Hepatobiliary and Pancreatic Malignancies: Epidemiology, Clinical Presentation, Diagnosis, and Staging

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Contents

1.1 Introduction

Hepatobiliary and pancreatic malignancies constitute a diverse range of disease processes, each with its own pathogenesis, presentation, and staging. This chapter will summarize the epidemiology, clinical presentation, diagnosis, and staging of hepatocellular carcinoma, carcinoma of the gall bladder and bile ducts, and pancreatic cancer.

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1.2 Hepatocellular Carcinoma

1.2.1 Epidemiology and Etiology

Worldwide, hepatocellular carcinoma (HCC) is the fifth and seventh most common cancer in adult men and women, respectively. It also constitutes the second leading cause of cancer-related deaths in men and the sixth leading cause of cancer-related deaths in women [1].

In the majority of patients, HCC occurs in the setting of chronic liver disease. Nearly 80% of cases are due to underlying chronic hepatitis B and C infection [2] although cirrhosis of almost any cause is known to predispose to HCC.

Men are more likely to develop HCC as compared to women [1] with a mean age at presentation of 50–60 years [3, 4].

The various etiological factors of HCC are listed in Table 1.1.

1.2.2 Clinical Presentation

Patients with HCC usually present in advanced stages of the disease because of the absence of pathognomonic symptoms [5, 6]. The median survival following diagnosis is approximately 6–20 months [7].

Patients are largely asymptomatic, apart from symptoms of existing chronic liver disease. A diagnosis of HCC should be suspected in situations of recent onset hepatic decompensation in a patient with compensated chronic liver disease. Table 1.2 lists the common presenting symptoms and signs. Tumor rupture with intraperitoneal bleed is a rare clinical presentation which requires urgent resuscitation, angioembolization, or even surgery.

HCC can occasionally be associated with paraneoplastic syndromes like hypoglycemia, erythrocytosis, hypercalcemia, or severe watery diarrhea.

Table 1.1 Etiological/predisposing factors for hepatocellular carcinoma

Hepatitis B viral infection
Chronic hepatitis C virus (HCV) infection
Hereditary hemochromatosis
Chronic hepatitis and cirrhosis
Aflatoxin
Contaminated drinking water
Betel nut chewing
Tobacco and alcohol abuse
Diabetes mellitus
Nonalcoholic fatty liver disease
Obesity
Iron overload
Alpha-1 antitrypsin deficiency
Acute intermittent porphyria
Gallstones and cholecystectomy
Dietary factors—consumption of red meat and saturated fat

Table 1.2 Hepatocellular carcinoma—clinical presentation

Symptoms
– Asymptomatic—incidental finding
– Jaundice, anorexia, weight loss, malaise
– Vague upper abdominal pain
– Upper abdominal mass
– Acute presentation—intralesional bleed with acute onset severe abdominal pain, intraperitoneal rupture with bleed
Signs
– Hepatomegaly (50–90%)
– Hepatic bruit (6–25%)
– Ascites (30–60%)
– Splenomegaly due to associated portal hypertension from underlying liver disease
– Fever (10–50%)—probably due to tumor necrosis
– Signs of chronic liver disease—jaundice, dilated abdominal veins, palmar erythema, gynecomastia, testicular atrophy, and peripheral edema
– Budd-Chiari syndrome due to invasion into the hepatic veins causes tense ascites and large tender liver
– Troisier's sign—left supraclavicular lymph node enlargement (Virchow's node)

1.2.3 Diagnosis and Staging

Triple-phase contrast-enhanced CT scan or MRI is the investigative modality of choice for HCC. A diagnosis of HCC can be made for a solid liver lesion with characteristic enhancement patterns, i.e., enhancement in the arterial phase and contrast washout in the venous phase. Both arterial enhancement and venous washout are essential to make a diagnosis of HCC.

As the majority of patients with HCC have pre-existing chronic liver disease, enrolling these patients into a surveillance program of 6-monthly ultrasound aids in early diagnosis. Fig. 1.1 shows the American Association for the Study of Liver Diseases (AASLD) algorithm for suspected HCC [8]. Differentiation between high-grade dysplastic nodules and HCC on biopsy may be challenging and requires evaluation by expert pathologists supplemented with staining for glypican 3, heat shock protein 70, and glutamine synthetase. If the biopsy is negative for HCC, patients should be followed by imaging at 3- to 6-month intervals until the nodule either disappears, enlarges, or displays diagnostic characteristics of HCC.

Serum alpha-fetoprotein (AFP) levels are not included in the diagnostic algorithm for HCC as elevated serum AFP may also be seen in patients with chronic liver disease without HCC such as acute or chronic viral hepatitis [9]. However, it is accepted that serum AFP levels greater than 500 μg/L, in a high-risk patient, are diagnostic of HCC [10]. Serum AFP has also emerged as an important prognostic marker in patients being evaluated for liver transplant. An AFP level >1000 μg/L is associated with a high risk for disease recurrence following transplant [11].

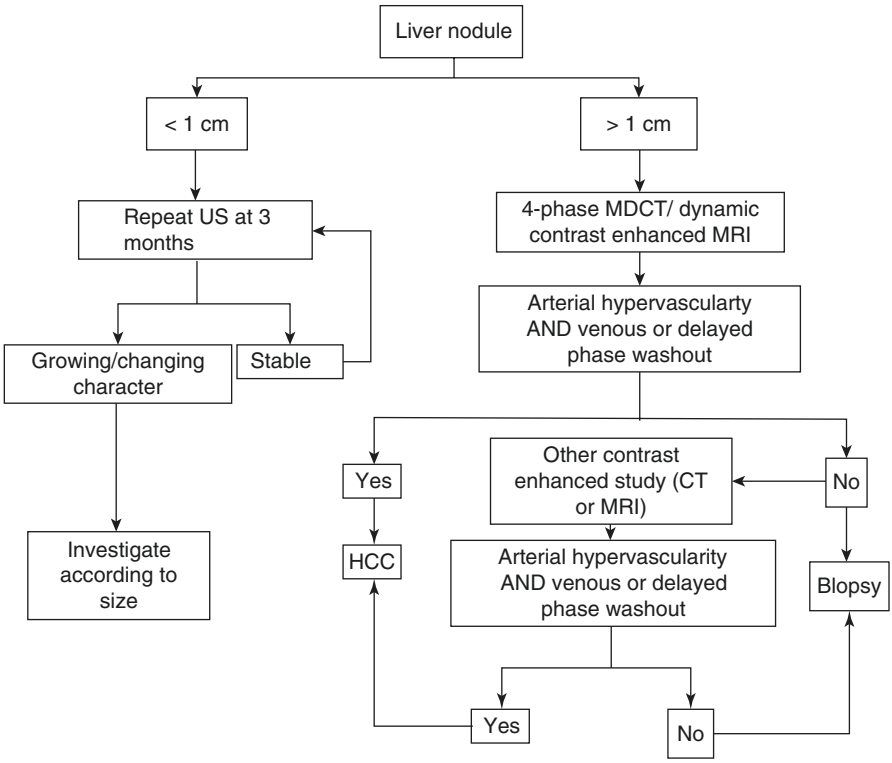

Fig. 1.1 AASLD algorithm for suspected hepatocellular carcinoma [8]. *CT* computed tomography, *MDCT* multidetector CT, *MRI*, magnetic resonance imaging, *US* ultrasonography

The most common sites of extrahepatic metastases in HCC are the lungs, abdominal lymph nodes, and bones, in that order. A CT chest is recommended for all patients being considered for curative resection. On account of low diagnostic yield a bone scan is only recommended for symptomatic patients.

Table 1.3 shows the TNM staging for HCC [12].

1.3 Carcinoma of the Gall Bladder and Bile Ducts

1.3.1 Epidemiology and Etiology

The incidence of gall bladder cancer shows a wide degree of geographical variation with the highest incidence recorded in parts of South America, India, Pakistan, Japan, and Korea [13]. The majority of patients with carcinoma of the gall bladder have gall stone disease. However, the incidence of gall bladder cancer in patients with gall stone disease is just 0.5–3% [14]. Table 1.4 lists the risk factors for gall bladder cancer.

Cholangiocarcinoma arises from the bile duct epithelium and has been classified as intra- and extrahepatic based on anatomical location. Extrahepatic cholangiocarcinomas

Table 1.3 Hepatocellular carcinoma—TNM staging [12]

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors not more than 5 cm		
T3a	Multiple tumors more than 5 cm		
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein		
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Table 1.4 Gall bladder cancer—risk factors

Gallstone disease
Porcelain gallbladder
Gallbladder polyps
Primary sclerosing cholangitis
Chronic infection—salmonella, *Helicobacter*
Congenital biliary cysts—choledochal cysts
Abnormal pancreaticobiliary duct junction
Medications—methyldopa, oral contraceptives, isoniazid
Carcinogen exposure—oil, paper, chemical, shoe, textile industries
Obesity and elevated blood sugar

are further classified as perihilar (up to the insertion of the cystic duct into the bile duct) and distal. Perihilar tumors in turn are further classified as per the Bismuth-Corlette system into four types (Table 1.5) [15]. Hilar cholangiocarcinomas are collectively known as Klatskin tumors.

Table 1.5 Bismuth-Corlette classification of perihilar cholangiocarcinoma [15]

Type 1—Tumors below the confluence of the right and left hepatic ducts
Type 2—Tumors reaching the confluence
Type 3—Tumors involving the confluence and either the right (3a) or left (3b) hepatic ducts
Type 4—Multicentric tumors or those involving the confluence and both the right and left ducts

Primary sclerosing cholangitis and fibropolycystic liver disease (e.g., choledochal cysts) are the major risk factors for cholangiocarcinoma. Intrahepatic cholangiocarcinoma is also associated with chronic liver disease and liver fluke infestation (e.g., clonorchis sinensis). Two familial syndromes, viz., Lynch syndrome and biliary papillomatosis [16], also predispose to cholangiocarcinoma.

1.3.2 Clinical Presentation

Patients with early-stage gall bladder cancer are usually asymptomatic, or present with symptoms of underlying gall stone disease. A large number of early-stage cancers present incidentally on imaging for other indications, or postoperatively, in the histopathology report of cholecystectomy for gall stone disease. Locally advanced disease may present with jaundice due to infiltration of the porta hepatis or compression at the porta due to metastatic lymphadenopathy. Duodenal or colonic obstruction due to a gall bladder primary usually represents inoperable disease.

Extrahepatic cholangiocarcinoma usually presents with biliary tract obstruction as evidenced by jaundice, pruritus, clay-colored stools, and high-colored urine. Associated symptoms include dull aching right hypochondrium pain, malaise, anorexia, and weight loss. Secondary infection of static bile in an obstructed biliary system leads to cholangitis, with a triad of right hypochondrium pain, fever, and jaundice.

Intrahepatic cholangiocarcinomas account for 20% of cases [17] and are largely asymptomatic. Early cases are usually diagnosed incidentally. Large intrahepatic masses may present with vague abdominal pain, anorexia, and weight loss.

1.3.3 Diagnosis and Staging

Ultrasonography is usually the first investigation to evaluate patients with symptoms suggestive of biliary tract pathology. An ultrasound will confirm the presence of biliary tract dilatation, localize the level of block, exclude gall stone disease, and detect metastatic disease in the form of liver metastasis, gross peritoneal deposits, or ascites. Gall bladder polyps more than 1 cm in diameter should be treated with cholecystectomy as they are likely to harbor invasive malignancy [18].

A suspicion of malignancy on ultrasound is further investigated with either a contrast-enhanced CT scan or an MRI. Gall bladder cancer may appear as an intraluminal mass, enhancing wall thickening of the gall bladder, a mass in the gall bladder fossa with or without liver parenchymal infiltration. Biliary ductal dilatation (>6 mm) with

enhancing wall thickening is suggestive of cholangiocarcinoma. Intrahepatic cholangiocarcinomas appear as a mass-forming lesion in the liver parenchyma.

Magnetic resonance cholangiopancreatography (MRCP) is particularly useful in patients with biliary tract obstruction, as it will not only accurately delineate the level of obstruction (and type of block) but will also reveal liver metastasis and aberrant bile duct anatomy. Endoscopic retrograde cholangiopancreaticography (ERCP) is useful in distal cholangiocarcinomas with obstructive jaundice, where delineating biliary anatomy and the level of obstruction, obtaining bile/brush cytology and therapeutic stenting, is possible in a single investigation.

Tissue diagnosis is not mandatory for resectable gall bladder masses suspicious for malignancy or for resectable cholangiocarcinomas, but should be obtained if neoadjuvant or palliative treatment is planned. Gall bladder cancers have a predilection for peritoneal seeding, and a percutaneous biopsy/FNAC is preferably avoided in a curative setting. Endoscopic ultrasound (EUS) is a useful tool in gall bladder cancer for characterizing gall bladder polyps, defining depth of wall infiltration, determining lymph node involvement, and obtaining an EUS-guided FNAC.

A baseline Ca 19–9 is obtained for all patients with gall bladder and biliary tract malignancy as it serves as a prognostic indicator with the caveat that biliary obstruction itself may contribute to a raised CA 19–9.

The role of PET scan in gall bladder and biliary tract malignancies is best limited to the detection of occult metastasis [19].

The AJCC TNM system is used for staging gall bladder (Table 1.6) and biliary duct cancers [12]. There are separate staging systems for intrahepatic, perihilar, and distal cholangiocarcinomas.

Table 1.6 TNM staging—gall bladder cancer [12]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

1.4 Pancreatic Carcinoma

1.4.1 Epidemiology and Etiology

Worldwide pancreatic cancer is the eighth leading cause of cancer-related deaths in men and the ninth in women [1]. New Zealand Maoris, native Hawaiians, and black Americans have the highest reported incidence [20]. Men are more commonly affected, and the disease is rarely seen before the age of 45 years.

Major risk factors for pancreatic cancer include cigarette smoking, chronic pancreatitis, diabetes mellitus, high body mass index, low physical activity, pancreatic cysts including IPMN (intraductal papillary mucinous neoplasm), and a family history of pancreatic cancer. Pancreatic cancer may also occur in the setting of familial syndromes like hereditary breast and ovarian cancer syndrome, Lynch syndrome, hereditary pancreatitis, Ataxia-telangiectasia, and Li-Fraumeni syndrome.

1.4.2 Clinical Presentation

The clinical presentation of cancer of the exocrine pancreas depends on the location of the tumor within the gland. Sixty to seventy percent of tumors are located in the head, 20–25% in the body and tail, and the rest involves the entire organ [21].

Periampullary and pancreatic head masses usually present with symptoms of obstructive jaundice, viz., yellow discoloration of sclera, clay-colored stools, steatorrhoea, and high-colored urine. Jaundice is usually painless and progressive in nature. A history of waxing and waning jaundice can often be elicited in periampullary tumors.

Pain is a common symptom and is located in the epigastrium with characteristic radiation to the back. Constitutional symptoms of anorexia and weight loss are also common, and recent onset diabetes mellitus could be the first presenting sign [22]. A palpable abdominal mass, free fluid in the abdomen, palpable left supraclavicular node (Virchow's node), and periumbilical nodule (Sister Mary Joseph nodule) are signs of advanced disease.

1.4.3 Diagnosis and Staging

A triple-phase, pancreas protocol, contrast-enhanced, multidetector row CT scan of the abdomen is the gold standard for imaging of pancreatic cancer. A malignant pancreatic mass is typically ill defined and hypodense as compared to the pancreatic parenchyma. Dilatation of the biliary and pancreatic ducts (double duct sign) is present in 62–77% of cases but is not diagnostic of pancreatic head malignancy

[23]. Assessment of resectability with respect to involvement of the superior mesenteric artery (SMA), superior mesenteric vein (SMV), portal vein, coeliac axis, and aorta is made on CT scan.

ERCP is an invasive procedure with a low but defined incidence of mortality (0.2%) and risks of pancreatitis, bleeding, and cholangitis. It is indicated when there is a suspicion of choledocholithiasis and where biliary drainage and stenting are required.

MRCP may be helpful in patients with bulky tumors with duodenal obstruction, in patients with prior gastrectomy (Billroth II) and to detect biliary duct obstruction in the setting of chronic pancreatitis.

Serum levels of CA 19–9 are obtained in all cases of pancreatic cancer as they have prognostic implications [24]. The level of Ca19–9 may also help to predict the possibility of occult metastasis, help in selection of patients for staging laparoscopy, indicate the likelihood of an R0 resection, and give an indication of long-term outcomes [25, 26].

Patients who are fit for major surgery with a resectable mass on CT scan do not require a preoperative biopsy to confirm malignancy. However, in young patients with history of ethanol abuse and in patients with history of other autoimmune diseases, a differential diagnosis of autoimmune pancreatitis should be considered. An EUS in these situations will help to further characterize the pancreatic mass and obtain an EUS-guided FNAC/biopsy. Tissue diagnosis is also mandatory in patients requiring neoadjuvant therapy and in unresectable lesions prior to starting treatment.

The AJCC TNM system is used for staging cancers of the exocrine pancreas [12] (Table 1.7).

Table 1.7 TNM staging—pancreatic cancer [12]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Key Points

- HCC constitutes the second leading cause of cancer-related deaths in men and the sixth leading cause of cancer-related deaths in women.
- Nearly 80% of HCC cases are due to underlying chronic hepatitis B and C infection.
- Triple-phase contrast-enhanced CT scan or MRI is the investigative modality of choice for HCC.
- The most common sites of extrahepatic metastases in HCC are the lungs, abdominal lymph nodes, and bones.
- The incidence of gall bladder cancer shows a wide degree of geographical variation with the highest incidence recorded in parts of South America, India, Pakistan, Japan, and Korea.
- Primary sclerosing cholangitis and fibropolycystic liver disease are the major risk factors for cholangiocarcinoma.
- Ultrasonography is usually the first investigation to evaluate patients with symptoms suggestive of biliary tract pathology.
- MRCP is useful in patients with biliary tract obstruction.
- Worldwide pancreatic cancer is the eight leading cause of cancer-related deaths in men and the ninth in women.
- A triple-phase, pancreas protocol, contrast-enhanced, multidetector row CT scan of the abdomen is the gold standard for imaging of pancreatic cancer.

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