Biliary tract neoplasms: diagnosis and staging

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Abstract
Most biliary tract neoplasms are malignant and have been traditionally divided into cancers of the gallbladder, the extrahepatic bile ducts, and ampulla of Vater. Although infrequent, bile duct carcinomas and cancer of the gallbladder are not rare. In the United States, an estimated 6000–7000 new cases of carcinoma of the gallbladder and 3000–4000 new cases of carcinoma of the bile ducts are diagnosed annually. Familiarity with the imaging characteristics of gallbladder and bile duct neoplasms is important to expedite the diagnosis and appropriate treatment of patients who often present with non-specific symptoms of right upper quadrant pain, jaundice, and weight loss.

Keywords: Gallbladder cancer; cholangiocarcinoma; MRCP; ERCP; MDCT; MRI; Ultrasound.

Introduction
Most biliary tract neoplasms are malignant and have been traditionally divided into cancers of the gallbladder, the extrahepatic bile ducts, and ampulla of Vater. Although infrequent, bile duct carcinomas and cancer of the gallbladder are not rare. In the United States, an estimated 6000–7000 new cases of carcinoma of the gallbladder and 3000–4000 new cases of carcinoma of the bile ducts are diagnosed annually. Familiarity with the imaging characteristics of gallbladder and bile duct neoplasms is important to expedite the diagnosis and appropriate treatment of patients who often present with non-specific symptoms of right upper quadrant pain, jaundice, and weight loss.

Gallbladder carcinoma

Clinical features
Carcinoma of the gallbladder is the fifth most common malignancy of the gastrointestinal tract and is found incidentally in 1–3% of cholecystectomy specimens and 0.5–7.4% of autopsies. Risk factors for this neoplasm include gallstones and a history of chronic cholecystitis and an estimated 22% of patients with porcelain gallbladder will develop carcinoma. Others risk factors include choledochal cysts, anomalous pancreatico-biliary duct junctions, and gallbladder polyps >1 cm in size. Gallbladder carcinoma has a peak incidence in the sixth and seventh decades of life, and is three to five times more predominant in females. Israelis, Japanese, Native Americans, Spanish Americans in the southwest United States, and Eskimos have an increased risk for developing this cancer.

Early diagnosis of gallbladder carcinoma is difficult because most patients present with non-specific findings of right upper quadrant pain, malaise, weight loss, jaundice, anorexia, and vomiting. This presentation is often confused with symptomatic cholelithiasis or chronic cholecystitis. At the time of diagnosis, most patients are considered unresectable because of direct extension into adjacent organs, local lymph node metastases, or distant metastatic disease. The 5-year survival rate for this tumor is less than 5%.

Pathologic features
As in the stomach and colon, there appears to be a metaplasia—dysplasia—carcinoma sequence in the development of most invasive carcinomas of the gallbladder. Adenocarcinomas are divided into infiltrative (65%),
Papillary (15%) (Fig. 1), and colloid (10%) subtypes and these gross pathologic divisions do influence outcome[3,4]. Papillary tumors typically are not associated with gallstones and are less likely to invade the liver and metastasize to lymph nodes. Infiltrative forms, which are strongly associated with gallstones, are more likely to infiltrate early, obliterate the gallbladder, invade the liver, and metastasize to lymph nodes. Nearly 60% of carcinomas originate in the fundus, 30% in the body, and 10% in the neck[3,4]. In some cases, the tumor may diffusely infiltrate the entire gallbladder, making its origin impossible to identify.

**Tumor staging**

The gallbladder has unique anatomic features that are conducive to direct invasion of surrounding structures. The gallbladder wall consists of a mucosa, a lamina propria, a smooth muscle layer, perimuscular connective tissue, and serosa without a submucosa. Also, no serosa exists at the attachment to the liver and along the hepatic surface. The connective tissue is continuous with the interlobular connective tissue of the liver[9–13].

Gallbladder carcinoma has been traditionally staged according to the American Joint Committee on Cancer (AJCC) (Tables 1 and 2). An alternative and commonly used system is the Nevin classification which includes five stages (Table 3). Survival is directly related to stage in both classification systems. The degree of invasion is also highly predictive of survival and success of operative management[9–13].

**Imaging features**

Ultrasound, computed tomography (CT), and magnetic resonance (MR) are the primary means of imaging gallbladder carcinoma[14–21]. This neoplasm has three major patterns of presentation pathologically and on cross-sectional imaging: focal or diffuse mural thickening; an intraluminal polypoid mass, usually larger than 2 cm.

**Figure 1** Gallbladder cancer: pathologic features. Surgical specimen shows frond-like mass in the gallbladder fundus (arrow).

**Table 1** Definition of TNM in current AJCC gallbladder carcinoma staging

| Stage | Definition |
|-------|------------|
| TX    | Primary tumor cannot be assessed |
| T0    | No evidence of primary tumor |
| Tis   | Carcinoma in situ |
| T1    | Tumor invades lamina propria (T1a) or muscle layer (T1b) |
| T2    | Tumor invades perimuscular connective tissue, no extension beyond serosa or into liver |
| T3    | Tumor perforates the serosa (visceral peritoneum) or directly invades one adjacent organ, or both (extension 2 cm or less into liver) |
| T4    | Tumor extends more than 2 cm into liver, or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of liver) |

| Stage | Grouping |
|-------|----------|
| 0     | Tis N0 M0 |
| 1     | T1 N0 M0 |
| 2     | T2 N0 M0 |
| 3     | T1 N1 M0 |
| 4a    | T4 N0 M0 |
| 4b    | Any T N2 M0 |

**Table 2** Stage grouping in current AJCC gallbladder carcinoma staging

| Stage | Grouping |
|-------|----------|
| In situ carcinoma |
| Mucosal or muscular invasion |
| Transmural direct liver invasion |
| Lymph node metastasis |
| Distant metastasis |

**Table 3** Modified Nevin staging for gallbladder carcinoma

| Stage | Description |
|-------|-------------|
| 1     | In situ carcinoma |
| 2     | Mucosal or muscular invasion |
| 3     | Transmural direct liver invasion |
| 4     | Lymph node metastasis |
| 5     | Distant metastasis |
originating in the gallbladder wall; and most commonly a subhepatic mass replacing or obscuring the gallbladder, often invading adjacent liver\(^8,9\).

**Carcinoma with mural thickening**

Gallbladder carcinoma presenting with focal or diffuse mural thickening is the least common presentation and the most difficult to diagnose. Normally the gallbladder wall is 3 mm or less in thickness and carcinomas that are confined to the mucosa or slightly raised lesions may not be visualized sonographically. The diagnosis may be difficult because of the small size of early masses and the subtle wall thickening associated with cancer can be obscured by gallstones. In addition, diffuse wall thickening is more commonly caused by acute and chronic cholecystitis, adenomyomatosis, inadequate gallbladder distention, hepatitis, low protein states, and other causes\(^19,20\).

Although CT is inferior to ultrasound in depicting mucosal irregularity, mural thickening, and cholelithiasis, it is superior for evaluating the thickness of portions of the gallbladder wall that are obscured by gallstones or mural calcification on ultrasound. CT may show focal or irregular mural thickening; in these cases, the images should be carefully inspected for bile duct dilation, local invasion, metastases, and adenopathy\(^15,16\). On MR, the primary tumor and metastatic lesions have slightly higher signal intensity on T2-weighted images\(^17\).

**Carcinoma as a polypoid mass**

Approximately 25\% of gallbladder carcinomas present as intraluminal masses. It is important to recognize this appearance because these polypoid lesions tend to be well differentiated and confined by the muscularis propria and thus have a better prognosis at the time of diagnosis\(^2\)-\(^5\).

Sonographically, polypoid carcinomas typically have a homogeneous tissue texture, are fixed to the gallbladder wall at their base, and do not cast an acoustic shadow. Gallstones are often present and the gallbladder may be normal in size or expanded by the mass, which can be hyperechoic, isoechoic, or hypoechoic relative to the liver.

A small polypoid carcinoma can be difficult to differentiate from a cholesterol polyp, adenoma, or adherent stone. Benign polyps typically are less than 1 cm in size; if a polyp is greater than 1 cm in diameter and not clearly benign, a cholecystectomy should be considered. Tumefactive sludge or blood clot can simulate a polypoid carcinoma. Change in the appearance with positional maneuvers indicates blood or sludge, whereas color flow within the abnormality suggests a mass\(^18,19\).

On CT and MR, polypoid cancers enhance homogeneously after administration of contrast medium, and the adjacent gallbladder wall may be thickened. Polypoid gallbladder carcinomas do not usually show necrosis or calcification on CT\(^16\)-\(^19\).

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**Figure 2** Gallbladder cancer presenting as a gallbladder fossa mass. Coronal reformatted CT scan shows mural thickening of the gallbladder associated with intraluminal gallstones and invasion of the adjacent liver (arrow) and pericholecystic fat.

**Carcinoma as a gallbladder fossa mass**

This is the most common form of gallbladder cancer (Fig. 2) and presents as a solid mass with variable echogenicity that may be homogeneous or inhomogeneous. The mass may be difficult to separate from the liver sonographically, especially when there is direct hepatic invasion\(^2\)-\(^5\). The absence of a clearly distinct gallbladder and the presence of gallstones can be helpful clues to the diagnosis. Infiltrating carcinomas that replace the gallbladder often show irregular contrast enhancement with scattered regions of internal necrosis on CT and MR.

**Pathways of tumor spread**

Gallbladder carcinoma spreads beyond the wall (Fig. 3) by several routes: (1) direct invasion of the liver, duodenum, colon or the subperitoneal space of the hepatoduodenal ligament; (2) lymphatic spread to regional lymph nodes in the lesser omentum; (3) hematogenous spread to the liver; (4) intraductal tumor extension; and (5) metastasis to the peritoneum\(^12\). The resectability rates for gallbladder cancer range from 15\% to 30\%.

Tumor invasion of the liver may require resection of segments IV, V, and VI, the right lobe, or the right lobe plus a section of segment IV. Multiple bilateral liver, peritoneal or distant metastases are considered contraindications to resection of the primary tumor. Encasement or occlusion of the main portal vein or the left hepatic artery, if right lobectomy is required,
Precludes resection. Local invasion of the proximal transverse colon may require local colonic resection. Extension into the duodenum requires pancreaticoduodenectomy, provided that the portal vein is tumor free.

Prognosis

Prognosis in gallbladder cancer is poor due to the late stage of presentation in most patients. The overall 5-year survival is less than 5% with an overall mean survival of 6 months. Patient survival has been shown to correlate with both the initial stage of disease and the operative management approach.

Cholangiocarcinoma

Clinical features

Cholangiocarcinoma is the most common extrahepatic biliary tumor and the vast majority of these cancers are adenocarcinomas arising from the epithelium lining the bile ducts. The term cholangiocarcinoma includes intrahepatic, perihilar (Klatskin tumors), and distal extrahepatic tumors of the bile ducts (Fig. 4). Approximately two-thirds of cholangiocarcinomas are perihilar tumors, about one-quarter are distal extrahepatic tumors and the remainder are intrahepatic in location.

Cholangiocarcinomas arise slightly more often in men, with a male/female ratio of 1.3:1, with an average age between 50 and 70 years. Risk factors for this neoplasm include primary sclerosing cholangitis, choledochal cyst, Caroli’s disease, familial adenomatous polyposis, congenital hepatic fibrosis, hepatolithiasis, ulcerative colitis, prior biliary-enteric anastomosis, infection with parasites Clonorchis sinensis and Pisicoris viverrini, asbestosis, and exposure to dioxin, methyldopa and isoniazid.

The constellation of signs and symptoms associated with cholangiocarcinoma depends upon the location of the tumor, the degree of biliary obstruction and the extent of invasion. Patients with intrahepatic cholangiocarcinomas tend to have dull visceral abdominal pain, ipsilateral hepatic lobar atrophy, compensatory contralateral hepatic lobe hypertrophy.

The most common presenting symptoms in patients with hilar and extrahepatic cholangiocarcinomas include abdominal pain (40%), pruritis (20%), anorexia, nausea and vomiting. The patients also have jaundice (82%) often accompanied by acholic stools and bilirubinuria, weight loss (37%), hepatomegaly (26%), and rarely a palpable mass (9%).

Unfavorable prognostic factors in cholangiocarcinoma include: multifocal disease, liver capsule invasion, preoperative CA19-9 levels >1000 U/ml, lack of a tumor-free margin, lymph node involvement, expression of MUC1 by cholangiocarcinoma cells, and mass-forming or periductal-infiltrating type growth.

Pathologic features

Cholangiocarcinoma is a relatively slow growing, locally destructive, well to poorly differentiated tubular adenocarcinoma arising from malignant transformation of cholangiocytes. These neoplasms are divided into three types: (1) mass-forming, (2) periductal-infiltrating, causing stricture, and (3) intraductal-growing. Mass-forming intrahepatic cholangiocarcinoma produces a gray-yellow mass (Fig. 5) with frequent satellite nodules. Central necrosis and fibrosis are common. In the periductal-infiltrating type, the tumor grows along the bile duct wall, resulting in concentric mural thickening and proximal biliary dilation. A dense fibroblastic reaction may encase the adjacent hepatic artery or portal vein, which may render surgical resection difficult.

Intraductal-growing papillary cholangiocarcinoma is characterized by the presence of intraluminal papillary tumors of the intra- and/or extrahepatic bile ducts with partial obstruction and proximal biliary dilation. The tumors typically are small, but often spread superficially along the mucosal surface, resulting in multiple tumors along the adjacent segments of the bile ducts, or a tumor cast. Some papillary tumors of the bile...
ducts produce a large amount of mucin, and may impede the flow of bile juice. Mucin may obstruct the papilla of Vater so that the bile ducts both proximal and distal to the tumor are dilated\textsuperscript{12–61}.

The distinction of cholangiocarcinoma into extra- and intrahepatic origin is important in medical and surgical management and to growing evidence that these two types of cholangiocarcinomas may be caused by different pathogenetic mechanisms including discrete genetic and/or environmental triggers\textsuperscript{12–61}.

**Imaging features**

Ultrasound, CT, and MR are the primary means of non-invasively diagnosing and staging cholangiocarcinoma and these studies need to depict the overall extent of...
the tumor with particular attention to involvement of the bile ducts, liver, portal vessels, and for the detection of distant metastases[9,23–25].

**Intrahepatic type**

Intrahepatic cholangiocarcinomas typically present as a poorly marginated mass on cross sectional imaging studies. Sonographically, these masses may have mixed echogenicity or may be predominantly hypoechoic or hyperechoic. The sonographic findings depend upon the amount of fibrous tissue, mucin, and calcification present within the tumor[9,28].

Cholangiocarcinomas manifest as a hypodense mass on multidetector computed tomography (MDCT) that can be well defined or infiltrative without a capsule on non-contrast enhanced scans. Following the intravenous administration of contrast medium, the periphery of these masses, in which active tumor is present, may show brisk enhancement that rapidly becomes isodense or hypodense during the portal venous phase. Because cholangiocarcinomas contain fibrous tissue, the central area of the tumor does not enhance during the arterial or portal venous phase but becomes hyperdense during delayed images obtained 5–10 min after injection. The central portion of necrotic or mucin-producing tumors will remain hypodense. The dense fibrotic nature of the tumor often causes capsular retraction, seen in up to 21% of cases[9,15,16].

On MRI (see Fig. 5), intrahepatic cholangiocarcinomas manifest as non-encapsulated, poorly defined masses that are hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images. These tumors can have a central scar which may be either hypo- or hyperintense on T2-weighted images. The heterogeneous appearance of these lesions on T2-weighted images can be explained the low signal intensity of fibrous tissue and the higher signal intensity of mucous and myxoid degeneration. As with CT, the periphery of the lesion may show contrast enhancement early and the fibrous components of the centre of the tumor enhance late (see Fig. 5). Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) images may show displacement of bile ducts away from the intrahepatic cholangiocarcinoma, obstruction of an intrahepatic duct, or a polypoid mass in the intrahepatic ducts[18,26–28].

**Hilar type**

Cholangiocarcinomas most often occur at the confluence of the right and left bile ducts and the proximal common hepatic duct, so-called Klatskin tumors (Fig. 6). Depending upon the pattern of tumor growth and location, these tumors may present as an infiltrating mass, a region of ductal thickening, or an intraductal mass. Because they do not cause jaundice until the later

**Figure 6** Klatskin tumor: cholangiographic features. ERCP (a) and MRCP (b) images show a stenosis due to tumor at the confluence of the right and left intrahepatic ducts and proximal common hepatic duct (Bismuth Type IV). (c) Coronal reformatted MR image shows the mildly dilated intrahepatic ducts proximal to the tumor (arrow) and normal caliber bile duct distal to the tumor.
stages of disease, tumors that arise from the right or left hepatic ducts tend to be large and infiltrate the surrounding hepatic parenchyma\(^9,24\). Intrahepatic duct dilation and lobar or segmental atrophy of the hepatic parenchyma suggests the site of origin of the neoplasm. Patients with common hepatic and common bile duct cancers present earlier with painless, obstructive jaundice. These lesions are smaller and have a somewhat better prognosis. Cholangiocarcinomas within the substance of the porta hepatis and pancreatic parenchyma are often difficult to visualize on cross sectional imaging because the tumors may be isodense or isointense with normal adjacent structures.

Lesion detectability on ultrasound has been reported as high as 87% and portal venous involvement is correctly diagnosed in 87% of cases with color Doppler ultrasound\(^{15}\). Klatskin’s tumors present sonographically with: duct dilatation; isolation of the right and left bile duct segments; mass or bile duct wall thickening at the hepatic hilum; lobar atrophy with crowded, dilated bile ducts\(^9,15\).

The multiplanar reconstructive capabilities of MDCT provides a sensitive and accurate means of evaluating Klatskin’s tumors. On non-contrast enhanced scans, these tumors typically are hypodense compared to the liver. Enhancement patterns depend upon the tumor type and histology. Infiltrating tumors produce focal mural thickening with obliteration of the lumen. About 80% of these tumors show increased enhancement relative to the liver on arterial and/or portal phase venous phase images. Due to their sclerotic nature, most lesions show tumor enhancement 8–15 min after contrast medium injection\(^9,15,16,29,30\).

Cholangiocarcinomas are either isointense or low in signal intensity relative to the liver on T1-weighted images. On T2-weighted images, the tumor signal intensity ranges from markedly increased to mildly increased relative to liver. Tumors with high fibrous content tend to have lower signal intensity on T1-weighted images. Cholangiocarcinomas enhance to a moderate degree on gadolinium-enhanced T1-weighted MR images with contrast accumulation that increases with time\(^{15–18,35}\).

Lobar hepatic atrophy with marked dilatation and crowding of bile ducts is seen on CT and MR scans in approximately one-fourth of patients with hilar cholangiocarcinomas. The cholangiocarcinoma is often hilar with dominant involvement of the duct supplying the atrophied segment. Lobar atrophy with biliary dilatation strongly suggests cholangiocarcinoma, although longstanding biliary obstruction from surgical trauma or focal biliary obstruction can cause similar findings. The liver parenchyma and the subperitoneal spaces of the gastrohepatic and hepatoduodenal ligaments are commonly invaded by Klatskin’s tumors. Lymphatic metastases most commonly involve the porta caval, superior pancreaticoduodenal, and posterior pancreaticoduodenal lymph nodes. In advanced stages of hilar cholangiocarcinoma, retroperitoneal adenopathy, peritoneal carcinomatosis and proximal obstruction may occur\(^9\).

The extent of tumor in the bile duct is one of the most important factors that determine resectability. There is characteristic stenosis of the central, right, and left common hepatic ducts, with smooth shoulders or irregular tapering of ducts seen on cholangiography. These neoplastic strictures tend to branch and may extend into second-order biliary radicles\(^{22–81}\). Direct cholangiography is of limited value in assessing submucosally spreading tumor and in lesions that extend beyond the porta hepatis because of incomplete filling of bile ducts proximal to the tumor. A combination of MRCP and conventional MR imaging can provide complete tumor staging that assesses liver, portal node, and portal vein involvement\(^{15–18}\).

Hilar cholangiocarcinomas can usually be differentiated cholangiographically from hilar lymphadenopathy or benign stricture. Lymphadenopathy compresses and displaces rather than invades the extrahepatic ducts. Benign strictures occur after cholecystectomy or distal gastric surgery, are short and cause smooth, symmetric narrowing of the common hepatic bile duct. Rarely, lymphoma or sarcoidosis involve the bile ducts may be indistinguishable from cholangiocarcinoma\(^9,15,16\).

### Extrahepatic type

Carcinomas of the distal common hepatic or common bile duct are usually small and have a better prognosis than more central tumors. Extrahepatic cholangiocarcinomas are distributed as follows: 50–75% occur in the upper third, 10–30% in the middle third, and 10–20% in the lower third of the extrahepatic bile duct\(^{22–81}\). ERCP and MRCP usually demonstrate a short stricture or polyloid mass (Fig. 7) which usually causes biliary obstruction. CT and MR imaging can depict one of the following appearances: an obstructing nodular mass; concentric or asymmetric thickening of the bile duct wall with enhancement at the transition zone; or intraductal polyoid tumors with proximal biliary dilation. Direct invasion of adjacent periductal and lymph node metastasis are commonly seen in the subperitoneal space of the hepatoduodenal ligament. Cholangiocarcinomas that arise in the intrapancreatic portion of the common bile duct are well depicted as low signal intensity masses against the background of the high signal intensity head of the pancreas on T1-weighted fat-suppressed images.

Diagnosing cholangiocarcinoma is notoriously difficult in patients with sclerosing cholangitis, who are at great risk (10%) for developing this neoplasm\(^{13,61}\). The patient may have a dominant benign biliary stricture that may be difficult to differentiate from cholangiocarcinoma. Sudden and unexpected clinical deterioration associated with progressive elevation of alkaline phosphatase and serum CA19-9 values greater than 100 U/ml in the absence of bacterial cholangitis strongly suggest
cholangiocarcinoma complicating sclerosing cholangitis. On cross sectional imaging studies, it is often difficult to appreciate malignant degeneration in sclerosing cholangitis. Worrisome imaging findings include progression of strictures on serial cholangiograms, marked biliary dilatation above a dominant stricture, and a polypoid ductal mass ≥1 cm in diameter.

Periampullary tumors

Tumors that arise within 1 cm of the papilla of Vater are considered periampullary carcinomas and include ampullary, pancreatic, bile duct (Fig. 8), and duodenal cancers. It is often difficult to determine the exact organ of origin of these neoplasms pathologically. There is a high incidence of these tumors in patients with familial adenomatous polyposis, and cancer is often preceded by ampullary or duodenal adenomas. Periampullary neoplasms tend to be polypoid, have a lower grade, present earlier and as a consequence have a better prognosis than more proximal biliary neoplasms.

Periampullary tumors present with biliary dilatation extending to the level of the ampulla of Vater in 75% of cases and pancreatic ductal dilatation in 67% of patients. These masses tend to be small and may not be seen on CT scans, in which case abrupt termination of the common bile duct without mass may be seen cholangiographically. Occasionally a villous polypoid lesion may be seen in the distal common bile duct and duodenum. Liver metastases or lymphadenopathy is present at the time of diagnosis in only a small percentage of cases.

Periampullary tumors appear as a low signal intensity mass in the region of the ampulla on T1-weighted fatsuppressed MRI. Since these lesions are hypovascular, they have low signal intensity relative to adjacent normal pancreatic parenchyma on immediate postgadolinium T1-weighted images. A thin rim of peripheral enhancement is often found on 2 min postgadolinium fat suppressed images. MRCP is often instructive in helping determine the precise location and organ of origin of periampullary carcinomas.

Prognosis

Intrahepatic cholangiocarcinomas usually present at an advanced stage. In resectable patients (15–20% of the total) the 3-year survival is 45–60% with a median
survival of 18–30 months. For unresectable patients, the median survival is 7 months. Five-year survival for patients with perihilar cholangiocarcinoma varies between 7 and 15%[2,7,8].

The most favorable resectability rates (50%) have been reported for distal cholangiocarcinomas. When resectable, the mean survival is 24 months with a 5-year survival of 15–28% in patients with distal extrahepatic cholangiocarcinoma and 50–60% in patients with periampullary tumors[2,7,8].

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