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REVIEW

Diagnostic-therapeutic management of bile duct cancer

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Abstract

Biliary tract cancer, or cholangiocarcinoma, comprises a heterogeneous group of malignant tumors that can emerge at any part of the biliary tree. This group is the second most common type of primary liver cancer. Diagnosis is usually based on symptoms, which may be heterogeneous, and nonspecific biomarkers in serum and biopsy specimens, as well as on imaging techniques. Endoscopy-based diagnosis is essential, since it enables biopsy specimens to be taken. In addition, it can help with locoregional staging of distal tumors. Endoscopic retrograde cholangiopancreatography is a key technique for the evaluation and treatment of malignant biliary tumors. Correct staging of cholangiocarcinoma is essential in order to be able to determine the degree of resectability and assess the results of treatment. The tumor is staged based on the TNM classification of the American Joint Committee on Cancer. The approach will depend on the classification of the tumor. Thus, some patients with early-stage disease could benefit from surgery; complete surgical resection is the cornerstone of cure. However, only a minority of patients are diagnosed in the early stages and are suitable candidates for resection. In the subset of patients diagnosed with locally advanced or metastatic disease, chemotherapy has been used to improve outcome and to delay tumor progression. The approach to biliary tract tumors should be multidisciplinary, involving experienced endoscopists, oncologists, radiologists, and surgeons.

Key words: Bile duct cancer; Cholangiocarcinoma; Management; Diagnosis; Incidence; Multidisciplinary treatment

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Core tip: This update provides a review of the diagnosis and management of biliary tract tumors. The document brings together the point of view of surgeons, oncologists, and gastroenterologists; therefore, it will be of use to clinicians who manage these challenging tumors. Treatment depends on staging. New diagnostic techniques such as cholangioscopy and new cancer treatments will play a key role in the not too distant future.

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INTRODUCTION

Biliary tract tumors, or cholangiocarcinomas (CCAs), comprise a heterogeneous group of malignant tumors that can affect any part of the biliary tree, from the interlobular canals of Hering to the primary biliary duct. Depending on their anatomic location, the tumors are classified as intrahepatic CCA (iCCA) (20% of cases), which originate in the biliary tree within the liver, and extrahepatic CCA (eCCA), which originate outside the liver parenchyma; the latter is further subdivided into perihilar cholangiocarcinoma (pCCA or Klatskin tumor, 50-60% of cases) and distal cholangiocarcinoma (dCCA, 20% of cases). CCA affects multiple sites in 5% of cases[1,2]. Taken together, these tumors constitute the second most frequent type of primary liver cancer and approximately 3% of all gastrointestinal neoplasms. The tumor is unusual in most countries, with an incidence of fewer than 6 cases per 100000 persons. Nevertheless, the incidence of CCA is exceptionally high in some countries and regions (*e.g.*, Chile, Bolivia, South Korea, and Thailand)[3]. The epidemiological profile of the disease varies widely across the world, thus reflecting exposure to different risk factors, such as specific infectious diseases, chronic inflammatory diseases of the biliary tract, and congenital malformations. Parasitic infection caused by *Opisthorchis viverrini* and *Clonorchis sinensis* is a common risk factor in eastern Asia, where CCA accounts for 85% of all primary liver cancers. Other risk factors include liver diseases (*e.g.*, chronic infection by hepatitis B and C viruses, primary sclerosing cholangitis [PSC], and congenital malformations of the biliary tract [such as Caroli disease and choledochal cysts]). In addition, several toxic and environmental factors are also associated with the probable development of CCA, including food contami-nated by nitrosamines, smoking, and alcohol[4].

DIAGNOSIS

CCA is generally asymptomatic in the early stages and is diagnosed when the disease has metastasized or when it compresses the bile duct. Diagnosis is usually confirmed by combining nonspecific biomarkers in serum and/or biopsy specimens and imaging techniques[2,5]. When the disease is symptomatic, the clinical picture is heterogeneous, with general malaise, cachexia, abdominal pain, night sweats, fatigue, and/or jaundice. In most cases, CCA occurs in the absence of frank chronic liver disease and other risk factors.

iCCA is an incidental finding in 20%-25% of cases, with formation of masses the most common macroscopic presentation. In more than 90% of cases, this appears as a nodule in imaging tests[6-8]. If it occurs in the context of a cirrhotic liver, the differential diagnosis is with hepatocarcinoma after exclusion of metastatic lesions. The most common imaging patterns for iCCA in cirrhotic liver are progressive and homogeneous contrast uptake during the delayed phase in magnetic resonance imaging (MRI) or peripheral arterial enhancement in computed tomography (CT)[9,10]. The histopathology-based differential diagnosis of iCCA with hepatocarcinoma or metastasis requires a panel of immunohistochemistry markers and a cytokeratin profile (CK7+, CK19+, CK20−)[11,12]. iCCA has 2 main histopathological subtypes, which

reflect the origin of the tumor on the intrahepatic biliary tree: One that emerges from the small intrahepatic bile ducts, the bile ductular type (mixed pattern); and one that emerges from the large intrahepatic bile ducts, the bile duct type (mucinous pattern)[13]. Bile duct–type iCCA has an almost exclusively mass-forming growth pattern, is often associated with chronic liver disease (viral hepatitis or cirrhosis), and is not preceded by preneoplastic lesions. In clinical-pathological terms, it is similar to hepatocarcinoma and is positive for cytokeratin (CK)[14,15]. Furthermore, conventional bile duct–type iCCA (mucinous) generally appears as a mass-forming pattern, periductal infiltration, or intraductal growth. It is more frequently associated with PSC and may be preceded by preneoplastic lesions. It shares phenotypical traits with pCCA and pancreatic cancer[16].

As for the pCCA subtype, painless jaundice is the most common clinical symptom of onset[6]. In radiology, it appears as stricture of the bile duct. In this case, magnetic resonance cholangiopancreatography has the highest diagnostic accuracy for localizing and sizing strictures. To make the definitive diagnosis, patients usually undergo endoscopic retrograde cholangiopancreatography (ERCP) and various other procedures, such as cytology, brush cytology, fluorescence *in situ* hybridization (FISH), and cholangioscopy and/or chromoendoscopy–guided biopsy. The objective of these approaches is to confirm the disease based on microscopic data, albeit with very low and unsatisfactory sensitivity. In fact, fewer than 40% of patients are referred for surgery without a definitive diagnosis, and after surgery, no evidence of malignancy is observed in resected tissue in 10% of cases[17-19].

Even more challenging is the diagnosis of CCA in patients with PSC. The neoplastic nature of the stricture cannot be confirmed by MRI, CT, endoscopic ultrasound, or positron emission tomography (PET). The only condition that does not require confirmation by histopathology is biliary stricture associated with perihilar mass, although this presentation is very rare. Endoscopic ultrasound (EUS)–guided fine needle aspiration (FNA) has been shown to have a good diagnostic yield when distinguishing benign biliary strictures from malignant strictures and carries no risk of procedure-related tumor seeding (sensitivity 53%-66%, specificity 89%-100%, PPV 100%, NPV 29%-67%)[20].

Serum levels of CA19.9 > 130 U/mL in PSC had a sensitivity of 79% and specificity of 98% for detection of CCA. However, the serum level of CA19.9 is skewed by high secondary elevation in cholangitis and cholestasis. Several serum biomarkers (trypsinogen-2, IL6, MUC5AC, CYFRA211, progranulin), urine (volatile organic compounds, proteomic profiles), and bile (IGF1, microRNA-loaded vesicles, proteomic profile) have been proposed, although none has been able to be applied in clinical practice[21,22].

In summary, the diagnosis of CCA is still based on a combination of clinical and radiological characteristics and nonspecific histological and/or biochemical markers.

ENDOSCOPIC DIAGNOSIS

The importance of endoscopy in the diagnosis of malignant biliary tumors lies in its ability to provide specific tissue samples, which are essential for confirming the diagnosis. Furthermore, and particularly in the case of EUS, it makes it possible to provide additional information for diagnosis based on CT and MRI and establishes appropriate locoregional staging[23]. It is important to point out that, given duodenal access, all of the endoscopy techniques we describe below are more accurate and efficacious in the diagnosis of dCCA (ERCP: Sensitivity 80%, specificity 75%; EUS-FNA: Sensitivity 53%-66%, specificity 89%-100%, PPV 100%, NPV 29%-67%; Cholangioscopy with biopsy: Sensitivity 92%, specificity 93%; Intraductal Ultrasound: Accuracy 82%-95%; Confocal laser endomicroscopy combined with EUS-FNA: Sensitivity 100%, specificity 69%, PPV 60%, PNV 100%, overall accuracy 79%)[2,24-26]. In addition, histopathology-based diagnosis (histology or cytology) represents a challenge in many cases owing to the high rate of false negatives (approximately 50%). Therefore, negative findings in tissue do not rule out malignancy, and up to 40% of cases are referred for surgery without a definitive diagnosis. Similarly, no cancer is observed in the surgical specimen in 10% of these cases[6]. Confirmation in tissue is especially useful in patients who are not candidates for surgical resection in advanced or inoperable cancer and in patients who are candidates for clinical trials, since it can be obtained from the primary tumor using ERCP or, preferably, EUS. Confirmation can also be obtained from metastatic lesions using ultrasound- or CT-guided percutaneous biopsy[2,23]. In patients who are candidates for radical surgery, biopsy and cytology are not mandatory. In addition, given the possibility of tumor seeding resulting from sampling, these procedures should be restricted to cases in

which the diagnosis is doubtful and where endoscopy is the procedure of choice and percutaneous access is to be avoided[23,24]. Therefore, the decision to perform a biopsy should be taken on a multidisciplinary basis, especially in patients with potentially resectable tumors[23].

ERCP plays a key role in the assessment and treatment of biliary strictures, including malignant biliary tumors. It provides fluoroscopic high-quality images of the biliary tract and can confirm findings based on histopathology data obtained using brush cytology or targeted transpapillary biopsy[23,25,26]. Biopsy is preferable to cytology, although the latter continues to be the most widely used technique given the risk of iatrogenic lesion with biopsy pincers[23,24]. It is important to remember the key role that ERCP plays in therapy, as it can achieve biliary drainage in most cases, especially in distal extrahepatic tumors. The advent of new additional techniques such as cholangioscopy, intraductal ultrasound, and confocal laser endomicroscopy has further improved its diagnostic and therapeutic capacity[26]. The accuracy for differentiating between malignant and benign strictures (*e.g.*, PSC) based on cholangiographic morphology (*e.g.*, irregularity, asymmetry, and extension) is unsatisfactory, even in the hands of expert endoscopists (accuracy ranges from 72% to 80%), thus highlighting the need for tissue samples to ensure an appropriate diagnosis[26]. However, unfortunately, the sensitivity of tissue diagnosis based on ERCP, especially cytology, is low (from 18% to 48%, increasing modestly to 59.4% when biopsy and cytology guided by ERCP are combined), although the specificity is very high (almost 100%)[2,24-26].

In the case of patients with negative cytology and/or biopsy results, addition of more recent cytological tests, which have not yet been uniformly validated, such as FISH, analysis of digital images, and flow cytometry, can increase sensitivity, albeit slightly (< 70%), while maintaining high specificity. In general, they can improve detection of cholangiocarcinoma in approximately 10%-30% of cases[25,26]. FISH, which evaluates the presence of chromosomal aneuploidy, confirms cancer in 60% of patients whose standard cytology result is negative[2,24].

Endoscopic ultrasound

The main methods of assessing biliary strictures are MRI and ERCP-guided cholangiography, although EUS can also play a key role, especially when the results of other studies are inconclusive[25]. This technique provides high-definition images of stricture morphology that make it possible to characterize the malignancy. It also provides excellent visualization of the distal extrahepatic biliary tree, gall bladder, regional lymph nodes, and vascular structures, although the presence of biliary stents can distort the image[2,26]. The main limitation of this approach is its relatively poor characterization of the proximal extrahepatic biliary tree/perihilar area and the intrahepatic tree. Therefore, this technique can hamper diagnosis of cholangiocarcinomas arising in this area[27]. Given its favorable anatomical discrimination, EUS is very appropriate for locoregional staging, with major implications for decisions on therapy. It has proven to be more accurate than CT and PET for assessment of regional lymph node metastasis in patients with mainly distal eCCA[25]. In up to two-thirds of patients with eCCA, the lesion is not visualized as a well-defined mass in transverse radiology images (CT or MRI). EUS is particularly useful in these cases, as it is capable of identifying cholangiocarcinoma with a sensitivity of 45%[24,26]. EUS can also play a role in the identification of cholangiocarcinoma in early stages. In this case, combination of EUS with MRI cholangiography improves sensitivity from 80% to 90% and specificity from 90% to 98%[25]. EUS- FNA has a sensitivity of 53%-66% and a specificity of 89%-100% when applied for the histology-based diagnosis of cCCA. In addition, it also has an adequate yield for more proximal lesions, albeit to a lesser extent. The technique is useful for obtaining microbiopsies and may be considered if brush cytology or ERCP-guided biopsy tests are negative or inconclusive[23-26], given that EUS-FNA improves sensitivity and has a positive predictive value of almost 100%. The negative predictive value, however, is relatively low (29%-67%), thus preventing us from excluding malignancy after a negative biopsy result. This sometimes requires additional testing, including exploratory laparoscopy[2,26]. Cases of tumor seeding (dissemination) have been reported along the route followed by the needle (especially in the peritoneum and omental fat), with recurrence of the tumor after resection. This risk seems to be low and is clearly lower than that of percutaneous biopsy (owing to the use of smaller-gauge needles and a shorter route), although it has yet to be confirmed in larger-scale studies[2,23,24,26]. Nevertheless, because of this concern, some centers do not perform liver transplant in patients with cholangiocarcinoma after EUS-FNA of the primary lesion[24,25]. Therefore, in many centers, EUS-FNA is not recommended for proximal tumors (intrahepatic or hilar) that are potentially resectable or transplantable, given that the route followed by the needle is not included in the resection, in contrast with distal lesions, in which the duodenum is

usually resected using the Whipple procedure[2,24,26]. No data have been reported on this problem in patients with distal extrahepatic cholangiocarcinoma. The most prudent approach in potentially operable proximal cholangiocarcinomas is probably to limit the use of EUS-FNA to cases of doubtful diagnosis in which obtaining samples by ERCP has not delivered a diagnosis. In inoperable cases, the importance of this phenomenon is lower; therefore, resectability should be evaluated before attempting percutaneous or EUS-guided biopsy[2,24,26].

Cholangioscopy

Cholangioscopy enables direct visualization of the intraductal mucosa and identification of abnormalities that are suggestive of malignancy, such as dilated and tortuous vessels, villous projections, ulcerated strictures, and intraductal nodules[28]. Therefore, it enables more reliable differentiation between malignant and benign lesions than conventional ERCP, thus increasing the sensitivity and specificity of the latter to 90%. It also facilitates targeted biopsy, thus improving diagnostic yield[2,25,26]. However, its interobserver agreement is modest, and more data are necessary to clarify its role in the diagnosis of cholangiocarcinoma. In addition, it is possible that the risk of acute cholangitis increases with respect to conventional ERCP[25,26]. Additional benefits can be obtained by combining new techniques with conventional cholangioscopy (*e.g.*, multimodal chromoendoscopy, autofluorescence imaging, and narrowband imaging), although these have yet to be validated in larger-scale studies[26,28,29].

Intraductal ultrasound

Intraductal ultrasound is performed using a transpapillary probe during ERCP. It provides useful information, especially in cases of a doubtful diagnosis, and is more accurate than ERCP-guided transpapillary biopsy and cytology for identification of tumors[25,26]. Intraductal ultrasound provides high-definition images of the extrahepatic biliary tract, portal vein, and right hepatic artery. Furthermore, it is more accurate than standard EUS for differentiating between benign and malignant disease in indeterminate strictures (89% *vs* 76%), for establishing the degree of resectability in the case of malignant tumors (82% *vs* 76%), and for staging hilar cholangiocarcinoma, with an accuracy of 95%-100%[25,26]. Its diagnostic superiority is more pronounced in the case of proximal biliary lesions, where EUS is most limited. However, it does not make it possible to obtain tissue samples, is less useful for staging of regional lymph node involvement, requires the use of ERCP, and is not widely available at present[26].

Confocal laser endomicroscopy

Confocal laser endomicroscopy is an imaging technique that is performed by introducing a transpapillary probe along the working channel of a side view endoscope. It provides a microscopic view of the surface of the biliary epithelium that can be considered "*in vivo*" histology. The technique has the potential to differentiate in real time between malignant and benign biliary strictures with high accuracy in cases that remain indeterminate after ERCP or EUS. However, evidence of its use in clinical practice must be confirmed in more powerful studies. In addition, the technique is not available in most centers[25,26,28].

STAGING

Correct staging of cholangiocarcinoma is essential when attempting to determine resectability and the outcome of treatment[6]. The system used at present is the TNM classification system (8th edition, 2017-2018) of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC)[30]. This classification is specific for each subtype of CCA, given the differences in subtype management (Tables 1-3).

pCCA can be further subclassified according to the Bismuth-Corlette classification[31] (Figure 1). This classification is widely used, although it is subject to limitations, for example, it does not take into account vascular involvement and distant metastasis[2]; therefore, this is of little use in guiding decisions on therapy[6]. In 2011, the Mayo Clinic proposed a new system for classification and standardization of pCCA that, while more complex than the previous one, aims to standardize, more accurately defines surgical options, and distinguishes between different prognoses. It is applied depending on the size of the tumor, disease extension in the main bile ducts, hepatic artery and/or portal vein involvement, lymph node involvement, distant metastasis, and remnant liver volume after resection[6,32].

iCCA presents 3 growth patterns with different prognoses: Mass-forming (MF-iCCA), periductal infiltration (PI-iCCA), and intraductal growth (IG-iCCA). MF-iCCA

Table 1 Eighth edition of the TNM classification of the AJCC/UICC (2017-2018)[30] - Intrahepatic cholangiocarcinoma

Primary tumor (pT)	Regional lymph nodes (pN)	Distant metastasis (pM)	Stage grouping
TX: Primary tumor cannot be assessed	NX: Regional lymph nodes cannot be assessed		Stage 0: Tis N0 M0; Stage IA: T1a N0 M0; Stage IB: T1b N0 M0; Stage IIA: T2 N0 M0; Stage IIIA: T3 N0 M0; Stage IIIB: T4 N0 M0; any T N1 M0; Stage IV: any T any N M1
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M0: No distant metastasis	
Tis: Carcinoma in situ (intraductal tumor)			
T1: Solitary tumor without vascular invasion T1a: Solitary tumor ≤ 5 cm without vascular invasion; T1b: Solitary tumor > 5 cm without vascular invasion	N1: Regional lymph node metástasis	M1: Distant metástasis	
T2: Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion			
T3: Tumor perforating the visceral peritoneum			
T4: Tumor involving local extrahepatic structures by direct invasión			
Note: Tumor growth patterns (mass forming versus periductal) are no longer part of staging criteria but should still be reported	Notes: Regional lymph nodes depend on tumor site. For left sided lesions, regional nodes include inferior phrenic, hilar and gastrohepatic lymph nodes. For right sided lesions, regional nodes include hilar, periduodenal and peripancreatic lymph nodes.		

is the most common form, PI-iCCA that which has the poorest prognosis, and IG-iCCA the least common form with the best prognosis. pCCA and dCCA can also present growth patterns similar to those of PI-iCCA or IG-iCCA. MF-iCCA generally arises in the small, peripheral ducts, whereas PI-iCCA and IG-iCCA arise in the large intrahepatic biliary ducts[2,6].

TNM staging is based on imaging tests. MRI cholangiography is the main test for determining the T stage (primary tumor). It evaluates the number of primary nodules, vascular invasion, direct extension in neighboring tissue, and bile duct involvement. EUS enables imaging and histology of regional lymph nodes (N stage) with greater accuracy than CT and PET and provides additional information for the T stage by assessing the relationship between the tumor and the vasculature (portal vein and hepatic artery). CT of the abdomen, pelvis, and thorax is the best method for discovering possible distance metastases (M stage), as well as for evaluating the relationship between the tumor and the vessels with the addition of intravenous contrast[2,23]. Unlike hepatocarcinoma, tumor size is not considered important in the T stage and has been eliminated as a prognostic factor[6].

Inconclusive MRI cholangiography should be followed by ERCP or percutaneous transhepatic cholangiography to evaluate the T stage, since this is fundamental when taking decisions on surgery[23]. The usefulness of combining PET with CT is debatable; this combination should only be used in specific cases[23]. Laparoscopy can be considered for staging in specific cases to rule out the presence of occult peritoneal metastasis if this information will affect the decision on the type of resection[2,23].

At diagnosis, the tumor has extended to the lymph nodes in up to 50% of patients, and the peritoneum is involved in 10%-20%. While distant metastasis is infrequent and late in this type of cancer, exhaustive M staging should be carried out, especially in potentially resectable cases[2]. Staging must also take into account the patient's general status (*e.g.*, ECOG), comorbid conditions, associated diseases, and liver function test results[23].

TREATMENT

Table 2 Eighth edition of the TNM classification of the AJCC/UICC (2017-2018)[30] - Perihilar cholangiocarcinoma

Primary tumor (pT)	Regional lymph nodes (pN)	Distant metastasis (pM)	Stage grouping
TX: Primary tumor cannot be assessed	NX: Regional lymph nodes cannot be assessed		Stage 0: Tis N0 M0; Stage I: T1 N0 M0; Stage II: T2a-b N0 M0; Stage IIIA: T3 N0 M0; Stage IIIB: T4 N0 M0; Stage IIIC: any T N1 M0; Stage IVA: any T N2 M0; Stage IVB: any T any N M1
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M0: No distant metastasis	
Tis: Carcinoma in situ/high grade dysplasia			
T1: Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue	N1: One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct (choledochal), hepatic artery, posterior pancreatoduodenal and portal vein lymph nodes	M1: Distant metástasis	
T2: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue or tumor invades adjacent hepatic parenchyma; T2a: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue; T2b: Tumor invades adjacent hepatic parenchyma	N2: Four or more positive lymph nodes from the sites described for N1		
T3: Tumor invades unilateral branches of the portal vein or hepatic artery			
T4: Tumor invades the main portal vein or its branches bilaterally or the common hepatic artery; or unilateral second order biliary radicles with contralateral portal vein or hepatic artery involvement			

CCA should be managed in tertiary hospitals with a multidisciplinary team experienced in endoscopic, percutaneous, and surgical approaches. Management depends on the classification of the tumor. Thus, patients with early-stage disease could benefit from surgery, with complete surgical resection being the cornerstone of cure. However, only a minority of patients are diagnosed in the early stages and are suitable candidates for resection[33]. In the subset of patients diagnosed with locally advanced or metastatic disease, chemotherapy has been used to improve outcome and delay progression[34]. There is a subgroup of patients who, owing to their comorbid conditions, will only be candidates for symptomatic/palliative treatment[23].

SURGICAL TREATMENT

Resection is the only option that provides a real possibility of long-term survival in patients diagnosed with CCA. Improved staging of these tumors and a more aggressive surgical approach have improved the outcome of surgery. Even so, in most series, only 30%-65% of patients with CCA have potentially resectable tumors. The possibility of a radical resection increases if hepatectomy is routinely combined with resection of the biliary tract. Similarly, resection of the caudate lobe helps to reduce the number of patients with affected surgical margins[35]. Morbidity and mortality are high after resection of CCA. The risk increases somewhat if the patient has both cholestasis and hypoalbuminemia during the preoperative period. Therefore, preoperative optimization is essential in such cases.

The indication and extension of surgery depends on the clinical status of the patient, functional liver reserve, and the location and extension of the tumor, which includes the association with vascular structures and negative metastatic disease. Block resection with macroscopically and microscopically negative margins (R0) is the main prognostic factor[36].

The criteria considered absolute for unresectability are the presence of nonresectable extrahepatic or hepatic metastases, bilateral extension of the tumor with involvement of the secondary biliary tract, complete occlusion of the main portal vein,

Table 3 Eighth edition of the TNM classification of the AJCC/UICC (2017-2018)[30] - Distal cholangiocarcinoma

Primary tumor (pT)	Regional lymph nodes (pN)	Distant metastasis (pM)	Stage grouping
TX: Primary tumor cannot be assessed	NX: Regional lymph nodes cannot be assessed		Stage 0: Tis N0 M0; Stage I: T1 N0 M0; Stage IIA: T1 N1 M0 or T2 N0 M0; Stage IIB: T2 N1 M0 or T3 N0-1 M0; Stage IIIA: T1-3 N2 M0; Stage IIIB: T4 N0-2 M0
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M0: No distant metastasis	
Tis: Carcinoma in situ / high grade dysplasia			
T1: tumor invades the bile duct wall with a depth less than 5 mm	N1: Metastasis in one to three regional lymph nodes	M1: Distant metástasis	
T2: Tumor invades the bile duct wall with a depth of 5 - 12 mm	N2: Metastasis in four or more regional lymph nodes		
T3: Tumor invades the bile duct wall with a depth greater than 12 mm			
T4: Tumor invades the celiac axis, superior mesenteric artery or common hepatic artery			

or thrombosis of the portal vein contralateral to the tumor. Criteria that can be considered relative for unresectability are insufficient liver remnant and cholestasis or cholangitis at diagnosis.

In patients who are candidates for surgery but have a relative criterion, ipsilateral portal vein embolization can lead to compensatory hypertrophy of the healthy remnant liver. Similarly, in patients with cholestasis, percutaneous drainage of the biliary tract can help to resolve congestive cholestasis, as well as episodes of cholangitis. It is also beneficial in undernourished patients or those with liver failure. When possible, drainage should be applied on the side of the liver that is not going to be resected; similarly, an external drain should only be placed with the aim of not crossing the tumor and thus preventing potential dissemination[37,38]. Drainage can increase postoperative complications and hamper surgery. In addition, it has been associated with an increased probability of peritoneal metastasis. Therefore, it should not be performed systematically and is not considered essential in the following cases: recent-onset jaundice (< 2-3 wk), total bilirubin < 11.7 mg/dL, absence of sepsis, and future liver reserve > 40%. Outside these criteria, the risk-benefit ratio seems favorable for placement of a drain. Furthermore, if portal vein embolization is necessary to increase the liver reserve, then presurgical biliary drainage should be performed in the absence of the previous criteria[39].

The classic approach, via laparotomy, has gradually been replaced in recent years by minimally invasive techniques such as laparoscopy and robot-guided surgery. The outcome of this approach when performed by experts is comparable to that achieved with conventional surgery, thus minimizing the morbidity associated with the classic surgical technique, reducing length of stay, and improving clinical outcome. Irrespective of the approach, a complete examination of the abdominal cavity is necessary to determine whether there is extrahepatic disease. Similarly, intraoperative ultrasound makes it possible to evaluate local resectability[40].

Surgical treatment of Bismuth-Corlette type I and II Klatskin tumor includes cholecystectomy, limited resection of the extrahepatic pathway, and lymphadenectomy with bilioenteric reconstruction (normally Roux-en-Y hepaticojejunostomy). Most authors recommend combining this approach with type II hepatectomy (Figure 2).

Surgical treatment of stage IIIa and IIIb tumors includes the following: Cholecystectomy, partial resection of the main biliary tract, lymphadenectomy of the hepatic hilum, right hepatectomy (IIIa), left hepatectomy (IIIb), resection of the caudate lobe, and bilioenteric reconstruction (hepaticojejunostomy). After excluding tumors with extensive portal and/or arterial involvement, type IVa tumors (TNM classification)[30] can be candidates for the same treatment as Bismuth-Corlette type III tumors, although in combination with extended hepatectomy and extensive lymphadenectomy to N2. Type IVb tumors (TNM classification) are not candidates for resection; therefore, a palliative stent should be placed as the best option for therapy[41,42].

Once surgery has begun, the main reasons for unresectability during the examination of the abdominal cavity are underestimation of the extension of the tumor in

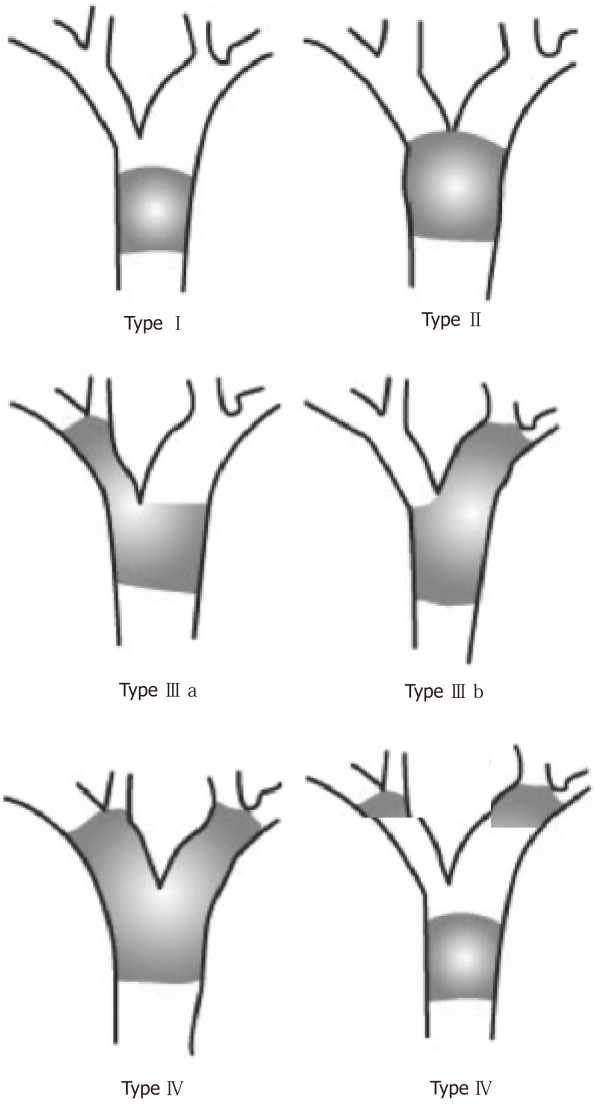

Figure 1 Bismuth-Corlette classification of pCCA (modified from Guidi *et al*[109]). Type I: The tumor is located below the confluence of the left and right hepatic ducts and involves the common hepatic duct. Type II: The tumor involves the bifurcation of the common hepatic duct but does not affect the left or right hepatic ducts. Type III: The tumor occludes the common hepatic duct and the right hepatic duct (IIIa) or left hepatic duct (IIIb). Type IV: The tumor involves both the right and the left hepatic ducts or there is bilateral involvement or involvement of multiple intrahepatic segments.

the preoperative diagnosis, severe vascular involvement, and metastatic disease. Staging laparoscopy can clarify the presence of occult metastases in up to one third of patients and should be considered in patients with a percutaneous drain, large tumors, or very high serum CA19.9 levels[37].

The combination of hepatectomy with portal vein or artery resection is technically possible in expert hands and in very specific patients. Resection of segment 1 should be protocol-based, irrespective of the hepatectomy to be performed, since CCA can spread to the caudate lobe via small direct branches from the main branches or even from the confluence itself. Therefore, 43% to 100% of cases could be affected[43].

The rate of R0 reaches 75% in experienced centers, with more than 50% of patients disease-free at 5 years.

Perihilar CCA that is technically unresectable in stages I-II could be treated with total hepatectomy, resection of the extrahepatic biliary tract, and liver transplant, although only in reference centers with an intensive neoadjuvant treatment protocol[37]. While much controversy surrounds the indication for liver transplant, this approach seems to be increasingly beneficial, since not only do we achieve radical resection of the tumor and microscopic disease that could go unnoticed during surgery, but there are also no limitations with respect to vascular involvement or with future liver remnant. The neoadjuvant treatment regimen used in these cases is so

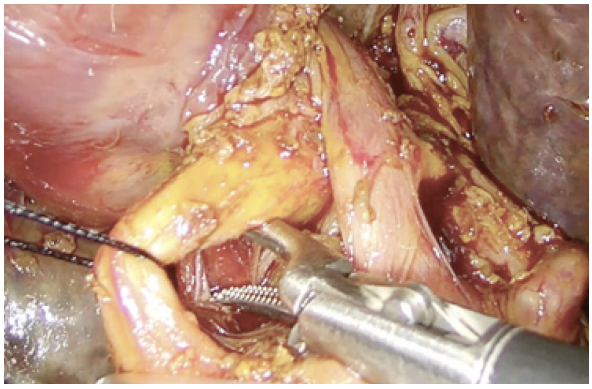

Figure 2 Lymph node dissection in the hepatic hilum (N1) during the resection of a Klatskin tumor.

hepatotoxic that it cannot be used in those patients who are to undergo partial hepatectomy. Furthermore, it combines radiotherapy, chemoembolization, and brachytherapy before transplant, thus achieving results of 90%, 80%, and 71% at 1, 3, and 5 years, respectively[39].

Surgical treatment of intrahepatic cholangiocarcinoma includes hepatectomy, which can be more or less extensive, with hilar and suprapancreatic lymph node dissection, either alone or in combination retroperitoneal lymph node dissection. For some authors, retroperitoneal lymph node dissection is only indicated in centrally located tumors. The finding of positive nodes in the hilar or suprapancreatic territory (N1) is not a contraindication for surgery, although it should be taken into account in cases of retroperitoneal involvement (N2). Similarly, macroscopic involvement of the para-aortic nodes, the celiac trunk, or the superior mesenteric artery should be considered a contraindication for surgery. A tumor resection margin of at least 1 cm is recommended. Up to 70% of the liver volume can be resected, providing that the healthy liver has a good functional reserve[39,44,45].

In recent years, increasing number of patients with unresectable intrahepatic and extrahepatic CCA are being included for liver transplant, always based on very rigorous clinical criteria. This is due, to a large extent, to lower numbers of recipients with hepatitis C virus cirrhosis, which in turn increases the number of organs to be transplanted, and to the development of chemotherapy drugs, which improve the survival of these patients.

The most common postoperative complications are hemorrhage, infection, liver failure, cardiorespiratory failure, and adrenal failure. Mean postoperative mortality is 8.2% (3%-17%), with morbidity of 50% (31%-85%). It is important to remember that since most of these publications are from experienced centers with a high surgical volume, global figures could be even higher[37].

ENDOSCOPIC AND RADIOLOGICAL MANAGEMENT

Indications for biliary drainage

Preoperative biliary drainage is recommended in patients with cholangitis, intense symptomatic jaundice, jaundice before neoadjuvant chemotherapy, delayed surgery, severe malnutrition, and liver or kidney failure, as well as in candidates for portal vein embolization[6,46]. Despite the fact that preoperative biliary drainage has been seen to reduce morbidity and mortality overall[3], there is some controversy over its indication in patients with severe jaundice: some studies have shown a greater risk of postoperative complications[47] and lower survival, possibly as a result of delaying surgery[48]. Nevertheless, a more recent retrospective study recommends preoperative biliary drainage in order to increase survival[49].

Drainage is also considered palliative treatment in patients with unresectable CCA, leading to greater survival and cost savings than in patients with similar characteristics who undergo surgery[4].

The main advantages of biliary drainage are improvement of jaundice, prevention of cholangitis, and prevention of the hepatotoxicity induced by the chemotherapy drugs used. We must not ignore the risks inherent to drainage, such as pancreatitis or possible contamination of a normally sterile site. Therefore, decisions on drainage should be taken after weighing up the risks and benefits in each case[1].

PALLIATIVE BILIARY DRAINAGE

The best strategy for biliary drainage should take 3 factors into account: (1) Possible contamination in sequestered biliary segments; (2) Potential surgical resection with curative intent; and (3) The need to optimize preservation of liver function with a view to initiating chemotherapy[50]. Therefore, a different approach must be used for decompression of the biliary tract, namely, ERCP, percutaneous drainage, or surgery (bypass).

ERCP-guided endoscopic biliary drainage

In line with the European Society of Gastrointestinal Endoscopy (ESGE), ERCP-guided decompression of the biliary tract is considered the technique of choice, with a lower rate of procedure-related complications, shorter hospital stay, and better survival rates than percutaneous or surgical interventions, thus making it the most cost-effective approach[3,8,9]. ERCP-guided drainage is the preferred approach in Bismuth-Corlette types I and II CCA. In conventional ERCP, the first step is to cannulate the biliary tract in order to insert the stent through the working channel of the endoscope. Despite the high success rates with ERCP-guided drainage, the biliary tract cannot be cannulated in some cases for technical reasons (infiltration of the ampulla of Vater, duodenal stricture due to bulky tumors, or anatomical abnormalities caused by previous interventions). The main options in these cases are percutaneous or surgical drainage. EUS-guided biliary drainage is a more recent technique that is being used for treatment of distal extrahepatic CCA[51-53]. In patients with anatomical abnormalities caused by Roux-en-Y hepaticojejunostomy or pancreaticoduodenectomy, we can use enteroscopy-assisted ERCP, which has proven less successful than other approaches. Therefore, in patients with cholangitis for whom biliary drainage cannot be delayed, the recommended approach is percutaneous or surgical drainage.

Percutaneous transhepatic cholangiography and internal/external biliary drainage

This approach is indicated after failure of ERCP-guided drainage and in cases of proximal extrahepatic biliary obstruction in which the stent cannot be placed using ERCP or in cases of intrahepatic biliary obstruction. The technique enables selective and direct access to intrahepatic bile ducts, thus avoiding contamination of the tract on crossing the papilla[54]. If the guidewire manages to reach the duodenum, an internal/external biliary drainage catheter is inserted. If this is not possible, an external drain can be inserted to decompress the biliary tract. This is a transient step until a second and definitive attempt can be made.

Endoscopic ultrasound–guided biliary drainage/EUS–assisted ERCP

This is becoming an attractive option for patients who cannot undergo conventional ERCP and who are not candidates for or refuse to undergo percutaneous or surgical drainage. The approach includes 3 techniques[55]:

EUS-guided rendezvous technique: Access to the biliary tract is via ultrasound and fluoroscopic guidance, ideally toward the common bile duct, which is more stable than the common hepatic duct, as it is surrounded by the pancreas. Once the location is determined after aspirating bile, the contrast is injected, and the guidewire is inserted toward the ampulla of Vater up to the duodenum. Endoscopy is then replaced by duodenoscopy (ERCP scope), the guidewire is inserted along the working channel, and the procedure is continued in the same way as conventional ERCP.

EUS-guided intrahepatic duct access: This technique is similar to transhepatic percutaneous drainage. The branches of the left hepatic duct are accessed via the abdominal wall with an endoscopy-guided 19F needle. The guidewire is then inserted toward the ampulla and the procedure is continued in the same way as a conventional ERCP.

EUS-guided extrahepatic duct access: This technique is indicated when it is not possible to access the second part of the duodenum owing to duodenal stricture. Access to the bile duct is *via* endoscope in the duodenal bulb, the guidewire is inserted toward the intrahepatic ducts, with a stent in place in order to maintain the choledochoduodenostomy.

Comparison of endoscopic and percutaneous biliary drainage

Percutaneous biliary drainage has traditionally been the preferred approach before surgical resection. Advances in and greater availability of endoscopy have led several authors to compare biliary drainage using an endoscopic stent with that based on a percutaneous stent. No differences were observed with respect to procedure-related

complications or mortality[56], and percutaneous drainage was not shown to be more successful than endoscopic drainage[57]. In a more recent systematic review, percutaneous drainage was associated with a lower frequency of cholangitis and pancreatitis and better success rate[58], although other retrospective studies warn of the risk of metastatic seeding and lower survival[59-61]. Similarly, the E-POD Hilar Study found no advantage for endoscopic nasobiliary drainage over endoscopic biliary stenting when both were performed as the initial procedure in patients with resectable CCA. Stenting was technically more successful than endoscopic nasobiliary drainage[62].

A recently published prospective study with the objective of comparing the incidence of severe complications had to be suspended early because of high mortality in the percutaneous drainage group (*vs* the endoscopic group)[63].

A prospective study that compared endoscopic drainage with surgery found no differences with respect to postsurgical complications and survival rate, although the cost was lower in the endoscopic group[64].

TYPES OF STENT

Depending on the stage at which CCA is diagnosed, the tumor can be managed with plastic stents or self-expandable metallic stents (SEMS). SEMS can be fully covered or uncovered.

Plastic stents

Plastic stents can be of various materials (polyethylene, Teflon, or polyurethane). Polyethylene stents are more flexible than Teflon stents and adapt better to the biliary tract. While 10F stents have been shown to be the most patent[46], they are generally patent for no more than 3-4 mo, and ERCP must often be repeated owing to occlusion of the stent by biliary sludge, tumor growth, or formation of biofilm.

Self-expandable metal stents

SEMS were developed to overcome the limitations of plastic stents. They are more patent with fewer complications, lower reintervention rates, and greater survival than plastic stents as a palliative option, with no significant differences with respect to cost[65-69].

The ESGE recommends the use of uncovered SEMS as a palliative treatment in patients with unresectable hilar biliary obstruction, although its patency may be limited by growth of the tumor within the stent, stent margins, obstruction with debris or food remains, or epithelial hyperplasia. The ESGE does not advocate this type of stent for drainage of biliary obstruction of unknown origin, and recommends using plastic stents or fully covered stents until the cause is determined[46].

Covered SEMSs can be used for distal malignant biliary obstruction. The ESGE recommends fully covered 10-mm SEMSs for preoperative biliary drainage in patients who are to receive neoadjuvant treatment, since they are patent for longer and are less likely to migrate[46]. Covered stents are not indicated in patients with hilar tumors, since they block the contralateral hepatic duct and the intrahepatic branches of the same lobe, thus potentially causing cholangitis. Similarly, they are not indicated in patients who have not undergone cholecystectomy, since they could cause cholecystitis by blocking the exit cystic duct. These stents have a lower rate of intrastent tumor growth and can be removed *via* endoscopy.

Covered SEMS were associated with a lower risk of intraluminal tumor growth than uncovered SEMS, although they carry a greater risk of migration, extraluminal tumor growth, and formation of sludge[70-72].

In addition to having the advantages of other covered stents, the recently developed multihole covered SEMS can be placed in patients with hilar tumors or gall bladder tumors, since they can be drained through the openings in the stent.

In unresectable CCA, the SEMS can be placed unilaterally, bilaterally, side-by-side, or stent-in-stent, although there is no consensus on the technique of choice[73]. There are also reports of percutaneous placement of a tri-metal stent in cases of inoperable perihilar tumors, with better results for biliary drainage and stent patency[74].

COMPLICATIONS AFTER BILIARY DRAINAGE

The main complications after biliary drainage are pancreatitis, cholangitis, cholecystitis, hemorrhage, and perforation.

As for the use of sphincterectomy before placement of the stent in order to prevent post-ERCP pancreatitis, a recent meta-analysis showed this was associated with a

greater risk of cholangitis and bleeding during the first 30 days after the procedure, with no significant differences in the rate of post-ERCP pancreatitis[75]; therefore, this procedure should be performed systematically.

OUTLOOK FOR THE FUTURE

New research lines in endoscopy-based locoregional treatment that go beyond decompression with stents include photodynamic therapy and, more recently, cholangioscopy-guided radiofrequency ablation, which has shown promising results in patients with locally advanced or unresectable tumors. Further studies are necessary to confirm the long-term benefits of both techniques[76].

ADJUVANT TREATMENT FOR RESECTED BILIARY TRACT MALIGNANCIES

The aim of adjuvant treatment in biliary tract cancer (BTC) is to treat micrometastatic disease, thus improving relapse-free survival and overall survival (OS). Although various studies have been published in recent years, no standard adjuvant regimen has been established for BTC.

A retrospective study of 62 patients with BTC and adverse features (N1, R1, liver metastases)[77] reported that 28 patients received GFP chemotherapy (gemcitabine plus low-dose 5FU plus cisplatin). Three-year OS was 62% in the adjuvant chemotherapy arm compared with 9% in the nonadjuvant arm ($P < 0.001$).

Another retrospective cohort study included 1335 patients with T1-3 N1 M0 gallbladder cancer and 1009 patients with intrahepatic CCA from the National Cancer Database. The authors concluded that the addition of adjuvant chemotherapy and radiotherapy improved OS in the subset of patients with gallbladder cancer, regardless of margin involvement, although this improvement was not seen with adjuvant chemotherapy alone. However, this benefit from adjuvant chemotherapy or radiotherapy was not seen in patients with intrahepatic cholangiocarcinoma[78].

The benefit of adjuvant chemotherapy was explored in the phase III BILCAP trial, in which 447 patients with resected BTC (368 with intrahepatic, hilar, or extrahepatic CCA) were randomly assigned to receive 8 cycles of capecitabine compared with placebo. The intent to treat analysis revealed a potentially clinically relevant but not statistically significant improvement in OS (median 51 mo *vs* 36 mo; HR = 0.81; 95%CI: 0.63-1.06). However, the benefit was statistically significant when a per protocol analysis was performed (median 53 mo *vs* 36 mo; HR = 0.75; 95%CI: 0.58-0.97)[79].

Results from another recently published phase III trial comparing adjuvant treatment with gemcitabine monotherapy versus placebo in patients with CCA showed no significant differences in OS between the 2 arms (median 62.3 mo *vs* 63.8 mo; HR, 1.01; 95% CI, 0.70-1.45)[80].

A phase III randomized study comparing adjuvant GEMOX (gemcitabine plus oxaliplatin) versus observation in 196 patients with resected BTC[81] found that median relapse-free survival was 30.4 mo in patients who received chemotherapy compared with 18.5 mo in those who did not (HR = 0.88; 95%CI: 0.62-1.25; $P = 0.47$). Similarly, median OS was not significantly different (75.8 mo *vs* 50.8 mo; HR = 1.08; 95%CI: 0.70-1.66; $P = 0.74$).

Finally, a meta-analysis that included 20 studies and more than 6000 patients suggested that patients with high-risk features such as those with node or margin positivity appeared to derive the clearest benefit from adjuvant strategies[82]. A statistically significant OS advantage was seen in node-positive disease for any adjuvant therapy modality (OR = 0.49; 95%CI: 0.30-0.80), with 77% of patients treated with chemotherapy alone. Similarly, efficacy outcomes were shown for margin-positive disease (OR = 0.36; 95%CI: 0.19-0.68). Of note, radiotherapy only benefited patients with R1 disease, while after R0 resection, it was associated with a trend toward worse OS.

Although this analysis supports adjuvant treatment for high-risk patients with BTC, it does not define the best treatment modality in this setting or the benefit of adjuvant therapy for patients with low-risk disease. High-quality randomized clinical trials are ongoing, although more are required[83,84].

Based on the previous results, the National Comprehensive Cancer Network (NCCN) guidelines suggest adjuvant concurrent FU-based chemoradiotherapy in patients with positive margins, carcinoma in situ at the margins, or positive lymph nodes after resection for CCA[85]. Guidelines from the European Society of Medical

Oncology (ESMO) suggest that in the absence of level 1 evidence, adjuvant therapy (chemotherapy, chemoradiotherapy, or radiotherapy) may be offered to patients based on the best data available after a risk-benefit assessment[23].

SYSTEMIC TREATMENT FOR ADVANCED DISEASE

Systemic chemotherapy is the treatment of choice for patients with locally advanced or metastatic disease and adequate performance status[23].

First- and second-line chemotherapy

Few prospective trials have been performed in the first-line setting in advanced BTC. The multicenter phase III ABC-02 study showed that the combination of cisplatin and gemcitabine achieved a median OS of 11.7 mo compared with 8.1 mo for gemcitabine in monotherapy[86]. A similar phase II study carried out in a Japanese population demonstrated a benefit in OS with the combination regimen[87].

Chemotherapy with gemcitabine and cisplatin has not been directly compared in phase III studies with other gemcitabine-containing regimens, except for gemcitabine plus S-1 in the Japanese phase III FUGA-BT trial. In a preliminary report presented at the 2018 Gastrointestinal Cancers Symposium, which is supported by the American Society of Clinical Oncology, this combination was not inferior in median OS (15.1 mo *vs* 13.4 mo; HR = 0.95; 95%CI: 0.78-1.15), median progression-free survival (PFS) (6.8 mo *vs* 5.8 mo), or overall response rate (ORR) (30 *vs* 32 percent)[88]. In patients with renal impairment, oxaliplatin can be replaced by cisplatin. In a phase II trial of GEMOX, median OS was 15.4 mo in the subgroup of patients with good performance status and adequate liver function[89]. In patients with a performance status of 2, gemcitabine monotherapy may be an option[86].

Based on recent studies, the addition of nanoparticle albumin-bound (nab)-paclitaxel to gemcitabine-cisplatin for the treatment of patients with advanced biliary tract cancer seems promising[90].

Despite the improvement in outcome with first-line treatment, the disease progresses in most cases. There are no prospective studies of specific chemotherapy regimens in this setting, since randomized clinical trials are difficult to perform owing to the rarity and heterogeneity of the tumors.

For patients progressing on gemcitabine and cisplatin chemotherapy, options for treatment may include a fluoropyrimidine alone or in combination with oxaliplatin[91]. Other options for patients whose gemcitabine plus oxaliplatin regimen fails include the combination of a fluoropyrimidine with cisplatin or irinotecan[92].

Molecularly targeted therapy

Recent molecular studies have increased our understanding of the pathogenetic mechanism of CCA.

Emerging data from next-generation sequencing analyses have identified actionable mutations that could be managed with several targeted agents in clinical development. The results of these analyses are promising. Other therapies such as immunotherapy in patients with microsatellite instability have also emerged in the landscape of BTC[93,94].

The FGF pathway regulates cell proliferation, migration, and angiogenesis. Alterations in genes encoding fibroblast growth factor receptors (FGFRs) can promote aberrant FGF pathway activation and the development of tumorigenesis[95]. FGFR fusions and translocations constitute driver mutations in CCA and are present in 13% to 17% of intrahepatic CCAs. BGJ398 is an oral selective pan-FGFR inhibitor with activity in tumor models harboring FGFR alterations. BGJ398 was evaluated in a multicenter phase II trial of 61 heavily pretreated patients with FGFR alterations[96]. The ORR was 14.8%, the disease control rate was 75.4%, and the estimated median PFS was 5.8 mo (95%CI: 4.3 to 7.6 mo).

Other agents against FGFR2 resistance mutations have shown activity in patients with advanced CCA. The phase I/II basket trial evaluated the novel FGFR inhibitor TAS-120 in 23 patients with FGFR2 fusion and other FGFR-altered CCAs. Four of 9 patients achieved a partial response. TAS-120 is currently being studied in a large basket trial with a planned enrollment of 800 patients[97].

Mutations in the isocitrate dehydrogenase (IDH) genes *IDH1* and *IDH2*, which occur in about 20% of intrahepatic CCAs, constitute promising targets for patients with BTC[92]. Ivosidenib (AG-120) is an oral, selective, reversible inhibitor of mutant IDH1 that is currently being evaluated in phase III studies of CCA and acute myeloid leukemia[98].

Studies of melanoma and colorectal cancer have suggested that tumors with *BRAF*-activating mutations are sensitive to MEK inhibition[99]. The efficacy and safety of

selumetinib, a MEK1/2 inhibitor, was explored in a multi-institutional phase II study of 28 patients with metastatic BTC. Three patients had a confirmed objective response, and a further 17 patients had stable disease[100]. The combination of dabrafenib (a *BRAF* inhibitor) and trametinib (a MEK inhibitor) in patients with *BRAF* V600E–mutant metastatic BTC was recently reported to be active. The preliminary report of a cohort of the phase II ROAR basket trial presented at the 2019 Gastrointestinal Cancers Symposium showed an ORR of 42%. In addition, the response lasted 6 mo or longer in 7 patients. Median PFS was 9.2 mo and median OS was 11.7 mo[101]. The authors concluded that dabrafenib plus trametinib should be considered a therapeutic option for patients with *BRAF*-mutant BTC.

Cholangiocarcinoma is considered as a chemoresistant tumour. Chemosensitization strategy to improve the response of CCA is recently under discussion[102].

Immunotherapy for patients with deficiency in the mismatch repair system

The immune system plays a role in the surveillance and eradication of malignant cells. Tumors that lack the mismatch repair system harbor more mutations than those without this deficiency, and the neoantigens generated can be recognized as immunogenic antigens. The biologic footprint of mismatch repair–deficient tumors is microsatellite instability (MSI). About 3% of CCAs are mismatch repair–deficient/MSI-high, which makes them susceptible to programmed cell death protein 1 (PD-1) inhibitors[103]. In a study of 86 patients with 12 different tumors (including advanced CCAs), pembrolizumab was administered to those with a deficiency in the mismatch repair system. Objective responses were observed in 54% of patients with non-colorectal cancer, and 21% had complete responses (1 patient with CCA)[104].

Targeting angiogenesis and EGFR

Vascular endothelial growth factor (VEGF) is overexpressed in BTC. Bevacizumab, a monoclonal antibody that blocks the VEGF receptor, has been evaluated in combination with a variety of chemotherapy agents with promising results. A single-arm phase II study of bevacizumab with gemcitabine and oxaliplatin showed efficacy against BTC, with a median PFS of 7 mo and OS of 12.7 mo[105]. However, these results should be interpreted with caution owing to the absence of an internal control arm to estimate the true benefit conferred by bevacizumab.

Erlotinib is a tyrosine kinase inhibitor that blocks the ATP binding site of the epidermal growth factor receptor (EGFR). This drug has been studied in combination with cytotoxic chemotherapy and bevacizumab. The addition of erlotinib to chemotherapy failed to prolong PFS compared with chemotherapy alone[106]. On the other hand, the combination of bevacizumab and erlotinib demonstrated clinical activity with a low frequency of grade 3/4 adverse effects in patients with advanced BTC[107].

Cetuximab and panitumumab are monoclonal antibodies that selectively block EGFR. The survival benefit of adding cetuximab to gemcitabine-oxaliplatin, could not be confirmed in a randomized phase II study that included 150 patients with advanced BTC[108].

The efficacy of panitumumab in combination with platinum-based chemotherapy was also explored in a randomized phase II study that included 89 patients with *KRAS* wild-type advanced BTC. Median PFS was similar en both groups, and no differences were observed in OS[109]. The results of these trials confirm the marginal role of anti-EGFR agents in the treatment of advanced BTC.

Finally, it is important to emphasize the need to identify patients who derive the most benefit from different treatment options assessed according to molecular profiles. By integrating comprehensive molecular characterization of tumors with targeted therapy, we hope to achieve the goal of precision medicine for patients with BTC.

CONCLUSION

Diagnosis of CCA is sometimes challenging for the clinician. The tumor must be managed in tertiary hospitals with a multidisciplinary team experienced in endoscopic, percutaneous, and surgical approaches. Depending on the location and local and distant extension, we can offer patients potentially curative surgery. In most cases, chemotherapy is used to improve survival and delay tumor progression. Some patients can only be offered symptomatic treatment owing to their comorbidities.

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