Review Article

Cancer review: Cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) is the most common biliary tract malignancy. CCA is classified as intrahepatic, perihilar or distal extrahepatic; the individual subtypes differ in their biologic behavior, clinical presentation, and management. Throughout the last decades, CCA incidence rates had significantly increased. In addition to known established risk factors, novel possible risk factors (i.e. obesity, hepatitis C virus) have been identified that are of high importance in developed countries where CCA prevalence rates have been low. CCA tends to develop on the background of inflammation and cholestasis. In recent years, our understanding of the molecular mechanisms of cholangiocarcinogenesis has increased, thereby, providing the basis for molecularly targeted therapies. In its diagnostic evaluation, imaging techniques have improved, and the role of complementary techniques has been defined. There is a need for improved CCA biomarkers as currently used ones are suboptimal. Multiple staging systems have been developed, but none of these is optimal. The prognosis of CCA is considered dismal. However, treatment options have improved throughout the last two decades for carefully selected subgroups of CCA patients. Perihilar CCA can now be treated with orthotopic liver transplantation with neoadjuvant chemoradiation achieving 5-year survival rates of 68%. Classically considered chemotherapy-resistant, the ABC-02 trial has shown the therapeutic benefit of combination therapy with gemcitabine and cisplatin. The benefits of adjuvant treatments for resectable CCA, local ablative therapies and molecularly targeted therapies still need to be defined. In this article, we will provide the reader with an overview over CCA, and discuss the latest developments and controversies.

Keywords: Cholangiocarcinoma, extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma

INTRODUCTION

Cholangiocarcinoma (CCA) is the most common biliary tract malignancy. Based on its location, CCA is classified as intrahepatic, perihilar or extrahepatic CCA – the latter two were previously grouped together as extrahepatic CCAs. The three CCA types differ in their cancer biology, clinical presentation and management. Tumors that arise from the bifurcation of the common hepatic duct were described in 1965 by Gerald Klatskin, hence termed as Klatskin's tumor.[1] Perihilar CCA is the most common type of CCA; clinically, it can be classified into Type I to IV based on the Bismuth–Corlette classification [Table 1]. Macroscopically, CCAs can be described according to their growth pattern as mass-forming, periductal infiltrating or intraductal papillary. Intrahepatic CCA shows predominantly a mass-forming growth pattern while extrahepatic CCA is predominantly periductal-infiltrating.[2] Histologically, 90% of CCA's are

adenocarcinomas with other variants including signet-ring type, clear cell type, papillary adenocarcinoma, intestinal type adenocarcinoma, oat cell carcinoma, adenosquamous carcinoma and squamous cell carcinoma.[3]

EPIDEMIOLOGY

CCA is the second most common primary hepatic malignancy accounting for 10–20% of primary liver cancers.[4] The average age at presentation is 50 years, with the majority of cases in the Western world diagnosed at or after the age of 65 years. Extrahepatic and perihilar CCA are the most common types with 6–8% of CCAs being intrahepatic, 50–67% perihilar and 27–42% distal extrahepatic.[5,6]

Intrahepatic cholangiocarcinoma
In the United States, incidence rates of intrahepatic CCA have increased by 165% between the late 1970's and the late 1990's from 0.32/100,000 to 0.85/100,000.[7] Annual prevalence rates in the US, between 1990 and 2000, were highest among Hispanics at 1.22/100,000 and lowest among African-Americans at 0.3/100,000.[8] The rise in its incidence has been observed globally, but the exact cause for this increase has not been conclusively determined. The highest CCA prevalence rates have been reported in Northeast Thailand, an area with a high prevalence of liver fluke infestations.[4,9] In the US, annual age-adjusted mortality rates have increased from 0.07/100,000 in 1973 to 0.69/100,000 in 1997.[10] There is a trend toward higher mortality among male as compared to female CCA patients. The 1-year-relative survival rates have improved from 16.4% in the 1970's to 27.6% in the 1990's, but there was no significant change in the 5-year survival rate (<5%).[4]

Extrahepatic cholangiocarcinoma
Epidemiologic data for extrahepatic CCA is frequently flawed due to its combined analysis with gallbladder carcinoma. Globally, extrahepatic CCA is the most common form of CCA; whereas in East Asian countries, intrahepatic CCA is more the common form.[11] In the US, the surveillance, epidemiology, and end results database showed an overall incidence of extrahepatic CCA of 1.2/100,000 in males and 0.8/1000,000 in females between 1973 and 1987.[12] Between 1992 and 2000, its incidence rates remained fairly stable (95% confidence interval [CI] - 1–3%, *P* = 0.33).[13] The majority of perihilar CCA cases are diagnosed after 65 years of age with a male predominance of 52%. The mortality rates have decreased from 0.6/100,000 in 1979 to 0.3/100,000 in 1998.[4,10] There was a modest improvement in 5-year survival rates, which was 11.7% between 1973–1977, and 15.1% in 1983–1987.[12] With the establishment of novel, potentially curative treatments (see below) survival rates of perihilar CCA will have to be re-examined.

ETIOLOGY

Several conditions have been linked to CCA carcinogenesis [Table 2]. Some are considered established risk factors such as primary sclerosing cholangitis (PSC) while some have a weak association and are therefore considered possible risk factors. Multiple studies have shown the association between PSC and CCA.[14-17] Individuals with PSC have a 13% lifetime risk of developing CCA.[15] In a study by Burak *et al.*, 161 patients with PSC were followed for 11.6 years; 7% of these patients developed CCA.[17] Liver fluke infestation is strongly associated with the development of CCA.[18] Prevalence rates of CCA are high in parts of the world with high prevalence rates of liver-fluke infestations, especially in regions where it is endemic such as in certain regions of South-East Asia.[4,9,11] The most commonly implicated species of liver flukes are *Opisthorchis viverrini* and *Clonorchis sinenesis*, which are acquired by oral ingestion of undercooked fish and can inhabit the gallbladder and biliary tree of the human host.[9,19,20] CCA can develop in the setting of choledochal cysts;[21] especially type I (solitary, extrahepatic) and type IV (extrahepatic and intrahepatic) cysts are associated with a high risk for cholangiocarcinogenesis and lifetime incidence rates of 6–30%.[22,23] While cyst excision reduces the risk for CCA, it does not eliminate it.[22] Caroli's disease, a rare congenital disorder characterized by nonobstructive dilatation of segmental intrahepatic bile ducts, has been linked with development of intrahepatic CCA.[23] The

Table 1: Bismuth-Corlette classification of perihilar CCA

Type	Anatomic location
I	Common hepatic duct distal to the biliary confluence
II	Involves the biliary confluence
IIIa	Biliary confluence and right hepatic duct
IIIb	Biliary confluence and left hepatic duct
IV	Extending to the bifurcation of left and right hepatic ducts or multifocal

CCA: Cholangiocarcinoma

Table 2: Risk factors associated with cholangiocarcinogenesis

Risk factors of cholangiocarcinogenesis
PSC
Liver flukes - *Opisthorchis viverrini* and *Clonorchis sinensis*
Hepatolithiasis
Caroli's disease
Congenital hepatic fibrosis
Choledochal cysts
Viral hepatitis B and C infection
Liver cirrhosis
Chemical compounds - dioxin, thorotrast
Obesity and diabetes

PSC: Primary sclerosing cholangitis

presence of gallstones in the intrahepatic biliary tree, known as "hepatolithiasis," has been associated with a 5% incidence of CCA.[24] Toxic agents like thorotrast and dioxin have been implicated in the development of CCA.[25,26] Congenital hepatic fibrosis is an uncommon clinical condition that has been associated with CCA.[27]

Recent data suggested associations between of hepatitis B virus (HBV) and HCV infections with cholangiocarcinogenesis, in particular with intrahepatic CCA.[28-30] In a recent meta-analysis an association between cirrhosis and CCA has been suggested.[31] Furthermore, associations between obesity and intrahepatic CCA have been reported.[31,32] In a meta-analysis of 5 cohort and 5 case–control studies, the odds ratio of CCA was 1.37 (95% CI of 1.22–1.55) among those with excess body weight compared to those with normal weight.[32] Some authors have also described an association between diabetes and extrahepatic CCA.[33,34] In a Taiwanese population based study of 5157 CCA cases, diabetes was associated with an increased risk for both intrahepatic (odds ratio [OR] = 2.0, 95% CI: 1.8–2.2) and extrahepatic (OR = 1.8, 95% CI: 1.6–2.0) CCA.[33] Incidence rates of intrahepatic CCA were lower in diabetics treated with metformin compared with those who were not.[35] However, these associations of CCA with the above described conditions need to be further validated.

PATHOGENESIS

Frequently, CCA develops in the context of chronic inflammation and cholestasis.[14] Proinflammatory cytokines such as interleukin-6 (IL-6) have been associated with cholangiocarcinogenesis.[36,37] For example, liver fluke infestation is a pro-inflammatory state that can induce local, advanced periductal fibrosis and these patients have been found to have nearly 8 times higher levels of IL-6 compared with patients without advanced periductal fibrosis.[38] IL-6 receptor-inhibition decreases cellular proliferation of CCA tumor cells. CCA cells synthesize and secrete IL-6, followed by subsequent auto-and paracrine stimulation of the IL-6 receptor. Negative feedback mechanisms regulating IL-6 signaling are frequently inactivated in CCA cells. Activation of the IL-6 receptor results in downstream activation of pro-carcinogenic pathways such as JAK/STAT3, p38MAPK, ERK1/2 and PI3K/Akt.[37]

Inducible nitric oxide synthase (iNOS) has also been implicated in cholangiocarcinogenesis.[37] iNOS over-expression was demonstrated in human CCA specimens, and its expression could be induced in CCA cell lines by proinflammatory cytokines.[39] iNOS induces nitrosylation of base excision

repair enzymes and caspase-9, thereby, inhibiting the function of DNA repair proteins and apoptotic proteins.[40,41] Once malignant transformation has occurred; cells gain the ability of uncontrolled proliferation, invasion across the basement membrane, and escape apoptotic pathways.[42] Among others, erb-2, cyclooxygenase-2 and epidermal growth factor receptors (EGFR) have been identified as key molecular contributors in CCA carcinogenesis.[42]

DIAGNOSIS

The clinical presentation of CCA patients is unspecific. Patients with intrahepatic masses may present with abdominal pain, malaise, night sweats, weight loss and loss of appetite. Patients with extrahepatic CCA tend to present with symptoms of obstructive jaundice and sometimes with complications like cholangitis. The differential diagnoses with these symptoms are broad [Table 3] and include conditions such as hepatocellular carcinoma (HCC), pancreatic cancer, liver fluke infestation, hepatic metastases, biliary stones, biliary strictures, cholangitis and IgG4-associated cholangiopathy.[43-45] Therefore, a high level of suspicion is required, in particular in patients at risk for CCA.

Radiological imaging

Ultrasonography is of limited value in the diagnosis of CCA and can, therefore, not be recommended for surveillance or diagnosis.[46] For the distinction between intrahepatic CCA from HCC, dynamic computer tomography (CT) and magnetic resonance imaging (MRI) are equally valuable for tumors of >2 cm. CT has accuracies of up to 93% in determining portal vein and arterial involvement and isparticularly useful in preoperative planning.[47] However, its sensitivity for identifying lymph node metastases is only 54%, and it tends to underestimate the tumor extent of perihilar CCA. MRI with magnetic resonance cholangio-pancreatography (MRCP) is a valuable imaging technique in the evaluation of the primary tumor of perihilar CCAs, with an accuracy of up to 95%.[48] Positron emission tomography (PET) can be used when other diagnostic tests are nonconclusive or provide contradictory results. In the

Table 3: Differential diagnoses of the evaluation of CCA

Differential diagnosis
Hepatocellular carcinoma
Liver metastases
Pancreatic cancer
Fasciola hepatica infection mimicking as CCA
Cholangitis
Cholecystitis or choledocholithiasis
Biliary strictures
IgG4-associated cholangiopathy

CCA: Cholangiocarcinoma

evaluation of intrahepatic CCA of >1 cm size, PET-CT has sensitivities and specificities of up to 95% and 100% for evaluation of the primary tumor, and 94% and 100% for distant metastases; respectively. However, in the evaluation of perihilar CCA, its sensitivity and specificity decreases to 69% and 67%, and its sensitivity for the detection of regional lymph nodes is 13–38%, respectively.[49] Cholangiography allows evaluation of the biliary tree and can be performed by percutaneous transhepatic cholangiography (PTC), MRCP or endoscopically using endoscopic retrograde cholangio-pancreatography (ERCP).

Endoscopic techniques
Endoscopic retrograde cholangio-pancreatography is used in the diagnosis of perihilar and distal extrahepatic CCA distal. In addition to its diagnostic value, ERCP and PTC allowbiliary stent-placement to relieve biliary obstruction. Cytologic analysis of brush samples from the biliary epithelium obtained during ERCP can aid in the diagnosis of CCA. While the specificity of cytology in the diagnosis of CCA is 61–100%, itssensitivityis only 9–24%.[50] Fluorescent *in-situ* hybridization (FISH) can increase the sensitivity of cytology by detecting aneuploidy in the epithelial cells.[51] Addition of FISH analysis can increase sensitivities and specificities for diagnosing CCA in PSC patients to 47% and 97%.[48,52]

Tumor markers
Carbohydrate antigen CA 19-9 is a commonly used tumor marker in the diagnosis of CCA.[53] However, other malignancies as well as inflammatory or infectious conditions (i.e. cholangitis) can also cause significant increases in CA 19–9 serum concentrations. On the other hand, patients who are Lewis antigen negative do not produce CA 19–9 regardless of tumor burden. A change in the CA 19--9 serum concentration by 63 U/L from baseline carries a sensitivity of 90% with a specificity of 98% for CCA.[54] Early detection of CCA in individuals with PSC is a necessary aspect of their management. Currently, there is no single effective surveillance test. Recently, a novel urine test was described which detects molecular peptide markers that differentiate CCA from PSC or benign biliary disorders with a sensitivity and specificity of 83% and 79%.[55] Angiopoietin-2 is secreted by the tumor vasculature and elevated serum concentrations were reported to predict underlying CCA.[56] However, further studies are needed to validate these results and to identify novel biomarkers of CCA.

STAGING AND PROGNOSIS

An optimal cancer staging system should provide the following information: (1) Prognosis and natural history of the disease, (2) guide therapy, and (3) allow objective comparison of therapies. Several different prognostic factors and staging systems have been proposed for the different types of CCA. However, the majority of these staging systems is limited by their need for histology, their suboptimal correlation to survival or the need for further validation.

Intrahepatic cholangiocarcinoma
Tumor number and differentiation, lymph node metastases, and vascular invasion were described as independent prognostic factors for intrahepatic CCA.[57] Tumor size as a prognostic factor has been controversial; however, recent studies indicate that increasing tumor size might be associated with worse tumor grade, and it has therefore been suggested tore-evaluate its value.[58]

Several different staging systems have proposed for intrahepatic CCA. In its most recent 7th edition, the American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) tumor node metastasis (TNM) system revised its CCA classification [Table 4].[60] It excludes tumor size due to the absence of tumor size as an independent prognostic factor for survival.[59-61] The staging system was validated to accurately predict survival.[62] Though frequently used, this system is limited in its preoperative value as it requires histologic diagnosis for both tumor *in situ* and T4 stages.[48] The National Cancer Center of Japan system is another staging system similar to the AJCC/UICC system,

Table 4: TNM and AJCC/UICC staging systems for intrahepatic CCA

TNM stage	Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intraductal tumor)
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
T4	Tumor with periductal invasion
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present
M0	No distant metastases
M1	Distant metastases

AJCC/UICC stage	Tumor	Node	Metastasis
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IVa	T4	N0	M0
	Any T	N1	M0
IVb	Any T	Any N	M1

TNM: Tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: International Union Against Cancer; CCA: Cholangiocarcinoma

but it is based on analysis of only 60 patients and has not been externally validated.[48] The Liver Cancer Study Group of Japan (LCJGSC) staging system is based on independent prognostic variables identified in a retrospective analysis of 136 CCA cases;[63] it includes tumor size, and portal vein, hepatic vein and serosal invasion.[61] However, its T-stages lacked the correlation to survival. Recently, the LCJGSC staging was modified by omission of serosal invasion and redefinition of stages IVA and IVB based upon nodal negative and positive disease. The modified LCJGSC staging system outperformed the AJCC/UICC staging system in its correlation to survival, especially in the advanced stages;[64] however, further validation is required.

Perihilar cholangiocarcinoma

For perihilar CCA, lymph node metastases, tumor differentiation, perineural invasion, surgical margins and bilirubin levels have been identified as independent prognostic factors.[65,66] Few studies also suggested performance status, comorbidities, and albumin serum concentrations as prognostic factors.[67,68] Currently, two major staging systems exist for perihilar CCAs: The Memorial Sloan-Kettering Cancer System (MSKCC) and the AJCC/UICC 7th edition staging system [Table 5].[60] The MSKCC system classifies tumors according to their tumor extent, portal venous invasion, and hepatic lobar atrophy [Table 6].[60] The major difference between the 6th and 7th edition of the AJCC/UICC staging system is the separation of the perihilar and distal extrahepatic CCAs as separate entities.[48] However, a very recent retrospective validation study evaluated the 7th edition AJCC/UICC staging system and showed that survival of T3 and T4 tumors were not significantly different, and survival of patients with stage III and IVA was similar.[69] Omission of Bismuth type IV from the T4 definition, and combining N1 disease as stage IVA disease improved the prognostic predictive power of this staging system;[69] however, these results need further validation. In a recent retrospective analysis of patients with Bismuth–Corlette type III perihilar CCA, the MKSCC in its tumor classification T-stage classification was correlated with overall survival following resection but not the AJCC/UICC system; however, neither staging system was correlated with recurrence-free survival.[70] Recently, two new staging systems were developed for perihilar CCA. A novel staging system was recently developed by the International CCA Group.[71] It includes components of the Bismuth–Corlette classification, the TNM and the MSKCC staging system. A total of 8 variables are the basis of this staging system: (1) Extent of bile duct involvement, (2) tumor size, (3) tumor morphology, (4) portal vein involvement, (5) hepatic artery involvement, (6) liver remnant volume, (7) underlying liver disease, (8) lymph node metastases and (9) distant metastases.[71] While promising, this staging system has yet to be internally and externally validated.

Table 5: TNM and AJCC/UICC staging systems for perihilar CCA

TNM stage	Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor confined to the bile duct, with extension up to the muscle layer of fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumors invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally or tumor invades the common hepatic artery or tumor invades second-order biliary radicals bilaterally or tumor invades unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases (including nodes along the cystic duct, common bile duct, hepatic artery and portal vein)
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
M0	No distant metastases
M1	Distant metastases

AJCC/UICC stage	Tumor	Node	Metastasis
0	Tis	N0	M0
I	T1	N0	M0
II	T2a-b	N0	M0
IIIa	T3	N0	M0
IIIb	T1-3	N1	M0
IVa	T4	N0-1	M0
IVb	Any T	N2	M0
	Any T	Any N	M1

TNM: Tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: International Union Against Cancer; CCA: Cholangiocarcinoma

Distal extrahepatic

For distal extrahepatic CCA, tumor invasion depth, lymph node metastases, microscopic vascular invasion, invasion into the pancreas, surgical resection margins and perineural invasion have been reported to be independent prognostic factors.[72,73] Currently, the AJCC/UICC 7th edition is the only staging system available for distal extrahepatic CCAs [Table 7].[60] Recent updates in the 7th edition included separation of extrahepatic CCA into distal and perihilar extrahepatic variants, which is a major improvement compared with prior staging systems.[48]

TREATMENT

Intrahepatic cholangiocarcinoma

Surgical treatments are the only potentially curative therapeutic options for intrahepatic CCAs. Unfortunately, only a minority of patients qualify for surgical resection. Surgical outcomes largely depend on successful R0 resection (negative surgical margins). Resectability rates range between 19 and 74%.

Table 6: MSKCC staging system for perihilar CCA. It accounts not only for longitudinal extension of the tumor, but also incorporates the radial extension of the mass to more accurately reflect the resectability of the lesion

Stage	Criteria
T1	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles
T2	Tumor involving biliary confluence ± unilateral extension to second-order biliary and ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to second-order biliary radicles; or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement

MSKCC: Memorial Sloan-Kettering Cancer Center; CCA: Cholangiocarcinoma

Table 7: TNM and AJCC/UICC staging systems for distal extrahepatic CCA

TNM stage	Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intraductal tumor)
T1	Tumor confined to the bile duct histologically
T2a	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum or other adjacent organs without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present
M0	No distant metastases
M1	Distant metastases

AJCC/UICC stage	Tumor	Node	Metastasis
0	Tis	N0	M0
Ia	T1	N0	M0
Ib	T2	N0	M0
IIa	T3	N0	M0
IIb	T1-3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

TNM: Tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: International Union Against Cancer; CCA: Cholangiocarcinoma

Recurrence rates are usually high around 60–65%.[74] Survival rates depend on R0 resection and lymph node status. Following R0 resection, 5-year survival rates are 23–42% versus 0% after R + resection.[5,75,76] Five-year survival rates in patients with N1 status following surgical resection is 0–9% and up to 43% in N0 disease.[75,77] Contraindications for surgical resection have been listed in Table 8.[78,79] The National Comprehensive Cancer Network guidelines version 2.2014 discuss adjuvant treatment as an option following R0, R1 and R2 resection based on a previous meta-analysis that indicated a benefit in patients with R1 disease.[80,81] However, there are no large randomized controlled trials demonstrating a survival benefit of neoadjuvant or adjuvant chemotherapy.

For patients not amenable to curative surgical treatment; the current standard of care is combination chemotherapy with gemcitabine plus cisplatin, which had been shown to significantly increase progression-free survival compared with gemcitabine-only regimen, based on the ABC-02 trial.[82]

In the palliative setting, local ablative therapies have been be considered such as radiofrequency ablation, transarterial chemoembolization (TACE), drug eluting bead-TACE (DEB-TACE), selective intra-arterial radiotherapy with ^{90}Y microspheres or external beam radiation therapy. Few studies suggested a benefit of such therapies in regard to tumor progression and survival. However, these studies were limited by their retrospective nature, small sample size, use of different chemotherapeutic agents and inclusion of other biliary tract cancers.[83] Currently, there are no prospective, randomized controlled trials that have shown a survival benefit of the above described local ablative therapies. Grade III/IV toxicity rates of up to 36% have been reported with the above described local ablative therapies.[83,84] Large randomized controlled prospective trials are needed before the routine use of these treatments can be recommended.

Five-year survival rates of cirrhotics without malignancy undergoing orthotopic liver transplantation (OLT) exceed 70%.[85] OLT for malignancies is only recommended if 5-year survival rates are similar to those expected after OLT for cirrhosis in the absence of malignancy.[85] OLT for HCC within Milan criteria is supported by its 5-year survival rates of more than 70%.[86] Few studies have retrospectively evaluated the benefit of OLT with or without adjuvant treatment for intrahepatic CCA; these studies were limited by their retrospective nature, small sample size, and differences in tumor characteristics and adjuvant treatments. Recurrence rates were as high as 35–75% and 5-year survival was reported as 34–51%.[78,87-91] Based on the high recurrence rate and the relatively low 5-year survival rates, OLT is currently not the standard of care for intrahepatic CCA. Further prospective studies will be needed to identify subgroups of intrahepatic CCA patients that may benefit from OLT and to establish protocols with efficacious neoadjuvant and adjuvant therapies.

Perihilar cholangiocarcinoma
Similar to intrahepatic CCA, in the case of perihilar CCA, surgical management is also the only potentially curative treatment. While surgical resection is, in general, the preferred surgical treatment modality, OLT is preferred in patients with PSC and/or cirrhosis due to the limited hepatic reserves in patients with advanced cirrhosis and the risk of subsequent de novo hepato-and cholangiocarcinogensis. Exclusion criteria for surgical resection are listed in

Table 9.[78,79] In cases in which resectability is prohibited by a low volume of the hepatic remnant, portal vein embolization of the affected lobe can be pursued to induce hypertrophy of the contralateral hepatic lobe.[79] OLT with neoadjuvant chemoradiotherapy can achieve 5-year recurrence-free survival rates of 68%.[79,92,93] The exclusion criteria for OLT for CCA have been listed in Table 10.[94]

In patients with resectable CCA and cholestasis, plastic or covered self-expandable stents can be placed without interfering with subsequent surgery. However, a debate of the potential of increased complications with preoperative biliary stenting persists based upon data from pancreatic carcinoma.[95] In patients with nonresectable CCA, drainage of >50% of the liver parenchyma can improve patient survival; in the palliative setting, uncovered self-expandable biliary stents are preferable. However, bilateral biliary stents increase the risk of stent-related complications (i.e. acute bacterial cholangitis) and immediate gram-negative targeted antibiotic treatment is recommended for patient with stents and signs suggestive of bacterial cholangitis.[93] When comparing metal stents with plastic stents, it has been found that metal stents improve outcomes.[96] Furthermore, if metal stents were to be employed, covered metal stents should be favored given their ability to prevent tumor in growth. However, this should be weighed against the risks of possible pancreatitis and cholecystitis.[93] In addition, bilateral stent placement for palliative purposes also improved outcomes when compared with unilateral stent placement.[96] Another local regional treatment option that can be considered is photodynamic therapy (PDT). This consists of systemic injection of a photosensitizing agent, which once exposed to specific wavelengths of light will generate free radicals resulting in tumor necrosis. Stenting with PDT has been compared to stenting without PDT. The results indicated a benefit in regard to survival, biliary drainage and quality of life; however this will need to be confirmed by larger studies.[97]

Extrahepatic cholangiocarcinoma

Extrahepatic CCA is optimally treated surgically. This is usually performed as a Whipple-resection.[79] Five-year survival is reported as 27–37%.[5,46] Neither neoadjuvant nor adjuvant treatments have been shown to provide a significant survival benefit in large randomized controlled clinical trials.[80]

Targeted therapies and future therapies

Several preclinical studies have shown the therapeutic potential of targeting molecular pathways in CCA. The EGFR pathway has been identified as a promising molecular

Table 8: Exclusion criteria for surgical resection of intrahepatic CCA

Contraindications for surgical resection of intrahepatic CCA
Diffuse bilobar involvement (satellite lesions)
Peritoneal carcinomatosis
Distant metastases
Underlying liver disease (advanced fibrosis, PSC, cirrhosis)
Future liver remnant <20%-30% and no or poor response to portal vein occlusion
Severe comorbidities

CCA: Cholangiocarcinomal; PSC: Primary sclerosing cholangitis

Table 9: Exclusion criteria for surgical resection of perihilar CCA

Contraindications for surgical resection of perihilar CCA
Bilateral tumor extension involving left and right secondary biliary radicles
Unilobar involvement with encasement of contralateral portal vein or hepatic artery
Bilateral vascular involvement
Distant metastases
Underlying liver disease (advanced fibrosis, cirrhosis)
Future liver remnant 20%-30% and no or poor response to portal vein occlusion
Severe comorbidities

CCA: Cholangiocarcinoma

Table 10: List of exclusion criteria for patients with CCA who do not meet criteria for liver transplantation

Exclusion criteria for OLT in CCA (Mayo Clinic protocol)
Intrahepatic CCA
Uncontrolled infection
Prior radiation or chemotherapy
Prior biliary resection or attempted resection
Intrahepatic metastases
Evidence of extrahepatic disease
History of other malignancy within 5 years
Transperitoneal biopsy (including percutaneous and EUS-guided FNA)

CCA: Cholangiocarcinoma; OLT: Orthotopic liver transplantation; EUS-guided FNA: Endoscopic ultrasound-guided fine needle aspiration

target for CCA.[98] In a large randomized controlled phase 3 trial, including 180 CCA patients, the addition of erlotinib was found to increase the complete and partial response rate from 14% to 31%, and increased progression-free survival from 3.0 to 5.9 months.[99] Other promising, druggable molecular targets for CCA include vascular endothelial growth factor receptor, Januskinase-1/2, STAT3, MET and IDH 1 and 2.[100,101] An interesting approach targets the microenvironment, such as cancer associated fibroblasts (CAF). CAF have been shown to promote tumor progression and CCA. Navitoclax, a BH3 mimetic, selectively induced apoptosis of CAFs resulting in inhibiton of tumor progression and prolongation of survival a preclinical *in vivo* model.[102] Results of several phase 2 trials are pending.[101]

CONCLUSIONS

In recent years, the incidence of CCA has significantly increased, thereby making it the most common biliary tract malignancy. Novel, possible risk factors have been identified, which are highly relevant in Western societies (i.e. obesity, diabetes, HCV) and might explain its recent rise in the incidence rate. Recent molecular studies have increased our understanding of this disease and helped to identify the link between cholestasis, inflammation, and cholangiocarcinogenesis. However, there is a need to further characterize the molecular networks driving its progression and identify different molecular subtypes that could direct management. Our diagnostic evaluation of CCA still has room for improvements and short-comings of current staging systems still need to be overcome. Novel treatments have been established that have helped to improve survival of carefully selected patients with perihilar CCA (OLT with neoadjuvant chemoradiation), and prolong survival of patients with unresectable disease. However, large randomized controlled, prospective clinical trials are needed to establish the benefit of adjuvant treatments, local ablative therapies, and molecularly targeted agents.

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