Review Article

Cancer review: Cholangiocarcinoma

Yezaz Ahmed Ghouri, Idrees Mian, Boris Blechacz1*

Department of Internal Medicine, The University of Texas Health Science Center, 1Department of Gastroenterology, Hepatology and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

E-mail: bblechacz@mdanderson.org
*Corresponding author

Published: 23 February, 2015
Received: 01 November, 2014
Accepted: 01 February, 2015

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 CCAs 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.[31]

**EPIDEMOLOGY**

CCA is the second most common primary hepatic
malignancy accounting for 10–20% of primary liver cancers.[14] 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.[34]

**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%).[14]

**Extrahepatic cholangiocarcinoma**

Epidemiologic data for extrahepatic CCA is frequently flawed
due to its combined analysis with gallbladder carcinoma. Globally,
exahepatic 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.[15] 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 sinensis*, 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
dilation of segmental intrahepatic bile ducts, has been
linked with development of intrahepatic CCA.[23]

| 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

**Table 1: Bismuth-Corlette classification of perihilar CCA**

A peer reviewed journal in the field of Carcinogenesis and Carcinoprevention
Incidence of diabetes was associated with an increased risk for both advanced periductal fibrosis and these patients have been found to have nearly 8 times higher levels of IL-6 compared with those who were not treated with metformin.

Recent data suggested associations between hepatitis B virus (HBV) and HCV infections with cholangiocarcinogenesis, in particular with intrahepatic CCA. 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. Incidence rates of intrahepatic CCA were lower in diabetics treated with metformin compared with those who were not. Therefore, 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. Proinflammatory cytokines such as interleukin-6 (IL-6) have been associated with cholangiocarcinogenesis. For example, liver fluke infection 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. 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.

Inducible nitric oxide synthase (iNOS) has also been implicated in cholangiocarcinogenesis. iNOS over-expression was demonstrated in human CCA specimens, and its expression could be induced in CCA cell lines by proinflammatory cytokines. iNOS induces nitrosylation of base excision repair enzymes and caspase-9, thereby, inhibiting the function of DNA repair proteins and apoptotic proteins. Once malignant transformation has occurred; cells gain the ability of uncontrolled proliferation, invasion across the basement membrane, and escape apoptotic pathways. Among others, erb-2, cyclooxygenase-2 and epidermal growth factor receptors (EGFR) have been identified as key molecular contributors in CCA carcinogenesis.

**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 infection, hepatic metastases, biliary stones, biliary strictures, cholangitis and IgG4-associated cholangiopathy. 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. 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 is particularly useful in preoperative planning. 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%. 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 choleodocholithiasis |
| 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.[40] 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 allow biliary 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%, its sensitivity is only 9–24%.[40] 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 to re-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         |
| 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.\cite{60,61} 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;\cite{62,63} it includes tumor size, and portal vein, hepatic vein, and peritoneal invasion.\cite{64} 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;\cite{65} 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.\cite{66,67} Few studies also suggested performance status, comorbidities, and albumin serum concentrations as prognostic factors.\cite{68,69} 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].\cite{69} The MSKCC system classifies tumors according to their tumor extent, portal venous invasion, and hepatic lobar atrophy [Table 6].\cite{70} 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.\cite{71} 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.\cite{72} 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; however, these results need further validation. In a recent retrospective analysis of patients with Bismuth–Corlette type III perihilar CCA, the MSKCC 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.\cite{73} Recently, two new staging systems were developed for perihilar CCA. A novel staging system was recently developed by the International CCA Group.\cite{74} 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.\cite{75} While promising, this staging system has yet to be internally and externally validated.

**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.\cite{76,77} Currently, the AJCC/UICC 7th edition is the only staging system available for distal extrahepatic CCAs [Table 7].\cite{78} 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.\cite{79}

**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%.
Recurrence rates are usually high around 60–65%. 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. Five-year survival rates in patients with N1 status following surgical resection is 0–9% and up to 43% in N0 disease. Contraindications for surgical resection have been listed in Table 8. 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. 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.

In the palliative setting, local ablative therapies have been considered such as radiofrequency ablation, transarterial chemoembolization (TACE), drug eluting bead-TACE (DEB-TACE), selective intra-arterial radiotherapy with Y90 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. 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.

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%. 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. OLT for HCC within Milan criteria is supported by its 5-year survival rates of more than 70%. 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%. 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 cholangiocarcinogenesis. Exclusion criteria for surgical resection are listed in

---

**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
Furthermore, if metal stents are to be employed, covered metal stents should be favored given their ability to prevent tumor ingrowth. However, this should be weighed against the risks of possible pancreatitis and cholecystitis. In addition, bilateral stent placement for palliative purposes also improved outcomes when compared with unilateral stent placement. 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.

**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: Cholangiocarcinoma; 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 extrabiliary disease                         |
| History of other malignancy within 5 years              |
| Transperitoneal biopsy (including percutaneous and EUS-guided FNA) |

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

Extrahepatic cholangiocarcinoma

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

**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 target for CCA. 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. Other promising, drugable molecular targets for CCA include vascular endothelial growth factor receptor, Januskinase-1/2, STAT3, MET and IDH 1 and 2. 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 inhibition of tumor progression and prolongation of survival in preclinical in vivo model. Results of several phase 2 trials are pending.
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 directly manage. 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.

REFERENCES

1. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatitis. An unusual tumor with distinctive clinical and pathological features. Am J Med 1965;38:241-56.
2. Hirohashi K, Uenishi T, Kubo S, Yamamoto T, Tanaka H, Shuto T, et al. Macroscopic types of intrahepatic cholangiocarcinoma: Clinicopathologic features and surgical outcomes. Hepatogastroenterology 2002;49:326-9.
3. Olness MJ, Erlich RA. A review and update on cholangiocarcinoma. Oncology 2004;66:167-79.
4. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis 2004;24:115-25.
5. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: Thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245:555-62.
6. Nakeeb A, Pist HA, Sohn TA, Coleman J, Abrams RA, Plantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-73.
7. Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: A true increase? J Hepatol 2004;40:472-7.
8. McLean L, Patel T. Racial and ethnic variations in the epidemiology of intrahepatic cholangiocarcinoma in the United States. Liver Int 2006;26:1047-53.
9. Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang YY, et al. Epidemiology of cholangiocarcinoma: An update focusing on risk factors. Cancer Sci 2010;101:579-85.
10. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353-7.
11. Bragazzi MC, Maria Consiglia Bragazzi, Vincenzo Cardinale, Guido Carpino, Rosanna Venere, Rossella Semeraro, et al. Cholangiocarcinoma: Epidemiology and risk factors. Transl Gastrointest Cancer 2012;1:21-32.
12. Carriaga MT, Henson DE. Liver, gallbladder, extrahaepatic bile ducts, and pancreas. Cancer 1995;75:171-90.
13. Welzel TM, McGlynn KA, Hsing AW, O'Brien TR, Pfeiffer RM. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahaepatic cholangiocarcinoma in the United States. J Natl Cancer Inst 2006;98:873-5.
14. Liu R, Cox K, Guthery SL, Book L, Witt B, Chadwick B, et al. Cholangiocarcinoma and high-grade dysplasia in young patients with primary sclerosing cholangitis. Dig Dis Sci 2014;59:2230-4.
15. Morris-Stiff G, Bhat C, Olliff S, Hubscher S, Gunson B, Mayer D, et al. Cholangiocarcinoma complicating primary sclerosing cholangitis: A 24-year experience. Dig Surg 2008;25:126-32.
16. Kerr SE, Farr Fritchler EG, Campion MB, Voss JS, Kipp BR, Halling KC, et al. Biliary dysplasia in primary sclerosing cholangitis harbors cytogenetic abnormalities similar to cholangiocarcinoma. Hum Pathol 2014;45:1797-804.
17. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol 2004;99:523-6.
18. Watanapa P, Watanapa WB. Liver fluke-associated cholangiocarcinoma. Br J Surg 2002;89:962-70.
19. Kurathong S, Lerdverasirikul P, Wongpaisoon V, Pramoolsinsap C, Kanjanapitak A, Varavithya W, et al. Ophistochirius viverrini infection and cholangiocarcinoma. A prospective, case-controlled study. Gastroenterology 1985;91:151-6.
20. Jang KT, Hong SM, Lee KT, Lee JG, Cho SH, Heo JS, et al. Intraductal papillary neoplasm of the bile duct associated with Clonorchis sinensis infection. Viroschews Arch 2008;453:859-98.
21. lipsetz PA, Pist HA, Colombani PM, Boitnott JK, Cameron JL. Choledochal cyst disease. A changing pattern of presentation. Ann Surg 1994;220:644-52.
22. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. Hepatology 2011;54:173-84.
23. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterology 2005;128:1655-67.
24. Chen MF, Jan YY, Wang CS, Hwang TL, Jeng LB, Chen SC, et al. A reappraisal of cholangiocarcinoma in patient with hepatitis B. Cancer 1993;71:2461-5.
25. Liu D, Moiomi H, Li L, Ishikawa Y, Fukumoto M. Microsatellite instability in thorotrast-induced human intrahepatic cholangiocarcinoma. Int J Cancer 2002;102:366-71.
26. Walker NJ, Crockett PW, Nyska A, Brix AE, Jokinen MP, Sells DM, et al. Dose-additive carcinogenicity of a defined mixture of “dioxin-like compounds”. Environ Health Perspect 2005;113:43-8.
27. Gunay-Aygun M, Gahi WA, Heller T. Congenital hepatic fibrosis overview. University of Washington, Seattle, Seattle (WA); 1993.
28. Matsumoto K, Onoyama T, Kawasa S, Takeda Y, Harada K, Ikeuchi Y, et al. Hepatitis B and C virus infection is a risk factor for the development of cholangiocarcinoma. Intern Med 2014;53:651-4.
29. Wu Y, Wang T, Ye S, Zhao R, Bai X, Wu Y, et al. Detection of hepatitis B virus DNA in paraffin-embedded intrahepatic and extrahaepatic cholangiocarcinoma tissue in the northern Chinese population. Hum Pathol 2012;43:56-61.
30. Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, et al. Risk factors for intrahepatic and extrahaepatic cholangiocarcinoma in the United States: A population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1221-8.
31. Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancer? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol 2012;57:69-76.
32. Li JS, Han TJ, Jing N, Li L, Zhang XH, Ma FZ, et al. Obesity and the risk of cholangiocarcinoma: A meta-analysis. Tumour Biol 2014;35:6831-8.
33. Chang JS, Tsai CR, Chen LT. Medical risk factors associated with cholangiocarcinoma in Taiwan: A population-based case-control study. PLoS One 2013;8:e69981.
34. Jing W, Jin G, Zhou Y, Zhang Y, Shao C, et al. Diabetes mellitus and increased risk of cholangiocarcinoma: A meta-analysis. Eur J Cancer Prev 2012;21:24-31.
35. Chaiterraki R, Yang JD, Harmsen WS, Stedeldahl SW, Mettler TA, et al. Risk factors for intrahepatic cholangiocarcinoma: Association between metformin use and reduced cancer risk. Hepatology 2013;57:648-55.
36. Sugawara H, Yasoshima M, Katayangki K, Kono N, Watanabe Y, Harada K, et al. Relationship between interleukin-6 and proliferation and differentiation in cholangiocarcinoma. Histopathology 1998;33:145-53.
57. de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Serum and bile markers for cholangiocarcinoma. Clin Liver Dis 2013;17:321-34.

50. Harewood GC, Baron TH, Stadheim LM, Kipp BR, Sebo TJ, Salomao DR. Comparative analysis of resection and liver transplantation for intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 2013;20:159-65.

46. Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: A new staging system for mass-forming intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 2014;21:499-508.

44. Kim YH, Kang KJ, Kwon JH. Four cases of hepatic fascioliasis mimicking cholangiocarcinoma. Korean J Hepatol 2005;11:169-75.

43. Klempnauer J, Ridder GJ, von Wasielewski R, Werner M, Weimann A, Pichlmayr R. Resectability of hilar cholangiocarcinoma: A comprehensive analysis of prognostic factors. J Clin Oncol 1997;15:947-54.

42. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Pedersen R, Klempnauer J, et al. Prediction of resectability and outcomes in patients with resectable hilar cholangiocarcinoma: A multicenter analysis by the Study Group for Hepatic Surgery of the American Association for the Study of Liver Diseases. Medicine 2013;92:460-6.

41. Turkmen S, Inan S, Turan M, Ozcan R, Tamer Y, Yagci S. Sclerosing cholangitis. Dig Dis Sci 2005;50:1734-40.

40. Vosskuhl K, Negm AA, Framke T, Weismüller T, Manns MP, Wedemeyer H, et al. Advanced periductal fibrosis from infection with the carcinogenic human liver fluke Opisthorchis viverrini correlates with elevated levels of interleukin-6. Hepatology 2009;50:1273-81.

39. Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res 2000;60:184-90.

38. Sripa B, Mairiang E, Thinkhamrop B, Laha T, Kaewkes S, Sithithaworn P, et al. Measurement of IgG4 in bile: A new approach for the diagnosis of IgG4-associated cholangiopathy. Endoscopy 2012;44:48-52.

37. Malhi H, Gores GJ. Cholangiocarcinoma: Modern advances in understanding a deadly old disease. J Hepatol 2006;45:856-67.

36. Hong SM, Pawlik TM, Cho H, Aggarwal B, Goggins M, Hruban RH, et al. Preoperative assessment of resectability of hilar hepatocellular carcinoma: Combined CT and cholangiography with revised criteria. Radiology 2006;239:113-21.

35. Lee HY, Kim SH, Lee JH, Kim SW, Jang JY, Han JK, et al. Preoperative assessment of resectability of hepatic hilar cholangiocarcinoma: Combined CT and cholangiography. Hum Pathol 2007;38:1137-44.

34. Nehls O, Gregor M, Klump B. Serum and bile markers for cholangiocarcinoma. Korean J Parasitol 2014;52:193-6.

33. Kim YH, Kang KJ, Kwon JH. Four cases of hepatic fascioliasis mimicking cholangiocarcinoma. Korean J Gastroenterol 2004;49:139-54.

32. Nathans D, SoSuvak R, Gharibyan A, Schwab M, et al. DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res 2000;60:184-90.

31. Levey C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD. The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Dig Dis Sci 2005;50:1734-40.

30. Metzger J, Negrin AA, Plentz RR, Reimann M, Wiesmüller TJ, Wedemeyer J, Karlsten TH, et al. Urine proteome analysis differentiates cholangiocarcinoma from primary sclerosing cholangitis and other benign biliary disorders. Gut 2013;62:122-30.

29. Voigtlander T, David S, Thamm K, Schlue J, Metzger J, Manss MP, et al. Angiopoietin-2 and biliary diseases: Elevated serum, but not bile levels are associated with cholangiocarcinoma. PLoS One 2014;9:e97046.

28. de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Intrahepatic cholangiocarcinoma: An international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 2011;29:3140-5.

27. Spoelstra G, Ejaz A, Kim Y, Sotiropoulos GC, Pau A, Alexandrescu S, et al. Tumor size predicts vascular invasion and histologic grade among patients undergoing resection of intrahepatic cholangiocarcinoma. J Gastrointest Surg 2014;18:1284-91.

26. Bridgewater J, Gallo PR, Khan SA, Llovet JM, Park JW, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014;60:1268-89.
of biliary tract cancer: A systematic review and meta-analysis. J Clin Oncol 2012;30:1934-40.

81. National Comprehensive Cancer Network (NCCN) clinical Practise Guidelines in Oncology, Hepatobiliary Cancers; 2014. Available from: http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf Version 2.2015. [Last cited on 2014 Feb].

82. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: A comparative multicentre study in Japan. Br J Cancer 2010;103:469-74.

83. Kuhlmann JB, Euringer W, Spangenberg HC, Breidert M, Blum HE, Harder J, et al. Treatment of unresectable cholangiocarcinoma: Conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. Eur J Gastroenterol Hepatol 2012;24:437-43.

84. Boehm LM, Jayakrishnan TT, Miura JT, Zacharias AJ, Johnston FM, Suraka GA, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. J Surg Oncol 2015;111:213-20.

85. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A, et al. Recommendations for liver transplantation for hepatocellular carcinoma: An international consensus conference report. Lancet Oncol 2012;13:e11-22.

86. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update. Hepatology 2011;53:1020-2.

87. Sapisochin G, Rodríguez de Lope C, Gastaca M, Ortiz de Urbina J, Suarez MA, Santoyo J, et al. “Very early” intrahepatic cholangiocarcinoma in cirrhotic patients: Should liver transplantation be reconsidered in these patients? Am J Transplant 2014;14:e660-7.

88. Sotiropoulos GC, Kaiser GM, Lang H, Molmenti EP, Beckebaum S, Foustas I, et al. Liver transplantation as a primary indication for inoperable cholangiocarcinoma: A single-center experience. Transplant Proc 2008;40:3194-5.

89. Fu BS, Zhang T, Li H, Yi SH, Wang GS, Xu C, et al. The role of liver transplantation for inoperable cholangiocarcinoma: A single-center experience. Eur J Surg 2011;47:218-21.

90. Ghali P, Marotta PJ, Yoshida EM, Bain VG, Marleau D, Peletkian K, et al. Liver transplantation for incidental cholangiocarcinoma: Analysis of the Canadian experience. Liver Transpl 2005;11:1412-6.

91. Robles R, Figueras J, Turrión VS, Margarit C, Moya A, Varo E, et al. Liver transplantation for peripheral cholangiocarcinoma: Spanish experience. Transplant Proc 2003;35:1823-4.

92. Hoffmann RT, Papatosta PM, Schin A, Bamberg F, Haug A, Dürr EM, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: Factors associated with prolonged survival. Cardiovasc Intervent Radiol 2012;35:105-16.

93. Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. Clin Gastroenterol Hepatol 2013;11:13-21.

94. Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. Transpl Int 2010;23:692-7.

95. van der Gaag NA, Rauws EA, van Eijk CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010;362:129-37.

96. Liberato MJ, Carena JM. Endoscopic stenting for hilar cholangiocarcinoma: Efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients. BMC Gastroenterol 2012;12:103.

97. Ortner ME, Caca K, Berr F, Lieberthru J, Mansmann U, Huster D, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: A randomized prospective study. Gastroenterology 2003;125:1355-63.

98. Andersen JB, Spee B, Blechacz BR, Avital I, Komuta M, Barbour A, et al. Genomic and genetic characterization of cholangiocarcinoma identifies therapeutic targets for tyrosine kinase inhibitors. Gastroenterology 2012;142:1021-31 e15.

99. Lee J, Park SH, Chang HM, Kim JS, Choi HJ, Lee MA, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2012;13:181-8.

100. Takahashi H, Ojima H, Shimizu H, Furuse J, Furukawa H, Shibata T. Axitinib (AG-013736), an oral specific VEGFR TKI, shows potential therapeutic utility against cholangiocarcinoma. Jpn J Clin Oncol 2014;44:570-8.

101. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet 2014;383:2168-79.

102. Mertens JC, Fingas CD, Christensen JD, Smoot RL, Bronk SF, Vermeers NF, et al. Therapeutic effects of deleting cancer-associated fibroblasts in cholangiocarcinoma. Cancer Res 2013;73:897-907.

How to cite this article: Ghouri YA, Mian I, Blechacz B. Cancer: A peer reviewed journal in the field of Carcinogenesis and Carcinoprevention

AUTHOR'S PROFILE

Dr. Boris Blechacz, MD, PhD: Assistant Professor, Department of Gastroenterology, Hepatology, & Nutrition, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Dr. Yezaz Ahmed Ghouri, MD: Senior Resident, Internal Medicine, The University of Texas Health Science Center, Houston, Texas.

Dr. Idrees Mian, MD: Senior Resident, Internal Medicine, The University of Texas Health Science Center, Houston, Texas.

http://www.carcinogenesis.com/content/14/1/1