, invasion of adjacent organs, and hepatic and peritoneal metastases. Due to low curative resection rates, the 5-year survival rate is poor at less than 5% for infiltrative advanced disease (stage 3 or 4).⁹

Morphology of Gallbladder Cancer

Gallbladder cancer usually presents one of three ways. The most common is a mass replacing the gallbladder in 40 to 65% of cases, followed by focal and asymmetrical mural thickening in 20 to 30% and as an intraluminal polypoid lesion in 15 to 25% of cases.¹⁰ Cholelithiasis, a known risk factor, is present alongside gallbladder cancer in 60 to 94% of cases.¹¹ Mural thickening and intraluminal polypoid lesions may mimic benign gallbladder diseases such as cholecystitis and polyps. Malignancy may also coexist with benign gallbladder diseases, making the detection and diagnosis of gallbladder cancer a particular challenge. ►Table 1 outlines morphology of gallbladder cancer, the common differential diagnoses to be aware of and imaging features that can help to differentiate benign from malignant disease.

Gallbladder Polyps

Particular emphasis is placed on the discussion of gallbladder polyps as they are a relatively common incidental findings during ultrasound (US) and many undergo follow-up, yet malignancy following on from such polyps are a relatively infrequent diagnosis, with some studies suggesting only 0.4% of resected gallbladder polyps sized over 1 cm are malignant. As such, current guidelines are questionable and management of polyps remains a particular clinical challenge as prolonged follow-up of small polyps are of questionable benefit and may lead to unnecessary surgical resection and anxiety for patients. Suggestions of management differ between different consensus groups.

Joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery (EAES), International Society of Digestive Surgery (EFISDS), and European Society of Gastrointestinal Endoscopy (ESGE) have released updated guidelines in 2021 for the management and follow-up of gallbladder polyps.¹²

The updated 2021 guidelines are summarized as follows¹²:

- Gallbladder polyps sized 1cm or more should undergo cholecystectomy (includes polyps <1cm that grow to 1cm during follow-up).

Table 1 Differential diagnoses to consider according to the morphological appearance of gallbladder cancer

Morphological appearance of gallbladder cancer	Differential diagnosis	Imaging features raising suspicion of malignancy
Mass replacing the gallbladder	<ul style="list-style-type: none"> • Primary or secondary hepatic malignancy: Hepatocellular carcinoma, cholangiocarcinoma or metastasis infiltrating the gallbladder • Tumefactive gallbladder sludge • Pericholecystic abscess from complicated cholecystitis 	Careful assessment for center of origin, enhancement patterns, and assessment of the gallbladder wall and cystic duct for wall thickening or mass lesions can help narrow the differential diagnosis
Mural thickening	<ul style="list-style-type: none"> • Acute or chronic cholecystitis • Adenomyomatosis • Xanthogranulomatous cholecystitis • Porcelain gallbladder • Diffuse thickening due to hepatic or systemic diseases: cirrhosis, hepatitis, cardiac/renal failure, hypoproteinemia 	<ul style="list-style-type: none"> • Focal and asymmetrical thickening (rather than diffuse) • Irregular contour of gallbladder wall • Marked mural thickening over 1cm • Focal, early and marked enhancement of the gallbladder wall • GB-RADS score can be used to risk stratify wall thickening <p>Note: Xanthogranulomatous cholecystitis may mimic malignancy due to irregular wall thickening, regional lymphadenopathy and local invasion, making differentiation difficult, but intramural xanthomas are usually hypodense lesions on CT</p>
Intraluminal mass/polypoid lesion	<ul style="list-style-type: none"> • Benign gallbladder polyp: adenomatous, hyperplastic, cholesterol • Gallbladder metastasis (melanoma most commonly) • Carcinoid tumor • Gallstones • Tumefactive gallbladder sludge 	<ul style="list-style-type: none"> • Polyps >1cm • Interval increase in polyp size • Sessile lesion • Solitary lesion • Enhancement greater than that of normal gallbladder wall • Immobile lesion despite changes in patient positioning

Abbreviations: CT, computed tomography; GB-RADS, Gallbladder Reporting and Data System.

- Polyps sized 6 to 9mm with risk factors for gallbladder malignancy (age over 60, PSC, Asian ethnicity, sessile lesion) should undergo cholecystectomy.
- Polyps sized 6 to 9mm with no risk factors for malignancy OR polyps 5mm or less with risk factors—follow-up US recommended at 6 months, 1 year, and 2 years. No follow-up beyond 2 years in absence of polyp growth.
- Polyps sized 5mm or less and no risk factors for malignancy—no follow-up.
- If the polyp grows by 2mm or more during 2-year follow-up, multidisciplinary team discussion is required to decide between cholecystectomy or continued follow-up imaging.

The Society of Radiologists in Ultrasound (SRU) released recommendations for the management of incidentally detected gallbladder polyps in 2022. Management is risk stratified according to polyps categorized as extremely low risk, low risk, and indeterminate risk polyps. Management is summarized as follows¹³:

Extremely low risk: Pedunculated ball-on-the-wall or thin stalk

- 15 mm or more—surgical review
- 10 to 14 mm—US follow-up at 6 m, 1 year and 2 years
- 9 mm or less—no follow-up

Low risk: Pedunculated with thick/wide stalk OR sessile

- 15 mm or more—surgical review
- 10 to 14mm—US follow-up at 6 m, 1 year, 2 years, and 3 years OR surgical review
- 7 to 9 mm—US follow-up at 1 year
- 6 mm or less—no follow-up

Indeterminate risk: Focal wall thickening 4 mm or more adjacent to the polyp

- 7mm or more—surgical review
- 6 mm or less—US follow-up at 6 m, 1 year, 2 years, and 3 years OR surgical review

For any risk category, surgical review is recommended if there is an increase in size of the polyp by 4mm or more in less than 1 year.

Imaging of Gallbladder Cancer

Patients often present with nonspecific clinical symptoms and there is no catch-all imaging modality to select from the outset to diagnose gallbladder cancer, particularly as patients may be diagnosed incidentally following investigation for another pathology entirely. Arriving at a diagnosis of gallbladder cancer relies on high clinical suspicion to investigate and a full workup involving clinical assessment, laboratory, and imaging findings.

The role of imaging lies in diagnosis, staging, guiding image targeted biopsy, and follow-up of residual or recurrent disease. A combination of imaging modalities is used, which together provide complementary information. This includes US, contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and positron emission tomography/CT (PET/CT).

Ultrasound

US is frequently the first modality to visualize the gallbladder and biliary tract in patients presenting with right upper quadrant pain or jaundice. It is widely available, non ionizing and offers dynamic real-time imaging.¹⁴ Gallbladder cancer may appear as a large mass replacing the gallbladder, focal mural thickening, or an intraluminal mass/polypoid lesion (► Fig. 1). The coexisting presence of gallstones is a common finding, which may decrease the sensitivity of detecting a suspicious mass by obscuring views due to acoustic shadowing.^{10,11}

US has high sensitivity and diagnostic accuracy of 85 and 80%, respectively, for detecting the primary tumor and extent of local invasion in locally advanced cases.¹⁵ However, in early-stage disease, lesions may be subtle and mural thickening due to cholecystitis or gallbladder cancer can be difficult to distinguish. Features such as irregular,

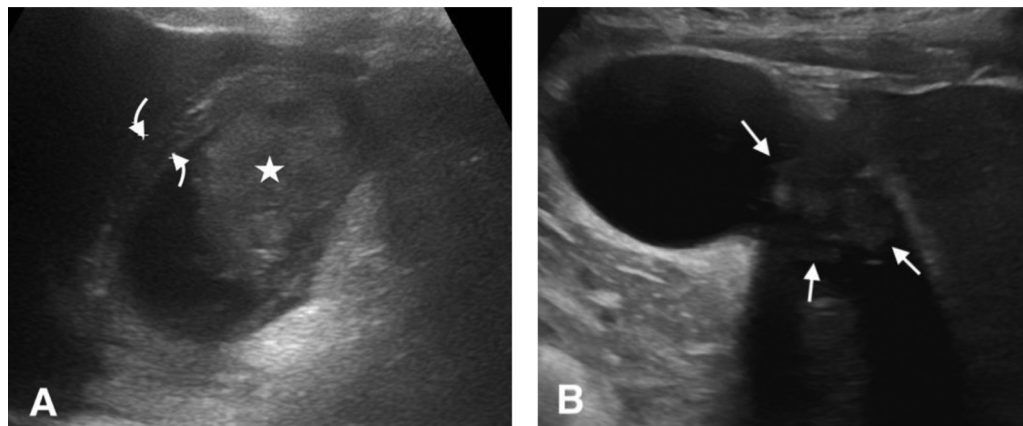


Fig. 1 Ultrasound showing the different morphology of gallbladder cancer. (A) Edema and focal thickening of the gallbladder wall (curved arrows) and an intraluminal mass lesion (star). Clinical history and ultrasound features were thought to be acute cholecystitis with tumefactive sludge at the time of presentation; however, this was pathologically proven T2 gallbladder carcinoma at cholecystectomy. (B) A 2.5 cm intermediate echogenic polypoid mass projecting into the body of the gallbladder (arrows).

asymmetric thickening and thickening greater than 1 cm should raise concern for malignancy.

The Gallbladder Reporting and Data System (GB-RADS) US risk stratification released in 2021 is the first of its kind to risk stratify gallbladder wall thickening into categories ranging from GB-RADS 0 to 5 to improve US interpretation, reporting, and improve accuracy in detecting malignant thickening. GB-RADS scores should be applied after acute, systemic, hepatic, and extracholecystic causes (such as hepatitis, viral disease, cardiac disease) of gallbladder thickening are excluded. Six categories are suggested for wall thickening with increasing risk of malignancy. Features are based on the type of wall thickening such as symmetry or asymmetry, extent of thickening: either focal or diffuse involvement, presence of a layered appearance, presence of intramural features such as cysts or echogenic foci, and the interface formed with the liver.¹⁶ ►Table 2 provides a summary of the GB-RADS score according to risk category, probability of malignancy, and suggested management.

Overall, US has limited assessment for quantifying disease extent, unable to detect distant sites of metastasis. US findings are mainly used to guide the next appropriate imaging modality.¹⁷

Endoscopic ultrasound (EUS) has emerged as a promising modality to assess local disease extent by assessing tumor depth invasion of the gallbladder wall and detect presence of lymphadenopathy at the porta hepatis and peripancreatic regions, both common sites of nodal disease. This technique allows cytological analysis by fine-needle aspiration (FNA) with a sensitivity of 76.9% for diagnosing gallbladder cancer.¹⁸

Computed Tomography

CECT is the modality of choice for detecting, characterizing, and staging gallbladder cancer and is crucial for preoperative planning. CT allows evaluation of direct invasion of the primary tumor into the liver and neighboring organs, identification of vascular and biliary involvement, nodal disease, and sites of distant metastasis.

Imaging features of gallbladder cancer include mural thickening over 1 cm, focal asymmetric or irregular mural thickening, or a low attenuation mass lesion that demonstrates enhancement either replacing the gallbladder or an intraluminal polypoid mass (►Figs. 2 and 3). CT has an overall accuracy of 71% for determining T staging, with accuracy depending on morphological type: 89% for intraluminal polypoid mass lesions, 83% for mass replacing the gallbladder, and much lower accuracy of 54% for lesions presenting as mural thickening.¹⁹ Differentiating benign from malignant causes of gallbladder mural thickening remains difficult due to common overlap of appearances. Invasion of neighboring organs, enlarged locoregional nodes over 1cm, biliary obstruction, and distant metastasis steer the diagnosis toward malignancy.

CT has a sensitivity of 72.7%, specificity of 100%, and accuracy of 85% in determining surgical resectability.²⁰ However, involved lymph nodes are challenging to determine with sensitivity of 36% for N1 and 47% for N2 disease, relying on morphology and size criteria above 1 cm to determine involvement.²¹ Detecting the presence and extent of peritoneal metastases is limited and despite high reported detection sensitivities of 85 to 93%, CT may underestimate the extent of peritoneal involvement when compared to

Table 2 GB-RADS score detailing the risk category, ultrasound findings, probability of malignancy, and suggested management

GB-RADS score	Risk category	Probability of malignancy	US findings	Suggested management
0	Inadequate scan (due to technical or patient factors).	N/A	Inadequate due to: large body habitus, poor patient positioning, contracted gallbladder from inadequate fasting, large stones that obscure the gallbladder wall due to acoustic shadowing, etc.	Repeat US if technical/patient factors allow or consider CT/MRI
1	Normal scan	N/A	Wall thickness 3mm or less in an adequately distended gallbladder	No follow-up
2	Benign findings	<2%	<ul style="list-style-type: none"> • Symmetric circumferential thickening or focal thickening with intramural changes • Layered appearance • Preserved interface with the liver 	No follow-up
3	Equivocal findings	2–50%	<ul style="list-style-type: none"> • Circumferential thickening without layered appearance • Focal thickening without intramural cysts/echogenic foci • Distinct interface with the liver 	Consider CT/MRI after MDT discussion
4	Malignancy likely	50–90%	<ul style="list-style-type: none"> • Circumferential or focal thickening without layered appearance • Loss of interface with liver 	CT/MRI
5	Malignancy highly likely	>90%	<ul style="list-style-type: none"> • Findings as in GB-RADS 4 with definite extramural extension 	CT/MRI

Abbreviations: CT, computed tomography; GB-RADS, Gallbladder Reporting and Data System; MDT, multidisciplinary team; MRI, magnetic resonance imaging; N/A, not available; US, ultrasound.

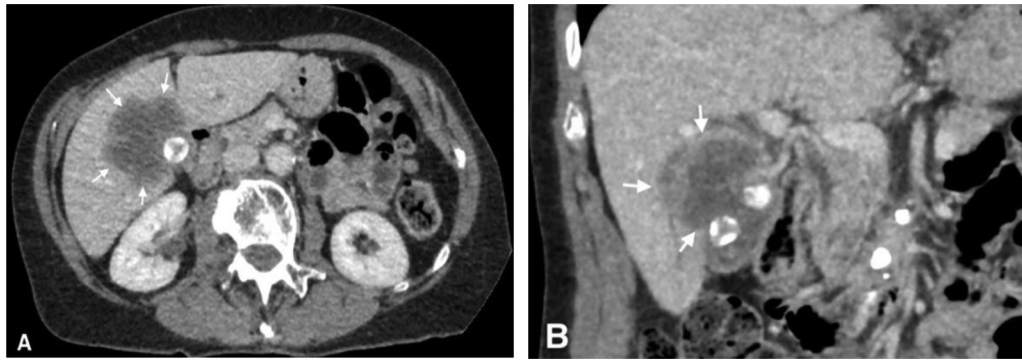


Fig. 2 Computed tomography (CT) showing a mass replacing the gallbladder. (A and B) Axial and coronal CT of the upper abdomen showing an ill-defined large mass lesion centered in the gallbladder with extension into the liver (arrows). This was pathologically proven stage T3 gallbladder carcinoma.

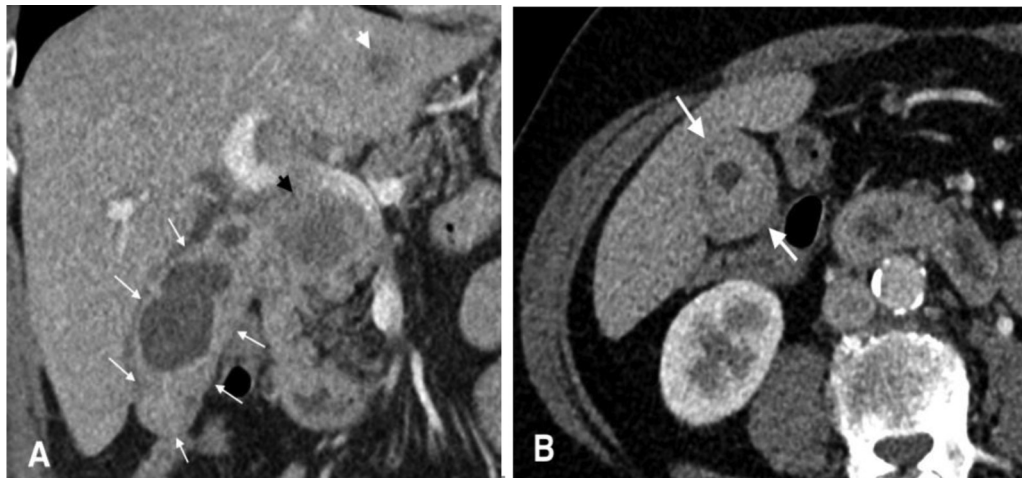


Fig. 3 Computed tomography (CT) showing asymmetric gallbladder mural thickening. (A) Coronal CT showing diffuse irregular, asymmetric gallbladder wall thickening (white arrows), a large pathological lymph node at the porta hepatis (black arrowhead), and a liver metastasis (white arrowhead). (B) Axial CT showing greater focal thickening at the gallbladder fundus measuring over 1 cm.

intraoperative laparoscopic findings.^{20,22} Nonetheless, most patients already have locally advanced primary tumor and nodal and distant metastasis; hence, determining the extent of involved nodes and peritoneal metastases often does not change management as patients are already considered unsuitable for surgical resection. In early-stage disease, PET/CT may be utilized to characterize indeterminate lesions and exclude occult metastasis.

Magnetic Resonance Imaging

MRI in combination with magnetic resonance cholangiopancreatography (MRCP) and dynamic post-contrast enhancement sequences have high accuracy of up to 84.9% for determining T stage disease.²³ Diffusion-weighted imaging aids in detection of nodal metastasis and hepatic invasion or metastasis, either by direct invasion or hepatic deposits, with higher reported sensitivity of 92% for nodal metastasis and 87.5 to 100% for hepatic invasion compared to CT. The arterial phase sequence on MRI and use of MRCP also better depicts arterial anatomy and biliary tract involvement, respectively, particularly useful in early-stage disease when surgical resection is considered. Features suggestive of biliary inva-

sion include biliary stenosis, luminal irregularly, or abrupt ductal caliber change.²⁴

Typically, tumors are hypointense to isointense signal on T1 and heterogeneously isointense to hyperintense signal on T2 (→Figs. 4 and 5). Enhancement is irregular from the periphery of the tumor from arterial phase and persists on portal venous and delayed phases.²⁴ Focal diffusion restriction on diffusion-weighted sequences helps in detecting and characterizing tumor involvement and studies have reported significantly lower apparent diffusion coefficient (ADC) values in malignant disease compared to benign disease to aid differentiation.²⁵

Advantages over CT are due to the superior soft tissue contrast resolution of MRI. Gallstones can easily be differentiated from polyps by their low T2 signal intensity and lack of enhancement, which may at times be tricky to differentiate on US if the gallbladder contains sludge or the gallstone is impacted in the gallbladder wall or on CT where smaller lesions may not be well demonstrated.²⁶ MRI can aid in differentiating malignant from benign causes of mural thickening such as cholecystitis, xanthogranulomatous cholecystitis, and adenomyomatosis.²⁷ Identification of lymph node

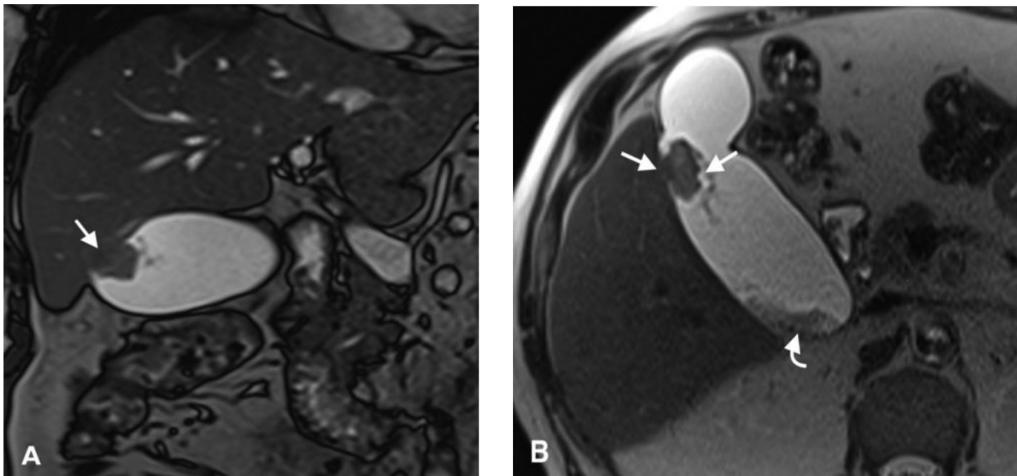


Fig. 4 Magnetic resonance cholangiopancreatography showing a large intraluminal polypoid mass. (A and B) Coronal and axial T2 images showing an isointense polypoid mass lesion (arrows) and tiny gallstones and sludge in the dependent portion of the gallbladder (curved arrow).

involvement is also superior with high sensitivity of 92% compared to CT sensitivity of 36 to 47%.²⁴

Positron Emission Tomography/Computed Tomography

PET/CT combines anatomical and functional information and is often used as a problem-solving tool to assess equivocal primary lesions and to guide appropriate clinical management by identifying occult or unsuspected sites of metastasis, important for N and M disease staging (► **Fig. 6**). PET/CT may also be used to identify residual or suspected recurrent disease in patients who have previously undergone surgical resection. Limitations include false-positives in benign inflammatory conditions that may cause FDG avidity and

mimic malignancy and false-negatives such as peritoneal deposits measuring less than 1 cm that may not be FDG avid.²⁸

Structuring Radiology Reports for Gallbladder Cancer

The role of the radiologist is to guide management and help surgeons determine which patients are suitable for surgical resection. Radiology reports ought to be well structured and include pertinent information to determine resectability. In particular, major vasculature such as the main portal vein, hepatic artery and their branches, biliary structures, and any variant vascular or biliary anatomy should be routinely commented on. ► **Table 3** shows a suggested reporting template for gallbladder cancer.

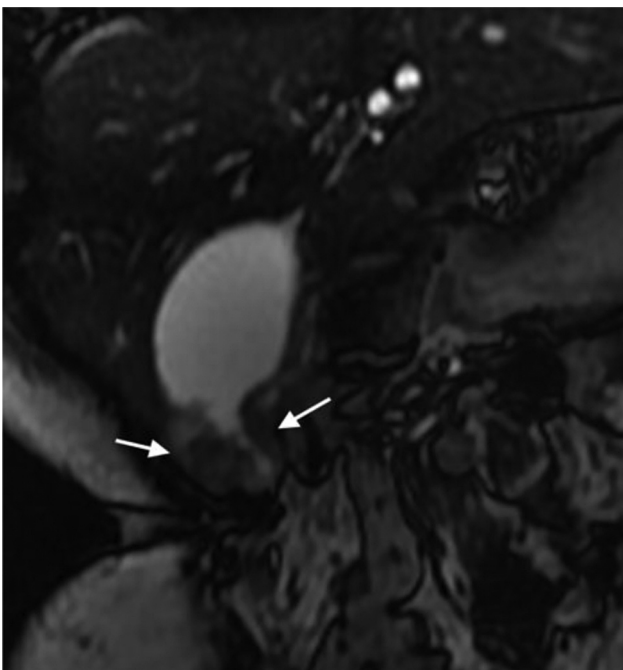


Fig. 5 Magnetic resonance imaging coronal T2 weighted image showing focal fundal gallbladder thickening. Note the asymmetric and irregular thickening either side of the gallbladder wall (white arrows).

Cholangiocarcinoma

Cholangiocarcinoma is a heterogenous group of primary malignant tumors that arise from bile duct epithelium anywhere along the biliary tract excluding the gallbladder, cystic duct, and ampulla of Vater. Adenocarcinoma accounts for 95% of cases. Prevalence is notably higher in certain parts of the East such as in Southeast Asia and the Middle East compared to the West, thought to be due to differences in local risk factors and genetic determinants. Presentation is typically in the seventh decade with a slight preponderance for elderly males.²⁹

The exact etiology is unknown, with many cases occurring sporadically in the presence of no known risk factors. Intraductal papillary neoplasm of the bile duct (IPNB) is regarded as a preinvasive precursor lesion of cholangiocarcinoma. Main risk factors include hepatolithiasis and clonorchiasis infection, with higher incidence of IPNB reported in the East, likely related to endemic hepatolithiasis and clonorchiasis infections. Reports of IPNB are mostly located within the liver with a predilection for left sided biliary ducts or at the hepatic hilum.³⁰

Identifiable risk factors for cholangiocarcinoma include conditions that cause chronic inflammation of biliary

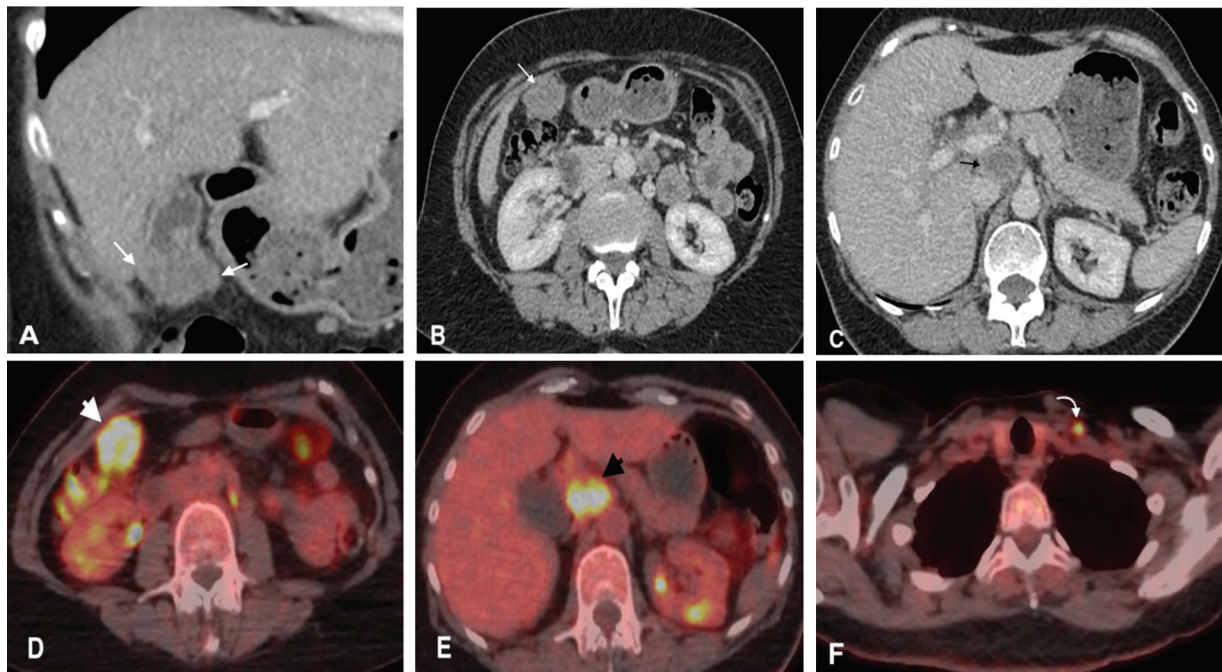


Fig. 6 Computed tomography (CT) and positron emission tomography/computed tomography (PET/CT) showing gallbladder cancer with lymph node involvement and an occult distant metastasis. (A and B) Coronal and axial CT images showing a large lobulated mass at the gallbladder fundus (white arrows). (C) Axial CT image showing a pathological lymph node at the porta hepatis (black arrow). (D, E, and F) Axial PET/CT images showing the fluorodeoxyglucose avid primary lesion (white arrowhead), pathological lymph node (black arrowhead) and a left supraclavicular metastasis; the latter an unsuspected site of metastasis not appreciated on initial staging contrast-enhanced CT (curved white arrow).

epithelium and bile stasis such as chronic biliary tract infections and inflammation, which promote carcinogenesis within the biliary tract.²⁹ In the West, the best-known risk factor is PSC with a lifetime incidence of cholangiocarcinoma ranging from 6 to 36%. Over 50% of patients are diagnosed with cholangiocarcinoma within a year of receiving a PSC diagnosis.³¹ Other well-known risk factors are infestation

from liver fluke (particularly Southeast Asia), chronic viral hepatitis, choledocholithiasis, hepatolithiasis, and primary biliary cirrhosis. Congenital malformations including bile duct cysts and Caroli disease carry an increased lifetime risk with incidence ranging from 6 to 30%.³²

Clinical presentation is often nonspecific. Symptoms may be constitutional, arise as a result of biliary obstruction or may manifest due to underlying predisposing pathology. In addition, symptoms depend on the anatomical site of origin of the primary tumor. Intrahepatic tumors tend to cause nonspecific symptoms such as abdominal pain, weight loss, and a palpable mass if large. Extrahepatic tumors typically cause biliary obstruction and symptoms include jaundice, pale stools, dark urine, and pruritus. The broad and nonspecific presentation means patients often present with late stage, advanced disease. The most common causes of death result from biliary sepsis, hepatic failure, or cancer cachexia.²⁹ Surgical resection remains the only curative treatment option and disease should ideally be diagnosed in the early stage. Investigation for biliary tract malignancy requires high clinical suspicion taking into account predisposing risk factors and laboratory, endoscopic, and imaging findings. Accurate radiological staging is paramount to identify patients suitable for surgical resection. Of particular importance is preoperative assessment of vascular and biliary structures to guide surgery.

Prognosis is poor with a 5-year survival of less than 5% in unresectable disease and survival still only 20 to 35% after surgery with curative intent and negative resection margins. A substantial proportion, approximately 40 to 50% of tumors,

Table 3 Suggested reporting template for gallbladder cancer

Site, size, and morphology of mass lesion
Enhancement pattern (e.g., from arterial phase and persists on portal venous and delayed)
Hepatic involvement—direct invasion and segments involved
Biliary duct involvement—site, length of involvement
Any variant biliary anatomy
Vascular involvement—main portal vein/left portal vein/right portal vein, hepatic artery proper/right hepatic artery/left hepatic artery
Any variant vascular anatomy
Local organ involvement—duodenum, colon, stomach, pancreas, diaphragm
Peritoneal spread—assess the hepatoduodenal ligament, lesser and greater omentum
Lymph nodes—size and location: regional vs non regional nodes
Distant metastasis—e.g., lung, bone, adrenals

initially deemed resectable at imaging, is surgically explored at staging laparoscopy and found to be unresectable despite thorough preoperative work up. Tumor recurrence rates are also high at 50 to 75% in the first 5 years of follow-up.^{33,34}

Classification of Cholangiocarcinoma by Location

Cholangiocarcinoma can be classified according to anatomical site of origin and according to morphological features.

Broadly, cholangiocarcinomas are intrahepatic or extrahepatic. Intrahepatic tumors constitute 10%, defined as tumors arising beyond the second order biliary ducts. Extrahepatic tumors constitute 90% and are further divided into distal and perihilar cholangiocarcinoma. Distal tumors constitute 20% and arise distal to the cystic duct insertion and up to the ampulla of Vater.³⁵ Perihilar constitute 70% and are anatomically defined as tumors arising between the second order biliary ducts and proximal to the insertion of the cystic duct. Perihilar tumors are further subtyped into four types by the Bismuth-Corlette classification according to anatomical extent and biliary duct infiltration. Type 1 involves the common hepatic duct below the confluence of hepatic ducts, type 2 involves the confluence of the left and right hepatic ducts, type 3a involves the main confluence and the bifurcation of the right hepatic duct, type 3b involves the main confluence and the bifurcation of left hepatic duct, and type 4 is either involvement of the main confluence and both right

and left hepatic ducts or multicentric tumors (→Fig. 7). The extent of tumor involvement is best assessed by MRCP and helps to determine preoperative resectability and extent of resection according to local tumor spread.³⁶

Morphological Growth Patterns of Cholangiocarcinoma

The Liver Cancer Study Group of Japan classifies cholangiocarcinoma according to three morphological growth patterns: mass-forming, periductal infiltrating, and intraductal growth. Each of these types may coexist.³⁷

Mass-forming cholangiocarcinomas account for 78% of intrahepatic cholangiocarcinoma and are usually large at presentation and of heterogenous composition due to varying degrees of central fibrosis.³⁸ Enhancement is typically peripheral on arterial phase followed by progressive central enhancement from portal venous to delayed phase. The degree of enhancement depends on the fibrous stromal content. Tumors with higher cellular components tend to enhance more in arterial phase and are associated with better prognosis than more fibrotic tumors that tend to enhance more in delayed phase.³⁹ More central lesions tend to cause biliary obstruction distally, while peripheral lesions near the hepatic capsule may cause capsular retraction (→Fig. 8). Satellite nodules adjacent to the main tumor are a common finding in 25 to 50% of cases as portal vein

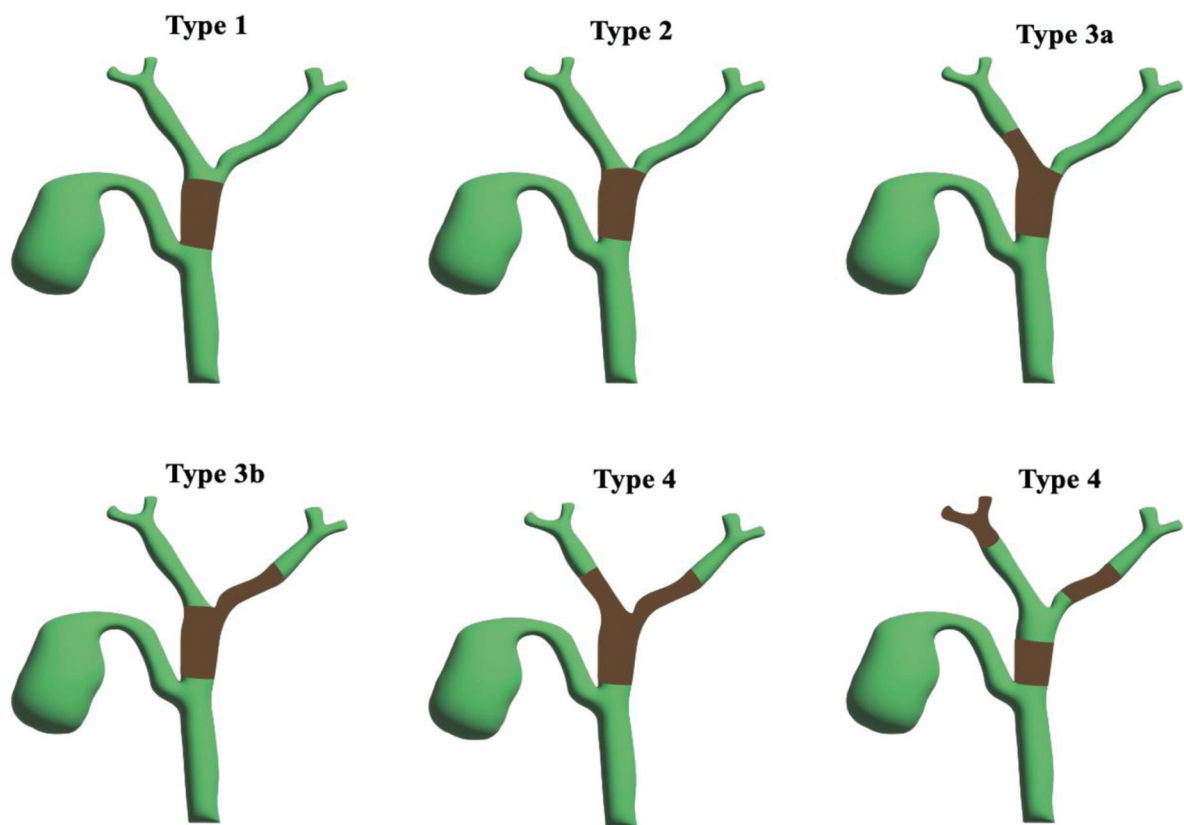


Fig. 7 The Bismuth-Corlette classification of perihilar tumors. Type 1 is tumor below the confluence of the right and left hepatic ducts. Type 2 is tumor involving the confluence of the right and left hepatic ducts. Type 3a is tumor involving the confluence and right hepatic duct. Type 3b is tumor involving the confluence and left hepatic duct. Type 4 is tumor involving the confluence and both right and left hepatic ducts or multicentric tumors.

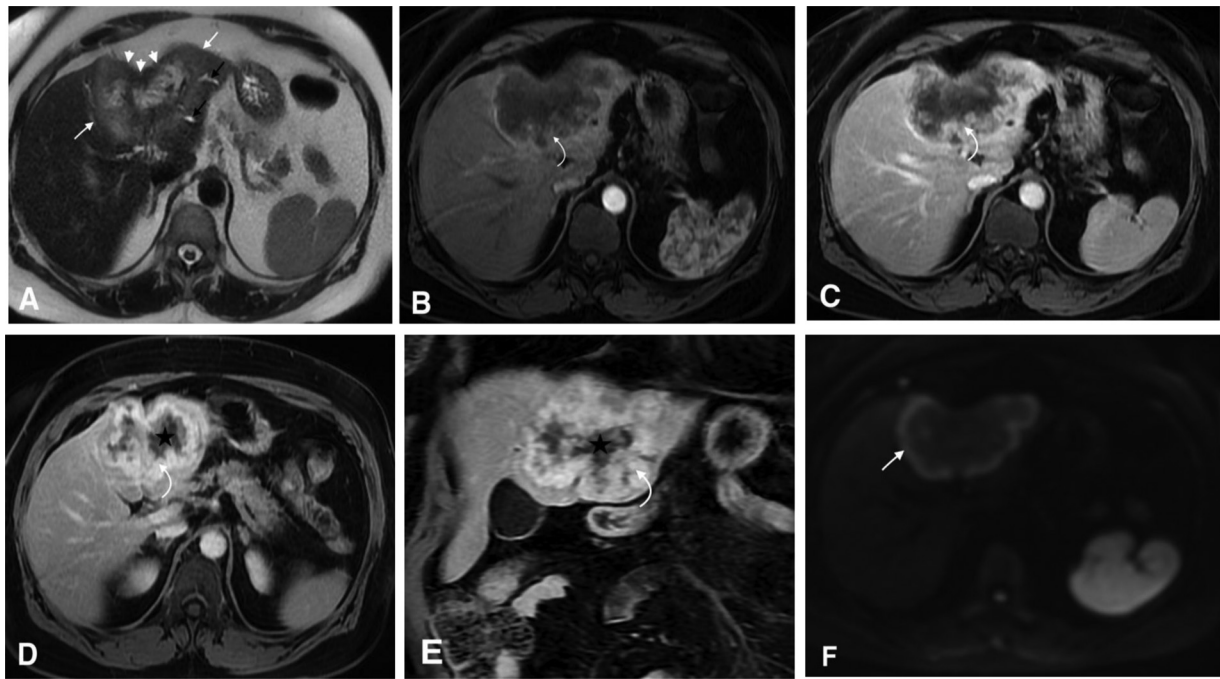


Fig. 8 Magnetic resonance imaging showing imaging features of mass-forming intrahepatic cholangiocarcinoma. (A) Axial T2 image of the large mass lesion of heterogenous iso/hyperintense signal (white arrows), capsular retraction (arrowheads) and dilated bile ducts peripheral to the mass (black arrows). (B and C) Progressive enhancement during arterial and portal venous phases (curved arrows). (D and E) 10-minute delayed phase images in axial and coronal showing marked enhancement (no contrast wash out) (curved arrows) except for the central most component containing fibrous stroma (star). (F) Diffusion-weighted imaging showing diffusion restriction in the peripheral portions of the mass in areas of higher cellularity (arrow).

branches are commonly invaded. Prognosis is poor due to the tendency to invade hepatic parenchyma and the portal vein.⁴⁰ Imaging features may overlap with other benign and malignant lesions. Hepatocellular carcinoma (HCC) is the main differential and enhancement characteristics are key to differentiation. HCC typically demonstrates arterial phase enhancement followed by rapid contrast wash out and may have a peripheral enhancing capsule on delayed phase contrary to the progressive central enhancement seen in cholangiocarcinoma^{41,42} (► Fig. 9).

Periductal infiltrating type is the most common type of hilar/perihilar cholangiocarcinoma and is associated with the worst prognosis. Extension typically occurs longitudinally along bile ducts causing thickening followed by stenosis of affected ducts and dilatation of ducts beyond the tumor (► Fig. 10). Propensity for extension into the submucosal layer and spread into perineural tissue and lymphatics towards the porta hepatis means extent of biliary involvement is frequently underestimated and difficult to determine on imaging alone.⁴³ Early-stage disease can be difficult to differentiate from benign strictures. Features favoring malignant strictures include long segment stricturing, duct thickening over 3mm, irregular and asymmetric bile duct luminal narrowing, prominent post contrast enhancement, presence of soft tissue, and locoregional lymphadenopathy.⁴⁴

Intraductal growth pattern may be difficult to detect on imaging. When visible, it appears as a small polypoid tumor or sometimes as multiple lesions within a segmental or diffusely dilated bile duct. Lesions are typically slow growing

and associated with the best prognosis as extension occurs superficially along mucosal surfaces without extension into the submucosal layer so there is higher likelihood of achieving tumor free resection margins.⁴⁵ The main differential is an intraductal stone and this can be differentiated on contrast sequences. Intraductal tumors demonstrate enhancement and asymmetric bile duct wall thickening, while stones demonstrate neither. ► Table 4 outlines the growth types, common differential diagnoses, and imaging features that can help to differentiate benign from malignant disease.

Imaging of Cholangiocarcinoma

Given the heterogenous nature of cholangiocarcinoma, imaging features vary greatly according to anatomical location and morphological growth pattern. Alongside characterization of the primary tumor, it is important to establish presence of satellite nodules, extent of bile duct involvement, involvement of hepatic vasculature, and nodal and distant metastasis. A combination of imaging modalities is used in the workup including US, EUS, CT, MRI with MRCP, and PET/CT. Percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) may be used for diagnostic and/or therapeutic purposes.

Ultrasound

US is the initial modality used for investigating right upper quadrant pain or jaundice and its primary role is in excluding benign causes of obstructive jaundice. Appearances of cholangiocarcinoma vary and US can identify the presence of

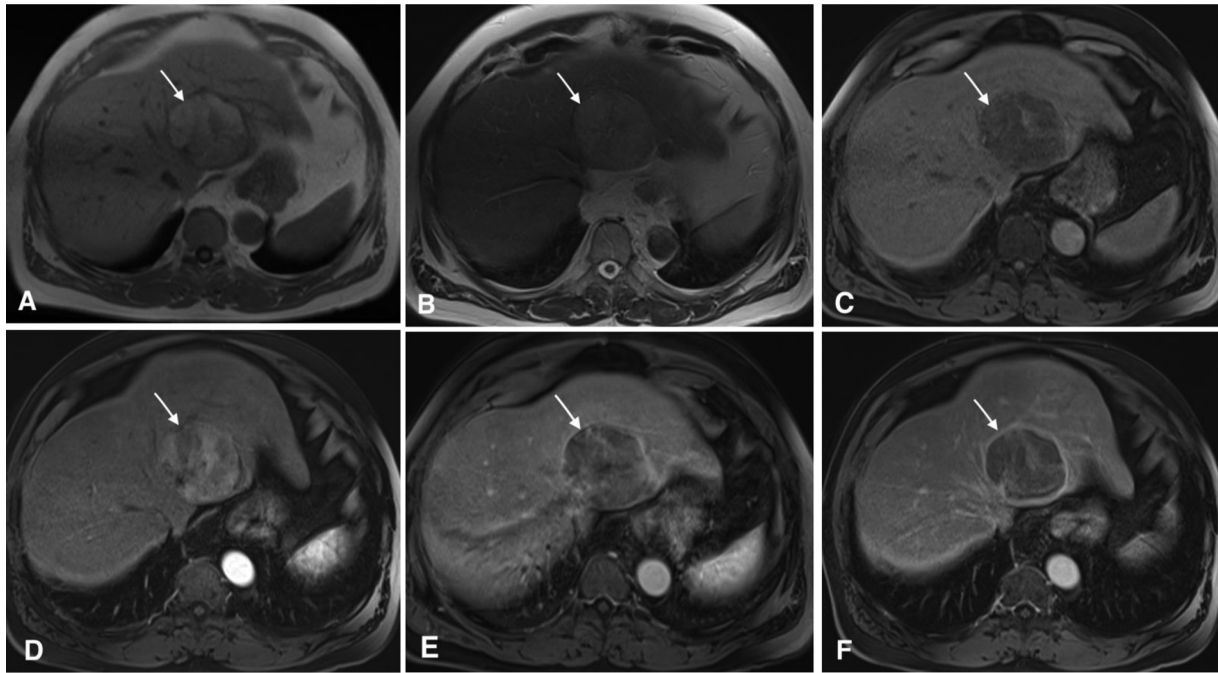


Fig. 9 Magnetic resonance imaging showing imaging features of hepatocellular carcinoma, one of the main differentials of mass-forming cholangiocarcinoma. Enhancement characteristics are key to differentiating between the two on imaging. (A and B) Axial T1 and T2 images showing a well-defined isointense lesion. (C–F) T1 precontrast, arterial, portal venous, and delayed images, respectively. There is arterial phase enhancement with rapid wash out on portal venous phase and a peripheral enhancing capsule on delayed phase.

biliary obstruction caused by the tumor but is insufficient for staging tumors. US helps in guiding the next choice of imaging modality.

Mass-forming tumors most commonly appear as irregular, well-defined, intermediate echogenic lesions with a hypoechogenic periphery of compressed hepatic parenchyma. If peripherally located, there may be capsular retraction due to fibrosis (→ Fig. 11). Periductal infiltrating tumors may not be directly discernible, but typically alter bile duct caliber causing stricturing at the level and dilatation distally (→ Fig. 12). Intraductal growth tumors typically alter bile duct caliber and if visualized are usually a hyperechogenic mass within the lumen.⁴⁶

EUS with FNA can be used to sample perihilar or distal lesions and suspicious lymph nodes and can diagnose peri-

hilar cholangiocarcinoma to an accuracy of 60 to 89%, although there is potential for peritoneal tumor seeding.⁴⁷

Computed Tomography

Multiphase imaging protocols allow characterization of cholangiocarcinoma and depict tumors in relation to major vasculature and bile ducts. The differential is wide for mass-forming intrahepatic cholangiocarcinoma and assessment of enhancement patterns on multiphase sequences is key to steering the diagnosis.

Imaging protocols involve at least triple phase imaging: arterial phase (25–30 seconds), portal venous phase (60–70 seconds), and a delayed phase (usually 3–10 minutes). The arterial phase demonstrates the hepatic artery and can be scrutinized closely in this phase, as well presence of variant

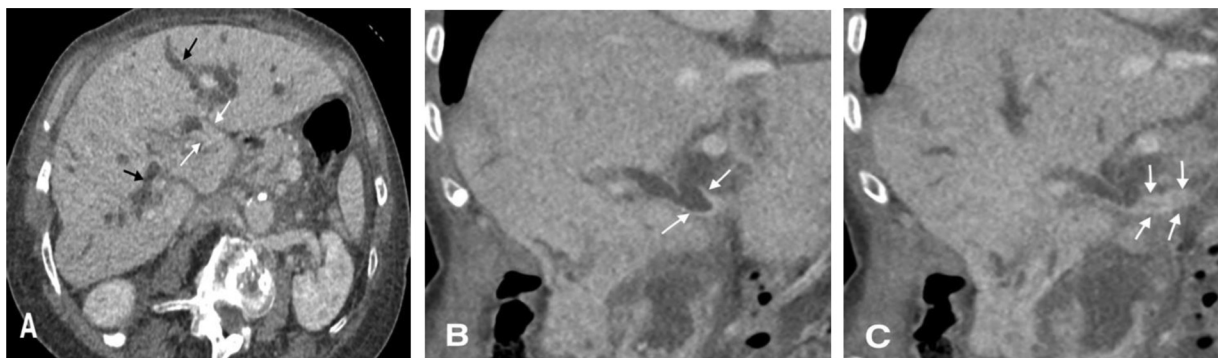


Fig. 10 Computed tomography showing periductal infiltrating perihilar cholangiocarcinoma. (A) Axial image showing thickening, enhancement, and luminal narrowing of the common hepatic bile duct (white arrow) causing intrahepatic bile duct dilatation (black arrows). (B and C) Coronal images showing the extent of bile duct affected.

Table 4 Differential diagnoses to consider according to the growth types of cholangiocarcinoma

Growth types of cholangiocarcinoma	Differential diagnosis	Imaging features favoring malignancy
Mass-forming	<ul style="list-style-type: none"> • HCC • Hepatic metastasis • Hepatic abscess • IgG4 inflammatory pseudotumor 	The differential is wide and key to differentiation are differences in enhancement patterns. Often biopsy is required to confirm diagnosis
Periductal infiltrating	Benign strictures: <ul style="list-style-type: none"> • PSC • Pyogenic cholangitis • IgG4 related sclerosing cholangitis • AIDS-related cholangitis • Iatrogenic 	<ul style="list-style-type: none"> • Long segment stricture • Bile duct thickening >3mm • Irregular and asymmetric bile duct luminal narrowing • Marked ductal enhancement • Soft tissue periductal lesion • Presence of nodal or distant metastasis
Intraductal growth	<ul style="list-style-type: none"> • Intraductal stones: hepatolithiasis/ choledocholithiasis 	<ul style="list-style-type: none"> • Enhancement on postcontrast sequences • Asymmetric wall thickening of the bile duct at that level

Abbreviations: AIDS, acquired immunodeficiency syndrome; HCC, hepatocellular carcinoma; IgG4, immunoglobulin G4; PSC, primary sclerosing cholangitis.



Fig. 11 Ultrasound showing a large mass-forming intrahepatic lesion centered in the left lobe and segment 4 (arrows). The lesion is predominantly intermediate echogenicity with central hypoechogenicity and is causing capsular retraction.

arterial anatomy. The portal venous phase is important to demonstrate the primary tumor size, site and morphology, involvement of the portal vein and its branches, presence of satellite nodules, involvement of the liver and extrahepatic spread to nodes, neighboring organs, peritoneum, and distant organs. The delayed phase completes assessment of enhancement characteristics as intrahepatic or hilar cholangiocarcinoma typically demonstrates late enhancement and the degree of enhancement depends on the fibrous stromal content.⁴⁸

CT has an accuracy of 60 to 88% for predicting resectability in mass-forming cholangiocarcinoma. Essential for preoperative planning is evaluation of tumor relation to major vasculature. Multiphase protocols allow evaluation of involvement of the portal vein with sensitivity of 89% and specificity of 92% and hepatic artery involvement with sensitivity of 84% and specificity of 93%. Vascular invasion is either visualized directly, or implied by segmental or lobar hepatic atrophy.^{49,50} However, CT accuracy for nodal and distant metastasis is low with sensitivity and specificity of

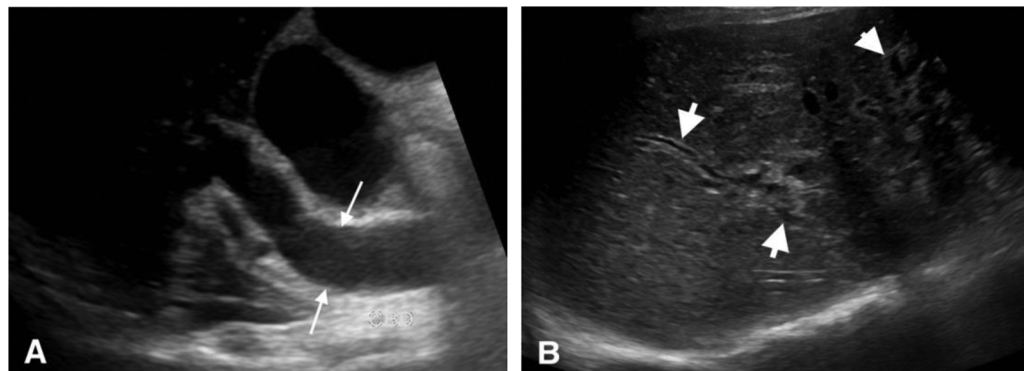


Fig. 12 Ultrasound showing dilated biliary ducts as a result of malignant biliary obstruction caused by cholangiocarcinoma (lesion not depicted). (A) Dilated common bile duct measuring 2 cm (arrows). (B) Dilated intrahepatic biliary ducts (arrowheads).

60.9 and 88%, respectively, for nodal disease and sensitivity and specificity of 67% and 94%, respectively, for distant metastasis. Therefore, patients with potentially surgically resectable disease may undergo PET/CT to characterize indeterminate lesions and detect occult sites of nodal or distant metastasis as part of the preoperative work up.⁵⁰

Magnetic Resonance Imaging

MRI and MRCP are used in combination to assess cholangiocarcinoma. MRI has accuracy of 77.8% similar to CT in predicting surgical resectability and in predicting biliary, hepatic artery, portal vein involvement all to an accuracy of over 82% and predicts lymph node metastasis to an accuracy of 74%.⁵¹

CT may underestimate extent of bile duct involvement and MRI with MRCP is often used to better depict and characterize extent of the involved bile ducts.⁵² MRCP provides the best noninvasive demonstration of the bile ducts, allowing for longitudinal extent of biliary involvement and visualization of bile duct variants, important in preoperative planning. Longitudinal extent of disease can be assessed, especially important in perihilar tumors, and MRCP can be used to subtype perihilar types according to the Bismuth-Corlette classification with an accuracy of 84%.⁵³ Both periductal infiltrating and intraductal growth types are best appreciated on MRCP and the use of MRI/MRCP has higher diagnostic accuracy compared to CT, which is able to better visualize small lesions. Enhancement typically begins in early phase with progressive and maximal enhancement on delayed phases.⁵⁴

MRCP sequences for evaluation of cholangiocarcinoma vary, but at minimum include a heavily T2-weighted sequence, a maximum intensity projection and thin three-dimensional volume rendered images to optimize visualization of the biliary tract while suppressing background signal. This allows smaller lesions and strictures along bile ducts to be demonstrated with greater sensitivity compared to CT (► Fig. 13). MRI protocols typically involve T1 and T2 signal-

weighted sequences, dynamic contrast enhancement sequences (usually arterial, portal venous and delayed phases at different intervals), and diffusion weighted imaging. Some institutions use hepatocyte-specific contrast agents and studies have suggested the use of such agents may allow more accurate assessment of disease extent, as marked enhancement of hepatic parenchyma in the hepatobiliary phase improves detection of satellite nodules and hepatic metastases, thereby aiding management and prediction of prognosis.⁵⁵

Positron Emission Tomography/Computed Tomography

PET/CT can be used to detect primary tumors with overall sensitivity and specificity of 81 and 82%. Higher detection rates are found in mass-forming intrahepatic tumors as such tumors are usually larger and are therefore more easily detected, in comparison to infiltrative lesions that spread along the duct and appear as streak-like uptake.⁵⁶

Rather than staging the primary tumor, the usefulness of PET/CT lies in determining N and M stage disease. Indeterminate or occult lesions can be characterized, resulting in an impact on clinical management in about a quarter to a third of patients. PET/CT has higher accuracy than CT in determining nodal metastasis (75.9 vs. 60.9%) and distant metastasis (88.3 vs. 78.7%).⁵⁷

Recognized false-positives are concurrent biliary duct inflammation, such as from biliary sepsis, PSC, following invasive procedures from biliary stent insertion or following chemotherapy treatment (► Fig. 14). False-negatives include limited detection of smaller malignant lesions measuring less than 1 cm and tumors with relatively high mucinous content.⁵⁸

PET/CT can be helpful in monitoring treatment response, as metabolic changes may precede anatomical changes and is helpful in detecting disease recurrence in cases of rising tumor markers when conventional imaging such as CT or MRI are negative. Detection of disease recurrence using PET/CT has a sensitivity of 94% and specificity of 100% compared to CT sensitivity of 82% and specificity of 43%.⁵⁹

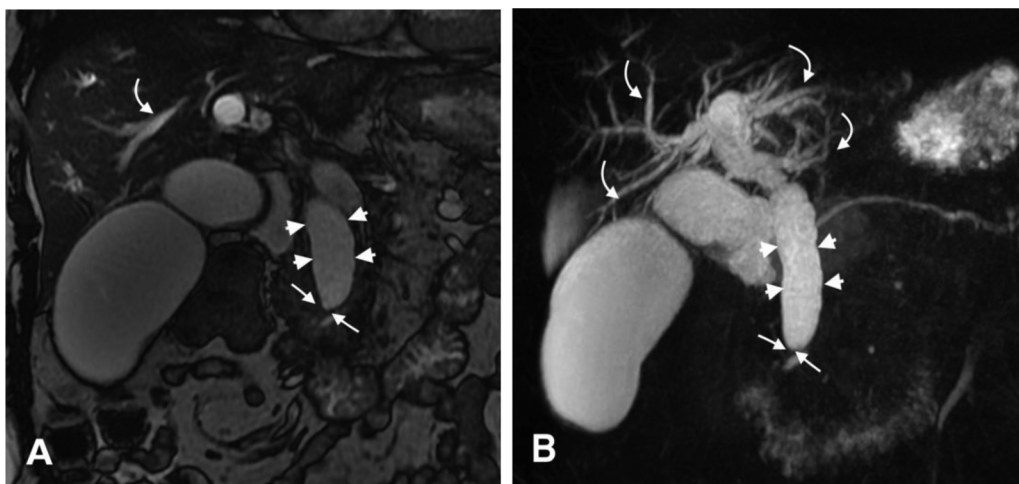


Fig. 13 MRCP showing distal cholangiocarcinoma. (A and B) Coronal T2 and three-dimensional maximum intensity projection images showing a distal common bile duct (CBD) stricture (arrows) causing abrupt caliber change and dilatation of the CBD (arrowheads) and intrahepatic bile duct dilatation (curved arrows).

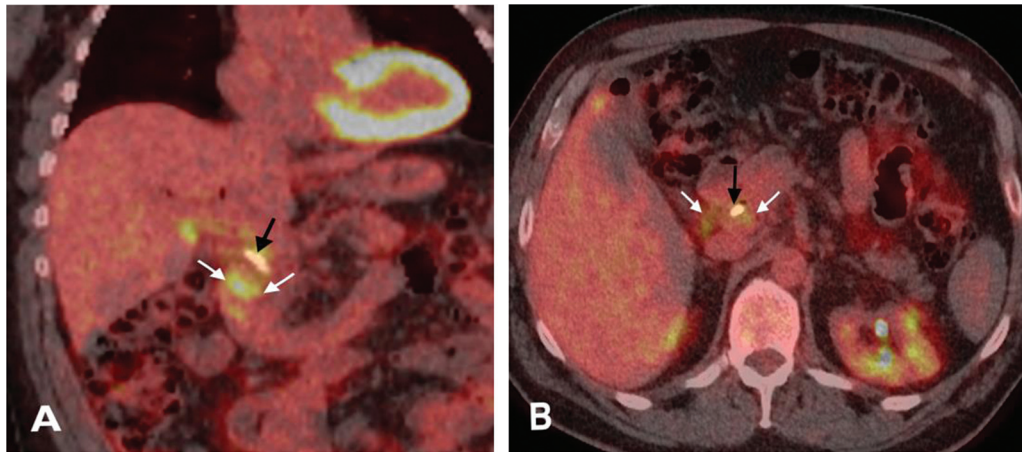


Fig. 14 Positron emission tomography/computed tomography (PET/CT) showing distal cholangiocarcinoma and a common bile duct (CBD) stent in situ. (A and B) Coronal and axial images showing a CBD stent in situ (black arrows) and fluorodeoxyglucose (FDG) uptake around the stent and CBD (white arrows). PET/CT may not reliably distinguish between inflammatory and malignant FDG uptake and in this case there was uptake from concurrent biliary duct inflammation from stent insertion.

Cholangiography

Cholangiography involves injecting contrast directly into bile ducts to depict the biliary tree and level of biliary obstruction as a result of disease. Approach to cholangiography is guided by the level of biliary obstruction and can include an antegrade approach such as PTC or a retrograde approach through ERCP. Such techniques are both diagnostic and therapeutic, but are mainly used for palliative therapeutic purposes rather than for diagnosis, as MRCP is a proven better substitute. Stents can be inserted to relieve biliary obstruction and samples taken for histology at areas of concern such as stricturing or irregular caliber bile ducts. Such techniques are invasive and associated with significant morbidity and mortality with complications including, cholangitis, hemorrhage, and stent blockage.⁶⁰

Determining Preoperative Resectability

Surgery is the cornerstone curative treatment option, yet cholangiocarcinoma remains a difficult tumor to accurately stage and treat. The goal of surgery is to achieve tumor resection with R0 resection margins, yet ensure enough normal hepatic parenchyma remains to maintain physiological function. Future liver remnant (FLR) volume can be calculated and this typically requires at least two hepatic segments or 25% of normal parenchyma, 40% if the liver is cirrhotic. If FLR is inadequate, selective portal vein branches can embolized to encourage remnant liver proliferation. Tumor resection with R0 margins becomes unlikely in the presence of bilateral arterial or portal vein invasion, lobar atrophy with contralateral vascular invasion, lobar atrophy with contralateral second-order bile duct involvement, distant metastasis and distant nodal metastases (paracaval, para-aortic and coeliac). Adjacent hepatic parenchymal involvement is usually not a criterion for unresectability, as radical surgery with extended hepatectomies can be performed as long as FLR is sufficient.^{61,62}

Table 5 Suggested reporting template for cholangiocarcinoma

Site (intrahepatic/perihilar/distal), size and number (if >1 lesion) of lesion
Morphology of tumor (mass-forming, periductal infiltrating or intraductal growth)
Enhancement pattern in arterial phase, portal venous phase and incremental delayed phases
Bile duct involvement—site, length of involvement including Bismuth-Corlette classification if perihilar
Vascular involvement—main portal vein, hepatic artery and branches
Hepatic involvement—direct involvement if mass-forming including segments involved
Segmental hepatic atrophy—(include calculation of FLR)
Any variant vascular or biliary anatomy
Local organ involvement
Peritoneal spread
Lymph nodes—size and location: local vs distant nodes
Distant metastasis—e.g., lung, bone, adrenals

Abbreviation: FLR, future liver remnant.

Structuring Radiology Reports for Cholangiocarcinoma

With the various imaging modalities available and selected according to clinical need, it is essential that radiologists include pertinent information in reports as this will guide management particularly in patients being considered for surgical resection. ► **Table 5** details a suggested reporting template for cholangiocarcinoma.

Conclusion

Patients with biliary tract malignancy continue to suffer poor prognosis due to the diverse nature of disease together with the nonspecific and often late clinical presentation. Surgical

resection remains the cornerstone of curative treatment yet the majority of patients have unresectable disease at presentation. Radiologists are paramount in guiding appropriate clinical management and ought to be familiar with the variable presentation of this heterogeneous malignancy.

Conflict of Interest

None declared.

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