REVIEW

Cholangiocarcinoma: A compact review of the literature

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Abstract

Cholangiocarcinoma (CC) is a devastating cancer arising from biliary epithelia. Unfortunately, the incidence of this disease is increasing in Western countries. These tumors progress insidiously, and liver failure, biliary sepsis, malnutrition and cancer cachexia are general modes of death associated with this disease. To date, no established therapy for advanced disease has been established or validated. However, our knowledge in tumor biology is increasing dramatically and new drugs are under investigation for treatment of this notorious tumor. In clinical practice, there are better diagnostic tools in use to facilitate an earlier diagnosis of CC, at least in those patients with known risk factors. CC is resectable for cure in only a small percentage of patients. Preoperative staging for vascular and biliary extension of CC is very important in this tumor. Laparoscopy and recently endosonography seem to protect against unnecessary laparotomies in these patients. During the last 15 years, aggressive surgical approaches, including combined liver resections and vascular reconstructive surgical expertise, have improved survival in patients with CC. Surgery is contraindicated in CC cases having primary sclerosing cholangitis (PSC). Although CC was previously considered a contraindication to liver transplantation, new cautious protocols, including neo-adjuvant chemoradiation therapies and staging procedures before the transplantation, have made it possible to achieve long-term survival after liver transplantation in this disease. New ablative therapies with photodynamic therapy, intraductal high-intensity ultrasonography and chemotherapy-impregnated plastic biliary endoprosthesis are important steps in the palliative management of extrahepatic CCs. Radiofrequency and chemo-embolization methods are also applicable for intra-hepatic CCs as palliative modes of treatment. We need more prospective randomized controlled trials to evaluate the role of the new emerging therapies for CC patients.

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INTRODUCTION

Cholangiocarcinoma (CC) is a malignant epithelial tumor of the biliary tree that accounts for approximately 10% to 15% of all hepatobiliary malignancies. CC mostly arises from the extra-hepatic biliary tree (50%-60% hilar CC, "Klatskin" tumors), spreads slowly and infiltrates periductal tissues. Hilar lesions are further subdivided based on location as indicated by Bismuth-Corlette classification (Figure 1). This form of CC characteristically presents with signs of ductal and vascular obliteration. Biliary tract sepsis, liver failure and/or cancer cachexia and malnutrition are the most important causes of death associated with these tumors[1]. The intra-hepatic form of CC appears as a mass lesion in the liver, which is mostly confused with metastatic tumor. These tumors usually progress insidiously, are difficult to diagnose and have grave prognosis. Unfortunately, the treatment alternatives are few. Effective surgery and other non-surgical treatment modalities for these patients with CC often fail due to characteristically late clinical presentation of this tumor.

Although our current understanding of tumor biology has far exceeded our past knowledge, the overall survival (including the resected patients) over the past 30 years is poor, with less than 5% of cases surviving for five years[1].

EPIDEMIOLOGY

Generally, CC is the second most common primary liver cancer after hepatocellular carcinoma (HCC) in most parts of the world. However, in some populations where HCC is uncommon, such as in Danish women, the prevalence of CC surpasses that of HCC[2]. Presentation is usually in the seventh decade in patients with CC, and it demonstrates slight male preponderance[3,4]. Fortunately, this tumor is a relatively rare kind of malignancy. In autopsy series, its prevalence is reported as around 0.01%-0.5%[5]. It represents 3% of all gastrointestinal system (GIS) cancers[6]. Of concern, some reports indicate that the incidence and mortality of intra-hepatic CC are increasing worldwide[7-9], while those of extra-hepatic CC are decreasing[7,8,10]. However, the increase in intra-hepatic CC is higher than the rate of decline in extra-hepatic CC. Whether this represents a real increase in this tumor or whether it can be attributed to better detection rates or changes in classification strategies is debatable. However, no increase has been noted in early stage or smaller-sized intra-hepatic CCs, perhaps indicating that these tumors are not better detected at present[11]. Thus, the underlying reason for the increasing incidence of intra-hepatic CC remains ambiguous.

RISK FACTORS AND PATHOPHYSIOLOGY

There are well-recognized risk factors for this tumor, such as congenital biliary anomalies, primary sclerosing cholangitis (PSC), hepatolithiasis, parasitic infections, chronic typhoid carriage, bile duct adenoma, biliary papillomatosis, drug exposure and genetic risks[12,13]. Chronic biliary inflammation is the common denominator in these conditions. An inflammatory milieu is believed to dysregulate or change the expression patterns of growth factors, pro-inflammatory cytokines and their receptors. Cytokines produced by cholangiocytes and activated macrophages can modulate gene expression and lead to activation of carcinogen metabolism. For example, interleukin (IL) -6 is a potent mitogen for cholangiocytes[14]. This cytokine can also induce nitric oxide (NO) synthase expression in cholangiocytes. NO can also directly injure the cellular DNA. Consumption of cellular detoxification and dysregulation of DNA repair and apoptosis are final steps of biliary carcinogenesis[5]. Bile acids also have been shown to activate inducible cyclo-oxygenase 2 and an anti-apoptotic molecule, myeloid cell leukemia protein 1 in cholangiocytes[15]. Thus, an inflammatory milieu and toxic bile constituents act together to promote carcinogenesis in the biliary tree. Histomorphological aspects in biliary carcinogenesis indicate that the intestinal metaplasia-dysplasia-carcinoma sequence can also be valid for CC[5].
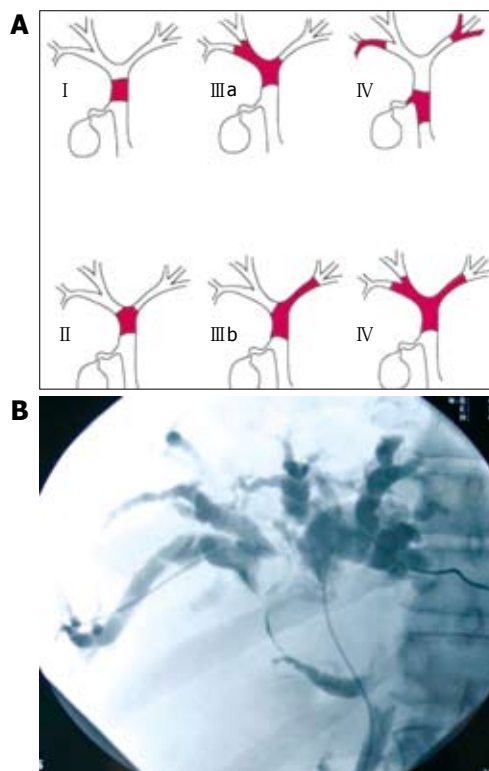
Figure 1 Hilar lesions are further subdivided based on location as indicated by Bismuth-Corlette classification. A: Bismuth-Corlette classification of hilar CC. Type Ⅰ involves the common hepatic duct, distal to the bifurcation of the biliary tree. Type Ⅱ affects the bifurcation. Type Ⅲa affects the right hepatic duct in addition to the bifurcation. Type Ⅲb affects the left hepatic duct in addition to the bifurcation. Type Ⅳ involves the bifurcation and both right and left hepatic ducts or indicates multifocal CC; B: Endoscopic retrograde cholangiography reveals hilar cholangiocarcinoma (Klatskin type 2) in one of our cases.

Congenital biliary cysts and pancreaticobiliary malfunction together have been obviously linked to biliary carcinogenesis, as both were present in 90% of cases in a reported clinical series[16]. Mixture of bile and pancreatic fluid due to impaired function of the Oddi sphincter induces chronic inflammation in the biliary tree with possible activation of carcinogenesis cascades.

PSC is one of the most common causes of CC in the Western world. As much as 42% of patients with PSC were reported to have CC in autopsy series[17]. Interestingly, the duration of PSC is not a risk factor for developing CC. Chronic inflammation and increased proliferation of biliary epithelium, along with increased production of endogenous mutagens in the bile, seemed to be related to carcinogenesis associated with PSC. Moreover, k-ras mutations were known to be common both in colon and biliary tree cancers in association with PSC[17].

Parasites such as *Opisthorchis viverrini* and *Clonorchis sinensis* have both direct strong carcinogenic effects and increase the susceptibility of cholangiocytes to endogenous and exogenous carcinogens. This is *via* chronic irritation and increased cellular turnover[18].

Hepatolithiasis leads to chronic proliferative cholangitis near to stone-bearing ducts and it has been reported in around 17.5% of patients with CC in some East Asian countries[19].

Chronic typhoid carriage and chronic cholangitis are representatives of chronic inflammatory conditions in the biliary tree and these conditions are accepted risk factors for developing CC.

Environmental toxins such as dioxin, and vinyl chloride, are known to be responsible for some cases of CC[20,21]. Thorotrast, which was used as a radiocontrast agent in the 1930s, is a potent carcinogenic agent for CC[22]. Nitrosamines, either taken exogenously or with tobacco use, or endogenously by nitrosation of nitrogenous compounds *via* NO, are potent carcinogens for biliary cancer[23,24].

Biliary papillomatosis, although a benign disease, has a moderately high malignant transformation rate[25]. Bile duct adenomas also carry appreciable risk for CC development[26].

Genetic polymorphisms in CYP1A2 and glutathione-S-transferase omega 1 and 2 have been related with this tumor[27]. These polymorphisms are believed to influence environmentally toxic substances, such as asbestos or dioxin.

A follow-up study of more than 1000 patients indicated late development of CC after biliary enteric diversion operations for benign biliary diseases[28,29].

Indeed, the majority of CC cases do not have these classic risk factors. Recently, a report from the United States included chronic viral hepatitis, cirrhosis and alcohol use among the risk factors for development of CC in elderly patients[30].

Obesity, moreover, was implicated as a risk factor for CC in a Korean study[1].

ROLE OF CLINICS AND LABORATORY TESTS IN DIAGNOSTIC EVALUATION

Extra-hepatic CC presents with classic signs of cholestasis including jaundice, dark urine, pale stools, pruritus, malaise and weight loss. Laboratory investigations reveal increased alkaline phosphatase, gamma-glutamyl transpeptidase and bilirubin. Prolonged obstruction of the main bile ducts can cause increased prothrombin time and a reduction in fat soluble vitamins. As the disease advances further, albumin, hemoglobin and lactate dehydrogenase can decrease. A glycoprotein tumor marker, CA 19-9, can be found elevated in 85% of such cases. A value of > 100 U/mL in PSC patients has a sensitivity of 89% and specificity of 86% for the diagnosis of CC. CC should not be diagnosed only on the basis of elevated CA 19-9. However, in patients without PSC, the sensitivity of CA 19-9 > 100 U/mL is 53%[31,32]. CEA is elevated in 30% of cases, while CA 125 is elevated in 40%-50% of patients with CC. CEA and CA 125 are also non-specific markers. A high index of suspicion is necessary to diagnose perihilar and extra-hepatic CCs because of other possible alternatives, including benign strictures, metastatic lymph nodes and/or gall bladder cancer. This is also true for PSC patients having dominant strictures. The confirmation of CC in these patients is quite challenging. Nevertheless, recent advances, especially in cytodiagnostic techniques, have contributed to establishing a correct diagnosis in nearly 80% of such cases.

Intra-hepatic CCs present mostly with non-specific symptoms, such as abdominal pain, weight loss, malaise and decreased appetite. Occasionally, an incidental abdominal mass detected during physical examination or radiologic evaluation is the single finding. Mildly elevated alkaline phosphatase and normal bilirubin levels are noticed on laboratory testing. CA 19-9 can also be found increased. These tumors are generally confused with metastatic adenocarcinomas. Indeed, a liver mass with adenocarcinoma histology, without an obvious primary source, should be seriously considered as intra-hepatic CC. A needle biopsy of the dominant liver mass is a straightforward diagnostic approach in these patients. Exclusion of another primary source can usually be accomplished by systemic physical examinations, chest X-ray, and tomography of the abdomen and pelvis.

Ultrasound is usually the first choice during investigation to visualize the location and extent of disease. Sonography can classify intra-hepatic CC as mass lesions. Contrast enhanced helical computerized tomography (CT) is very sensitive for detecting intra-hepatic CC larger than 1 cm. CT can also locate the site of obstruction and the presence of lymphadenopathy[33,34]. CT angiography can also detect vascular encasement[35]. Helical CT is only 60% correct in determining resectability. Although the experience with CT cholangiography is limited, this technique has been reported to be superior to conventional spiral CT examination. Ninety-four percent diagnostic accuracy has been noted for the diagnosis of malignant biliary lesions with CT cholangiography[36]. Magnetic resonance imaging (MRI) with MR Cholangiopancreatography (MRCP) has mostly replaced CT in diagnosis and staging evaluation of CC[37-39]. MR investigations can detect the site and extent of tumor involvement in the absence of PSC. MR angiography can show vascular involvement in these cases[40]. Thus, MRI studies have the advantage of showing vascular anatomy, cross-sectional imaging of the liver and cholangiography with a single technique and may exemplify an optimal imaging technique for this disease. However, in one study, MR cholangiography was reported to under-stage malignant hilar strictures in as high as 20% of patients[41]. Endosonography (EUS) is the most recent addition to the list of imaging modalities in diagnosis and staging of CCs[42]. EUS-guided fine needle aspiration (FNA) of hilar lymph nodes can be very important for staging procedure in CCs. EUS with FNA can diagnose Klatskin cases with 89% diagnostic accuracy even in the presence of negative brush cytology[43]. This technique does not induce contamination of the biliary tree, which can easily occur with endoscopic retrograde cholangiography (ERC). However, the hazard with this technique has been indicated as peritoneal tumor seeding[43]. Though a normal positron emission tomography (PET) scan with (18F)-fluorodeoxyglucose (FDG) can not exclude cancer and false-positives are highly common due to inflammatory conditions, PET may be useful for detecting metastatic disease[44]. FDG-PET/CT combination in detecting

Table 1	Memorial Sloan Kettering T stage for hilar CC
Stage	**Criteria**
T1	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicals
T2	T1 ± ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to second-order biliary radicals; or unilateral extension to second-order biliary radicals with contralateral portal vein involvement; or unilateral extension to second-order radicals with contralateral hepatic lobar atrophy; or main or bilateral portal vein involvement

Klatskin tumors was highly recommended in such patients[45].

Other methods to depict the biliary tree are ERC and percutaneous transhepatic cholangiography. These techniques allow visualization of a very detailed topography of the biliary tree. ERC is one of the main tools in the diagnosis of CCs. It can easily detect a stenosing tumor along the bile ducts. Unfortunately, both techniques carry a risk of bacterial cholangitis, a rather common complication after ERC. Using these techniques, brush cytology can provide cell samples to analyze and diagnose the biliary tract malignancy. Unfortunately, brush cytology has been reported to carry a very low diagnostic yield, ranging from 9%-24%. This was reported to be independent of the quantity of the specimen cellularity[46]. New technologies, such as the use of fluorescence *in situ* hybridization and digital image analysis methods, were reported to be more sensitive than the routine cytology. In one study, these technologies doubled the diagnostic accuracy of brush cytology[47]. The combined use of cholangioscopy improved the diagnostic yield of ERC for CCs. Cholangioscopy can detect the tumor vessel and improve diagnostic potential of direct cholangiographic examination[48]. Intraductal ultrasonography has also been reported to increase diagnostic accuracy of direct cholangiography[49].

OTHER POSSIBLE DIAGNOSES

Most patients with hilar stenosis and jaundice have CC. On the other hand, 10%-15% of cases had alternative diagnoses, including gall bladder carcinoma, Mirizzi syndrome and benign focal stenosis. The thickened and irregular gall bladder wall, infiltration to the right portal vein origin and liver segments 4 and 5, and occlusion of the common hepatic and cystic ducts suggest the presence of gall bladder cancer. Mirizzi syndrome results from periductal inflammation and fibrosis due to a large gall stone impacted at the neck of the gall bladder. Benign focal strictures involving the hilar region are uncommon. Other causes of the strictures affecting the whole biliary tree and benign in nature are postoperative strictures, chronic infectious cholangitis due to gall stones and flukes, ischemic cholangiopathy, chemoradiotherapy, vasculitis, human immunodeficiency virus cholangiopathy, infections such as tuberculosis and histoplasmosis, bile duct varices, papillary stenosis, and sphincter of Oddi dysfunction[50]. These strictures, though benign in nature, can masquerade malignancy on ERC as they may give a "pseudocholangiocarcinoma sign", which is sometimes difficult to differentiate from a true sign of CC. This sign was first reported by some authors in a patient with bile duct varices due to portal vein thrombosis and portal cavernomatous transformation[51].

STAGING AND TREATMENT MODALITIES

Resection and/or liver transplantation are the only curative options for CC. Accurate preoperative staging will determine the treatment approach in these patients. Although a pathologic staging system has been developed for ductal CC, it has a limited value in clinically assessing extra-hepatic CC. TNM classification does not correlate with resectability in patients with extra-hepatic CC. Conversely, the Memorial Sloan-Kettering staging system evaluates the biliary and vascular involvement of these tumors and clearly correlates with resectability and survival (Table 1). Indeed, clinical staging has three important points in presurgical evaluation of these cases. The first is the determination of proximal and distal extent of the disease. The second and third goals are to assess vascular involvement and the presence of metastasis, which can be done by Doppler ultrasound or MRI, CT and EUS examinations. FDG-PET scanning changes the surgical management in a third of patients, with an overall sensitivity for metastasis in 65%. FDG-PET has high false positivity in PSC patients and patients with biliary stents[52]. Laparoscopy for staging improved overall accuracy in choosing the optimal management formula in these cases. In one study, laparoscopy prevented unnecessary laparotomies in 42% of cases[53].

Surgery is the most suitable option for patients with intra-hepatic CC. With curative surgery, three-year survival rates have been reported to be approximately 40%-60%[54]. Surgery performed with curative intents is the best option for hilar and other extra-hepatic ductal CC cases without PSC. Surgery in patients with positive margins show no better results than with palliative therapies[54]. To obtain tumor-free margins, partial liver resections are often necessary. The liver resection has a great impact on obtaining negative margins in patients undergoing a potentially curative resection for hilar CC (Table 2)[55-60]. A combined data from United States and European experiences proved that five-year survival is higher in patients undergoing liver resection than in those not[61]. An analysis of recent surgical series indicated that five-year survival data is around 40% (Table 3)[62-66]. Most surgeons advocate caudate lobe resections, as the drainage of hilar biliary structures is directly

Table 2 Summary of some studies indicating potential influence of liver resection on tumor margin-negative resections and 5-year survival data on hilar CC (1986-1999)

	Resection	Liver resection	Operative mortality	Margin- (%)	5-yr survival Margin-	5-yr survival Margin+
Kosuge et al 1999[55]	65	80	9	52	56	13
Burke et al 1998[56]	30	73	6	83	40	0
Miyazaka et al 1998[57]	76	86	13	71	26	0
Nagino et al 1998[58]	138	90	9	76	21	-
Klempnauer et al 1996[59]	151	78	10	76	31	5
Nimura et al 1986[60]	100	91	10	55	35	0

Table 3 Summary of some recent studies indicating 1-, 3- and 5-yr survival data on margin-negative tumor resections of hilar CC (2000-2005)

	Resections	1-yr survival (margin-)	3-yr survival (margin-)	5-yr survival (margin-)
Jarnagin et al 2005[65]	25	100	80	45
	81	85	45	30
Silva et al 2005[64]	19	83	58	41
Kondo et al 2004[63]		-	-	40
Neuhaus et al 2003[62]	133	70	42	36
Tsao et al 2000[66]	25	-	-	43

into the caudate lobe bile ducts. In cases with involvement of the distal common bile duct, pancreatoduodenectomy is performed additionally to obtain negative margins. In patients with tumor-free margins after surgery, five-year survival is around 20%-40% and operative mortality 10%[54]. The presence of one of the following indicates unresectability: Bilateral involvement of secondary biliary radicals, invasion of the main portal vein proximal to its bifurcation, unilateral hepatic lobar atrophy together with invasion of contralateral portal vein and/or contralateral secondary biliary radicals, and metastatic involvement of N2 lymph nodes, liver, lung or peritoneum. Indeed, the invasion of the main portal vein may not be an absolute contraindication to surgery as surgeons can prefer to extend their surgical expertise by portal vein resection and its reconstruction in such cases. Though the significance of biliary drainage before surgery is controversial, preoperative biliary drainage of the obstructed lobe *via* percutaneous or endoscopic methods in hilar CCs is generally not indicated. Postoperative morbidity in such cases mostly arises from the introduction of bacteria into the biliary tree *via* preoperatively placed stents. Usually, drainage of the contralateral lobe, free of tumor, is preferred by most surgeons if the involved liver lobe is to be resected and there is deep jaundice. Some authors have shown that lack of intestinal bile delays liver regeneration associated with cyclin E-associated kinase inactivation after surgery[67].

In patients with PSC and CCs, surgery has the worst results. Five-year postoperative survival in these cases has been reported as low as 10%[17,68]. Postoperative recurrent cholangitis attacks, intolerance of partial hepatectomy, due to concomitant advanced fibrosis and high risks of *de nova* CC elsewhere in the biliary tree, are the main obstacles precluding surgery in PSC cases with CCs[69,70]. Thus, liver transplantation can be an alternative option in these cases.

Previously, CC was considered a contraindication for liver transplantation. However, three centers from the United States reported long-term survival following liver transplantation[71-73]. The Mayo Clinic reports five-year survival rates of more than 80% for patients with TNM stage 1 and 2 disease after liver transplantation[72]. The liver transplant protocols in these cases include preoperative chemo-irradiation therapy and exploratory laparotomy. Thus, longer survival expectations for CC cases can be possible with these new fastidious liver transplantation protocols. A recent study compared two treatment modalities, liver transplantation with neoadjuvant protocols and resection surgery, in extra-hepatic CC cases. Five-year survival rates were 82% for 38 patients who underwent liver transplantation and 21% for 26 cases who were resected[74]. Adjuvant treatment modalities such as external beam and intraluminal radiation therapies showed no benefit in two separate reports from Johns Hopkins[75,76]. There is currently no role for adjuvant chemotherapy. However, another study revealed positive effects of radiation therapy on survival in histologically positive tumor margin[76]. Similarly, one study demonstrated higher resectability in patients given neoadjuvant radiation therapy before exploration[76]. However, these studies were non-randomized and most consisted of small patient groups.

In patients with unresectable disease, the initial approach is to provide the patient with supportive care and, if necessary, to plan some form of biliary drainage. Palliative therapies provide less than 18 mo of survival. Intractable pruritus, cholangitis, and need for intraluminal radiotherapy and chemotherapy make it necessary to decompress the biliary tree. The patients with unresectable hilar tumors may not be suitable for an endoscopic approach, due to high failure rates and subsequent cholangitis with this technique. However, there are new metal stent designs for the biliary tree that can provide high success rates of endoscopic insertion without complications. For example, a newly designed Y-shaped metal stent with central wide-open mesh provided 80% technical success in bilateral stent insertion for advanced hilar CCs[77]. Percutaneous biliary drainage and subsequent placement of a self-expandable metallic stent can also be easily and successfully applied in patients with hilar tumors. The patency rates of metallic endoprosthesis at the hilus is approximately 6 mo, which is significantly lower than that reported for similar stents placed in the

distal bile duct. A small pilot study investigated the role of a new percutaneous drainage tube coated with carboplatin[78]. The carboplatin-coated tube continuously released a fixed amount of carboplatin for 4 wk in five patients. Partial response was reported in three (60%) of the cases. Operative segment III bypass provides excellent biliary drainage and is less prone to occlusion than metal stents. In one study, the one-year patency of segment 3 bypass was reported to be 80%[79].

Palliative external radiation therapy and percutaneous intraluminal iridium-192 for patients with unresectable locally advanced tumors, but without evidence of widespread disease, did not improve survival compared with biliary decompression[75,80-84]. In a group of 12 patients treated with this regimen, the median survival was around 14.5 mo[80]. Another report indicated improved survival in irradiated compared to non-irradiated patients. However, both groups had less than one-year survival[75]. A group of authors reported a beneficial effect of radiotherapy only in patients with aneuploid Klatskin tumors[85]. Radiation therapy is clearly not indicated in widespread disease. Successful ablation of intra-hepatic CC cases with radiofrequency ablative therapy was reported previously[86]. Photodynamic therapy is another palliative approach. This therapy is accomplished by the systemic administration of a photosensitizer that accumulates in the malignant cells. Red laser light-induced photoactivation at the time of ERC destroys the malignant cells. This therapy facilitates biliary decompression, and pilot studies have suggested a survival benefit and improvement in cholestasis, performance status and quality of life with this approach[87-90]. Another palliative treatment option is endoscopic administration of high-intensity ultrasound to induce coagulative necrosis of tumoral tissue. Local tumor destruction, with a high-intensity ultrasound probe during ERC, has been reported to induce complete regression of extra-hepatic CC in a pilot study[91]. For mass-forming tumors, transarterial chemoembolization or radiofrequency ablation may be useful. However, these therapies have been tested in small patient groups. Results with chemotherapy appear to be disappointing. Gemcitabine appears to be the most effective single agent[92]. Systemic chemotherapy combined with regional chemoembolization was proven feasible in a small group of patients[93]. New promising drugs are under investigation for their anti-tumoral effects on CCs. A very recent *in vitro* study clearly indicated a high apoptotic effect of proteasome inhibitors on CC cell lines[94].

CONCLUSION

CC is a devastating tumor with a high mortality rate. Its incidence is increasing and there is no new proven medical treatment modality. It is notorious as being difficult to diagnose as well as treat. Strategies are needed to detect these tumors at an early stage to apply radical curative therapy modalities. EUS-guided FNA is the most promising approach in this respect. Liver transplantation protocols must be supported, as necessitated by the recent reports of success using these protocols. Investigations of neoadjuvant and adjuvant treatment alternatives should continue and new *in vitro* effective anti-tumoral agents should be investigated in *in vivo* studies.

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