Updated Management of Malignant Biliary Tract Tumors: An Illustrative Review

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ABSTRACT

The management of malignant biliary tumors (MBTs) is complex and requires a multidisciplinary approach. Guidelines and methods of staging for biliary tumors have recently been released by main international societies, altering the clinical and radiologic approach to this pathologic condition. The aim of the present review is to detail the updated role of imaging in preoperative staging and follow-up and to illustrate clinical/therapeutic pathways. In addition, future perspectives on imaging and targeted/embolization therapies are outlined.

ABBREVIATIONS

AJCC = American Joint Committee on Cancer, CBD = common bile duct, CC = cholangiocarcinoma, CMS = covered metal stent, dCC = distal cholangiocarcinoma, FRL = future remnant liver, GBA = gallbladder adenocarcinoma, iCC = intrahepatic cholangiocarcinoma, MBT = malignant biliary tumor, OLT = orthotopic liver transplantation, PBD = preoperative biliary drainage, pCC = perihilar cholangiocarcinoma, PET = positron emission tomography, PVE = portal vein embolization, PV = portal vein, R0 = negative resection margin, TNM = tumor/node/metastasis [staging]

In recent years, joint clinical/radiologic management of malignant biliary tumors (MBTs) has evolved to improve patient survival and quality of life. MBTs account for approximately 4% of all malignant neoplasms of the gastrointestinal tract and are generally characterized by poor prognosis (1), as fewer than 20% of patients are suitable candidates for curative treatment (2,3). Cholangiocarcinoma (CC) and gallbladder adenocarcinoma (GBA) are the most common biliary tumors.

Guidelines for classification, imaging, staging, and management of hepatobiliary cancers have been recently updated by the National Comprehensive Cancer Network (4). Although the American College of Radiology has released criteria regarding radiologic management of benign and malignant biliary obstruction (5,6), there remains a paucity of universal radiologic guidelines (7–10) regarding management of malignant biliary neoplasms. Technical aspects and recommendations regarding biliary drainage in malignant biliary obstruction have been published by major endoscopic societies (American Society of Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy) and interventional radiologic societies (Cardiovascular and Interventional Radiological Society of Europe and Society of Interventional Radiology) (9–12). Asian-Pacific guidelines focused on the endoscopic and interventional management of hilar CC (13).

It is recognized that imaging studies and clinical workup—and, consequently, treatment protocols—will vary according to the patient's clinical status and tumor staging. An integrated approach involving surgery, chemotherapy, radiation therapy, and new interventional radiologic techniques represents the developing frontier of therapeutic options. In this institutional review board–approved review, we seek to review the

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key aspects of clinical management and imaging techniques regarding the most common MBTs.

CC: CLASSIFICATION, STAGING, AND IMAGING

CCs comprise all tumors originating from the bile-duct epithelial sheet. More than 90% of these have histologic features of adenocarcinoma and are classified according to their pattern of growth: (*i*) mass-forming, (*ii*) periductal infiltrating, (*iii*) intraductal-growing, or (*iv*) undefined, meaning more than one of the aforementioned types (eg, mass-forming and intraductal-growing) (14). Recent evidence underlined that the mass-forming, periductal infiltrating type was associated with a worse prognosis than other types, with higher recurrence rates after resection (14).

Because of mucin production and the infiltrating nature, bile duct filling defects evident on imaging may indicate thrombus, redundant mucin, or bile duct calculi. CCs may develop in any site of the biliary tree and are currently classified as intrahepatic, perihilar, and distal (the latter two types are also defined as extrahepatic), with anatomic boundaries as follows: (*i*) the second-order bile ducts delimit intrahepatic CC (iCC) from perihilar CC (pCC); (*ii*) the cystic duct is the point of distinction between pCC and distal CC (dCC); and (*iii*) the ampulla of Vater is the distal landmark of dCC (of note, tumors of the ampulla of Vater are considered separately from CC).

iCC

Usually, iCC is primarily detected at imaging as an isolated intrahepatic mass, and the differential diagnosis for these appearances includes hepatocellular carcinoma. Computed tomography (CT) and magnetic resonance (MR) imaging are helpful for diagnosis and staging of the primary tumor, but both imaging techniques have low specificity; CT demonstrates superior performance in depicting vascular involvement (14). The key pattern for diagnosis is that the iCC increasingly enhances during the arterial, venous, and particularly the delayed phase (**Fig 1**). On the contrary, hepatocellular carcinoma is characterized by brisk contrast enhancement during the arterial phase and prompt washout in the delayed phase (14). Recent studies (15,16) found that adverse prognostic factors in iCC include the number of lesions, vascular invasion, and nodal involvement (ie, tumor/node/metastasis [TNM] nodal stage N1). Interestingly, tumor size has not clearly been shown to be relevant (15,16), and this is recognized in the American Joint Committee on Cancer (AJCC) staging guidelines (17).

Farges et al (18) found the AJCC staging to be more accurate in predicting outcome in patients with iCC compared with other staging systems. Using the AJCC staging, patients with stage I disease had a 5-year survival rate of 62%, whereas patients with stage II disease had a 27% 5-year survival rate (18). The overall AJCC staging system is depicted in **Table 1**.

Complete surgical resection remains the only curative treatment for iCC, even though most patients are not candidates for surgery. Multifocal tumors and metastatic hilar lymphadenopathy are currently considered relative contraindications to surgery. Nodal metastases beyond the porta hepatis and distant metastatic disease contraindicate resection. Local factors such as lymphovascular, perineural invasion and tumor size $>$ 5 cm have also been reported as independent factors of recurrence and reduce overall survival following resection (4).

Extrahepatic CC

Extrahepatic CC is currently classified as pCC or dCC (3).

pCC. Three staging systems for pCC are available: Bismuth–Corlette classification, Seventh Edition AJCC TNM staging, and Jarnagin–Blumgart classification. The Bismuth–Corlette system (19) is a long-established method for the staging of this tumor, but it does not include important prognostic pathologic factors such as vascular invasion, lymph node involvement, distant metastases, and liver atrophy. In addition, this system remains deficient in predicting resectability and survival (19). The AJCC Seventh Edition system was introduced more recently and includes consideration of regional and distant lymph node involvement and distant metastases. The latest Jarnagin–Blumgart staging for resectable pCC permits prediction of resectability and likelihood of metastatic disease and survival (20). Accuracy of prognostic prediction with this staging system has been found to be superior to that seen with the TNM system (eg, accuracy for stage II: Jarnagin–Blumgart, 78.6%; TNM, 56.3% [20]). A comparison between Jarnagin–Blumgart staging and complete TNM staging is provided in **Table 2**.

Hilar CCs are classified in three stages (tumor stages T1–T3) according to the location and extent of bile duct involvement, presence of portal vein (PV) involvement, and hepatic lobar atrophy. The total score is yielded by the cumulative score (ie, 0, 1, or 2) of preoperative staging (stage T1, T2, or T3), intraoperative findings (ie, differentiation), and resection margin (ie, from a negative resection margin [R0] to a resection margin positive for macroscopic residual disease, or the presence of metastasis). Each total score is assigned a prognosis with survival time: for example, if the total score is 0 (stage I), survival is estimated to be $>$ 3 years; if the total score is 4 (stage III), there is an inferior prognosis with survival $\leq$ 1 year. The complete staging system is described in **Table 3**.

pCC is usually well-detected by CT and MR imaging, and these represent fundamental modalities for comprehensive staging of the disease. MR cholangiopancreatography is

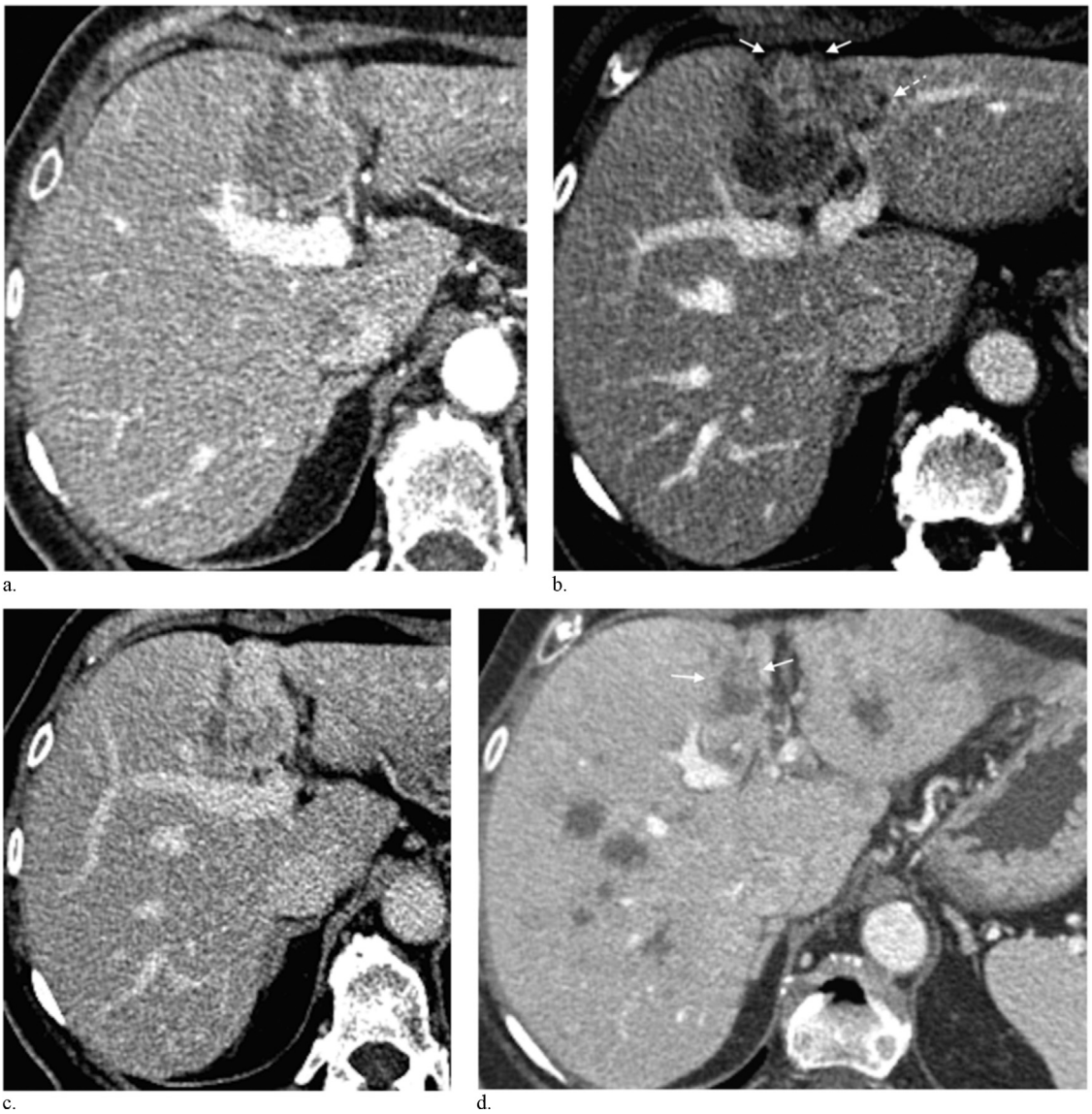

Figure 1. Images from a 73-year-old woman referred with anemia and fatigue, with a history of cholecystectomy and CBD stones. **(a)** Axial contrast-enhanced CT in arterial phase shows mild enhancement of the lesion. Increasing enhancement is noted during the venous **(b)** and delayed **(c)** phases. There is infiltration of the liver capsule (solid arrows, **b**) and infiltration of the PV branch for segment IV (dashed arrow, **b**). No lymph nodes are evident, and there is no apparent distant metastasis, indicating stage III disease (T3N0M0). US-guided biopsy confirmed the diagnosis of CC, and the patient underwent chemoradiation therapy. **(d)** Follow-up CT after 6 months of chemoradiation therapy shows shrinkage and morphologic change of the tumor (arrows), but multiple satellite lesions are present throughout the liver parenchyma.

the imaging modality of choice for pCC: its accuracy in assessing local extent and resectability (vascular and lymph node involvement) is as high as 95% and is comparable to that of endoscopic retrograde cholangiopancreatography (ERCP). CT is fundamental in the assessment of distant metastatic disease (peritoneum, bone, lung). Resectability may be assessed with CT with an accuracy rate ranging between 60% and 88% and negative predictive values of 85%–100%; however, lymph node metastasis detection is less accurate (accuracy of 58%) (14).

New imaging parameters to be assessed in pCC include (*i*) whether the tumor involves the hilum with or without unilateral extension to second-degree biliary ducts (stage T1), (*ii*) the presence of ipsilateral PV branch involvement and/or ipsilateral lobe atrophy (stage T2; Fig 2), and (*iii*) the presence of contralateral PV branch involvement or contralateral lobe atrophy or main or bilateral PV involvement (stage T3). (*iv*) Although lymph node involvement is not assessed by the Jarnagin–Blumgart staging system, it remains important to detect local (ie, stage N1) or distant (ie, stage N2) lymph node metastases. Resectability is determined by the assessment of those criteria; when using the classic Bismuth–Corlette classification, tumors of stage III/IV are typically considered unresectable (Fig 3).

Table 1. AJCC 7th Edition TNM Staging for Intrahepatic Cholangiocarcinoma

Final Stage	Tumor Stage	Node Stage	Metastasis Stage
I	T1: solitary tumor without vascular invasion	N0: no regional lymph node metastasis	M0: no distant metastasis
II	T2a: solitary tumor with vascular invasion T2b: multiple tumors with/without vascular invasion	N0: no regional lymph node metastasis	M0: no distant metastasis
III	T3: tumor perforating visceral peritoneum or involving local extrahepatic structures by direct invasion	N0: no regional lymph node metastasis	M0: no distant metastasis
IVA	T4: tumor with periductal invasion	N0: no regional lymph node metastasis	M0: no distant metastasis
	Any	N1: no regional lymph node metastasis	M0: no distant metastasis
IVB	Any	Any	M1: distant metastasis

AJCC = American Joint Committee on Cancer; TNM = tumor/node/metastasis [staging].

Table 2. Jarnagin–Blumgart Classification and AJCC 7th Edition Staging System for Perihilar Cholangiocarcinoma

Jarnagin–Blumgart Classification		AJCC 7th Ed. Staging			
Stage	**Criteria**	**Tumor Stage**	**Node Stage**	**Metastasis Stage**	**Final Stage**
T1	Tumor involving biliary confluence with/without unilateral extension to second-degree biliary ducts	T1: tumor confined to bile duct with extension up to muscle layer or fibrous tissue	N0: no regional lymph node	M0: no distant metastasis; M1: distant metastasis (liver, peritoneum, bone, lung)	Stage I
T2	Tumor involving biliary confluence with/without unilateral extension to second-degree biliary ducts and ipsilateral PV involvement with/without ipsilateral hepatic lobe atrophy	T2a: tumor invades beyond wall of bile duct to surrounding fat tissue T2b: tumor invades adjacent hepatic parenchyma	N0: no regional lymph node		Stage II
T3	(*i*) Tumor involving biliary confluence with/without unilateral extension to second-degree biliary ducts; (*ii*) unilateral extension to second-degree biliary ducts with contralateral PV involvement; (*iii*) unilateral extension to second-degree biliary ducts with contralateral hepatic lobe atrophy; or (*iv*) main/bilateral PV involvement	T3: tumor invades unilateral branches of PV or hepatic artery T4: tumor invades main PV	N0: no regional lymph node N1: regional lymph node metastasis (nodes along CBD, cystic duct, hepatic artery, PV N2: metastasis to distant lymph nodes (periaortic, pericaval, SMA, celiac trunk)		Stage IIIA (T3N0M0) Stage IIIB (T1–T3, N1, M0) Stage IVA (T4, N0/1, M0) Stage IVB (any T, N2, M0; any T, any N, M1)

AJCC = American Joint Committee on Cancer; CBD = common bile duct; PV = portal vein; SMA = superior mesenteric artery.

dCC. dCC is defined by tumor involving the common bile duct (CBD) from the cystic duct to the ampulla of Vater. It may present with similar clinical features as pCC, although fever is more common in dCC. Typically, dCC may present with two predominant imaging characteristics: (*i*) high-attenuation mass or thickened wall (biliary intraepithelial neoplasia; Fig 4) and (*ii*) low-attenuation polypoid mass (intraductal papillary

Table 3. Scoring Criteria for New Staging System for Perihilar Cholangiocarcinoma

Score	Jarnagin–Blumgart Classification	Intraoperative Findings	Resection Margin	Total Score	Stage	Prognosis	Predicted Survival (y)
0	T1	High/moderate differentiation without distant metastasis	R0	0	I	Good	> 3
1	T2	Poor differentiation	R1	1	II	Moderate	1–3
2	T3	Distant metastasis	R2	2–6	III	Poor	< 1

R0 = negative resection margin; R1 = resection margin positive for local disease.

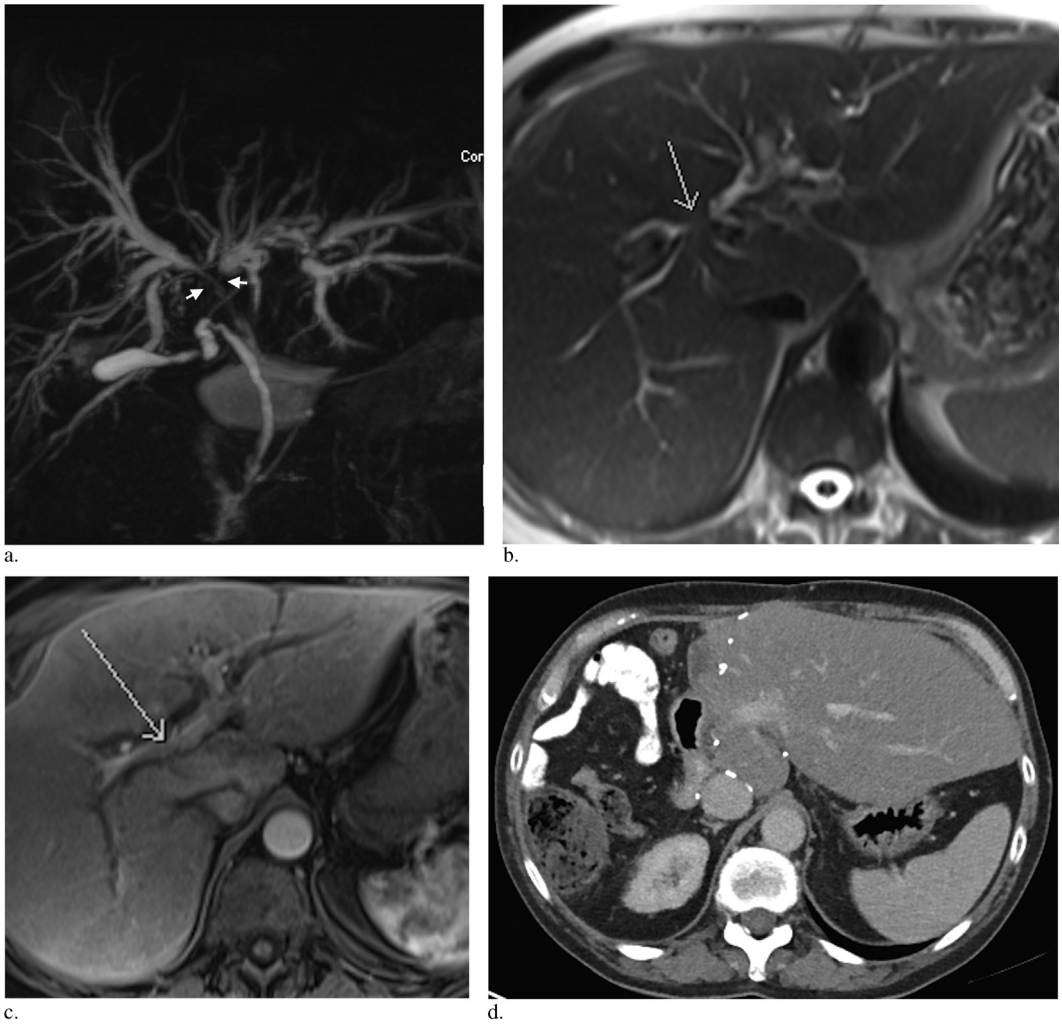

Figure 2. Images from a 60-year-old woman presenting with jaundice. **(a)** Coronal T2-weighted MR image demonstrates an ill-defined stricture at the level of the hilum (arrows) and intrahepatic bile duct dilation. **(b)** Axial T2-weighted image confirming the lesion infiltrating the biliary confluence as well as the right main biliary duct (arrow). **(c)** Postcontrast T1-weighted fat-saturated image shows the tumor infiltrating the periportal space, abutting—but not invading—the right PV (arrow), and clear of the main PV. The appearances are consistent with a Bismuth–Corlette type II tumor. There is no evidence of local lymphadenopathy or metastatic disease, for a classification of stage II disease (T2N0M0) according to Jarnagin–Blumgart and AJCC classification, amenable to surgical resection. No cholangitis or other indications for preoperative biliary drainage were present. Therefore, an extended right hemihepatectomy was performed. **(d)** There was no evidence of recurrence on CT at 2 years after resection.

neoplasms; however, the differential diagnosis includes the benign counterpart, papilloma or papillomatosis) (14).

dCC is characterized by depth of invasion, pancreatic invasion, and frequent lymph node metastasis; of note, metastatic lymph node spread is more commonly observed in dCC than in iCC and pCC. Tumor depth invasion, lymph node metastases (number of lymph nodes), perineural microscopic vascular invasion (PV invasion), invasion into the pancreas, and R0 resection were found to be significant predictors of survival (3,21,22).

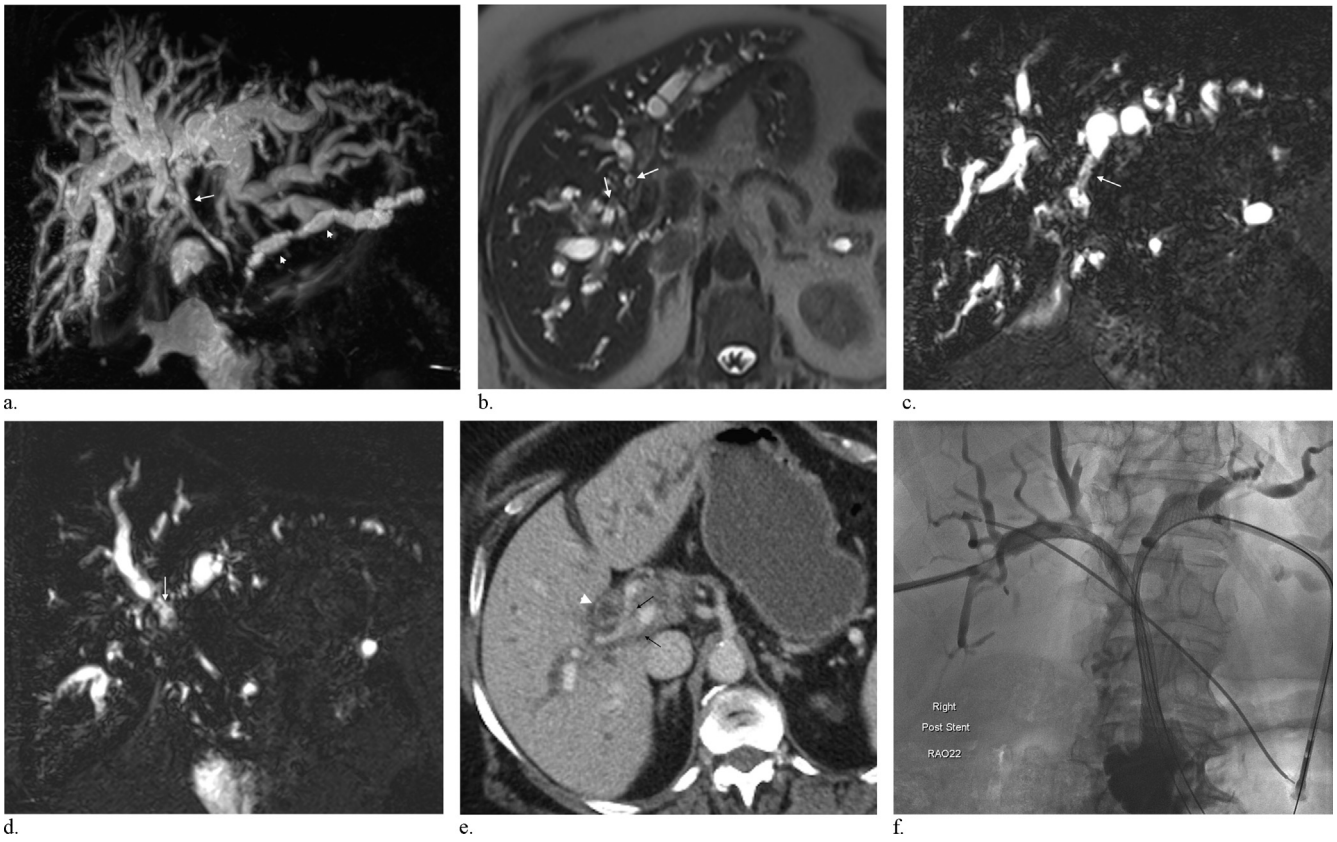

Figure 3. Images from a 65-year-old woman presenting with jaundice and pruritus. **(a)** Coronal T2-weighted MR cholangiopancreatography image demonstrates narrowing of the hepatic hilum (arrow) and intrahepatic bile duct dilation. The main pancreatic duct is also dilated mainly as a result of chronic pancreatitis (arrowheads). **(b)** Axial and **(c,d)** coronal T2-weighted images demonstrate disease extension to the bifurcation of the right and left hepatic ducts (arrows), consistent with Bismuth type IV disease. **(e)** Postcontrast CT demonstrates an ill-defined mass that infiltrated the hepatic artery (black arrows) and the PV (arrowhead). No significant nodes or metastases were detected, indicating stage IV disease (T4N0M0). Therefore, the tumor is considered inoperable. In view of the intrahepatic strictures, the patient underwent PTC and bilateral stent implantation. **(f)** PTC via bilateral percutaneous approach was performed, and two transpapillary 10-mm × 10-cm Wallstent stents (Boston Scientific, Marlborough, Massachusetts) were inserted, extending in the intrahepatic bile ducts. The percutaneous tracts were plugged with Gelfoam (Pharmacia & Upjohn, Kalamazoo, Michigan). The patient was discharged without complications, and chemotherapy was commenced.

The new Seventh Edition AJCC/Union for International Cancer Control staging system introduced staging for dCC that is separate from that for pCC (**Table 4**). The new dCC staging system considers assessment of the following parameters by CT/MR imaging: (*i*) tumor confined to the bile duct (stage T1); (*ii*) tumor invasion beyond the wall of the bile duct (stage T2); (*iii*) tumor invasion of the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis or superior mesenteric artery (stage T3); (*iv*) invasion of the celiac axis or superior mesenteric artery (stage T4); (*v*) presence of regional (porta hepatis/peripancreatic) lymph node involvement (stage N1); and (*vi*) presence of distant metastases (stage M1).

GBA: Staging and Imaging

Tumor stage has been demonstrated as the strongest prognostic factor for patients with GBA (4). A nationwide analysis in the United States (23) showed 5-year survival rates of 60%, 39%, and 15% for stage 0, I, and II GBA, respectively, with survival rates decreasing to 5% and 1% for patients with stage III and IV disease, respectively.

Staging of GBA is made according to the revised 2010 AJCC document in which stage groupings have been changed to distinguish hilar node involvement from involvement of other nodes and to improve correlation with resectability criteria and clinical outcome (3,23) (**Table 5**). Limited surgical resection is often performed in early-stage GBA (stage 0/I), whereas middle- to advanced-stage GBA (stages II/III) often requires extended resection (beyond segment IVb and V) and bile duct resection. However, these treatments have shown to increase perioperative morbidity and are therefore performed only in selected cases (24).

Multidetector CT is the most frequently used imaging technique for staging and assessment of local invasion (accuracy rate, 84%). MR imaging/MR cholangiopancreatography may be considered as additional imaging tests to better assess the bile duct and vascular invasion. At imaging, GBA may appear as (*i*) intraluminal polypoid lesion (stage Tis, T1), (*ii*) focal or

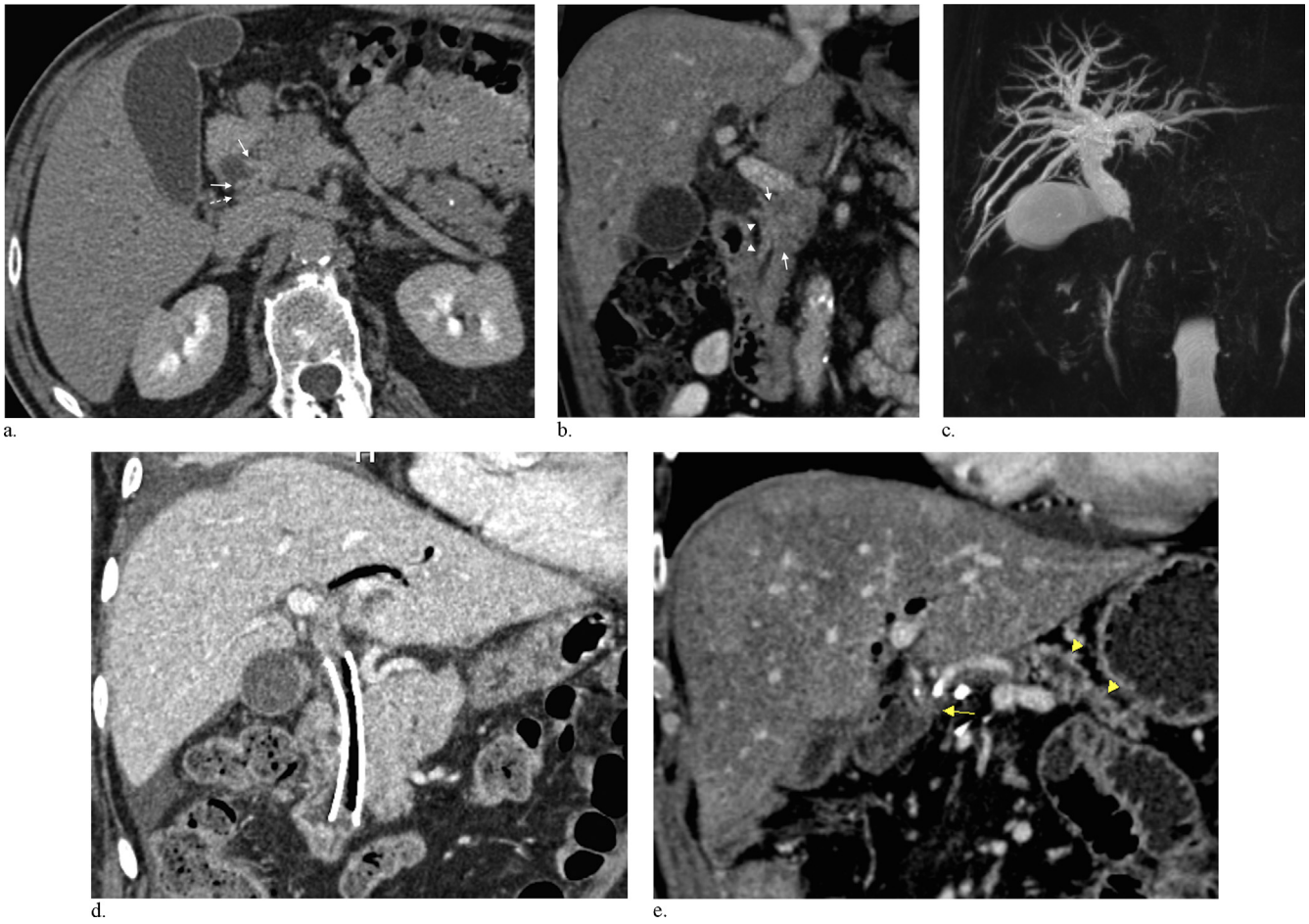

Figure 4. Images from a 67-year-old man referred with jaundice and recurrent cholangitis. **(a)** Axial CT image in delayed phase shows thickening of the distal CBD (solid arrows) with adjacent enlarged lymph node (dashed arrow). **(b)** CT coronal view shows that the thickened wall (arrowheads) is attached to the pancreatic parenchyma (arrows). **(c)** T2-weighted MR cholangiopancreatography sequence shows obstruction of the distal CBD and marked dilation of the intrahepatic bile ducts. The tumor was classified as stage IIA (T3N0M0). **(d)** CT coronal view shows the presence of a metallic stent within the middistal CBD after ERCP. Note that the stent has been placed distally to the hilum to allow resection. **(e)** Postsurgical coronal CT image shows the short biliary–jejunal anastomosis (arrow) and the remainder of the pancreas anastomosed to the jejunum, with dilated pancreatic duct (arrowheads).

Table 4. AJCC 7th Edition Staging System for Distal Cholangiocarcinoma

Final Stage	Tumor Stage	Node Stage	Metastasis Stage
IA	T1: tumor confined to bile duct	N0: no regional lymph node metastasis	M0: no distant metastasis
IB	T2: tumor invades beyond wall of bile duct	N0: no regional lymph node metastasis	M0: no distant metastasis
IIA	T3: tumor invades pancreas, duodenum, gallbladder, or other adjacent organs without involvement of celiac axis or SMA	N0: no regional lymph node metastasis	M0: no distant metastasis
IIB	T1–T3	N1: regional lymph node metastasis present	M0: no distant metastasis
III	T4: tumor involves celiac axis or SMA	Any	M0: no distant metastasis
IV	Any	Any	M1: distant metastasis

AJCC = American Joint Committee on Cancer; SMA = superior mesenteric artery.

diffuse asymmetric gallbladder wall thickening (stage T1–T3), or (*iii*) a mass completely occupying or replacing the gallbladder lumen (stage T3–T4; Fig 5) (3,24). Obstruction of the extrahepatic bile ducts causing jaundice may occur as a result of intraductal spread along the cystic duct toward the perihilar region (simulating pCC) that is considered to represent stage T3 disease (stage III). At this stage, the tumor may be

Table 5. AJCC 7th Edition Staging System for Gallbladder Adenocarcinoma

Final Stage	Tumor Stage	Node Stage	Metastasis Stage
IA	T1: tumor invades lamina propria or muscular layer	N0: no regional lymph node metastasis	M0: no distant metastasis
II	T2: tumor invades perimuscular connective tissue; no extension beyond serosa or into liver	N0: no regional lymph node metastasis	M0: no distant metastasis
III	T3: tumor perforates serosa (visceral peritoneum) and/or directly invades liver and/or one other adjacent organ or structure, eg, stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts	N0: no regional lymph node metastasis	M0: No distant metastasis
IVA	T4: tumor invades main PV or hepatic artery or invades two or more extrahepatic organs or structures	N0: no regional lymph node metastasis	M0: no distant metastasis
	Any	N1: regional lymph node metastasis	M0: no distant metastasis
IVB	Any	Any	M1: distant metastasis

AJCC = American Joint Committee on Cancer; PV = portal vein.

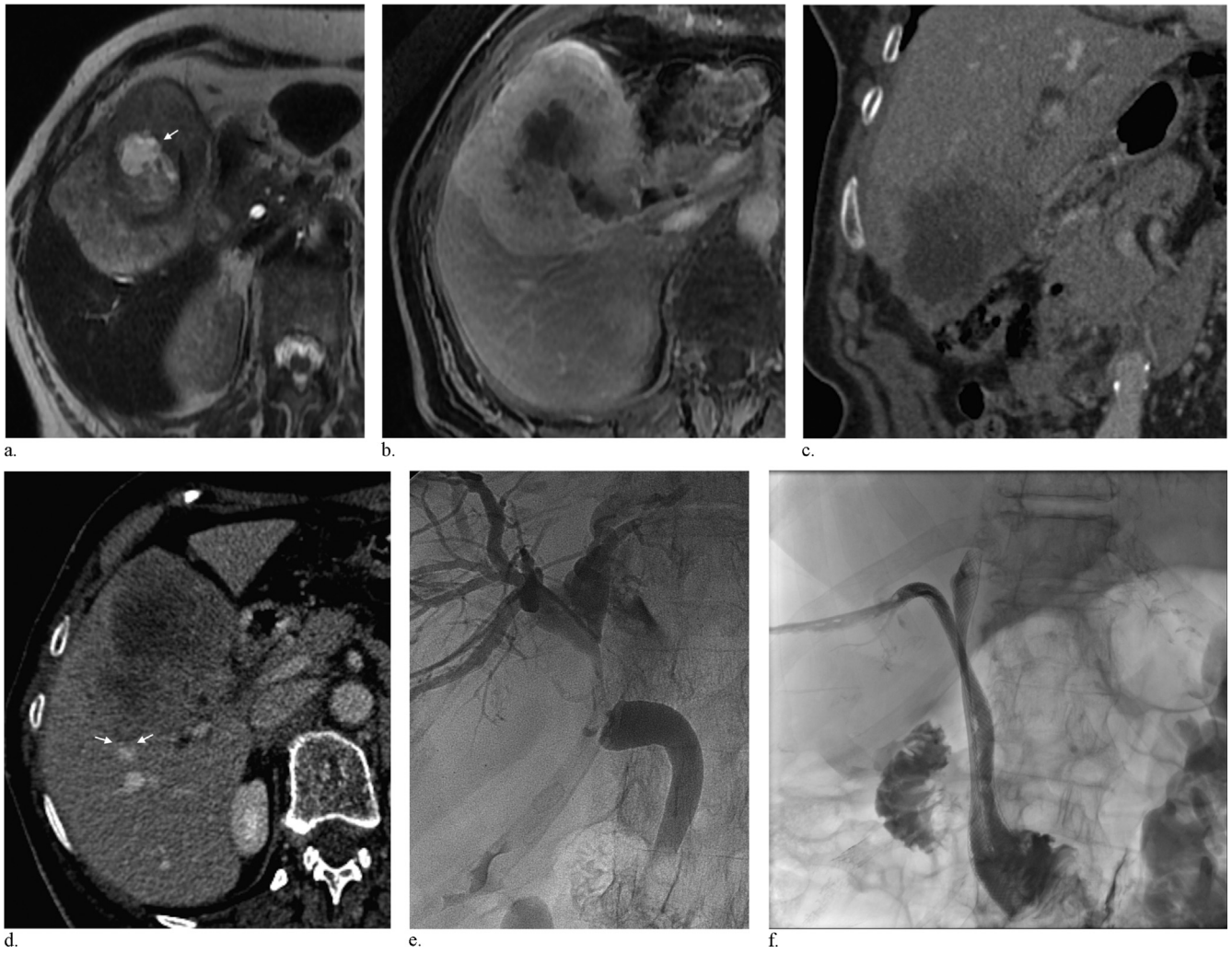

Figure 5. Images from a 71-year-old woman referred with jaundice and colic pain. **(a)** T2-weighted axial MR image shows the mass arising from the thickened gallbladder wall (arrow), invading segments IV/V. **(b)** Delayed fat-saturated T1-weighted postcontrast image shows retention of gadobenate dimeglumine within the tumor. **(c)** Coronal CT view demonstrates a hepatic lesion that infiltrates the right colic flexure. **(d)** Axial CT image in portal-venous phase shows infiltration of the right PV branch (arrows). The tumor was classified as stage IVA (T4N0M0). **(e)** PTC shows tight subhilar stricture of the CBD. **(f)** Bilateral self-expandable metal stents were inserted percutaneously to allow bilirubin normalization and chemotherapy administration.

considered "borderline" resectable, although the final decision is to be made on a multidisciplinary basis.

Local lymph nodes are involved in 50% of patients at diagnosis (stage N1); involvement of distant lymph nodes is considered to represent stage N2 disease and is associated with the worst prognosis (stage IVB), similar to cases of distant metastases (stage M1) (4). Management according to respective staging is depicted in Figure 6.

CC and GBA: Clinical Management and Therapeutic Options

Presenting symptoms may vary according to the extent of disease: clinical presentation of iCC is rarely accompanied by jaundice caused by obstruction of bile ducts unless it extends to the hilum, CBD, or enlarged metastatic lymph nodes, causing hilar compression. The most common presentation of iCC is characterized by nonspecific symptoms such as abdominal pain, weakness, night sweating, and cachexia.

Extrahepatic tumors and GBA may cause symptoms and signs of biliary obstruction, including pruritus and jaundice, that often present belatedly. In particular, GBA can mimic symptoms of biliary colic and chronic cholecystitis. Additionally, recurrent cholangitis, intrahepatic bile duct stones, and abnormal liver function may coexist. Interestingly, fever is more frequently apparent in pCC than dCC. Predominant clinical patterns of presentation are (*i*) incidental mass or obstruction signs on imaging and (*ii*) presence of symptoms (3).

Patients with iCC, eCC, or GBA, should be initially assessed in a consultation that includes clinical examination, liver function tests, cancer antigen assessment (carcinoembryonic antigen, cancer antigen 19.9), and imaging such as MR cholangiopancreatography and CT. In iCC cases, preoperative biopsy, diagnostic laparoscopy to exclude unresectable disseminated disease, esophagogastroduodenoscopy, colonoscopy, and hepatitis serology may be considered. In extrahepatic CC, additional endoscopic ultrasound (US) for local

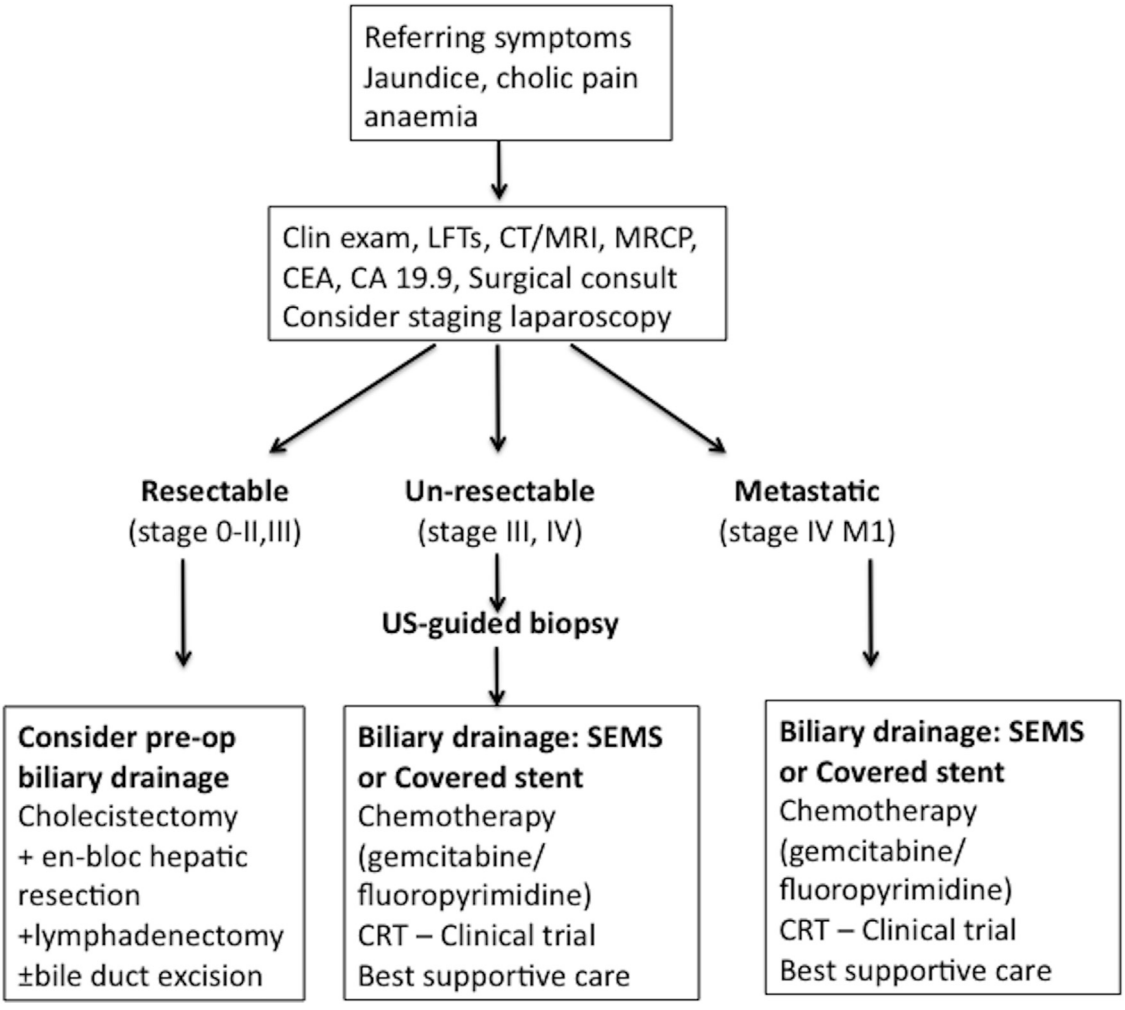

Figure 6. Flowchart showing clinical/radiologic management of GBA. PET/CT may contribute to staging by detecting lymph node involvement and distant metastasis, but it does not have a definite role yet. CA = cancer antigen; CEA = carcinoembryonic antigen; CRT = chemoradiation therapy; LFT = liver function test; MRCP = magnetic resonance pancreatography; SEMS = self-expandable metal stent.

staging may be appropriate. Following assessment, CC and GBA may be classified as resectable, unresectable, or metastatic. Clinical/radiologic management is illustrated in Figures 6–8.

Resectable disease. If the iCC or pCC is resectable, the patient can undergo a lobar, segmental, or wedge resection with portal lymphadenectomy, which is considered useful for appropriate treatment and staging information (4). Otherwise, dCC is treated with pancreaticoduodenectomy, often with lymphadenectomy and resection of the nerve plexus alongside major vessels (25). Preoperative biliary drainage (PBD) before resection may be indicated (25).

In resectable GBA, cholecystectomy and en bloc hepatic resection (resection of segments IV/V), lymphadenectomy, and/or bile duct excision represents the surgical approach of choice. An extended hepatic or bile duct resection may be necessary to guarantee an R0 margin (4,26). The role of extended regional lymphadenectomy on clinical outcome remains equivocal (27). Five-year disease-free survival rates after GBA resection have been reported to be as high as 65% (28).

PBD is a subject of contentious discussion. The primary drawbacks include increased perioperative risk of cholangitis, neoplastic seeding, and bleeding (13). Moreover, PBD may significantly increase the duration of hospital stay (27,28). There remains limited published literature regarding the influence of PBD on quality of life. The current evidence on PBD is insufficient to support or refute routine preoperative biliary drainage for patients with obstructive jaundice. Consequently, systematic preoperative biliary drainage is not recommended, but may be appropriate in selected patients (27–29). Benefits of internal PBD include correction of nutritional and biochemical abnormalities before surgery. In pCC, it permits time to perform PV embolization (PVE) in an effort to increase the future remnant liver (FRL) (3,4). There is inadequate evidence to demonstrate whether PVE increases resectability, achievement of R0 margin, or survival (29–32).

International endoscopic guidelines advise that PBD in hilar strictures caused by pCC (Bismuth class $\geq$ 2) or GBA should be performed via percutaneous route instead of via ERCP. However, in patients with dCC, preoperative drainage should be first attempted with

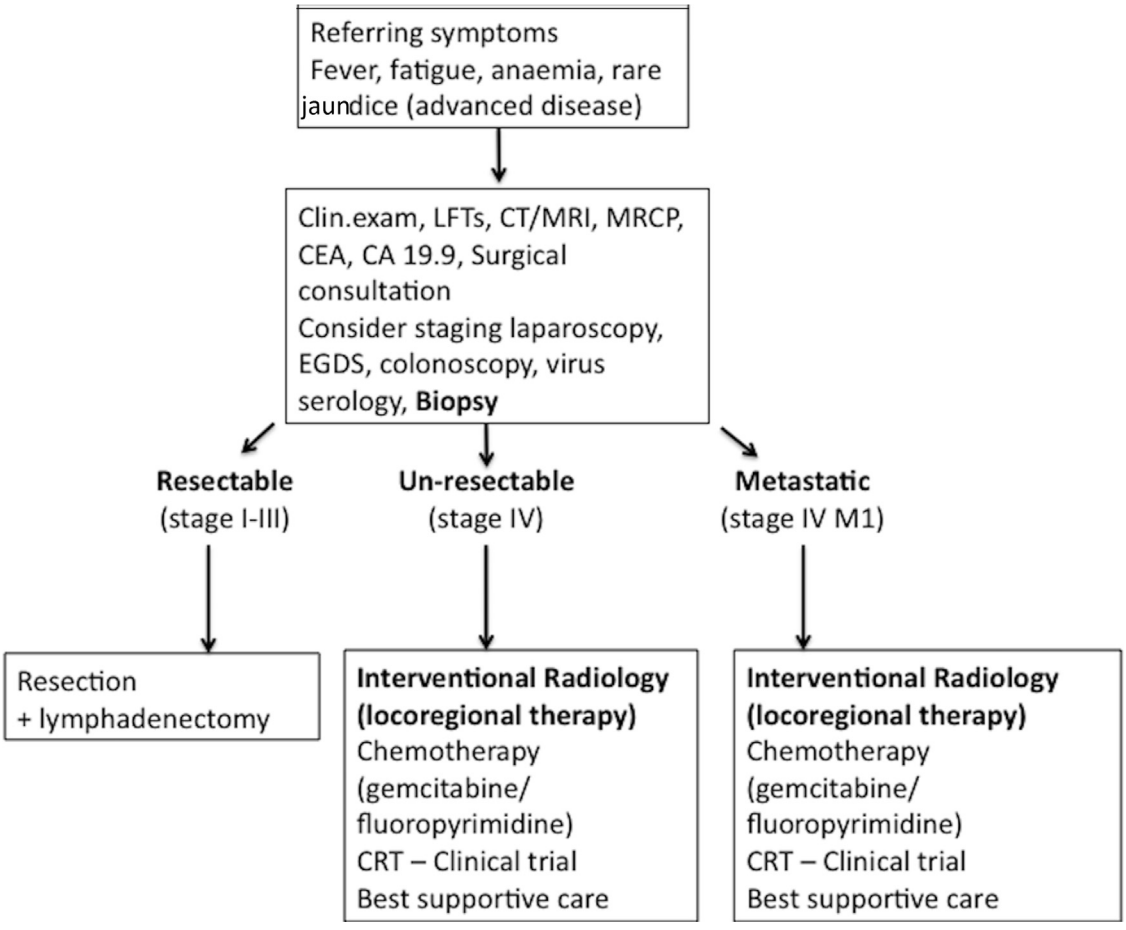

Figure 7. Flowchart showing clinical/radiologic management of iCC. PET/CT may contribute to staging detecting lymph node involvement and distant metastasis, but it does not have a definite role yet. CA = cancer antigen; CEA = carcinoembryonic antigen; CRT = chemoradiation therapy; EGDS = esophagogastroduodenoscopy; LFT = liver function test; MRCP = magnetic resonance pancreatography; SEMS = self-expandable metal stent.

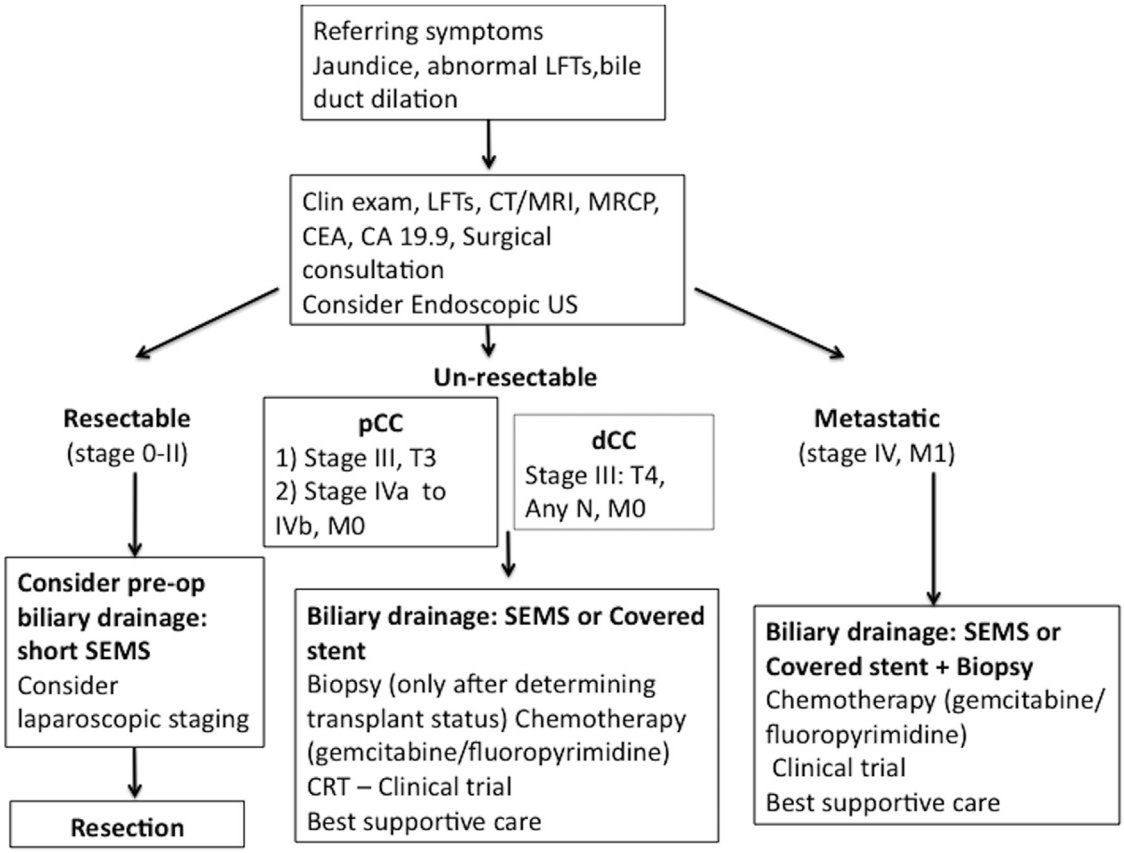

Figure 8. Flowchart showing clinical/radiologic management of extrahepatic CC. pCC is staged based on Jarnagin–Blumgart staging and AJCC Seventh Edition staging. Note that OLT is suitable only in selected patients with pCC (see text). CA = cancer antigen; CEA = carcinoembryonic antigen; CRT = chemoradiation therapy; LFT = liver function test; MRCP = magnetic resonance pancreatography; SEMS = self-expandable metal stent.

ERCP and sphincterotomy. In particular, placement of short covered stents distal to the biliary bifurcation (leaving at least 2 cm of the common hepatic duct below the bifurcation) does not affect the technical outcome of the duodenopancreatectomy and the biliary anastomosis (3,11–13,32–34). It is recognized that surgical resection is no more complex when performed in the presence of a short bare metal stent rather than a plastic stent (34).

Current recommendations advise PBD to be performed in (*i*) candidates for neoadjuvant therapies (*ii*) acute cholangitis and liver/renal disfunction (*iii*) intense pruritus and delayed surgery (*iv*) allow PVE to improve FRL and allow surgical resection (11–13,29,30,32). In the case of R0 resection or microscopic residual disease or positive regional nodes, the patient should undergo adjuvant treatment and clinical imaging follow-up every 6 months for 2 years if clinically appropriate. If there is macroscopic residual disease after resection, the patient should undergo adjuvant therapy alone (4). Therapy-related outcomes in resectable MBTs are shown in **Table 6** (3,15,24,25,29–31).

Unresectable/metastatic disease. In patients with unresectable or metastatic disease, subsequent management may involve interventional radiologic techniques. Patients with extrahepatic CC and GBA may require a tissue diagnosis, and endoluminal biopsy in CC is often necessary. Percutaneous transhepatic cholangiography (PTC) with metallic stent placement should be the first palliative intervention in view of the higher success rate of initial biliary drainage compared with ERCP (11–13,30,35).

In patients with inoperable dCC, biliary drainage should be attempted endoscopically first: initial insertion of a 10-F plastic stent is recommended if the diagnosis of malignancy is not established or if expected survival is less than 4 months. In patients with an established diagnosis of malignancy, initial insertion of a 10-mm-diameter self-expandable metal stent is recommended if expected survival is greater than 4 months (11–13). Only when an endoscopic approach fails, a percutaneous approach with PTC and subsequent stent insertion should be considered (11). Covered stents and partially covered stents demonstrated longer patency times than uncovered stents, with a low risk of migration (36–38).

The most important factor affecting survival is the normalization—not only improvement—of bilirubin levels (39,40). A survival analysis (41) identified that survival rates were significantly higher in patients with total bilirubin levels lower than 4 mg/dL compared with patients with higher postoperative bilirubin levels

Table 6. Resectable Malignant Biliary Tumors and GBA: Resuming Treatments and Outcomes (3,15,24,25,29–31)

Staging	Therapy	Outcome
GBA Stage 0–II (III)	Extended gallbladder resection	5-y disease-free survival rate as high as 65% (24)
Intrahepatic CC (stage I–III)	Resection and lymphadenectomy	5-y survival 31% (15)
Perihilar CC (stage 0–II)	Liver resection with/without bile duct resection with/without PBD	2-y survival 87.4% (3); 5-y survival 22%–50% with R0 and 0%–20% with R1 (29–31)
	PVE and PBD, then surgical resection	PVE increases resection rate (29–31); similar overall survival vs non-PVE surgery (29,30)
Distal CC (stage 0–II)	Pancreaticoduodenectomy with/without lymphadenectomy with/without PBD	5-y median survival 37% (25)

CC = cholangiocarcinoma; GBA = gallbladder adenocarcinoma; PBD = preoperative biliary drainage; PVE = portal vein embolization; R0 = resection margin negative; R1 = resection margin positive for local disease.

with whole or partial liver drainage. The British Biliary Drainage and Stenting Registry (42) outlined that, in patients with proximal hilar lesions, bilateral drainage or stent implantation resulted in a significantly greater reduction in bilirubin level (76.2%) than when only one lobe of the liver was drained or treated with a stent (34.4%; $P = .001$). Together, these findings suggest that the optimal approach to patients with a hilar stricture is to attempt bilateral drainage in the first place (35). Relief of obstruction with a stent may palliate pain, resolve cholangitis, and improve quality of life, and may be beneficial in the context of chemotherapy.

Available treatment options for unresectable or metastatic disease include (*i*) clinical trials, (*ii*) fluoropyrimidine- or gemcitabine-based chemotherapy or fluoropyrimidine chemoradiation, (*iii*) best supportive care, and (*iv*) orthotopic liver transplantation (OLT) (4). In addition, patients with iCC may also be suitable candidates for interventional radiologic treatments, including radiofrequency ablation, transarterial chemoembolization, drug-eluting bead chemoembolization, and transarterial radioembolization with yttrium 90 (^{90}Y). Ipsilateral PVE to increase the FRL followed by resection may also represent a valid therapeutic option to reserve for selected patients (3).

OLT is the last curative resource for unresectable pCC with negative lymph nodes and no metastatic disease: the survival rate may be as high as 42% at 5 years (3). Advantages of OLT over resection include the potential treatment of otherwise unresectable disease (Bismuth IV, stage IIIA/IVA, N0, M0) and the treatment of patients with underlying chronic liver disease (13). Notably, biopsy is not indicated before OLT because of the risk of neoplastic seeding. A new protocol combining neoadjuvant chemoradiation therapy and OLT yielded 5-year survival rates as high as 70% (43), but future research in this field is required (4). Therapy-related outcomes in unresectable/metastatic MBTs are shown in **Table 7** (2,23,38,43–46).

FUTURE CHALLENGES

Recent advances in imaging techniques and targeted and minimally invasive therapies are at the forefront of the future management of biliary tract tumors. Increasingly used imaging techniques include positron emission tomography (PET)/CT and endoscopic US. Current evidence suggests that the role of PET imaging in CC and GBA is not yet established, but concordant studies indicate that it has a role in detecting regional nodal metastasis or distant metastases in patients with otherwise resectable disease (3,47). Hence, it may have the potential to replace staging laparoscopy.

Endoscopic US is mainly indicated in extrahepatic CC and is more accurate than US and CT in the diagnosis and staging of malignant biliary obstruction (75% with endoscopic US vs 38% with US and 62% with CT) (48). Recently, endoscopic US showed at least comparable sensitivity—Weilert et al (49) reported 79% sensitivity for both techniques—in tissue sampling of extrapancreatic CC; however, there are low negative predictive values of 29%–67% and a higher risk of false-negative results in patients with a high degree of suspicion of malignancy (49). However, endoscopic US has an increasing role in clinical decision-making in cases of CC, allowing improved assessment of metastatic lymph nodes (ie, N stage) and local invasion (ie, T stage) and in providing a differential diagnosis in indeterminate biliary strictures (48). An evolving application of endoscopic US concerns endoscopic US–guided biliary drainage to be performed when ERCP fails. Currently, this technique is still in its infancy and is practiced only at specialized tertiary centers (50). As a consequence, percutaneous biliary drainage remains the principal alternative treatment (4).

Interventional radiology can offer a number of applications in patients with CC: newer embolization techniques such as chemoembolization with DC-Bead (BTG, London, United Kingdom) (44,45) and ^{90}Y radioembolization (46) are now valuable options in unresectable iCC. Median survival after radioembolization is 15.5 months, which is actually similar to that after systemic cisplatin/gemcitabine chemotherapy (11.7 mo) and chemoembolization (13.4 mo). Therefore, further studies are necessary to define the role and efficacy of those techniques. Stronger evidence is available for preoperative PVE associated with biliary drain insertion in

Table 7. Unresectable and Metastatic Malignant Biliary Tumors and GBA: Resuming Treatments and Outcomes (2,23,38,43–46)

Staging	Therapy	Biliary Stent Patency	Outcome (Survival)
GBA (stage III/IV, M1)	Biliary drainage (SEMS); chemotherapy, chemoradiation	Similar to pCC (studies include pCC and GBA)	5-y survival up to 5% (23)
Intrahepatic CC (stage III/IV)	Chemoembolization/ radioembolization or chemotherapy	NA	Chemotherapy, 11.7 mo (3); chemoembolization, 13.4 mo (44,45); radioembolization, 15.5 mo (46)
pCC (stage III/IV, M0/1)	Biliary drainage; chemotherapy, chemoradiation	Cumulative patency rate (BMS): 69.4% at 3 mo; 44.4% at 6 mo (35)	Median survival 7.9–14.6 mo; 1-y survival up to 12.9% (3)
pCC (stage III/IV, M0)	OLT Neoadjuvant chemoradiation, OLT (43)	NA	5-y survival up to 42% (3) 5-y survival 65%–70% (43)
Distal CC (stage III/IV, M1)	Biliary drainage (BMS/CMS); chemotherapy, chemoradiation	BMS (193–285d); CMS (225–357 d) (38)	Median survival: BMS, 180.5–184 d (38); CMS, 222–227.3 d (38)

BMS = bare metal stent; CC = cholangiocarcinoma; CMS = covered metal stent; GBA = gallbladder adenocarcinoma; NA = not applicable; OLT = orthotopic liver transplantation; pCC = perihilar cholangiocarcinoma; SEMS = self-expandable metal stent.

patients with jaundice and resectable hilar CC and GBA to increase the FRL (46,51,52).

Finally, molecular-targeted therapy has the expectation of replacing and improving outcomes of conventional chemotherapy. Ongoing phase II and III trials are demonstrating promising results for drugs with different molecular targets (eg, erlotinib, lapatinib, sorafenib, and selumetinib) alone and in combination with conventional chemotherapy (53).

CONCLUSIONS

Current management of MBTs is influenced by continuous progression in imaging and therapeutic techniques. Updated imaging and clinical guidelines may help the clinician and the radiologist to select the appropriate pathway of workup and treatment. The primary aim remains to deliver the optimum treatment, whether it is curative resection, transplantation, or palliation, to ultimately improve outcome and quality of life.

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