Cholangiocarcinoma

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Cholangiocarcinoma (CCA) is the primary cancer of the bile ducts. Although it comprises only 10%–15% of hepatobiliary neoplasms, its incidence is increasing.[1,2] CCA arises from malignant transformation of cholangiocytes, the epithelial cells that line the biliary apparatus. Traditionally, CCA is divided into intrahepatic and extrahepatic disease according to its location within the biliary tree. Intrahepatic CCA occurs within the hepatic parenchyma, forms classic mass lesions, and often presents with advanced clinical features. Extrahepatic CCA arises in large bile ducts (ie, left and right hepatic ducts and common hepatic and common bile ducts). These tumors present with features of biliary obstruction. In epidemiological databases, tumors of the left and right hepatic ducts are often classified as intrahepatic tumors because they can extend into the hepatic parenchyma; this classification should be discouraged as it is confusing. There are similarities between intrahepatic and extrahepatic CCA; however, each entity has distinct epidemiological and clinical features. More importantly, the etiopathogenetic pathways of intrahepatic vs extrahepatic CCA are probably independent.[1] Because of scientific progress in the past decade, a better understanding of the pathobiology of CCA is emerging. As we begin to shed light on the pathogenesis of CCA, we hope that its early detection and therapy will improve.[3]

Epidemiology

Overall, CCA is a rare neoplasm. Nevertheless, during the past 3 decades, its incidence has increased.[2,4] In the United States, approximately 5000 new CCA cases are diagnosed yearly.[2] Two thirds of CCAs involve the extrahepatic bile ducts, whereas the remaining one third affects the intrahepatic biliary tree.

Studies indicate that intrahepatic and extrahepatic CCA have a distinct epidemiology. As a result, incorrect classification between these 2 types may have affected the reported epidemiological observations of CCA. In the United States, the age-adjusted incidence rates of intrahepatic CCA increased from 0.32 in 100,000 in 1975–1979 to 0.85 in 100,000 in 1995–1999.[2] Conversely, the incidence of extrahepatic CCA declined from 1.08 in 100,000 in 1979 to 0.82 in 100,000 in 1998[2] (Figure 1). Below we present the epidemiology of intrahepatic and extrahepatic CCA separately.

During the 1970s, the average age at diagnosis of intrahepatic CCA was the sixth decade of life. In the late 1980s and during the 1990s, however, the age at diagnosis of intrahepatic CCA shifted toward the seventh decade of life. This age change of the affected individuals may reflect aging of the adult population, with subsequent development of CCA, and close follow-up and therapy of known risk factors (such as primary sclerosing cholangitis [PSC] and choledochal cysts) in young individuals. In the United States, the male–female ratio for intrahepatic CCA is approximately 1.5. The age-adjusted incidence of intrahepatic CCA in Caucasians and African Americans is comparable; Asians, however, have twice the incidence of Caucasians. The only ethnic group with a reported gradual increase in the age-adjusted incidence of intrahepatic CCA is Caucasian. The incidence of intrahepatic CCA varies across the world.[2] It is highest in northeast Thailand (96/100,000 in men and 38/100,000 in women), probably because of the high prevalence of liver fluke infestations.

The mortality related to intrahepatic CCA is also increasing worldwide.[5–7] In fact, the percentage of intrahepatic CCA–increased mortality is greater than that observed for hepatocellular carcinoma. In the United States, the age-adjusted mortality rate for intrahepatic CCA increased from 0.07 in 100,000 in 1973 to 0.69 in 100,000 in 1997.[6] The 5-year survival of patients with intrahepatic CCA remains unacceptably low and virtually unchanged over the past 20 years. Survival has not dramatically improved despite diagnosis at less advanced

Abbreviations used in this paper: CCA, cholangiocarcinoma; CT, computerized tomography; DIA, digitized image analysis; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FISH, fluorescence in situ hybridization; 5-FU, 5-fluorouracil; MR, magnetic resonance; MRCP, magnetic resonance cholangiopancreatography; OLT, orthotopic liver transplantation; PDT, photodynamic therapy; PSC, primary sclerosing cholangitis.

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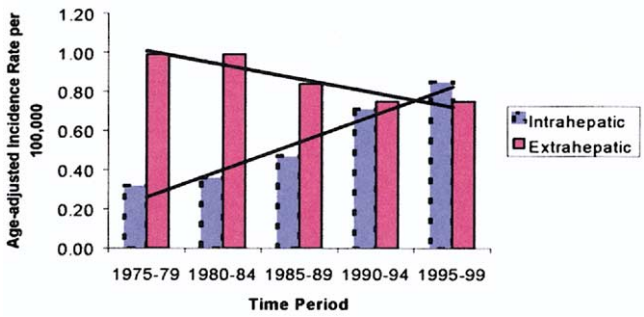

Figure 1. Incidence of intrahepatic and extrahepatic CCA in the United States from 1975 to 1999. Note that the term *intrahepatic CCA* includes hilar lesions (modified from Shaib et al[2]).

stages, better surgical approaches, and promising new therapies (eg, biliary stenting and photodynamic therapy [PDT]).

The incidence of extrahepatic CCA also varies across the globe. In the United States, the reported age-adjusted incidence of extrahepatic CCA is 1.2 in 100,000 for men and 0.8 in 100,000 for women.[8] Nonetheless, the overall incidence of extrahepatic CCA is declining. Moreover, the age-adjusted mortality rate of extrahepatic CCA is also decreasing in the Western countries,[5] with the exception of Italy and Japan. In the United States, the age-adjusted mortality rates declined from 0.6 in 100,000 in 1979 to 0.3 in 100,000 in 1998.[6] To this end, current evidence indicates minor improvements in 5-year survival rates of extrahepatic CCA from 11.7% in 1973–1977 to 15.1% in 1983–1987.[8]

Risk Factors

Table 1 reports the risk factors that thus far have been associated with the development of CCA. Still, for most CCA cases the cause is unknown, and these individuals lack exposure to or association with known risk factors. PSC is a definite risk factor for CCA.[9,10] In a PSC patient, the risk for developing CCA is approximately 1.5% per year after diagnosis of the cholestatic liver disease.[11] Among the patients with PSC who will acquire CCA, approximately 30% will be diagnosed with malignancy of the bile ducts within 2 years after diagnosis of PSC.[10,11] It is interesting to note that the risk of developing CCA is not associated with the duration of PSC.[11]

Hepatobiliary flukes, namely, *Opisthorchis viverrini* and *Clonorchis sinensis*, are strongly associated with CCA. These worms inhabit the bile ducts and occasionally the gallbladder after ingestion of undercooked fish. Patients with choledochal cysts (ie, congenital cystic dilatation of the ducts) have a 10%–15% lifetime risk of developing CCA.[12] Hepatolithiasis (ie, intrahepatic bile duct stones) is frequent in Asia but sparse in Western Europe and the United States. Hepatolithiasis is usually associated with peripherally located intrahepatic CCA.[13] Exposure to Thorotrast (a colloidal suspension of $^{232}ThO_2$) has been linked to the development of CCA. Thorotrast was used as radiology contrast agent in the early to mid 20th century. Thorotrast likely causes microsatellite instability and subsequently CCA, probably via clonal expansion of cholangiocytes and inactivation of hMLH1.[14] Environmental exposures such as dioxin and vinyl chloride have been suggested to cause CCA.[15,16] Recently, hepatitis C virus infection has been proposed as an etiologic factor of intrahepatic CCA.[17]

In conclusion, common features among many CCA risk factors are chronic biliary inflammation and cholestasis. Both of these events contribute to malignant transformation of the cholangiocyte.

Molecular Pathogenesis

During the last 10 years, considerable progress has been made in beginning to understand the pathogenesis of CCA. In general, malignant transformation of the cholangiocyte occurs in an environment of chronic biliary inflammation, chronic cholestasis, or both. We now appreciate several risk factors that predispose to the development of CCA (Table 1). In fact, the milieu of chronic biliary inflammation, and cholestasis, leads to the production of cytokines and reactive oxygen species, and this causes protracted cellular (ie, cholangiocyte) stresses and irreversible DNA damage.[1] As a result, cholangiocytes attain subcellular and cellular phenotypes that result in malignant transformation. Molecular mechanisms responsible for bile duct carcinogenesis likely include the interaction of genetic variants and somatic cell alterations. Figure 2 illustrates the proposed pathways that partake in cholangiocarcinogenesis. These paths include mechanisms that result in cholangiocyte: (1) self-sufficiency and proliferation, (2) apoptosis resistance, (3) escape from senescence, and (4) tumor invasiveness and metastasis.

Table 1. CCA Risk Factors

Age >65 y
Primary sclerosing cholangitis (PSC)
Liver fluke infestation
Opisthorchis viverrini
Clonorchis sinensis
Caroli disease
Choledochal cysts
Bile duct adenoma and biliary papillomatosis
Chronic intraductal stones (ie, hepatolithiasis)
Liver cirrhosis
Surgical biliary/enteric drainage procedures
Chemicals/agents (ie, Thorotrast, dioxin, or vinyl chloride)

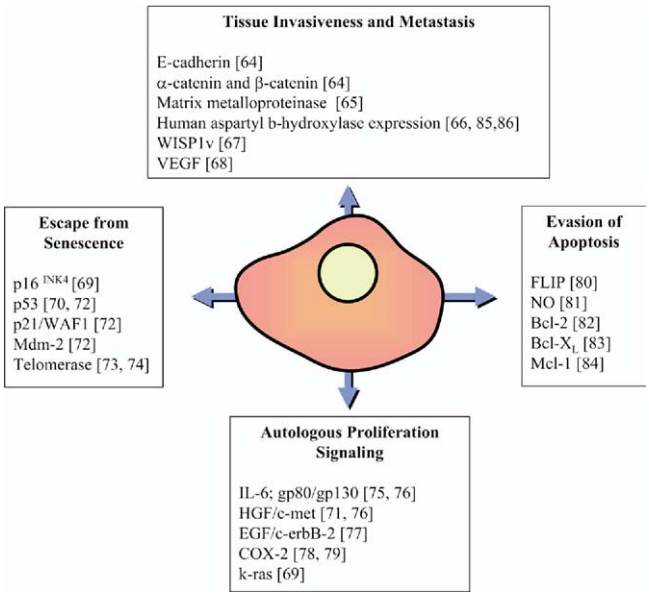

Figure 2. Molecular alterations of cholangiocyte malignant transformation. CCA possess molecular mechanisms to manifest self-sufficiency in growth and proliferation, avoid apoptosis, escape from senescence, and invade tissues and metastasize. The illustration depicts the molecular pathways of malignant cells that likely interact to produce the CCA phenotype. WISP1v, WNT1-inducible signaling pathway protein 1; VEGF, vascular endothelial cell growth factor; WAF1, wild-type p53-activated fragment 1; Mdm-2, murine double minute-2 gene; FLIP, flice-inhibitory protein; NO, nitric oxide; Bcl-2, B-cell lymphoma/leukemia 2; Bcl-X_L, BCL2-related protein, long isoform; Mcl-1, myeloid cell leukemia 1; COX-2, cyclooxygenase 2; IL-6, interleukin 6; HGF, hepatocyte growth factor; EGF, epidermal growth factor (modified from Gores[1]). (Numbers in brackets denote relevant references).

Pathologic Classification

According to its location in the biliary tree, CCA is classified into extrahepatic and intrahepatic types (Figure 3). The extrahepatic type accounts for approximately

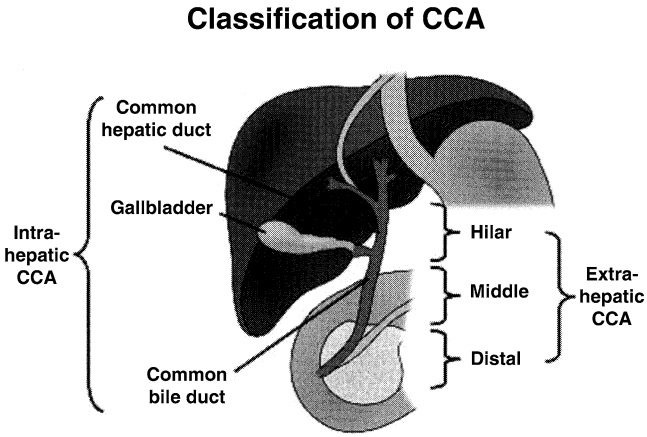

Figure 3. The term CCA refers to tumors involving the entire (ie, intrahepatic and extrahepatic) biliary tree. Intrahepatic CCA denotes malignancy affecting the intrahepatic bile ducts. Extrahepatic CCAs are divided into hilar (ie, Klatskin), middle, and distal tumors.

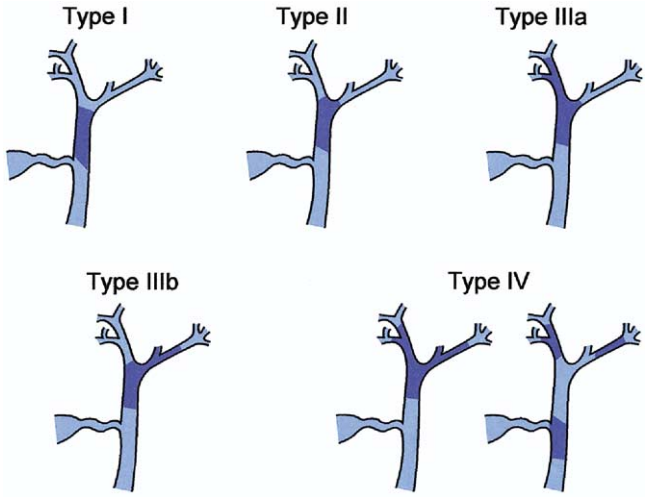

Figure 4. Classification of hilar CCA by Bismuth–Corlette. There are 4 types of hilar CCA. Type I affects the common hepatic duct; type II involves the common hepatic duct and the confluence of the right and left hepatic ducts; types IIIa and IIIb occlude the common hepatic duct and either the right or left hepatic duct, respectively; and type IV involves the biliary confluence and extends to both the right and left hepatic ducts or refers to multifocal bile duct tumors.

two thirds of all CCA and is further divided into: (1) hilar or Klatskin, (2) middle, and (3) distal tumors. Klatskin tumors represent approximately 60% of all extrahepatic CCA. Figure 4 illustrates the Bismuth–Corlette classification of hilar CCA. Macroscopically, extrahepatic CCA presents as sclerosing, nodular, or papillary phenotypes. The sclerosing type is the most frequent and results in annular thickening of the bile ducts because of infiltration and fibrosis of the periductal tissues. The intrahepatic CCA are classified into the following 4 growth types: (1) mass forming, (2) periductal infiltrating, (3) mass forming plus periductal infiltrating, and (4) intraductal.[18]

Whether CCA is intrahepatic or extrahepatic, the usual microscopic appearance is an adenocarcinoma. The most common histological appearance is a well- to moderately differentiated tubular adenocarcinoma within a prominent, dense, desmoplastic stroma. Poorly differentiated CCA is not uncommon and is characterized by individual malignant cells dispersed in a fibrous stroma. The tumor is often associated with prominent perineural invasion. Other histological variants of CCA include papillary adenocarcinoma, signet-ring carcinoma, squamous cell or mucoepidermoid carcinoma, and a lymphoepithelioma-like form.

Clinical Presentation, Laboratory Findings, Imaging Studies, and Diagnosis

Patients with extrahepatic CCA present with jaundice, dark urine, pale stools, pruritus, malaise, and

weight loss. Laboratory tests show obstructive cholestasis with increased alkaline phosphatase and bilirubin. The serum marker CA 19-9 may be increased. CA 19-9, the most frequently tested marker for pancreatobiliary malignancies,[19] detects circulating high-molecular-weight mucin glycoproteins coated with sialylated blood group epitopes (ie, sialyl Lewis).[20] CA 19-9 blood levels are dependent on the red blood cell Lewis phenotype.[21] Approximately 7% of the population are Lewis negative, and, thus, these individuals will have a nondetectable CA 19-9 even in the presence of malignancy.[22] CA 19-9 is not specific for CCA. Cancers of the pancreas, stomach, and colon; bacterial cholangitis; smoking; and gynecologic malignancies can cause increased CA 19-9. Bacterial cholangitis is a frequent cause of increased CA 19-9 serum levels in this patient population.

Intrahepatic CCA presents with nonspecific symptoms including abdominal pain, diminished appetite, weight loss, malaise, and night sweats. Sometimes an incidental abdominal mass detected during either a physical examination or imaging study is the only finding of CCA in asymptomatic patients. Laboratory tests usually show an increased alkaline phosphatase with a normal bilirubin. Serum tumor markers, such as CA 19-9, may be increased.

In extrahepatic CCA, imaging studies show dilatation of the biliary ducts and often define the anatomic level of biliary obstruction. The position and extent of extrahepatic CCA along the biliary system is defined by endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), or percutaneous transhepatic cholangiography. Despite being invasive, ERCP permits brush cytology and biopsies of the bile ducts for histological assessment. Figure 5 shows a percutaneous transhepatic cholangiogram of a patient with hilar CCA. Tissue-proven diagnosis of extrahepatic CCA can be daunting because it is a highly desmoplastic tumor composed of aggregations of a few malignant cholangiocytes within excessive fibrous tissue. The desmoplastic reaction surrounds the bile ducts and extends into the submucosa, and, thus, biliary cytology is positive for CCA in only approximately one third of the cases.[3] A combination of brush cytology and endoscopic biopsy may increase the yield of CCA-positive findings to 40%–70%.[3]

In CCA, computerized tomography (CT) scans and magnetic resonance (MR) imaging aid in the diagnosis and evaluation for possible tumor resection. On abdominal CT, the primary lesion of extrahepatic CCA is usually not visible given its infiltrative nature, which causes stricturing along the bile ducts. Nevertheless, CT can show the effect of CCA obstruction on the bile ducts

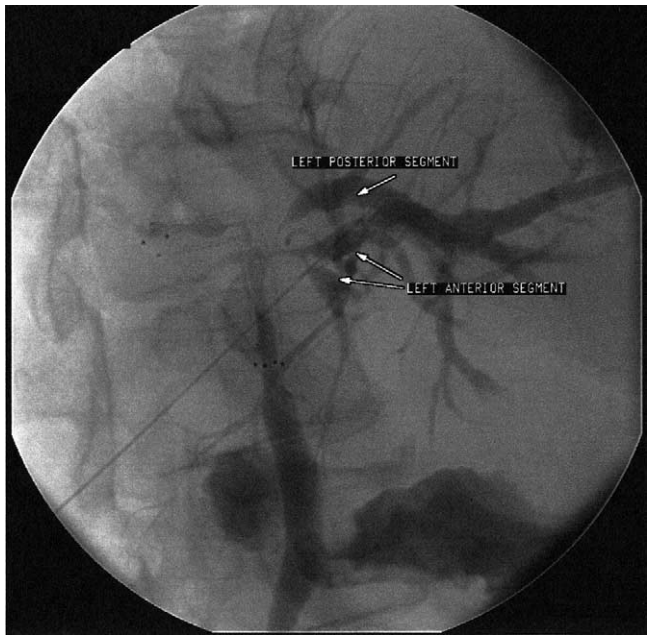

Figure 5. Percutaneous transhepatic cholangiogram showing a hilar CCA causing obstruction of the biliary bifurcation and the right and left hepatic ducts with extension into the left anterior and posterior segments. Note the presence of a metallic stent in the right hepatic duct and bifurcation.

(ie, dilation) and hepatic lobes (ie, atrophy/hypertrophy complex; see below). On CT examination, intrahepatic CCA presents with delayed venous phase enhancement of a hypodense lesion after contrast administration. On cross-sectional MR imaging, CCA appears as a hypointense lesion on T1- weighted images and as a moderately intense signal on T2-weighted images. In hilar CCA, MRCP may show irregular thickening of the bile duct wall if the lesion is >5 mm, in addition to proximal biliary dilatation.[23]

Unilobular bile duct obstruction usually results in atrophy of the affected hepatic lobe followed by hypertrophy of the nonaffected lobe. This phenomenon is known as the *atrophy-hypertrophy complex*.[24] On cross-sectional imaging the presence of an atrophied hepatic lobe alone without an atrophy-hypertrophy complex suggests vasculature encasement of the affected lobe by CCA.

New diagnostic methods, such as digitized image analysis (DIA) and fluorescence in situ hybridization (FISH), offer promise to evaluate extrahepatic bile duct lesions for cellular aneuploidy and chromosomal aberrations.[25] To perform DIA and FISH assays, bile duct brushing/aspirate specimens are collected at the time of ERCP, and cells are fixed on a slide. DIA is a digital camera–assisted image of the cell nucleus that captures pictures as light is transmitted through the slide specimen. This laboratory-based technique allows DNA con-

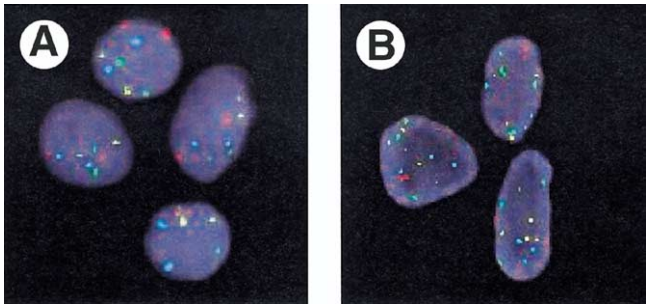

Figure 6. Fluorescence in situ hybridization of normal and malignant cholangiocytes. Fluorescently labeled DNA probe decorating genomic loci on 4 separate chromosomes are shown. The red color probe indicates chromosome 3, the green color probe specifies chromosome 7, the gold color probe points to chromosome 9, and aqua identifies chromosome 17. Normal cholangiocytes (*A*) have 2 duplicates of each probe, as anticipated for normal diploid cells. Malignant cholangiocytes (*B*) show gains of chromosomal probes, thus suggesting polysomy.

tent quantification, assessment of chromatin distribution, and nuclear morphology.[26] In a recent prospective study, DIA was compared with routine brush cytology for the detection of cancer in suspicious biliary tract strictures.[27] This study showed that DIA was significantly more sensitive (39.3%) than routine brush cytology (17.9%; $P = .014$). The specificity of DIA was 77.3%, whereas the specificity of cytology was 97.7% ($P = .003$). The lower DIA specificity was attributed to the high proportion of patients with PSC in that study.[27] Nevertheless, the sensitivity was greater, and the accuracy of DIA was comparable to that of cytology (56% vs 53%).

The FISH assay uses fluorescently labeled DNA-based probes to detect chromosomal aberrations in cholangiocytes. Bile duct cells with chromosomal gains suggest malignancy. To date, FISH has been performed with 4 fluorescently labeled DNA probes hybridized to the centromere of chromosomes 3, 7, and 17 and the p16 gene on chromosome 9 (9p21). After hybridization, the cells are stained with the nuclear counterstain 4′,6-diamidino-2-phenylindole, and fluorescence microscopy is used to screen the slide for abnormal cholangiocytes (Figure 6). A FISH assay is declared positive when ≥5 cells display gains of ≥2 chromosomes or when ≥10 cells show a gain of a single chromosome. A positive FISH study, however, cannot define the position of the bile duct malignancy. In a recent comparison study of FISH to standard cytology for detection of malignant bile duct strictures, the sensitivity of FISH and cytology were 34% and 15%, respectively ($P < .01$). The specificity of FISH was 91%, and the specificity of cytology was 98% ($P = .06$).[28] It seems, therefore, that biliary FISH is more sensitive and virtually as specific as standard cytology for the discovery of malignant bile duct strictures.

Endoscopic ultrasonography (EUS) has been used in assessing the nature of biliary strictures. In a recent study of 28 patients, EUS-guided fine-needle aspiration (FNA) biopsy of suspected CCA has shown a specificity, sensitivity, and positive predictive value of 86%, 100%, and 100%, respectively.[29] From the same study, EUS with FNA was reported to have a positive effect on the clinical management of 84% of patients with CCA.[29] These studies were performed in non-PSC patients; therefore, their role in identifying CCA in PSC patients is unclear. Also, the risk of peritoneal seeding with this technique in patients with potentially resectable disease needs to be taken into account.

The diagnosis of CCA is usually made by evaluating the clinical examination and biochemical results and by obtaining endoscopic and imaging procedures (ie, ERCP and CT/MR imaging of abdomen) to delineate the biliary anatomy. In clinical practice, it is common to make the diagnosis of CCA on the basis of clinical/laboratory/imaging studies without tissue-proven evidence of tumor. However, it should be noted that 10% of malignant-appearing biliary strictures are benign in surgical series.[30,31] In patients with PSC, the diagnosis of superimposed CCA can be very demanding. The patient may have dominant biliary stricture, and it is not easy to differentiate whether it is a benign lesion or CCA. In a patient with PSC, sudden and unexpected clinical deterioration, which is associated with progressive increases of alkaline phosphatase and serum CA 19-9 (>100 U/mL), in the absence of bacterial cholangitis, indicates probable development of CCA.[32,33] Indeed, the sensitivity and specificity of a CA 19-9 value >100 U/mL for detecting CCA in patients with PSC are 75%–89% and 80%–86%, respectively.[32,33]

Staging

CCA staging is clinically important to identify candidates for surgical resection. Tables 2 and 3 describe the TNM classification for intrahepatic and extrahepatic CCA, respectively. The worth of TNM system for extrahepatic CCA is limited, because it relates to histopathology and not to the extent of disease. Knowing the disease extension is pivotal in making decisions regarding surgical resection of the tumor. Table 4 shows proposed preoperative T-stage criteria for hilar CCA. During the clinical staging of extrahepatic CCA, the proximal and distal margins of the tumor should be clearly identified. ERCP, MRCP, or, less common, percutaneous transhepatic cholangiography can be used to map the boundaries of bile duct tumor. It is also important to exclude CCA

Table 2. TNM Pathologic Classification of Intrahepatic CCA[34]

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1

T1, solitary tumor without vascular invasion; T2, solitary tumor with vascular invasion or multiple tumors, none >5 cm; T3, multiple tumors >5 cm or tumor involving a major branch of the portal or hepatic vein(s); T4, tumor(s) with direct invasion of adjacent organs other than gallbladder or with perforation of visceral peritoneum; N0, no regional lymph node metastasis; N1, regional lymph node metastasis; M0, no distant metastasis; M1, distant metastasis.

vascular encasement of the contralateral (ie, nonaffected) liver lobe before committing to partial hepatectomy and to verify vascular patency of the portal vein and hepatic artery. This usually can be accomplished by Doppler ultrasonography and/or CT or MR vascular studies. Finally, regional metastases should be ruled out. Studies have shown that EUS is better compared with conventional cross-sectional abdominal imaging (ie, CT or MR imaging) to exclude metastatic disease. This is particularly important for questionable regional lymph nodes, which can be biopsied during EUS to rule out metastasis. Indeed, 15%–20% of CCA patients with unremarkable abdominal imaging studies have metastatic lymph node involvement according to EUS evaluation.[25]

Therapy

Surgical resection is the best available and potentially curative therapy for both intrahepatic and extrahepatic CCA. Almost all intrahepatic and most extrahepatic CCA require major hepatectomy for complete surgical removal of the malignancy. Thus, many patients are not deemed surgical candidates because of comorbidities or advanced age, despite evidence of resectable disease. Regrettably, more than half of CCA patients present with advanced, unresectable malignancy. In such cases, palliative therapies such as biliary stenting and photodynamic therapy (PDT) provide symptom relief and may improve survival. A clinical controversy is the presence of an intrahepatic mass that may mimic intrahepatic CCA vs metastatic disease of an unknown primary tumor. In our view, a patient who presents with a dominant liver mass and no evidence of detectable extrahepatic disease by physical examination, laboratory studies, and body imaging most likely has intrahepatic CCA.

Table 3. TNM Pathologic Classification of Extrahepatic CCA[34]

Stage	Tumor	Node	Metastasis
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1 to T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Tis, carcinoma *in situ*; T1, tumor confined to the bile duct histologically; T2, tumor invades beyond the wall of the bile duct; T3, tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left); T4, tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall; N0, no regional lymph node metastasis; N1, regional lymph node metastasis; M0, no distant metastasis; M1, distant metastasis.

Table 4. Proposed Preoperative T-Stage Criteria for Hilar CCA[35]

Stage	Criteria
T1	Tumor involving biliary confluence with or without unilateral extension to second-order biliary radicles
T2	Tumor involving biliary confluence with or without unilateral extension to second-order biliary radicles and ipsilateral portal vein involvement with or without 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 portal vein involvement or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy or main or bilateral portal vein involvement

At present, chemotherapy and/or radiation therapies for CCA have not been evaluated in the context of randomized, controlled trials, and, therefore, their efficacy remains dubious, including the use of adjuvant chemotherapy after surgical resection to diminish the risk of CCA recurrence.[3] Finally, at selected liver transplant centers, a small fraction of well-chosen patients with hilar CCA may undergo orthotopic liver transplantation (OLT), with excellent survival results. Figure 7 provides an algorithm for the overall management of CCA.

Surgical Therapy

Extrahepatic cholangiocarcinoma. Most extrahepatic CCAs are hilar tumors. CCA involving the distal bile ducts usually necessitates pancreaticoduodenectomy. Below we discuss the surgical therapy for hilar tumors.

Staging of extrahepatic CCA is a critical step before consideration for surgical resection. Clinical staging criteria for hilar CCA have been proposed (Table 4). It is interesting to note that these criteria correlate with tumor resectability (ie, 60% in stage T1 and 0% in stage T3) and patient survival.[35] The evaluation for resectabil-

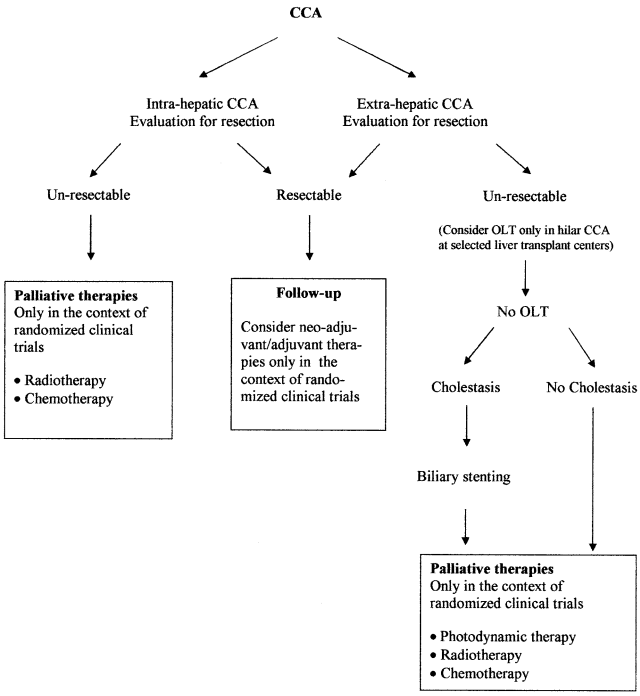

Figure 7. An overview of clinical management for CCA. OLT, orthotopic liver transplantation.

ity requires careful patient selection and meticulous interpretation of imaging studies. During preoperative evaluation, approximately one third of CCA cases will be deemed unresectable. Table 5 lists the criteria for nonresectable CCA. Moreover, during laparoscopy, 25%–30% of patients who were thought to be candidates for surgical resection will be found to have unresectable CCA.[35,37] Therefore, laparoscopy before resection of extrahepatic CCA has become the standard surgical approach.

In general, patients with resectable extrahepatic CCA necessitate partial hepatectomy to achieve tumor-free margins. This is important because patients with positive surgical margins have survival comparable to those receiving palliative therapy alone.[35,38,39] Patients with tumor-free margins have a 20%–40% 5-year survival rate.[35,38] To accomplish a biopsy-proven negative surgical margin, the surgeon needs to perform resection of the tumor/extrahepatic bile ducts along with subhilar lymphadenopathy. Data indicate that concurrent en bloc partial hepatectomy is associated with a higher degree of negative resection margins.[35,39] Extrahepatic CCA involving the biliary confluence affects the main caudate duct and, thus, requires caudate lobe removal.[35,40] An area of controversy in patients with CCA who present with obstructive jaundice is the need for preoperative biliary stenting. Although stenting of the bile ducts alleviates cholestasis in most cases, it poses the potential risk of infection and may make determining the intraoperative disease extent difficult. Patients with CCA limited to the common bile duct likely do not benefit from preoperative stenting. Patients who require hepatic resection may benefit from stenting of the remaining liver if it is also obstructed. Cholestasis may not resolve rapidly and can impair liver regeneration.[41]

Resection of extrahepatic CCA is a major operation with a 5%–10% mortality rate and notable morbidity even at large medical centers with expertise in hepatobiliary surgery.[35] Infections are the dominant cause of postoperative mortality.[35] Regional lymph node metastases are associated with reduced 3- and 5-year survival.[42] However, it is unknown whether extended lymph node resection during surgery improves patient survival. Beyond the curative intent, hepatobiliary surgery (ie, choledochojejunostomy or hepaticojejunostomy) may have a palliative effect on obstructive jaundice in extrahepatic CCA. However, current endoscopic modalities (ie, biliary stenting, PDT, and brachytherapy) and the high cost, morbidity, and mortality of operations have rendered the surgical approaches less favorable for palliation of jaundice.

Intrahepatic cholangiocarcinoma. Surgery is also the best option for effective and potentially curative therapy for intrahepatic CCA. Intrahepatic CCAs are large tumors at the time of diagnosis that necessitate major liver resection. Prognostic factors that indicate a poor outcome after surgical resection of intrahepatic CCA are shown in Table 6. Metastasis of CCA to the regional lymph nodes affects survival; however, the effect of surgical node dissection on patient survival is unclear. After surgical resection of intrahepatic CCA, the median and 5-year survival rates range from 12 to 28 months and from 29% to 36%, respectively. The different types of intrahepatic CCA have now been defined and include a classic mass lesion, periductal infiltrating disease, mass lesion plus periductal infiltrating disease, and intraductal papillary neoplasms. After surgical resection, patients with a mass lesion plus periductal infiltrating disease had

Table 5. Criteria of Nonresectable CCA[36]

1. Hepatic duct involvement up to secondary biliary radicals bilaterally
2. Encasement or occlusion of the main portal vein proximal to its bifurcation[a]
3. Atrophy of 1 hepatic lobe with encasement of contralateral portal vein branch
4. Atrophy of 1 hepatic lobe with contralateral involvement of secondary biliary radicals
5. Distant metastases (peritoneum, liver, lung)

[a]Relative criterion. Portal vein resection and reconstruction may be possible.

Table 6. Prognostic Factors Associated With Unfavorable Outcome After Surgical Treatment of Intrahepatic CCA

Preoperative CA 19-9 levels >1000 U/mL
Multifocal disease
Liver capsule invasion
Lack of cancer-free surgical margins
Regional lymph node metastases
Mass-forming or periductal infiltrating-type CCA growth
Expression of MUC1 by CCA cells

a shorter survival than those with mass-forming tumors.[18]

Palliative Therapeutic Approaches

Many patients with intrahepatic or extrahepatic CCA have unresectable disease at the time of diagnosis. In addition, because CCA affects usually the elderly, a significant percentage of surgical candidates have comorbidities that preclude an operation for tumor resection. Palliative therapies aim at improving or resolving obstructive jaundice and subsequently ameliorating patient symptoms. Palliative therapies of obstructive jaundice include biliary stenting, PDT, and intraluminal brachytherapy. Although the nonsurgical approaches to treat obstructive jaundice can be performed endoscopically or percutaneously, we discuss here only endoscopic-guided therapies.

Biliary stents. In patients with CCA, relief of obstructive jaundice improves symptoms and quality of life, but not survival. Biliary stents are an effective modality in relieving malignant bile duct obstruction with subsequent amelioration of jaundice. Biliary drainage of only 25%–30% of the hepatic parenchyma is required to achieve resolution of jaundice. Parameters to be considered before palliative endoscopic therapy with biliary stents include location and extent of bile duct obstruction, hepatic lobe atrophy, type of biliary stents (ie, plastic vs metallic) number of biliary stents (ie, single vs double drainage), and patient life expectancy.[43] Obtaining a cross-sectional imaging study before an ERCP provides guidance for the endoscopist to choose the optimal bile ducts for stenting, thus avoiding atrophied hepatic segments and minimizing the risk of postprocedural cholangitis.[43,44] Having this information before an ERCP not only improves the success rate of stenting obstructed bile ducts but also facilitates the resolution of jaundice.[45] The type and number of biliary stents to treat obstructive jaundice in CCA should be individualized. For instance, a patient jaundiced because of Bismuth type I hilar CCA can receive successful palliative treatment with a single biliary stent. Nevertheless, there is no consensus for biliary stenting of Bismuth type II, III, or IV hilar CCA. In a prospective, randomized controlled trial of patients with hilar CCA (ie, Bismuth I to III), it was concluded that unilateral drainage was adequate to alleviate biliary obstruction; moreover, endoscopic attempts to place a second biliary stent were likely to result in early complications (eg, bacterial cholangitis) without evidence of a patient survival benefit.[46]

Both plastic and metallic biliary stents have been used to alleviate CCA. Plastic stents have a smaller diameter and become occluded more easily compared with self-expandable metal stents.[43] The latter are also cost-effective in patients with CCA who survive for more than 3 months.

Photodynamic therapy. PDT has also been used to alleviate malignant obstruction of the extrahepatic bile ducts.[47] During the first visit, the patient undergoes systemic preadministration of a nontoxic photosensitizing drug, which accumulates mainly in the CCA. Two days later, the patient has ERCP to activate the photosensitizer intraductally via direct nonthermal laser application. During activation, the photosensitizing agent reaches an excited reactive state (triplet state); subsequently, the energy is transferred from the triplet state of the photosensitizer to molecular oxygen. This process creates singlet molecular oxygen ($^1O_2$), which results in direct or indirect photodamage of the targeted tissue (ie, CCA). Specifically, the photosensitizer accrues in the mitochondria and causes apoptosis of malignant cholangiocytes and surrounding tissues, thus resulting in tumor regression (Figure 8).

The most common photosensitizer in use is a derivative of hematoporphyrin (porfimer sodium; Photofrin; Axcan, Birmingham, AL). Sodium porfimer is given intravenously at 2 mg/kg body weight. In CCA, studies have shown that porfimer enrichment is adequate for PDT between day 1 and 4 after intravenous administration. Intraluminal photoactivation is achieved by laser light (wavelength, 630 nm; light dose, 180 J/cm^2). The tumoricidal depth penetration of PDT with porfimer is approximately 4–6 mm. Parameters that determine the depth and extent of tissue damage by PDT include the type and quantity of the photosensitizer used, the oxygen concentration in the affected tissue, and the intensity, absorption, and distribution of laser light. The PDT indications and contraindications are listed in Table 7.

Patients injected with porfimer can tolerate normal artificial room light. Nevertheless, they must keep out of bright, direct, or indirect sunlight because sunlight exposure can cause significant skin phototoxicity. Intraductal PDT therapy can produce mild to moderate epigastric pain for up to 3 days after the endoscopic procedure. In

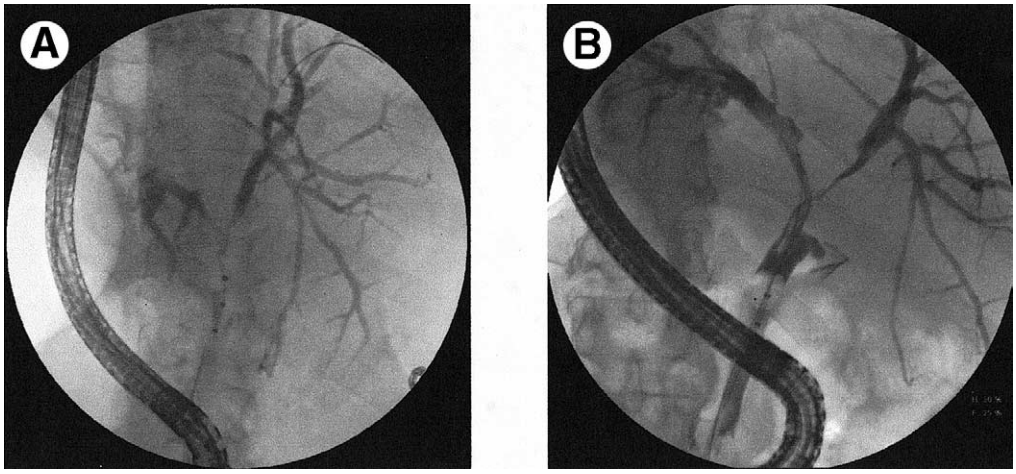

Figure 8. Photodynamic therapy (PDT) in a patient with unresectable hilar CCA. (*A*) ERCP before PDT. (*B*) ERCP 6 months after PDT. Note the improvement of the previously strictured left hepatic duct.

the first 2–3 days after PDT, a transient increase of aspartate aminotransferase and leukocytosis is anticipated. Biloma and hemobilia have been reported as PDT complications. No biliary perforation has been reported after PDT. The rate of cholangitis is not increased after PDT as compared with placement of biliary stents alone. The reported 30-day mortality after PDT was approximately 2%[47] because of 2 fatal episodes of pulmonary embolism, which were probably related to paraneoplastic thromboses rather than to PDT.

To "bleach out" the accumulated porfimer in the skin, patients should follow specific instructions. This goal can be accomplished by short exposures (5–10 minutes) after day 4 to mild evening sunlight before sunset. If the initial exposure is endured without skin sunburn, gradual re-exposure is recommended until bright sunlight is tolerated.

Table 7. PDT Indications and Contraindications for Hilar CCA[48]

Indications
Preliminary indication: nonresectable hilar CCA with unrelieved cholestasis
Relative indications (ie, within clinical trials)
Nonresectable hilar CCA with successful biliary drainage
Inoperable comorbid patient with resectable hilar CCA
Borderline resectability of hilar CCA (neoadjuvant PDT for purging of intrahepatic ducts from tumor cells beyond the tumor margins)
Contraindications
Porphyria (all genetic types)
Recent use of photosensitizing or dermatotoxic drugs (eg, bleomycin)
Insertion of a coated metal stent
Severe hepatic or renal failure
Relative contraindications
Peritoneal carcinomatosis (cholestasis palliated)
Karnofsky performance status <30%
Biliary empyema or liver abscess

Nonrandomized pilot studies of PDT for unresectable CCA have shown promising results on: (1) improvement or resolution of cholestasis, (2) stabilization of the Karnofsky performance status at almost normal or moderately diminished rates, and (3) improvement or preservation of quality of life.[48] Recently, a multicenter prospective, randomized trial has evaluated the effect of biliary stenting followed by PDT (group A) compared with biliary stenting alone (group B) in patients with unresectable CCA.[49] Group A showed prolonged survival (n = 20; median survival, 493 days; 95% confidence interval, 276–710 days) compared with group B (n = 19; median survival, 98 days; 95% confidence interval, 87–107 days; $P < .0001$).[49] This study failed to improve biliary obstruction and jaundice in group B (bile duct stenting alone). Thus, it is likely that the survival benefit reported in group A (biliary stenting and PDT) relates to amelioration of cholestasis rather than tumor burden.[50] Additional prospective, randomized trials of PDT for unresectable CCA are needed to further assess the utility of this promising approach.

Intraluminal brachytherapy. During intraluminal brachytherapy, premounted iridium-192 seeds are deployed within a catheter and placed across malignant biliary strictures via ERCP or percutaneous transhepatic cholangiography.[51,52] It is expected that brachytherapy provides focal, greater, and more effective doses of radiation than external beam radiation therapy. It is thus anticipated that intraluminal brachytherapy extends the palliation of obstructive jaundice while avoiding unnecessary radiation injury of the surrounding tissues/organs. Until now, the results of intraluminal brachytherapy have varied.[52,53] More studies are required to evaluate the effectiveness of this palliative treatment.

Liver Transplantation for Unresectable Cholangiocarcinoma

The initial experience with OLT for CCA was unsatisfactory.[54–60] Recurrence of CCA was common, and the 5-year survival rates were only 5%–15%. To this end, most liver transplant centers consider CCA a contraindication for OLT. It is interesting to note that, however, a selected group of patients who underwent OLT and had negative surgical resection margins and negative regional lymph nodes had long-term survival.[61] Furthermore, in a small number of patients treated with radiation, brachytherapy, and 5-fluorouracil (5-FU), the observed 5-year survival rate was 22%.[62] Because of these favorable observations, an experimental liver transplantation protocol was developed at the Mayo Clinic that was aimed at treating selected patients with early-stage unresectable hilar CCA or CCA arising in the background of PSC.

To be eligible for this protocol, the diagnosis of CCA needs to be confirmed by biopsy, brush cytology, or demonstration of cellular aneuploidy in the presence of malignant stricture based on cholangiographic studies. If a mass lesion is present in the perihilar region, then the diameter should be <3 cm on cross-sectional imaging studies. The CCA also has to be considered unresectable by the hepatobiliary team after meticulous clinical, laboratory, and imaging evaluation. Intrahepatic and extrahepatic CCA metastases have to be excluded by CT of the abdomen and chest, abdominal ultrasound, EUS with FNA of the regional lymph nodes, and total body bone scan. Tumor vascular encasement causing an absence of blood flow without evidence of vessel invasion is not a contraindication to enrollment.

Qualified CCA patients have to be suitable for radiation therapy, chemotherapy, and liver transplantation, as determined by the interdisciplinary transplantation team. Patients who meet eligibility criteria receive neoadjuvant chemotherapy and radiation therapy. External beam radiation therapy is administered (a total dose of 4500 cGy in 30 sessions) over 3 weeks. 5-FU is given intravenously at 500 mg/m^2 daily as a bolus for 3 consecutive days during the initiation of external beam radiation therapy. Complications of external beam radiation therapy include nausea, vomiting, leukopenia, cholangitis, gastrointestinal ulceration, and liver abscess. After completion of external beam radiation therapy, patients receive brachytherapy for the tumor by using a transcatheter loaded with iridium-192 seeds (total dose of 2000–3000 cGy). During brachytherapy, patients are treated with 5-FU 225 mg/m^2 daily. Subsequently, patients continue to receive the previously described dose of 5-FU or capecitabine (2000 mg/m^2 daily) 2 out of 3 weeks until OLT is performed.

After completing neoadjuvant chemoradiation therapy, patients undergo staging laparotomy with biopsy of the regional hepatic lymph nodes, other intra-abdominal lymph nodes, or nodules suggestive of tumor. Patients with negative staging operations proceed with OLT. Cadaveric livers or living donor right liver grafts can be used. After transplantation, patients receive standard immunosuppression regimens.

As of May 1, 2004, 56 patients with CCA were enrolled in this liver transplantation protocol at the Mayo Clinic in Rochester, Minnesota. Forty-eight patients underwent staging laparotomy, of whom 14 (29%) were found to have progression of CCA on laparotomy and were excluded from the protocol. Between 1993 and 2003, 28 patients underwent OLT; 6 died after OLT, and 22 are currently alive. The actuarial patient survival after liver transplantation was 88% at 1 year and 82% at 5 years. The time from enrollment to OLT was approximately 4 and 10 months during the first 5 years and the second 5 years of the protocol, respectively. After the described neoadjuvant chemoradiation protocol, the outcome of OLT in selected patients with CCA was similar to that after liver transplantation for other chronic liver diseases. Of note, the outcome of our liver transplantation protocol for CCA surpasses the outcome of surgical resection with curative intent—the gold standard therapy for CCA. A comparable liver transplantation protocol for CCA has been developed at the University of Nebraska and has also shown favorable patient survival outcome.[63]

Future Directions

In view of the increasing incidence of CCA, we need better early detection methods and new, effective therapies to improve the survival of patients with this distressing disease. To date, patients with CCA lack a survival benefit if treated with chemotherapy or radiation therapy.[3] Randomized, controlled clinical trials are necessary to evaluate novel chemotherapeutic agents in conjunction with radiation therapy. We hope that as the pathogenesis of CCA is elucidated, better pharmacological and other therapies will be devised to inhibit the critical pathways of carcinogenesis in these tumors.

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