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CHOLANGIOCARCINOMA: MODERN ADVANCES IN UNDERSTANDING A DEADLY OLD DISEASE

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Abstract

Cholangiocarcinomas are tumors that arise anywhere in the biliary tract, presumably of cholangiocyte origin. The global incidence of this rare disease is on the rise. Several known risk factors exist, and link chronic biliary inflammation to the pathogenesis of cholangiocarcinoma. Among these, amplification of the epidermal growth factor receptor, the interleukin-6 signaling pathway, inducible nitric oxide, erb-2, and cyclooxygenase-2 are well defined. Most patients present late, with a median survival of months. Although, imaging studies and clinical context often indicate cholangiocarcinoma, pathologic and cytologic diagnosis is difficult to obtain. Advanced cytologic tests with fluorescent in situ hybridization or digital image analysis can increase diagnostic sensitivity. Surgical resection is the current therapy of choice for both intrahepatic and ductal cholangiocarcinomas. However, the 5 year survival is poor, with 60 to greater than 90% recurrence rates. In a single center experience, liver transplantation with neoadjuvant chemoradiation, for highly selected patients has a 5 year disease free survival of greater than 80%. Future targeted therapies will depend on a better understanding of the cellular and molecular biology of cholangiocarcinomas.

Introduction

Cholangiocarcinomas are neoplasms with biliary epithelial cell or cholangiocytes differentiation, and are thought to arise from cholangiocytes. Most commonly, tumors occur at the biliary confluence (Klatskin or hilar cholangiocarcinoma), though in some instances tumors occur within the liver or distal to the hilum. The incidence is low, approximately 8 per million in the United States (1). Though it is a rare malignancy, the incidence of cholangiocarcinoma is increasing globally (2,3), and it remains the second most common primary hepatobiliary malignancy. Since the description of Klatskin et al (4), several advances have been made in the understanding and treatment of this devastating disease. Several recognized risk factors account for a minority of cancers. Most cholangiocarcinomas arise in the absence of any known predisposition (5). The molecular and cellular perturbations that characterize this malignant phenotype have been the focus of many investigators. These studies have partially elucidated abnormalities in growth regulatory genes in established cancers, and the mechanistic relationship between chronic biliary inflammation and cholangiocarcinogenesis. This information will ultimately help in the development of chemopreventive and therapeutic strategies.

Classification

Cholangiocarcinomas can be classified into 3 distinct categories by anatomic location. These are intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma and distal extrahepatic bile

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duct cancers (Fig. 1). Hilar cancers, also known as Klatskin tumors, occur at the confluence of the right and left hepatic ducts, are the most frequent (50-60%) and can involve the liver by direct extension (6). Because of the proximity of hilar and left and right branch tumors to the liver, they are included in intrahepatic cholangiocarcinomas in the SEER (Surveillance Epidemiology and End Results) database frequently used for epidemiologic studies. This practice is confusing and should be avoided. In this review intrahepatic cholangiocarcinoma refers only to tumors that originate within the hepatic parenchyma. Of the non-hilar tumors, 10% are intrahepatic and 20-30% are extrahepatic distal bile duct tumors. Further classification of both intrahepatic and extrahepatic tumors is based on gross tumor morphology. Three categories of cholangiocarcinoma have been identified based on their growth pattern: mass-forming, periductal-infiltrating, or intraductal-growing cholangiocarcinomas (7). In an alternative system extrahepatic tumors alone are classified into nodular, sclerosing, or papillary (Fig. 1), a description that respectively matches the broader morphologic classification (8). Hilar lesions are further classified as suggested by Bismuth-Corlette (Fig. 2), a pragmatic classification which corresponds to surgical decision making rather than tumor biology. Histologically, most tumors (>90%) are well to moderately differentiated tubular adenocarcinomas. The other outstanding histologic feature is the presence of a desmoplastic reaction. The fibrosis is variable, but may be profound in some cases, leading to a low diagnostic yield of random biopsies. Papillary adenocarcinoma, signet-ring carcinoma, squamous cell or muco-epidermoid carcinoma and a lymphoepithelioma-like form are rare histologic variants.

Risk Factors

Risk factors for development of cholangiocarcinoma are age, primary sclerosing cholangitis (PSC), chronic choledocholithiasis, hepatolithiasis, bile duct adenoma, biliary papillomatosis, Caroli's disease, choledochal cyst, thorotrast, smoking, hepatitis C virus infection, parasitic biliary infestation, and chronic typhoid carrier state (6). Chronic hepatitis C virus (HCV) infection was reported as a risk factor for intrahepatic cholangiocarcinoma initially in the East (9). Subsequently, it was identified as a risk factor even in the United States. HCV core protein has been detected in patient samples of cholangiocarcinoma (10). Primary sclerosing cholangitis is an uncommon disorder, associated with inflammatory bowel disease, usually ulcerative colitis. The prevalence of cholangiocarcinoma in this population ranges from 5-15%, with a cumulative annual risk of 1.5% per year of disease (11,12). In East Asia, parasitic biliary infection with *Clonorchis sinensis* and *Opisthorchis viverrini*, acquired by the consumption of raw fish, is endemic in certain areas (5). The parasite persists and progressively accumulates in the biliary system for years leading to a chronic inflammatory response and increased risk of cholangiocarcinoma. In one endemic area the adjusted prevalence odds ratio for cholangiocarcinoma was 14.1% (13). A likely distinct type of cholangiocarcinoma arises in the setting of fibropolycystic malformations of the biliary tree; indeed there is a 1% per year cumulative increase in cancer risk in patients with choledochal cysts. While biliary obstruction and inflammation play a role, other factors increase the risk of cancer, as cholangiocarcinomas can occur decades after surgical resection of the cyst (14). One unifying feature of all these risk factors for cholangiocarcinoma is the presence of chronic biliary inflammation.

Inflammation and Carcinogenesis

Molecular perturbations that lead to emergence of a cancerous phenotype involve the following pathways: growth autonomy, escape from senescence, unlimited replication, blockade of growth inhibitory signals, altered microenvironment and evasion of cell death. In chronically inflamed biliary epithelium several changes culminate in the upregulation of growth and prevention of cell death (Fig. 3). In a chronic inflammatory environment, epithelial cells are constantly stimulated to participate in the inflammation by generating chemokines and cytokines (15). The cancers arising in this background retain secretion of these inflammatory mediators presumably because they provide growth and survival advantages. In this regard,

interleukin 6 (IL-6) appears to be a pivotal cytokine for cholangiocarcinogenesis. Indeed cholangiocarcinoma cells constitutively secrete IL-6 (16). In a presumably autocrine fashion, IL-6 activates pro-survival p38 mitogen activated protein kinase (17). Upregulation of Mcl-1, an anti-apoptotic protein of the Bcl-2 family, and Akt activation are downstream consequences of this cytokine signaling cascade (16,18). Indeed, transforming growth factor β (TGF β), a tumor suppressor, can inhibit carcinogenesis by blocking IL-6 signaling (19). Loss of TGF β signaling, therefore, may allow full prooncogenic activity of IL-6. Furthermore, IL-6 also plays a role in senescence abeyance by promoting expression of telomerase (20). Periductal-infiltrating and papillary cancers grow in an environment enriched in bile, suggesting not only resistance to the toxicity of bile but perhaps a tropism for bile. Indeed, bile acids transactivate the epidermal-derived growth factor receptor (EGFR) and also enhance expression of Mcl-1 (21). Both IL-6 and EGFR have been shown to influence the expression of cyclooxygenase-2 (COX-2) (22). COX-2 and inducible nitric oxide synthase (iNOS) activation are the end result of this pro-inflammatory biliary epithelial milieu. Increased iNOS expression occurs in cholangiocytes in PSC and cholangiocarcinoma and elevated circulating nitrate levels occur in patient with liver fluke infestation (23). Nitric oxide (NO) has known pleiotropic effects. NO can directly or via formation of reactive peroxynitrite species lead to deamination of guanine and DNA adduct formation promoting DNA mutations (24,25). NO can also nitrosylate and inactivate DNA repair proteins permitting the accumulation of DNA mutations necessary for cancer development. NO can also nitrosylate caspase 9 leading to inhibition of apoptosis (26). Importantly, iNOS promotes COX-2 upregulation, presumably in the inflamed biliary tract, based on demonstration of this concept in immortalized, non malignant cholangiocytes (27). iNOS can also stimulate expression of Notch, a developmentally important receptor, strongly implicated in the genesis of pancreatic cancer (27). Thus, iNOS has pleiotropic effects in biliary tract carcinogenesis. The ligand independent activation of EGFR by bile acids also leads to the activation of COX-2. COX-2 catalyzes the synthesis of prostanoids from arachidonic acid (28). In colon cancer, COX-2 derived prostanoids bind to prostanoid receptors activating the transcription factor β -catenin; which if unregulated, is highly oncogenic. Likely similar signaling pathways also exist in cholangiocytes/cholangiocarcinomas. The role of β -catenin in cholangiocarcinoma, which plays a key role in hepatocellular and colorectal carcinoma (29), merits further investigation.

Other molecular abnormalities associated with cholangiocarcinoma affect both growth factor receptor tyrosine kinase (RTK) and tumor suppressor genes. Besides IL-6/IL-6 receptor/glycoprotein 130, activating mutations and overexpression of EGFR, hepatocyte growth factor/c-met (HGF), erb-2, K-ras, and BRAF have been described in cholangiocarcinoma (30-34). The proto-oncogene c-erbB-2 (also known as HER-2/neu) is activated in patients with cholangiocarcinoma. Furthermore, in experimental models, the sole introduction of this gene into a biliary epithelial cell line led to transformation and recapitulation of several features of cholangiocarcinoma. Inactivation of tumor suppressor genes occurs frequently as well. Alterations in the p16^{INK4a} and p14/MDM/p53 signaling pathway by homozygous deletion, exon mutations, promoter mutations, and methylation have been described in patients with PSC (35-38). Promoter mutations leading to loss of transcriptional activity of the tumor suppressor p16^{INK4a} occur not only in PSC but also in PSC-associated cholangiocarcinoma, suggesting a role molecular carcinogenesis. Alterations in adhesion molecules and angiogenic factors that support the malignant phenotype have also been described. Decreased expression of E-cadherin, α -catenin, and β -catenin leads to weaker intercellular adhesion (39,40). Overexpression of aspartyl (asparaginy) β -hydroxylase, a molecule that favors tumor invasion, also occurs in cholangiocarcinoma (41). Lastly, apomucins (MUC) play a role in immunophenotyping and have prognostic relevance (42). MUC1 expression is well described in intrahepatic cholangiocarcinoma. Tumors with high levels of expression, either mass-forming or periductal-infiltrating, have a poorer prognosis than intraductal-papillary tumors that display a lower level of MUC1 expression. In another surgical series, metastases 3 years

after surgical resection were higher in the MUC1 positive group of patients with intrahepatic cholangiocarcinoma (43).

Clinical Features

The presentation of Cholangiocarcinoma is primarily governed by anatomic location. Rarely, an asymptomatic cholangiocarcinoma is found during the evaluation of abnormal liver tests. Intrahepatic cholangiocarcinomas present as mass lesions; obstructive symptoms are rare. Fever, night sweats and weight loss may occur in addition to right upper quadrant abdominal pain. On the contrary, hilar and distal extrahepatic bile duct cancers present with symptoms of biliary obstruction, cholangitis and right upper quadrant pain. Other symptoms may coexist, related to hepatitis c infection, cirrhosis, or systemic metastases.

Diagnosis

Imaging modalities are the mainstay of diagnosis. Magnetic resonance imaging (MRI) with concurrent magnetic resonance cholangiopancreatography (MRCP) is the radiologic modality of choice (Fig. 4)(44-46). It allows visualization of the location and extent of biliary disease as well as hepatic parenchyma. Cholangiocarcinomas appear hypointense on T₁-weighted images and hyperintense on T₂-weighted images. Image enhancement can be observed using superparamagnetic iron and delayed gadolinium images (47,48). MR angiography can be performed to assess vascular encasement (49). Hepatic parenchyma, intrahepatic tumors, biliary dilatation, and lymph nodes can also be assessed via Computed tomography (CT). CT angiography allows excellent visualization of the vasculature (50). Ultrasound is non-specific; it may identify intrahepatic mass lesions, and bile duct dilatation proximal to the obstructing lesion. Endoscopic ultrasound guided regional lymph node sampling can be performed in early disease to assess respectability or eligibility for transplantation (51). However, endoscopic aspiration of hilar masses is not recommended because of the potential for tumor seeding.

Biliary instrumentation is necessary in the setting of biliary obstruction. It should also be performed to sample suspicious lesions for histologic and cytologic analyses. In one study, the sensitivity of routine cytology varied from 9-24% and specificity varied from 61-100% (52). In addition to routine pathology and cytology, advanced cytologic techniques can now be recommended for the evaluation of aneuploidy, a hallmark of cancer. These techniques are fluorescence insitu hybridization (FISH) (Fig. 5) and digital image analysis (DIA) (53,54). FISH utilizes fluorescent probes to identify chromosomal amplification (i.e., the actual number of a given chromosome in a cell) and DIA quantitates nuclear DNA as a ratio of normal ploidy (2N). The addition of either DIA or FISH to routine cytology increases the sensitivity without compromising the specificity for diagnosis of cholangiocarcinoma. The highest sensitivity for the diagnosis of malignant biliary stricture in patients with and without PSC is attained by the combination of DIA and FISH. Either DIA or FISH positivity had 67% sensitivity in the diagnosis of cholangiocarcinoma in PSC patients with normal cytology; however the specificity was 75%. When combined, DIA and FISH had a sensitivity of 14% in patients with PSC with normal cytology for the diagnosis of cholangiocarcinoma while retaining a specificity of 98% (unpublished observation).

Serologic testing is supportive and in most instances done prior to or concurrent with imaging studies, though not necessary for the diagnosis of cholangiocarcinoma. The focus of this discussion is on tumor associated markers and not routine liver test abnormalities. CA 19-9, CA 125 and CEA are the most studied tumor associated markers with cholangiocarcinomas. Of all three, CA 19-9 has the most utility. In patients with PSC a value of >100 U/ml has a sensitivity of 89% and specificity of 86%, and in patients without PSC the sensitivity is 53%, for the diagnosis of cholangiocarcinoma (7,55). Increasing the cutoff to >129 U/ml in patients PSC provided a sensitivity of 78.6%, and improved the specificity to 98.5%, and a positive

predictive value of 56.6% (56). In patients with advanced disease, the level may be strikingly elevated, though not universally. CEA and CA-125 are non-specific as they are elevated in patients with cholangiocarcinoma and other gut-derived malignancies, and they have a low sensitivity as well (57). The caveat to the interpretation of an elevated CA 19-9 is the coexistence of bacterial cholangitis, which may not always be overt. Hepatolithiasis also commonly leads to increased levels of CA 19-9, and also CA 125 and CEA. Therefore, cholangiocarcinoma should not be diagnosed on the basis of these tests alone except in patients with known risk factors or virtually diagnostic imaging studies. In an unrelated at-risk population, a study from Thailand, demonstrated the utility of testing serum interleukin-6 levels in conjunction with CA 19-9 in patients with chronic biliary parasitosis. A CA 19-9 value >100 U/ml combined with an IL-6 value > 50 pg/ml had a sensitivity of 80% and accuracy of 76% (58).

In summary, there are multiple parallel diagnostic algorithms to confirm cancer in suspicious cases. Cancer should be carefully sought and confirmed or excluded in patients with high grade strictures, elevated CA 19-9 and suspicious masses. Though histologic diagnosis is the gold standard, per-cutaneous or trans-luminal approach is not recommended because of the risk of tumor seeding. Ideally, biliary tissue should be obtained by ERCP. Non-diagnostic biopsy or cytology should not exclude the diagnosis of cholangiocarcinoma. Screening biliary instrumentation in stable, asymptomatic PSC patients is not recommended due to the concurrent risk of pancreatitis (>7% in patients with PSC, Dr. K. Lindor, personal communication), however, when clinically indicated advanced testing should be utilized to diagnose early cancers in PSC patients. Asymptomatic high risk patients maybe surveyed non-invasively, such as with a serum CA 19-9 value and MRCP annually to achieve early cancer detection, although there are no outcome studies or cost-effectiveness information to advocate this approach.

Staging

There is no unified single staging system for all cholangiocarcinomas, reflecting the different patho-biology of intrahepatic and extrahepatic tumors. The staging of Cholangiocarcinoma has also been dynamic. There have been several modifications and alternatives proposed, with the objective of improving the prognostic and therapeutic predictions for each cancer stage. For staging intrahepatic cholangiocarcinoma the proposed system correlates with survival after hepatic resection (59). Stage I disease is a solitary tumor without vascular involvement, Stage II disease is a solitary tumor with vascular encasement/invasion, Stage IIIA disease is multiple tumors with or without vascular involvement, Stage IIIB disease is any tumor with regional lymph node metastasis, and Stage IV disease is any tumor with distant metastases.

The natural history of extrahepatic cholangiocarcinoma is short, and median survival ranges in months. The only effective treatment is surgical resection (and possibly liver transplantation), therefore, the evolution of staging systems for hilar cholangiocarcinoma has been towards a system that determines resectability. American Joint Committee on Cancer Staging staging system, based on the TNM classification, considers tumor pathology, and the presence of lymph node or extra-lymphatic metastases. It does not correlate with resectability. This led to the development and modification of the Memorial Sloan-Kettering staging system (Fig. 6), also known as T-stage criteria for hilar cholangiocarcinoma (60). As shown in Figure 6, T1 and T2 tumors as well as T3 tumors involving the main portal vein are considered resectable, the later only with portal reconstruction. This is based on the extent of biliary and vascular involvement, and correlates with resectability and survival.

Therapy

Curative surgical resection

Surgical resection is indicated in patients with cholangiocarcinoma in the absence of underlying liver or biliary tract disease. Solitary intrahepatic cholangiocarcinoma lesions are amenable to surgical resection. A partial hepatectomy with removal of the involved bile ducts is performed. Five year patient survival ranges from approximately 20-43%, the higher survival stems from careful patient selection (61-64). In the remainder, recurrent disease is the norm. Strategies to prolong disease free survival using neoadjuvant therapy or adjuvant therapy with radiation or chemotherapy are not effective. The best predictors of survival are the absence of lymph node involvement, negative tumor margins up to 1cm, solitary lesions, and lack of microscopic vascular invasion. Perineural involvement and tumor site do not affect survival. Liver transplantation is contraindicated in these patients due to the universal recurrence rates and lack of effective neoadjuvant or adjuvant therapy.

Extrahepatic lesions are evaluated for resection in the absence of local or distant metastases. For locally contained disease, respectability is primarily determined by the extent of biliary or vascular involvement. Furthermore, resection is feasible only in the absence of underlying liver disease and PSC. The former, a contraindication to partial hepatectomy and the latter to prevent recurrence in predisposed at-risk epithelium. Bilobar involvement precludes curative surgery, as both the right and left lobes of the liver cannot be removed. This can manifest as bilateral portal vein branch involvement, involvement of the main portal vein, and bilateral involvement of secondary biliary radicals. Furthermore, unilobar involvement or atrophy with contralateral vascular involvement also represents disease advanced beyond respectability. Unilobar disease is considered resectable, even with ipsilateral encasement of the hepatic artery or portal vein branch, and/or involvement of ipsilateral secondary biliary radicals with associated lobar atrophy. A concomitant partial hepatectomy is the single most important factor leading to improved outcomes after resection of extrahepatic bile duct tumors (65,66). Several strategies have been developed to improve outcomes. One such strategy is partial hepatic resection with concomitant en-bloc resection of vascular structures and accompanied by reconstruction along with biliary excision for complex hilar tumors (60,67). Indeed, even in patients with Bismuth-Corlette Stage II tumors involving the confluence of the right and left hepatic ducts, caudate lobe resection is recommended because the bile ducts from the caudate lobe drain directly into the confluence and cancer frequently extends up these ducts into the caudate lobe. Another strategy focuses on enhancing compensatory hepatic hypertrophy by pre-operative portal vein embolization to enable extended hepatectomy (resection of ≥ 5 hepatic segments) (68,69). Complete resection of distal bile duct tumors requires more extensive surgery, usually with pancreatoduodenectomy. Even with detailed preoperative staging and curative intent, the 5 year survival for hilar cholangiocarcinoma ranges from 20-40% (60,65,70). Surgical tumor margin is the best predictor of survival; the RO group (no microscopic disease at surgical margin) of patients has the best 5 year survival in all published surgical series. Because of high rates of recurrence, several neoadjuvant therapies have been studied, including radiation, photodynamic therapy and chemotherapy. None of these have demonstrated clear benefit. Distal bile duct cancers have a 5 year survival rate of 37%. Survival is predicted as for proximal cancers by tumor free surgical margins and additionally by lymph node involvement.

Resection in patients with PSC is discouraged as cholangiocarcinoma in often multifocal in this setting, the underlying parenchymal disease may preclude resection and recurrent disease with death following resection occurring in $>90\%$ of patients. In PSC patients with early cholangiocarcinoma, liver transplantation is the preferred definitive therapy (vide infra). In the absence of local or distant metastases, resectability of extrahepatic lesions is determined by the extent of involvement of the biliary tree and hepatic vasculature.

Transplantation

Unresectable cholangiocarcinoma is an emerging indication for liver transplantation, both deceased donor or living donor. The earliest case reports for transplantation for cholangiocarcinoma were dismal. Disease recurrence was the norm. There has been a resurgence in this modality based on recent experience. Two groups of patients stand to benefit from this modality. The first group are those with locally contained unresectable disease with otherwise normal biliary and hepatic structure and function. The other group is patients with underlying biliary inflammation, such as PSC, and/or hepatic dysfunction precluding surgery. The first description of a case series of 11 patients transplanted for cholangiocarcinoma with neoadjuvant chemoradiation demonstrated a 45% tumor free survival with a median follow up of 7.5 years (range 2.8-14.5 years) (71). The experience of another specialized center in such a series of carefully selected patients has reported excellent disease free 5 year survival (82%) following a protocol of neoadjuvant external beam radiation therapy, trans-catheter intrabiliary radiation, chemotherapy and pre-transplant staging exploratory laparotomy (72, 73) (Fig. 7). Indeed, over the same time period, with intent to treat analysis, survival with liver transplantation greatly exceeded that obtained with surgical resection.

Adjuvant therapy

Given the high rate of post-resection disease recurrence, adjuvant radiation therapy and chemotherapy have been explored as a means of improving disease free survival. There are no randomized controlled trials of either modality for post-operative therapy in patients with curative resection. In case series, radiation beam does not improve survival (74), and may even lead to hepatic decompensation (75). Conflicting data exist regarding the role of chemotherapy. Some studies have shown improved survival whereas others have shown no benefit. (76-78). The authors do not advocate adjuvant therapy for this cancer. Brief mention should be made about the safety of neoadjuvant photodynamic therapy (discussed in detail below). In one case series, the safety of bilioenteric anastomosis with photodynamic therapy pre-treated biliary epithelium has been demonstrated.

Symptom Palliation

Since the natural history of this disease is short and most patients present with advanced disease, they are candidates mostly for palliative therapy. The goals then are symptom resolution and quality of life. Biliary obstruction is the major cause of morbidity in this population. This can be treated by a surgical, endoscopic or percutaneous approach. Surgical biliary bypass is associated with a high perioperative morbidity and mortality. Endoscopic biliary stenting is associated with negligible morbidity and mortality. Furthermore, it can be performed as an outpatient procedure. Biliary drainage can also be easily achieved percutaneously, however it has the disadvantage of external drains, bile leakage and patient discomfort. It may be the only option in patients with complete biliary obstruction. By either modality, adequate drainage of one functional hepatic lobe is sufficient to relieve cholestasis (79). Stents can be bare or coated and metal or plastic. Metal stents remain patent longer than plastic stents and should be considered in patients with an anticipated survival of less than 6 months. Plastic stents need to be changed periodically, often at 3 monthly intervals (80).

Tumor palliation

Significant progress has been made in understanding this disease, and patients are being diagnosed earlier at specialized centers. However, a significant proportion of patients present with advanced disease. They are not candidates for curative surgery nor transplantation. The palliative options, consisting of chemotherapy, radiation therapy or photodynamic therapy are of limited benefit, as cholangiocarcinomas respond poorly to existing therapies. Trials of various combinations of these therapeutic options are lacking.

Photodynamic therapy (PDT) is based on the systemic administration of a photosensitizing agent and endoscopic tumor directed red laser light treatment resulting in selective tumor toxicity. Initial studies demonstrated the safety of this procedure in patients with advanced, non-resectable, hilar cholangiocarcinomas. Cholangitis and dermal phototoxicity related respectively to biliary instrumentation and the administration of photosensitizer occur in few patients. In patients with Bismuth-Corlette III or IV tumors, and insufficient biliary drainage with endoscopic stent placement alone, PDT in addition to stenting led to successful biliary drainage and improved quality of life with no 30 day mortality. Several other case series have confirmed that the responses to photodynamic therapy include improved biliary drainage and quality of life (81-83). Furthermore, in a prospective, open-label trial of PDT + endoscopic stenting compared to stenting alone, improved patient survival was demonstrated, 493 days median survival in the PDT group versus 98 days median survival in the stenting alone group ($p < 0.0001$) (81).

Other local ablative therapies including radiofrequency ablation for small intrahepatic cholangiocarcinoma (84-86), and transcatheter arterial embolization are described. (87). Initial trials of chemotherapy were 5-fluorouracil (5FU) based. The response rates with 5FU alone were 10% at best. Several 5FU based combinations, including doxorubicin, mitomycin C, methyl-CCNU, streptozotocin, and cisplatin + epirubicin were of no added benefit (88,89). This led to the use of gemcitabine, which has become the mainstay of chemotherapy (90-92). Response rates ranging from 16% to 36% have been reported, based on different drug administration protocols. However, even with an initial 36% response rate, median survival was poor (6.5 months). It has also been tried in combination with other agents such as cisplatin, and 5-fluorouracil, and the of Gemcitabine ± Cisplatin is now in Phase III trials. Several other agents are in Phase I/II trials.

The emergence of novel therapeutic options based on tumor biology is the goal of the genomic and proteomic era of medicine. Several potential targets exist. Biological therapy targeting epidermal growth factor-receptor (EGF-R), commonly amplified in cholangiocarcinoma, is an attractive candidate. Similarly, chemoprevention with COX-2 antagonists is successful in preventing cholangiocarcinoma growth in cell culture models and in experimental animal models. Other targets such as prostanoid antagonists or iNOS inhibitors need to be evaluated in experimental models.

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Fig. 1.

Classification of cholangiocarcinoma. Cholangiocarcinomas are broadly classified into intrahepatic (also known as peripheral) or extrahepatic tumors. Each is morphologically classified further into mass-forming, periductal-infiltrating or intraductal-growing. This classification also corresponds to the depiction of extrahepatic tumors as nodular, sclerosing or papillary.

Fig. 2. Bismuth-Corlette classification of hilar cholangiocarcinoma. Type I hilar cholangiocarcinoma involves only the common hepatic duct, distal to the confluence of the left and right hepatic ducts (biliary confluence). Type II involves the biliary confluence. Type IIIa affects the right hepatic duct in addition to the biliary confluence and Type IIIb involves the left hepatic duct in addition to the biliary confluence. Type IV tumors either involve both the right and left hepatic ducts in addition to the biliary confluence or are multifocal.

Fig. 3.

Molecular features of cholangiocarcinogenesis. Epithelial changes driven by chronic inflammation that promote tumor formation are depicted here. Autonomous proliferation is promoted by the following: interleukin 6(IL6), its receptor glycoprotein (gp130), epidermal growth factor receptor (EGFR), Her-2 (neu) gene product (c-erb-2), inducible nitric oxide synthetase (iNOS), cyclooxygenase-2 (COX-2), and the oncoprotein K-ras. Evasion of apoptosis is promoted by: myeloid cell leukemia 1 (Mcl-1), Bcl-XL, Bcl-2, nitric oxide (NO) and cellular FLICE inhibitory protein (cFLIP). Escape from senescence is promoted by: p16INK4a, p53, p21, Mdm-2 and telomerase. Lastly, invasion and metastases are promoted

by alterations of: E-cadherin, β -catenin, α -catenin, matrix metalloproteinase (MMP), vascular endothelial growth factor (VEGF) and aspartyl β -hydroxylase.

Fig 4.

Magnetic resonance imaging of a hilar cholangiocarcinoma. Representative MRI imaging with gadolinium enhancement with Feridex and with MRCP are shown. (A) A 4 cm mass is seen centrally with abrupt cutoff of the left hepatic ducts. The mass and thickening also extend along the right posterior ductal system. Intrahepatic bile ducts are dilated. (B) MRCP shows bilateral intrahepatic biliary dilatation with abrupt cutoff corresponding to the 4 cm mass shown in A.

Fig. 5.

Fluorescence in situ hybridization of biliary brushing. A representative fluorescence photomicrograph of biliary brushings from a patient with cholangiocarcinoma is shown here. Each colored spot represents one chromosome, therefore, 2 spots per color are indicative of the normal diploid state. In this example, >2 spots are seen for more than 1 color (indicating more than 1 chromosome pair is abnormal), leading to a diagnosis of polysomy.

Fig. 6. T-stage modification of the Memorial Sloan Kettering criteria for resectability of extrahepatic cholangiocarcinoma. T-1 tumors do not involve vascular structures. They are limited to the hilum with unilateral involvement up to secondary biliary radicles. T-2 tumors involve the biliary confluence and additionally unilateral portal vein branch or secondary biliary radicles or ipsilateral lobar atrophy, all indicative to hilar disease with unilateral biliary or vascular involvement. T-3 tumors have evidence of bilateral biliary or vascular involvement in addition to a tumor at the biliary confluence. In some T-3 tumors the main portal vein alone is involved, in this case resection with portal vein reconstruction may be a possibility.

Fig. 7.

Survival following transplantation for unresectable cholangiocarcinoma. A total of 94 patients underwent staging surgery from 1993-2006. Survival rate since time of diagnosis for patients who received liver transplantation (solid line) and those that were not transplanted (dotted line) because of the presence of extrahepatic disease on staging is shown.