Epidemiology, pathogenesis, and classification of cholangiocarcinoma

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INTRODUCTION

Cholangiocarcinomas (bile duct cancers) arise from the epithelial cells of the intrahepatic and extrahepatic bile ducts. Although these cancers are rare in the United States, they are highly lethal because most are locally advanced at presentation.

The epidemiology, pathology, pathogenesis, and classification of cholangiocarcinoma will be discussed here. Clinical manifestations, diagnosis, and treatment are reviewed separately. (See "Clinical manifestations and diagnosis of cholangiocarcinoma" and "Treatment of localized cholangiocarcinoma: Adjuvant and neoadjuvant therapy and prognosis" and "Treatment options for locally advanced, unresectable, but nonmetastatic cholangiocarcinoma" and "Systemic therapy for advanced cholangiocarcinoma".)

Cancers of the gallbladder and ampulla of Vater are discussed as separate disease processes, although these structures are part of the biliary drainage system. (See "Gallbladder cancer: Epidemiology, risk factors, clinical features, and diagnosis" and "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging".)

ANATOMY, TUMOR CLASSIFICATION, AND STAGING

Biliary tract cancers were traditionally divided according to their anatomical primary site into cancers of the gallbladder, the extrahepatic ducts, and the ampulla of Vater, while intrahepatic tumors of the bile system were classified as primary liver cancers. More recently, the term cholangiocarcinoma has been used to refer to bile duct cancers arising in the intrahepatic, perihilar, or distal (extrahepatic) biliary tree, exclusive of the gallbladder or ampulla of Vater.

Anatomically, intrahepatic cholangiocarcinomas originate from small intrahepatic ductules (termed peripheral cholangiocarcinomas) or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. The extrahepatic bile ducts are divided into perihilar (including the confluence itself) and distal segments, with the transition occurring at the point where the common bile duct lies posterior to the duodenum, proximal to the insertion of the cystic duct into the common bile duct (figure 1) [1].

In general, perihilar disease represents approximately 50 percent; distal disease, 40 percent; and intrahepatic disease, less than 10 percent of cholangiocarcinoma cases [2].

Bismuth-Corlette classification for perihilar tumors — Cancers arising in the perihilar region have been further classified according to their patterns of involvement of the hepatic ducts (the Bismuth-Corlette classification) (figure 2) [3]:

- Tumors below the confluence of the left and right hepatic ducts (Type I)
- Tumors reaching the confluence (Type II)
- Tumors occluding the common hepatic duct and either the right or left hepatic duct (Types IIIa and IIIb, respectively)
- Tumors that are multicentric, or that involve the confluence and both the right or left hepatic duct (Type IV)

Bile duct tumors that involve the common hepatic duct bifurcation are referred to as Klatskin tumors or hilar cholangiocarcinoma regardless of whether they arise from the intrahepatic or extrahepatic portion of the biliary tree [3]. Perihilar tumors account for approximately 50 percent of all cholangiocarcinomas, while approximately 40 percent are distal extrahepatic tumors, and 10 percent or fewer are intrahepatic [2].

TNM staging classifications — The newest version of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) cancer staging manual provides separate staging systems for cancers of the perihilar (table 1), distal (table 2), and intrahepatic bile ducts (table 3), which all differ in their definitions of tumor (T) stage and in their prognostic stage groupings. The rare combined hepatocellular and cholangiocarcinomas

(mixed hepatocholangiocarcinomas) are included in the intrahepatic bile duct classification. (See 'Combined hepatocellular-cholangiocarcinoma' below.)

There are major changes for all three sites compared with the seventh (2010) edition of the AJCC staging manual:

- For distal bile duct tumors, regional nodal (N) staging has been expanded according to the number of involved nodes, rather than just their presence or absence, and T staging now depends on the depth, in millimeters, of tumor invasion into the bile duct wall (table 2) [4].

- For perihilar tumors, the N category has been reclassified based upon the number of involved lymph nodes, instead of the location of the involved nodes, and Bismuth-Corlette type IV tumors have been removed from the T4 category; in addition, the prognostic stage groups have been changed (table 1) [1].

- For intrahepatic tumors, there are no changes to the N categories (nodal involvement [N1] versus no nodal involvement [N0]), but the T1 category has been split to reflect the prognostic importance of tumor size, and the T2 category is modified to reflect the equivalent prognostic value of vascular invasion and tumor multifocality (table 3) [5].

These prominent changes in the staging classification of bile duct cancers over time have improved the prognostic stratification of the Tumor, Node, Metastasis (TNM) staging system. As examples:

- Stratification of survival according to the newest 2017 T stage designations for distal cholangiocarcinomas (which are now based upon depth of tumor invasion rather than what structures were invaded) is provided in the figure (figure 3) [4,6], while stratified survival according to N category is depicted in this figure (figure 4) [4].

- Survival stratified according to the new prognostic stage groupings for tumors of the perihilar bile ducts is provided in a separate figure (figure 5) [1], as is survival stratified according to T stage for intrahepatic cholangiocarcinomas (figure 6) [5].

- A comparison of five-year survival stratified by stage groupings according to the 2010 and 2017 editions of the AJCC staging classification for intrahepatic cholangiocarcinoma in a series of 1154 patients undergoing potentially curative resection for intrahepatic cholangiocarcinoma at 14 major hepatobiliary centers is provided in the table (table 4) [7].

The continued evolution of the staging classification for bile duct cancers at all sites has obvious implications for interpretation and comparison of outcomes from trials and retrospective series that use older TNM staging criteria.

A criticism of the TNM staging system is that vessel invasion, as detected on the final pathology specimen, affects T stage category, but it is not used to assess local resectability. As such, the stage groupings do not serve as a guide for choosing local therapy. A modification to the tumor staging system for perihilar tumors has been proposed that incorporates the Bismuth-Corlette classification and a more detailed assessment of major vascular invasion, as well as liver remnant volume and underlying liver disease [8].

EPIDEMIOLOGY

Cholangiocarcinomas account for approximately 3 percent of all gastrointestinal malignancies, with a prevalence in autopsy studies of 0.01 to 0.46 percent [9].

- **United States**
  - Incidence data from the American Cancer Society are difficult to interpret because intrahepatic bile duct cancers have been included with primary liver cancers, while extrahepatic biliary cancers are in a separate category that includes gallbladder cancer:
    - In the United States, approximately 41,000 primary liver and intrahepatic bile duct cancers are diagnosed annually [10]. Data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program suggest that approximately 15 percent of these are intrahepatic cholangiocarcinomas [11,12].
    - Approximately 12,000 cases of extrahepatic biliary tract cancers are diagnosed annually in the United States [10], two-thirds of which are gallbladder cancers. The remainder, approximately 3000 cases per year, are extrahepatic cholangiocarcinomas.
  - Data from an analysis of the United States SEER database from 2001 to 2015 suggest an incidence of 1.26 cases of cholangiocarcinoma per 100,000 people per year, and that two-thirds of cases are intrahepatic [13].
- **Internationally** – Internationally, the incidence of cholangiocarcinoma varies significantly. While the incidence is low in high-income countries (from 0.35 to 2 cases per 100,000 population per year), in endemic regions of Thailand and China, the incidence is up to 40-fold higher [14-16].

Globally, the burden of gallbladder and other biliary tract cancers has risen over the last 30 years [17]. In particular, the incidence and mortality of intrahepatic cholangiocarcinoma has been rising over the past four decades in most countries [11,12,14,18-25] (although not Denmark [18]). Rates of extrahepatic cholangiocarcinoma had been declining internationally up to approximately the year 2000 [11,12,18-23], but more recent reports suggest an increased incidence over the last 20 years [24].

Some of these apparent differences may be due to changes in ICD (International Classification of Disease) classification [26]. Klatskin tumors often invade the liver by the time of presentation which may result in some extrahepatic cholangiocarcinomas misclassified as intrahepatic in origin, thereby contributing to possible underestimation of the incidence of extrahepatic cholangiocarcinomas. In addition, at least some of the increase in intrahepatic cholangiocarcinomas may be attributable to new diagnostic methods for obstructive jaundice that identify biliary malignancies that previously might have gone undiagnosed [27]. However, the rising rates of intrahepatic cholangiocarcinoma have not been associated with an increase in the proportion of early stage or smaller size lesions [12]. Furthermore, incidence rates do not seem to be plateauing.

Other studies suggest that the increasing incidence of cholangiocarcinoma may be related to a concomitant increase in certain risk factors such as cirrhosis, alcoholic liver disease, and hepatitis C virus infection [24,28]. (See 'Risk factors' below.)

As a general rule, the incidence of biliary tract cancers increases with age [29]; the typical patient with cholangiocarcinoma is between 50 and 70 years of age. However, patients with cholangiocarcinomas arising in the setting of primary sclerosing cholangitis (PSC) and those with choledochal cysts present nearly two decades earlier [9,30]. In contrast to gallbladder cancer, where female gender predominates, the incidence of cholangiocarcinoma is slightly higher in men [29]. This probably reflects the higher incidence of PSC in men [31]. (See "Primary sclerosing cholangitis: Epidemiology and pathogenesis".)

RISK FACTORS

A number of risk factors for cholangiocarcinoma have been recognized, although a specific risk factor cannot be identified for many patients [32]. In the United States and Europe, the main risk factors are primary sclerosing cholangitis (PSC) and fibropolycystic liver disease (eg, choledochal cysts). There is a clear and strong association between chronic intrahepatic stone disease (hepatolithiasis, also called recurrent pyogenic cholangitis) and cholangiocarcinoma [33]. Chronic liver disease (cirrhosis and viral infection) is now recognized as a risk factor,

particularly for intrahepatic cholangiocarcinoma [33]. (See 'Primary hepatobiliary disease' below.)

In certain regions (eg, Thailand) chronic infection with liver fluke is the driving risk factor. (See 'Parasitic infection' below.)

Finally, at least four genetic conditions, Lynch syndrome, *BRCA*-associated protein-1 (BAP1) tumor predisposition syndrome, cystic fibrosis, and biliary papillomatosis, appear to increase the risk for cholangiocarcinoma. (See 'Genetic disorders' below.)

Primary hepatobiliary disease

Primary sclerosing cholangitis — PSC is an inflammatory disorder of the biliary tree that leads to fibrosis and stricturing of the intrahepatic and/or extrahepatic bile ducts. PSC is strongly associated with inflammatory bowel disease, notably ulcerative colitis (UC); approximately 40 to 50 percent of patients have symptomatic colitis, while the incidence of colitis is around 90 percent in patients with PSC [34]. (See "Primary sclerosing cholangitis: Epidemiology and pathogenesis".)

There is a well-established association between PSC and cholangiocarcinoma, especially perihilar disease. Nearly 30 percent of cholangiocarcinomas are diagnosed in patients with PSC, with or without UC. The annual incidence of cholangiocarcinoma in patients with PSC has been estimated to be between 0.6 and 1.5 percent per year, with a lifetime risk of 5 to 15 percent [35-41]. However, the incidence is much higher (30 percent or more) in autopsy series [42]. Cholangiocarcinomas develop at a significantly younger age (between the ages of 30 and 50) in patients with PSC than in those without this condition. It is also more difficult to diagnose because of the diffusely abnormal biliary tree [43]. Over one-third of cases are diagnosed within two years of the initial diagnosis of PSC, and the risk appears unrelated to the duration of the inflammatory disease [30,37,42]. However, a population-based patient series from the Netherlands has questioned previous notions that late presentation of cholangiocarcinoma is a rare event, reporting that 37 percent of cholangiocarcinomas present more than 10 years after the diagnosis of PSC [44]. Thus, clinical and biochemical deterioration at any point in the disease course should prompt evaluation for a potentially malignant cause. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis" and "Clinical manifestations and diagnosis of cholangiocarcinoma", section on 'When to consider cholangiocarcinoma'.)

The reason why patients with PSC develop cholangiocarcinoma is not well understood, although there have been several observations.

- One case-control study attempted to identify specific risk factors by comparing 20 patients with PSC and hepatobiliary carcinoma (17 of whom had cholangiocarcinoma) with 20 age- and sex-matched patients with PSC without cancer [37]. No clinical or biochemical risk factors for the development of cancer could be identified in the year before cancer diagnosis. However, the number of patients who smoked or were former smokers was significantly higher in the cancer group.

- Alcohol consumption has been suggested to be a risk factor for the development of cholangiocarcinoma in patients with PSC [37]. One study compared 26 patients with PSC and cholangiocarcinoma with 87 patients with PSC but without tumors [45]. Only alcohol consumption was significantly associated with the development of cancer (odds ratio [OR] of 2.95; 95% CI 1.04-8.3). However, these authors could not test for a dose-response relationship due to inadequate data, and they could not confirm the link between smoking and cholangiocarcinoma in PSC.

- Certain genetic polymorphisms have been implicated as risk factors for cholangiocarcinoma in PSC [46].

The development of cholangiocarcinoma is heralded by rapid clinical deterioration with jaundice, weight loss, and abdominal discomfort; tumors are often detected at an advanced stage. (See "Clinical manifestations and diagnosis of cholangiocarcinoma", section on 'When to consider cholangiocarcinoma'.)

Issues related to cancer screening, typically by serial assay of the tumor marker carbohydrate antigen (CA) 19-9, in patients with PSC are discussed elsewhere. (See "Clinical manifestations and diagnosis of cholangiocarcinoma", section on 'CA 19-9' and "Primary sclerosing cholangitis in adults: Management", section on 'Cancer screening'.)

Fibropolycystic liver disease — Congenital abnormalities of the biliary tree (Caroli syndrome, congenital hepatic fibrosis, choledochal cysts) carry an approximately 15 percent risk of malignant change in the adult years (average age at diagnosis 34) [47-49]. (See "Biliary cysts" and "Caroli disease".)

Choledochal cysts are congenital cystic dilatations of the bile ducts, while Caroli disease is a variant of choledochal cyst disease that is characterized by multiple cystic dilations of the intrahepatic biliary ducts [50]. The overall incidence of cholangiocarcinoma in patients with untreated cysts is as high as 28 percent [48,49].

Although the mechanism underlying carcinogenesis in these patients is unclear, it could be related to biliary stasis, chronic inflammation from reflux of pancreatic juice, or abnormalities in

bile salt transporter proteins that result in unstable bile content, or deconjugation of carcinogens that were previously conjugated in the liver [47].

Cholelithiasis, cholecystitis, and hepatolithiasis — While cholelithiasis is a well-described strong risk factor for gallbladder cancer, the association between gallstones and cholangiocarcinoma is less well established. However, at least four epidemiologic studies note an increased risk for cholangiocarcinoma among patients with symptomatic gallstone disease or cholecystitis, but of a lower magnitude than for gallbladder cancer [51-54]. (See "Gallbladder cancer: Epidemiology, risk factors, clinical features, and diagnosis", section on 'Gallstone disease'.)

There is a clear and strong association between chronic intrahepatic stone disease (hepatolithiasis, also called recurrent pyogenic cholangitis) and cholangiocarcinoma [55-62]. Stone disease affecting only the intrahepatic bile ducts is exceedingly rare in the West but is endemic in certain parts of Southeast Asia. In Taiwan, 50 to 70 percent of patients undergoing resection for cholangiocarcinoma have associated hepatolithiasis [57,58], while in Japan, the incidence is much lower (6 to 18 percent) [59-61]. (See "Recurrent pyogenic cholangitis".)

The etiology of hepatolithiasis is not known, but congenital ductal abnormalities, diet, and chronic inflammation from bacterial or parasitic infections have all been implicated. The calculi are usually composed of calcium bilirubinate (brown pigment stones) rather than cholesterol. The biliary stones are thought to cause bile stasis, predisposing to recurrent bacterial infections and chronic inflammation.

It may be difficult to identify cholangiocarcinomas arising as a complication of hepatolithiasis. However, the diagnosis should be suspected in a patient over the age of 40 who has a long history of hepatolithiasis, weight loss, elevated serum alkaline phosphatase, a serum carcinoembryonic antigen (CEA) level above 4.2 ng/mL, and hepatolithiasis in either the right or both lobes of the liver [63].

Chronic liver disease — Hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as liver cirrhosis regardless of etiology, have been examined as risk factors for intrahepatic cholangiocarcinoma [28,62,64-66].

Viral hepatitis — An association between HCV infection and cholangiocarcinoma was initially suggested in 1991 [67]. Since then, several reports have noted a higher than expected rate of HCV-associated cirrhosis in patients with cholangiocarcinoma, although the risk is much lower than for hepatocellular cancer [12,28,65,68-78]:

- A prospective case control study from Japan reported the risk of developing cholangiocarcinoma in patients with cirrhosis related to HCV was 3.5 percent at 10 years [65].

- A large cohort study in the United States found a significant association between intrahepatic cholangiocarcinoma and HCV after adjustment for potential confounders, including cirrhosis (adjusted relative risk [RR] 2.55, 95% CI 1.31-4.95) [77].

- Similarly, a large cohort study of older United States adults derived from the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database found that HCV positivity was associated with a significant increase in the risk of both extrahepatic (adjusted odds ratio [aOR] 1.90, 95% CI 1.41-2.57) and intrahepatic (aOR 3.40, 95% CI 2.52-4.58) cholangiocarcinomas [78].

An association between HBV infection and cholangiocarcinoma has also been suggested, although the data are less compelling than for HCV [62,74,79,80].

Nonviral chronic liver disease — As with hepatocellular carcinoma, chronic liver disease of nonviral etiology also appears to be associated with intrahepatic cholangiocarcinoma [12,28,62,64-66,68,81]. In a case-control study, risk factors that were significantly more prevalent among patients with intrahepatic cholangiocarcinoma included nonspecific cirrhosis (aOR 27.2) and alcoholic liver disease (aOR 7.4) [28]. A Danish cohort study that followed 11,605 persons with cirrhosis from any cause for an average of approximately six years found a significant 10-fold higher risk for intrahepatic cholangiocarcinoma among these patients compared with the general population [66].

Precursor (intraductal) lesions — There are three known precursors to invasive cholangiocarcinoma: intraductal papillary neoplasm of the bile ducts (picture 1) [82,83], the rare intraductal tubulopapillary neoplasm of the bile ducts (picture 2) [83,84], and the much more common biliary intraepithelial neoplasia (picture 3) [85,86]. (See 'Papillary' below and "Pathology of malignant liver tumors", section on 'Biliary intraepithelial neoplasia' and "Pathology of malignant liver tumors", section on 'Intraductal papillary neoplasm of bile duct' and "Pathology of malignant liver tumors", section on 'Intraductal tubulopapillary neoplasm of bile duct'.)

Genetic disorders — At least four genetic disorders are associated with an increased risk of cholangiocarcinoma: Lynch syndrome (hereditary nonpolyposis colorectal cancer), BAP1 tumor predisposition syndrome, cystic fibrosis, and a rare inherited disorder called multiple biliary papillomatosis.

Lynch syndrome — Patients with Lynch syndrome, an autosomal dominant disorder that is caused by a germline mutation in one of several DNA mismatch repair (MMR) genes, are at risk for colon cancer and a variety of extracolonic cancers, including hepatobiliary neoplasms. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Extracolonic manifestations'.)

BAP1 tumor predisposition syndrome — An increased risk of cholangiocarcinoma has been reported in families that carry germline missense variants of the *BRCA*-associated protein 1 (*BAP1*) gene (the clinical phenotype is called "BAP1 tumor predisposition syndrome") [87]. In one report of 40 probands, two (5 percent) developed cholangiocarcinoma, compared with none of the 113 ungenotyped relatives. Interestingly, in The Cancer Genome Atlas (TCGA), somatic mutations in the *BAP1* gene were reported in 11 of 51 cholangiocarcinomas [88], and a putative role for *BAP1* as a tumor suppressor gene in cholangiocarcinoma has been suggested [89].

Multiple biliary papillomatosis — Multiple biliary papillomatosis is characterized by multiple adenomatous polyps of variable distribution and extent in the intrahepatic bile ducts, and repeated episodes of abdominal pain, jaundice, and acute cholangitis [90]. Biliary papillomatosis should be considered a premalignant condition and considered for resection since a high proportion of these lesions (83 percent in one study [90]) undergo malignant transformation [91,92].

Cystic fibrosis — Patients with cystic fibrosis have an increased risk of biliary tract cancers. In a meta-analysis, the standardized incidence ratio was 17.87, 95% CI 8.55-37.36, and it was two- to fivefold higher in patients who had undergone lung transplantation compared with those who did not undergo transplantation [93]. (See "Cystic fibrosis: Overview of gastrointestinal disease", section on 'Gastrointestinal cancer'.)

Toxic exposures

- **Thorotrast** – A clear association exists between exposure to Thorotrast (a radiologic contrast agent banned in the 1960s for its carcinogenic properties) and subsequent cholangiocarcinoma; malignancy usually develops 30 to 35 years after exposure [94].
- **Occupational exposures** – An increased incidence of cholangiocarcinoma has been less strongly associated with several occupations, including the auto, rubber, chemical, and wood-finishing industries.
- **Smoking and alcohol** – Individual studies on the association between smoking/alcohol intake and risk of cholangiocarcinoma have been conflicting. A pooled analysis of 26 prospective studies concluded that alcohol consumption was only associated with

intrahepatic cholangiocarcinoma, with an increased risk for individuals consuming five or more versus zero drinks per day (HR 2.25, 95% CI 1.46-3.78) [95]. By contrast, ever, former, or current smoking was associated with an increased risk of extrahepatic bile duct and ampulla of Vater cancer, with dose-response effects for duration and intensity of smoking. Current smoking and smoking intensity were also associated with intrahepatic cholangiocarcinoma risk (for >40 cigarettes per day versus never smokers, HR 2.15, 95% CI 1.15-4.0).

- **Iron overload** – Increased iron levels (both in patients with hereditary hemochromatosis and nonhemochromatosis populations) increase the risk of primary liver cancer, including cholangiocarcinoma [96,97]. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis".)

Infections

Parasitic infection — In Asia (particularly Thailand), infection with liver flukes of the genera Clonorchis and Opisthorchis is associated with cholangiocarcinoma of the intrahepatic bile ducts [64,98,99]. Humans are infected by consuming undercooked fish, with the adult worms inhabiting and laying eggs in the biliary system. These organisms induce a chronic inflammatory state in the proximal biliary tree, presumably leading to malignant transformation of the lining epithelium. Carcinogens that are produced by bacteria in fish and other foods, smoking, alcohol, and HBV infection might also act as cofactors [47,100,101].

HIV infection — HIV infection was an independent risk factor for intrahepatic cholangiocarcinoma in the Medicare population in the case control study described above (aOR 6.4) [28]. However, the validity of the association is uncertain given the relatively small number of cases that were identified and the possibility that at least some of the HIV infected cases may have had coexisting, undiagnosed risk factors (such as HCV infection).

H. pylori infection — Several studies report an association between biliary tract carcinoma and infection with *Helicobacter pylori* [74,102-105]. Although a cause and effect relationship has not been proven, some have suggested that *H. pylori* may be involved in the pathogenesis of biliary neoplasms through enhanced biliary cell inflammation and proliferation [104].

Other factors

Elevated blood glucose — An association between diabetes mellitus and cancer of the biliary tract has been suggested in several case-control and cohort studies. In a meta-analysis of 15 such studies, individuals with diabetes had a significantly increased risk of cholangiocarcinoma relative to nondiabetics (summary RR 1.60, 95% CI 1.38-1.87) [106]. The risk was significantly

elevated for both intrahepatic and extrahepatic cholangiocarcinomas. Whether elevated blood sugar or other diabetes-associated conditions (eg, obesity, hyperlipidemia) represent the true risk factors for cholangiocarcinoma is not clear.

An association between consumption of sweetened beverages (which raises blood glucose concentration) and extrahepatic cholangiocarcinoma was suggested in a prospective analysis of 70,832 Swedish adults enrolled in the Swedish Mammography Cohort and Cohort of Swedish Men who were free of cancer and diabetes and who completed a food frequency questionnaire at baseline [107]. Incident cases of biliary tract cancer were ascertained through linkage with the Swedish Cancer Register. With a mean follow-up of over 13 years, after adjustment for other risk factors, women and men in the highest category of combined sugar-sweetened and artificially sweetened beverage consumption had a significantly higher risk of extrahepatic cholangiocarcinoma (multivariable hazard ratio [HR] for two or more 200 mL servings per day of sweetened beverages compared with no consumption was 1.79, 95% CI 1.02-3.13). The corresponding HR for intrahepatic cholangiocarcinoma was 1.69, 95% CI 0.41-7.03.

Obesity — Obesity has been linked to an increased risk for cholangiocarcinoma, particularly intrahepatic cholangiocarcinoma [68,108].

Metabolic syndrome — A study that included 743 patients with intrahepatic cholangiocarcinoma found that the presence of metabolic syndrome (defined by the presence of three of the following: elevated waist circumference/central obesity, dyslipidemia, hypertension, or impaired fasting glucose) was a risk factor for intrahepatic cholangiocarcinoma (aOR 1.56) [109].

Medications — A few medications have been linked to an increased incidence of cholangiocarcinoma, although causality is not proven.

- **DPP-4 inhibitors** – For adults with type 2 diabetes, dipeptidyl peptidase-4 (DPP-4) inhibitors may increase the risk of cholangiocarcinoma, although data are mixed [110,111]. In a large cohort study with over 600,000 person-years of follow-up, patients with type 2 diabetes who were treated with DPP-4 inhibitors had an increased risk of cholangiocarcinoma compared with patients receiving other antidiabetic medications (adjusted HR 1.77, 95% CI 1.04-3.01) [110]. An earlier study failed to show such an association [111]. (See "Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus".)

- **Oral contraceptives** – At least one study found that long-term use of oral contraceptives (9+ years) was associated with a significantly increased risk of intrahepatic

cholangiocarcinoma (HR 1.62, 95% CI 1.03-2.55) [112]. Prior data had shown a relationship between exogenous hormone use and an increased risk of all primary liver cancers [113].

HISTOLOGY AND IMMUNOHISTOCHEMISTRY

Cholangiocarcinomas can be classified according to their location along the biliary tree (figure 1 and figure 2). The majority (75 percent in one report [31]) are found in the upper one-third of the biliary tract, and two-thirds involve the bifurcation of the common hepatic duct (Klatskin tumors). Intrahepatic nonperihilar tumors (ie, peripheral cholangiocarcinomas) are the least common, accounting for fewer than 10 percent of cases in most series. Up to 7 percent of tumors are multicentric at the time of diagnosis [114].

Cholangiocarcinoma — The majority of cholangiocarcinomas (>90 percent) are adenocarcinomas, with squamous cell carcinoma being responsible for most of the remaining cases; adenosquamous cancers are rare. They are graded as well, moderately, or poorly differentiated. Histologic findings and immunohistochemical stains that can assist in the differential diagnosis of cholangiocarcinoma from other malignancies, particularly those that arise in liver, are discussed elsewhere. (See "Pathology of malignant liver tumors", section on 'Cholangiocarcinoma'.)

Intrahepatic adenocarcinomas are divided into large duct type (picture 4) and small duct type (picture 5) [115]. Morphologically, both intrahepatic and extrahepatic biliary adenocarcinomas can be sclerosing, nodular, or papillary [115,116].

Sclerosing — Sclerosing (scirrhous) tumors are characterized by an intense desmoplastic reaction. The extensive fibrosis makes preoperative diagnosis by biopsy and cytology more difficult than for other tumors (see "Clinical manifestations and diagnosis of cholangiocarcinoma"). These tumors also tend to invade the bile duct wall early and, as a result, are associated with low resectability and cure rates. Intraductal spread may mimic primary sclerosing cholangitis (PSC) on cholangiographic studies, complicating the radiographic diagnosis. Unfortunately, most cholangiocarcinomas are of this type. In one report, 94 percent of 194 perihilar tumors were sclerotic adenocarcinomas, as were 79 of 80 distal tumors and all nine intrahepatic cholangiocarcinomas [114].

Nodular — Nodular cholangiocarcinomas present as a constricting annular lesion of the bile duct. These are highly invasive tumors, and most patients have advanced disease at the time of diagnosis; thus, the resectability and cure rates are very low.

Papillary — Papillary tumors are the rarest form of cholangiocarcinoma. These usually present as bulky masses in the common bile duct lumen, which cause biliary obstruction early in the course of the disease. For this reason, they have the highest resectability and cure rates [117,118].

Characteristics that are common to all three tumor types include slow growth, a high rate of local invasion, mucin production, and a tendency to invade perineural sheaths and spread along nerves. By contrast, distant metastases are distinctly uncommon in cholangiocarcinoma.

Most intrahepatic cholangiocarcinomas are adenocarcinomas with variable desmoplastic reaction, although there are several special or unusual histological features depending on the site of origin [119]. At the large intrahepatic bile ducts, papillary growth and periductal infiltration is typical, while tumors arising from ductules share a similar phenotype with hepatocellular carcinoma (HCC). In addition to invasive cancer, intrahepatic cholangiocarcinomas that arise in the setting of chronic biliary disease (eg, hepatolithiasis) are characterized by precancerous lesions including biliary intraepithelial neoplasia and intraductal papillary neoplasms of the bile ducts. (See "Pathology of malignant liver tumors", section on 'Biliary intraepithelial neoplasia' and "Pathology of malignant liver tumors", section on 'Intraductal papillary neoplasm of bile duct'.)

Immunohistochemistry — There are no known proteins that are differentially expressed by normal and malignant biliary epithelium and, therefore, no pathognomonic immunohistochemical test that can be used to confirm the cell type of origin. However, positive results of several types of immunohistochemical staining may be used to support a diagnosis of malignant biliary epithelium. In particular, cytokeratin-7 (CK7) positivity is consistent with biliary tract origin (table 5). However, metastatic cancers of the lung and breast are also CK7 positive, and the diagnosis of a cholangiocarcinoma is frequently a diagnosis of exclusion. This subject is discussed in detail elsewhere. (See "Pathology of malignant liver tumors", section on 'Histology and immunohistochemistry'.)

Combined hepatocellular-cholangiocarcinoma — Combined hepatocellular-cholangiocarcinoma, also referred to as primary liver carcinoma with biphenotypic differentiation or hepatocholangiocarcinoma, is now acknowledged as a distinct subtype of cholangiocarcinoma [120-122]. These tumors consist of intimately admixed elements of both HCC and cholangiocarcinoma. They are distinguished from separate HCC and cholangiocarcinomas arising in the same liver lobe (which may be separated or intermixed "collision" tumors). (See "Pathology of malignant liver tumors", section on 'Combined hepatocellular-cholangiocarcinoma'.)

These tumors are staged as intrahepatic cholangiocarcinomas and not HCCs. (See 'TNM staging classifications' above.)

The cell of origin is debated, but the available evidence supports the view that combined hepatocellular-cholangiocarcinoma arise from a common hepatic stem cell. It is generally accepted that adult hepatic stem cells are capable of biliary or hepatocyte differentiation [123,124]. Further, investigators have shown that in at least one case, combined hepatocellular-cholangiocarcinoma was derived from a single clone, and primary cell lines derived from resected combined tumors can be induced to differentiate to the characteristics of HCC and cholangiocarcinoma under different growth conditions [125,126]. Finally, molecular studies suggest that tumors that exhibit both biliary and hepatocyte differentiation exhibit stem cell/progenitor features, a down-regulation of the hepatocyte differentiation program, and a commitment to the biliary lineage [127].

Combined hepatocellular-cholangiocarcinomas have distinct imaging characteristics, and they are typically treated surgically. Although multimodality therapy is often employed [128,129], its benefit is unproven. The prognosis is thought to be intermediate between that of pure HCC and intrahepatic cholangiocarcinoma [129-133]. Patients with advanced disease should be treated according to the principles established for advanced cholangiocarcinoma [134]. (See "Clinical manifestations and diagnosis of cholangiocarcinoma", section on 'MRI and MRCP' and "Systemic therapy for advanced cholangiocarcinoma".)

MOLECULAR PATHOGENESIS

A detailed discussion of the molecular pathogenesis of cholangiocarcinomas is beyond the scope of this discussion and is well-reviewed elsewhere [135,136]. What follows is a brief overview of the salient points.

There are two precursors to cholangiocarcinoma: intraductal papillary mucinous neoplasm of the bile duct and the much more common biliary intraepithelial neoplasia. Biliary intraepithelial neoplasia is graded based on the extent of cellular atypia, mirroring the spectrum of precursor lesions for pancreatic cancer [137]. Intraductal papillary mucinous neoplasm of the bile duct is a macroscopic lesion similar to its pancreatic counterpart [138]. (See "Pathology of malignant liver tumors", section on 'Intraductal papillary neoplasm of bile duct' and "Pathology of malignant liver tumors", section on 'Biliary intraepithelial neoplasia' and "Pathology of exocrine pancreatic neoplasms", section on 'Pancreatic intraepithelial neoplasia' and "Pathology of exocrine pancreatic neoplasms", section on 'Intraductal papillary mucinous neoplasms'.)

Conversion from normal to malignant bile epithelium through one of these precursor lesions probably requires a stepwise accumulation of successive genetic abnormalities, similar to the sequence of events that underlies colorectal carcinogenesis [135,139,140]. However, the level of understanding of the molecular pathogenesis of cholangiocarcinoma is significantly less than that of other gastrointestinal cancers. Molecularly, the precursors of carcinoma remain poorly characterized, although they appear to harbor mutations in p53 and loss of *SMAD4* [141,142]. (See "Molecular genetics of colorectal cancer".)

A variety of molecular defects involving both oncogenes (*RAS*, *ERBB2*, *BRAF, EGFR*, *PIK3CA*, *CTNNB1*) and tumor suppressor genes (eg, p53, *SMAD4*, *CDKN2A*) have been described in specimens of invasive biliary tract tumors. As an example, approximately one-third of tumors overexpress p53 (implying the presence of mutations in this tumor suppressor gene), while abnormal expression of KRAS is found in 45 to 54 percent of intrahepatic cholangiocarcinomas and 10 to 15 percent of extrahepatic cholangiocarcinomas [135]. These genetic alterations seem to be associated with a more aggressive tumor phenotype [143,144].

The contribution of these genetic changes to cholangiocarcinoma genesis and their relationship to chronic inflammation, ethnic background, and carcinogen exposure remain uncertain (see 'Risk factors' above). At least some data suggest that p16INK4a promoter point mutations contribute to initiation and progression of cholangiocarcinoma in the setting of primary sclerosing cholangitis (PSC) [145,146].

Mutations in the gene encoding isocitrate dehydrogenase 1 (IDH1) have been identified in 25 percent of intrahepatic cholangiocarcinomas and not extrahepatic cholangiocarcinomas or gallbladder carcinomas [147]. In this study, the frequency of *IDH1* and *IDH2* gene mutations was greater than the combined frequency of activating mutations in other genes (*AKT1*, *KRAS*, *NRAS*, and *BRAF*) in intrahepatic cholangiocarcinomas. This suggests potential for targeting this pathway in intrahepatic cholangiocarcinoma.

Although current knowledge is limited, it is hoped that advances in the understanding of the genetic pathways that contribute to the development of cholangiocarcinomas will identify driver mutations that can be successfully targeted for therapeutic benefit [148]. However, at present, there are no molecular markers that are currently used for prognosis or selecting treatment.

SUMMARY

- The term cholangiocarcinoma refers to bile duct cancers arising in the intrahepatic, perihilar, or distal (extrahepatic) biliary tree, exclusive of the gallbladder or ampulla of

Vater. Cancers arising in the perihilar region are further classified according to their patterns of involvement of the hepatic ducts (the Bismuth-Corlette classification) (figure 2).

The Tumor, Node, Metastasis (TNM) staging classification from the joint American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) includes separate staging systems for intrahepatic, perihilar, and distal bile duct tumors, which differ in their definitions of primary tumor stage and their prognostic stage groupings. (See 'Anatomy, tumor classification, and staging' above.)

- The incidence of biliary tract cancer increases with age; the typical patient with cholangiocarcinoma is between 50 and 70 years old. The incidence rates of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma have been rising over the past two to four decades in most countries. (See 'Epidemiology' above.)

- A number of risk factors for cholangiocarcinoma have been recognized, although a specific risk factor cannot be identified for many patients. (See 'Risk factors' above.)

  In the United States and Europe, the main risk factors are primary sclerosing cholangitis and choledochal cysts (fibropolycystic liver disease). (See 'Primary sclerosing cholangitis' above and 'Fibropolycystic liver disease' above.)

  Southeast Asia has a very high incidence of cholangiocarcinoma that is due to a high prevalence of hepatobiliary flukes. (See 'Parasitic infection' above.)

  There is a clear and strong association between chronic intrahepatic stone disease (hepatolithiasis, also called recurrent pyogenic cholangitis) and cholangiocarcinoma. (See 'Cholelithiasis, cholecystitis, and hepatolithiasis' above.)

  Chronic liver disease (cirrhosis and viral infection) is a risk factor, especially for intrahepatic cholangiocarcinoma. (See 'Risk factors' above.)

- At least two genetic disorders are associated with an increased risk of cholangiocarcinoma: Lynch syndrome (hereditary nonpolyposis colorectal cancer) and a rare inherited disorder called multiple biliary papillomatosis. (See 'Genetic disorders' above.)

- The majority of cholangiocarcinomas (>90 percent) are adenocarcinomas, with squamous cell carcinoma being responsible for most of the remaining cases. Intrahepatic adenocarcinomas can be of the small duct or large duct type. Morphologically, cholangiocarcinomas may present as one of three types: nodular, sclerosing, or papillary. (See 'Cholangiocarcinoma' above.)

Combined hepatocellular-cholangiocarcinoma, also referred to as primary liver carcinoma with biphenotypic differentiation, is now acknowledged as a distinct rare subtype of cholangiocarcinoma. Prognosis is intermediate between that of hepatocellular cancer and intrahepatic cholangiocarcinoma. (See 'Combined hepatocellular-cholangiocarcinoma' above.)

- A variety of molecular defects involving both oncogenes and tumor suppressor genes have been described in specimens of invasive biliary tract tumors. Conversion from normal to malignant bile epithelium through one of these precursor lesions probably requires a stepwise accumulation of successive genetic abnormalities. However, the level of understanding of the molecular pathogenesis of cholangiocarcinoma is significantly less than that of other gastrointestinal cancers. (See 'Molecular pathogenesis' above.)

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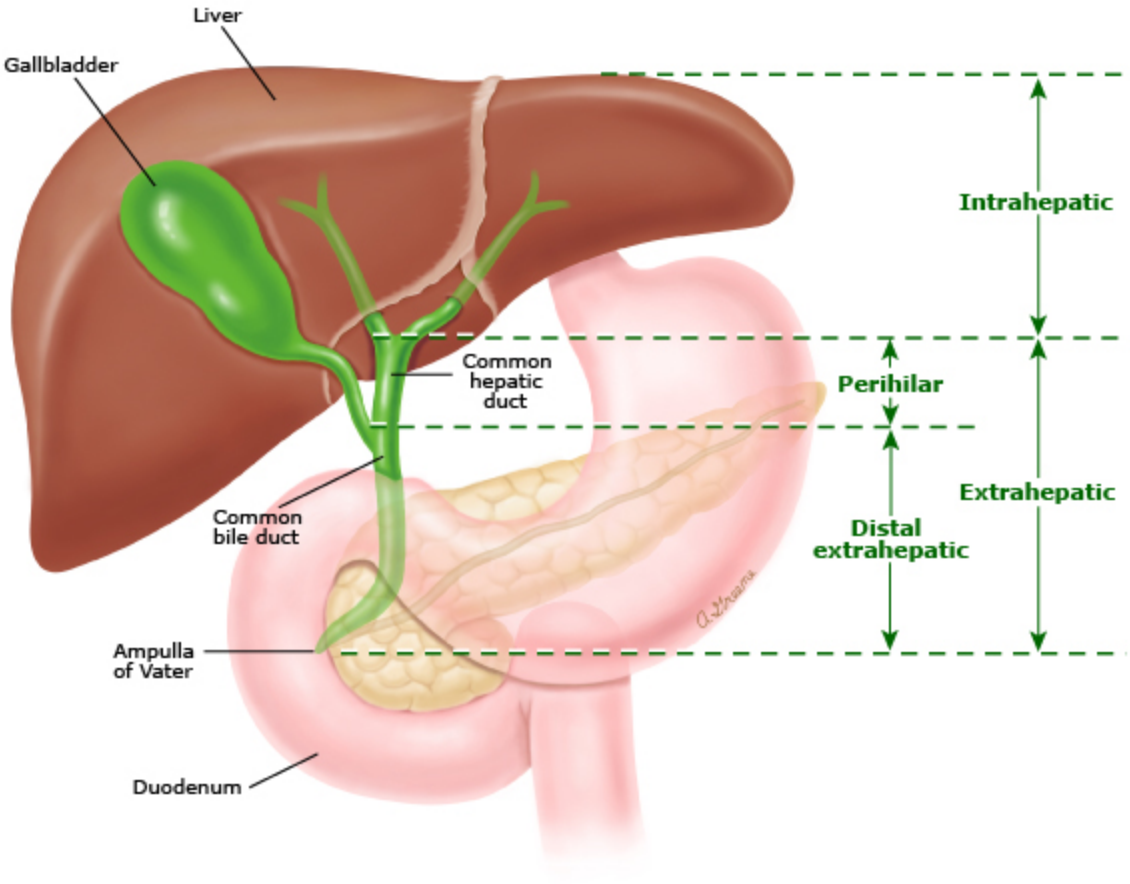
Topic 663 Version 65.0

GRAPHICS

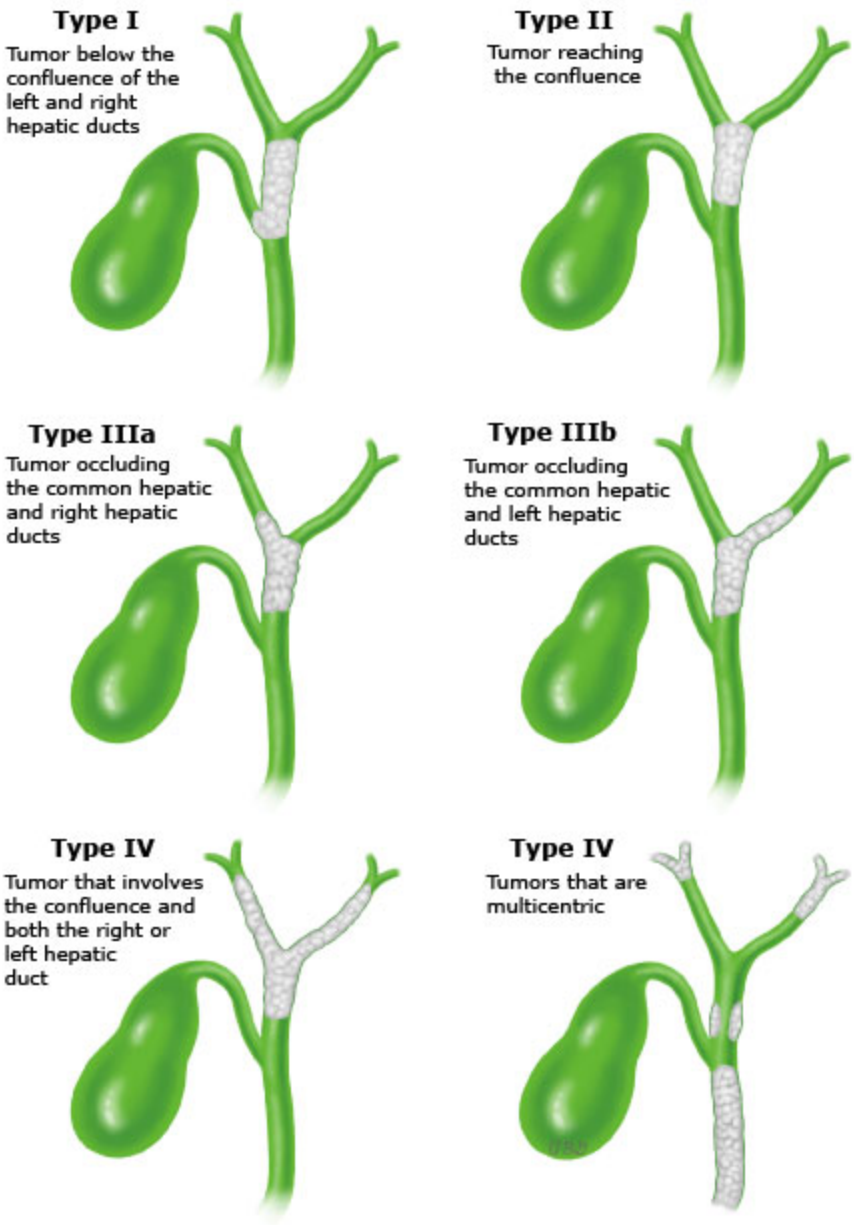
Anatomic classification of cancers of the human biliary tract



Classifications defined by: American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition, Amin MB (Ed), Chicago: Springer Science+Business Media, LLC, 2017.

Graphic 52489 Version 6.0

Bismuth-Corlette classification of biliary tract cancers



The Bismuth-Corlette classification of biliary tract. White areas represent tumor and green areas normal bile duct.

Modified from de Groen PC, Gores GJ, LaRusso NF, et al. N Engl J Med 1999; 341:1368.

Graphic 75886 Version 5.0

Perihilar bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0

T1	N0	M0	I
T2a-b	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIC
Any T	N2	M0	IVA
Any T	Any N	M1	IVB

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110944 Version 8.0

Distal bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor invades the bile duct wall with a depth less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5 to 12 mm
T3	Tumor invades the bile duct wall with a depth greater than 12 mm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T1	N2	M0	IIIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T2	N2	M0	IIIA
T3	N0	M0	IIB

T3	N1	M0	IIB
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110943 Version 7.0

Intrahepatic bile duct cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis present

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB

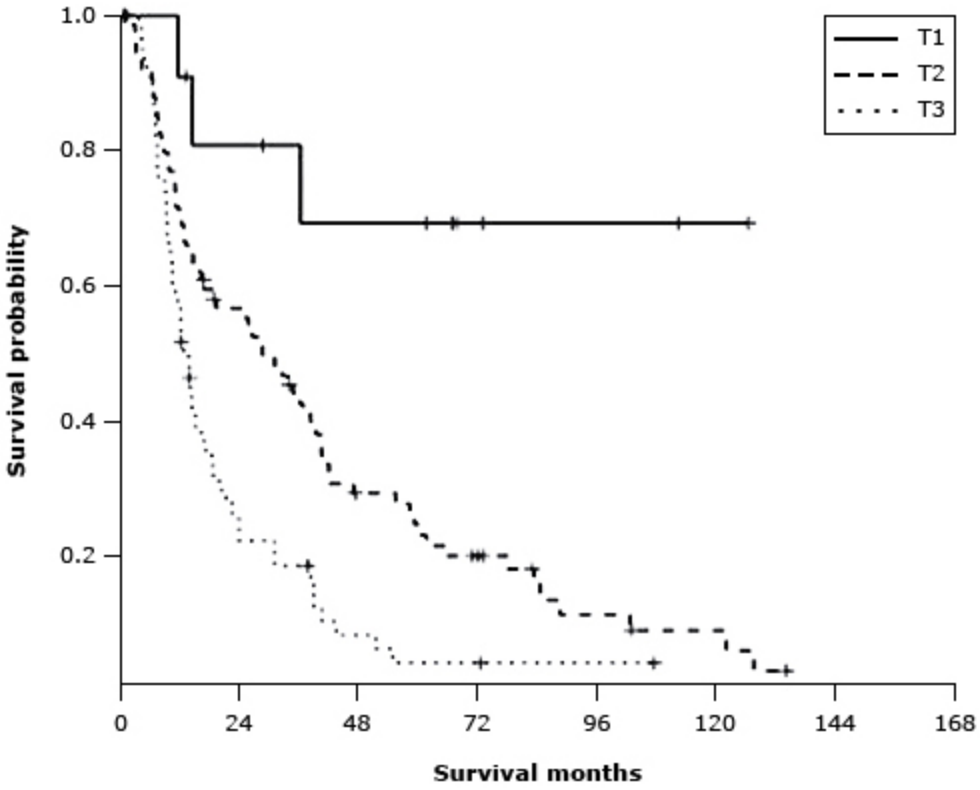
Any T	N1	M0	IIIB
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 110945 Version 7.0

Survival of cholangiocarcinoma of the distal bile duct based on AJCC 8th edition tumor (T) categories



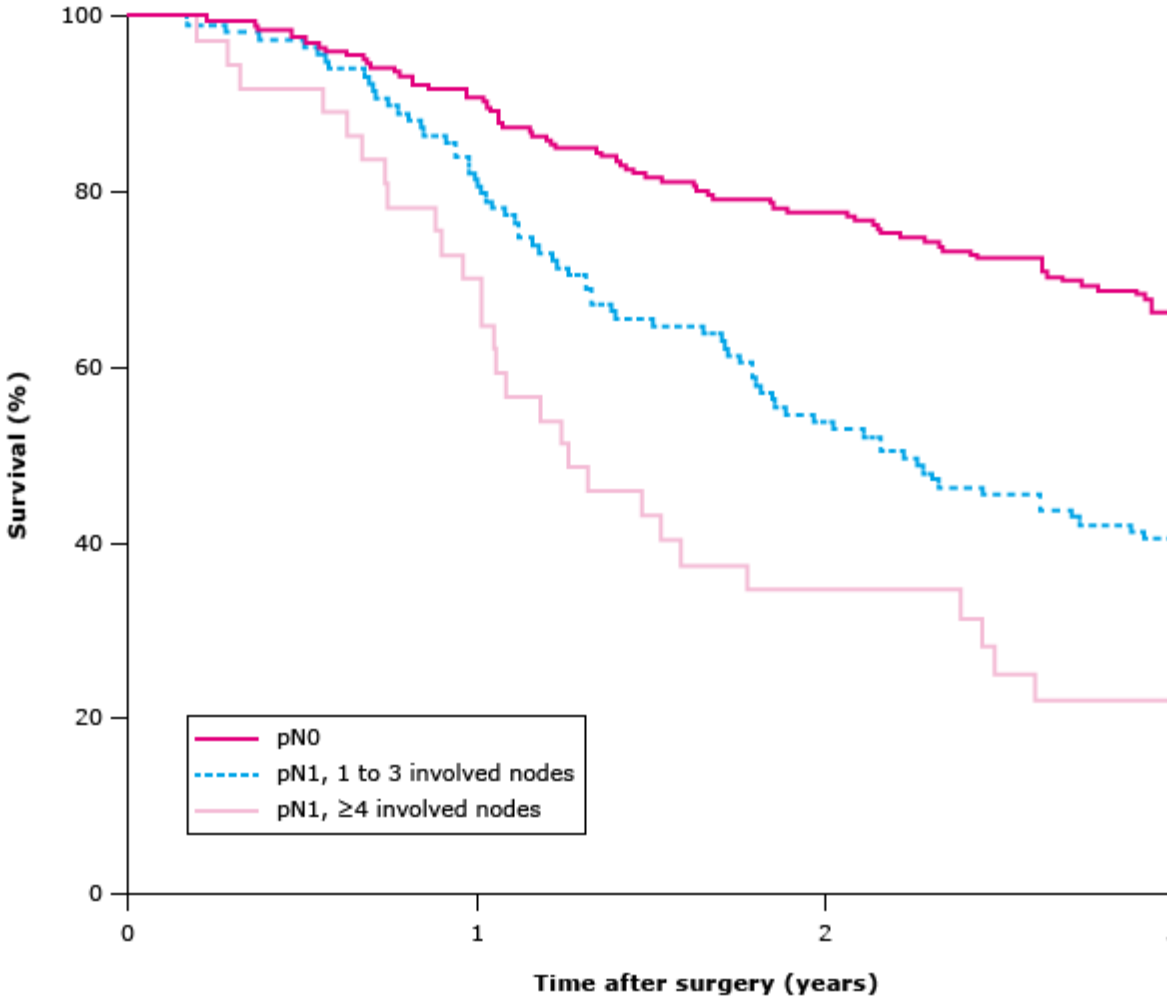
Survival based on T stage category. Results from 147 United States patients who underwent resection of distal bile duct carcinoma confirm earlier study results from 222 Korean patients regarding the use of depth of tumor invasion to predict prognosis and stratify T category.

AJCC: American Joint Committee on Cancer.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 111032 Version 7.0

Survival after potentially curative resection in a multi-institutional series of 37 undergoing pancreaticoduodenectomy for a distal bile duct cancer



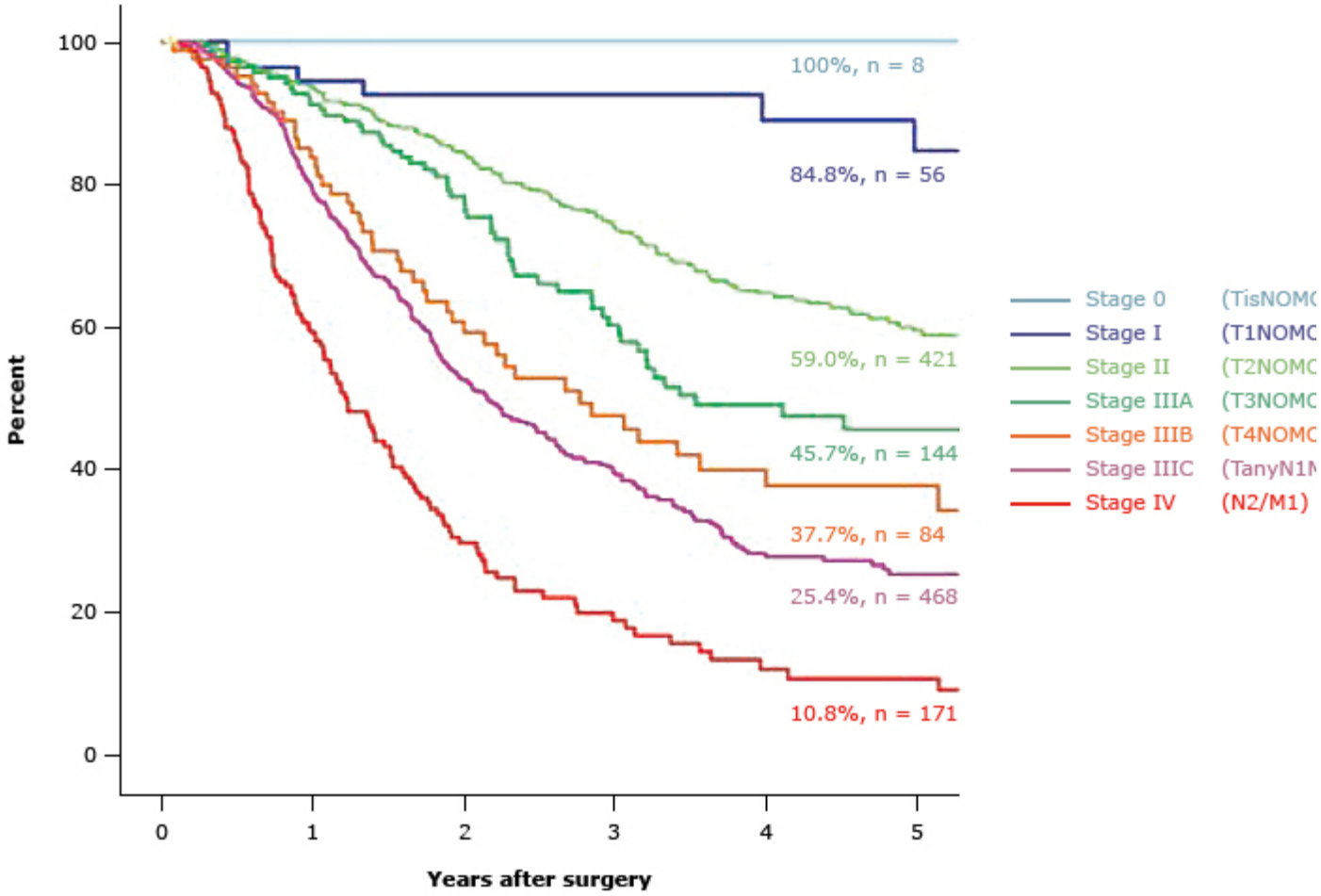
Number at risk

pN0	213	190	159	1
pN1, 1 to 3 involved nodes	120	100	65	4
pN1, ≥4 involved nodes	37	27	11	

Survival according to the number of involved nodes in 370 patients. P<0.001 (pN0 versus pN1, 1 to 3 involve pN0 versus pN1, 4 or more involved nodes) (log rank test).

Graphic 111045 Version 1.0

Overall survival after resection of a perihilar cholangiocarcinoma in a series of patients, stratified according to AJCC 8th edition prognostic stage groupings

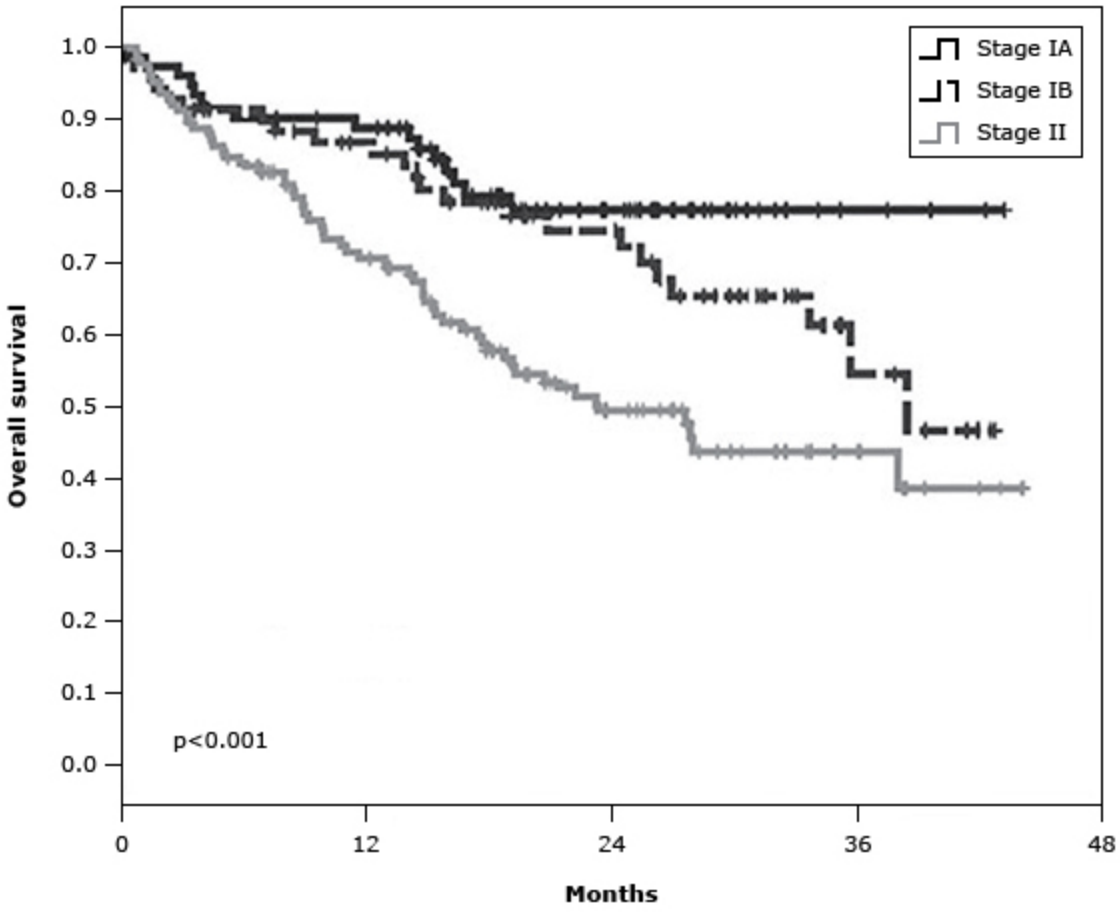


Overall survival after surgical resection of perihilar cholangiocarcinoma at Nagoya University, Japan. Change 7th Edition include removal of Bismuth-Corlette type IV tumors from the T4 category and downstaging of T4 stage IVA to IIIB.

AJCC: American Joint Committee on Cancer.

Graphic 111047 Version 6.0

Stratification for survival in a series of 861 patients with intrahepatic cholangiocarcinoma based on revised AJCC/UICC 8th edition definitions for stage IA, IB, and II disease



Stratification of survival for 861 N0M0 patients with confirmed intrahepatic cholangiocarcinoma based on new stage IA, IB, and II classification using National Cancer Data Base (NCDB) registry data.

AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 111048 Version 6.0

Stage-stratified comparison in 5-year survival outcomes between the 7th (2010) and 8th (2017) edition of the AJCC staging system, Kaplan-Meier analysis

	N (%)	5-year (%)	95% CI
AJCC 7th edition*			
I	93 (18.1)	58.8	44.9-70.3
II	110 (21.4)	38.8	26.5-51.0
III	70 (13.6)	39.7	24.1-54.9
IVa	242 (46.9)	18.4	11.9-6.1
AJCC 8th edition¶			
Ia	15 (5.1)	90.0	47.3-98.5
Ib	18 (6.1)	50.6	19.9-75.0
II	37 (12.5)	55.1	34.5-71.7
IIIa	22 (7.4)	49.7	16.6-76.2
IIIb	204 (68.9)	16.2	9.5-24.5

AJCC: American Joint Committed on Cancer; N: number of patients.

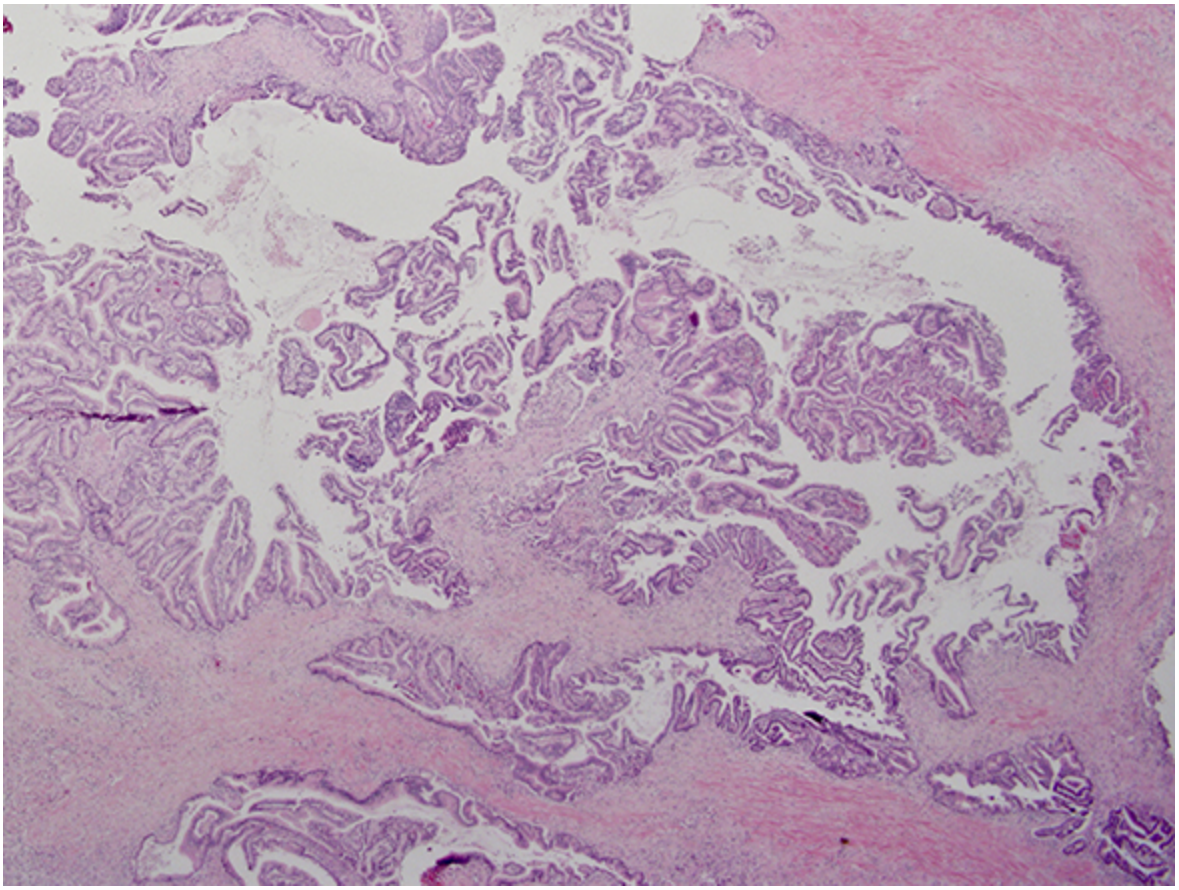
* N = 515.

¶ N = 296.

From: Spolverato G, Bagante F, Weiss M, et al. Comparative performances of the 7th and the 8th editions of the American Joint Committee on Cancer staging systems for intrahepatic cholangiocarcinoma. J Surg Oncol 2017; 115:696. http://onlinelibrary.wiley.com/wol1/doi/10.1002/jso.24569/abstract. Copyright © 2017 Wiley Periodicals, Inc. Reproduced with permission of John Wiley & Sons Inc. This image has been provided by or is owned by Wiley. Further permission is needed before it can be downloaded to PowerPoint, printed, shared or emailed. Please contact Wiley's permissions department either via email: permissions@wiley.com or use the RightsLink service by clicking on the 'Request Permission' link accompanying this article on Wiley Online Library (http://onlinelibrary.wiley.com).

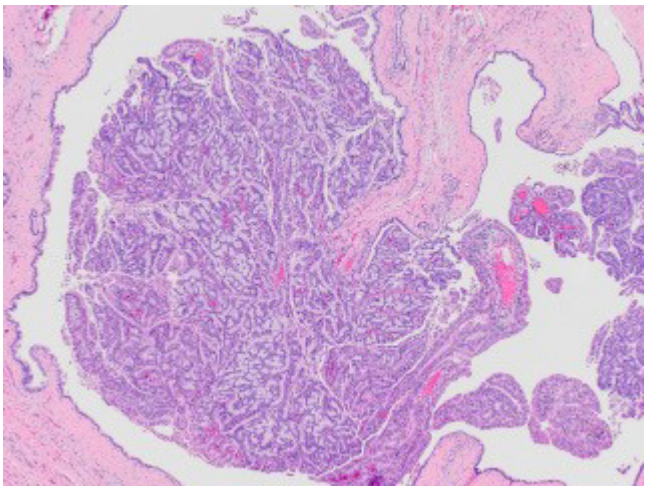
Graphic 113799 Version 1.0

Histology, intraductal papillary neoplasm of the bile duct



Graphic 97392 Version 1.0

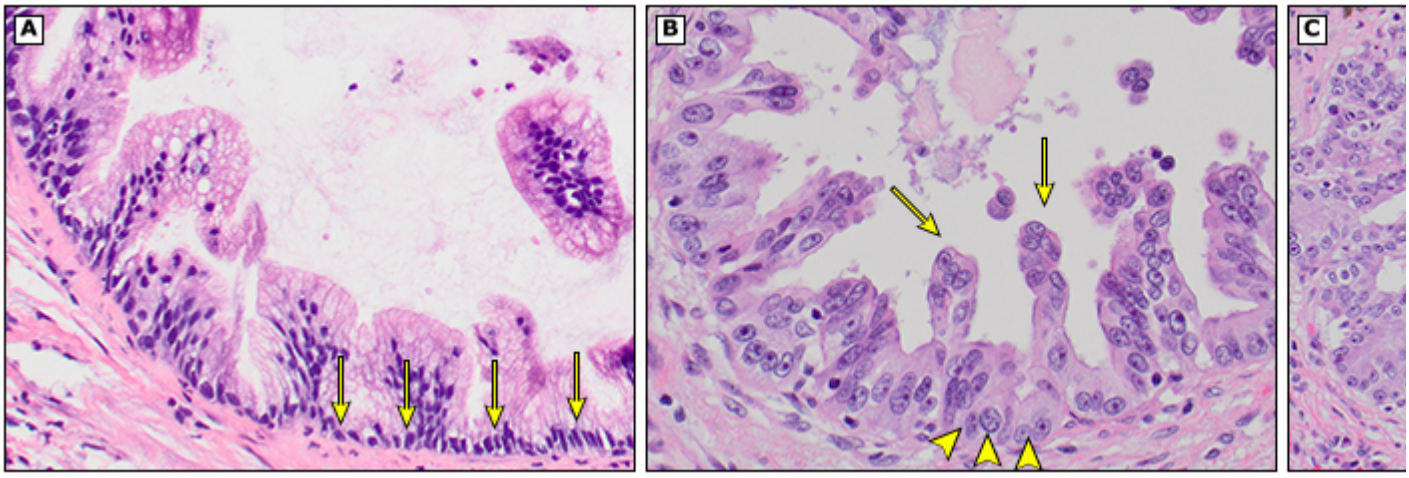
Intraductal tubulopapillary neoplasm of the bile duct, a precursor lesion to cholangiocarcinoma



Histology of intraductal tubulopapillary neoplasm: Dilated bile duct with intraductal polypoid mass, composed of back-to-back tubular units and occasional papillary formation. The native bile duct epithelium is preserved.

Graphic 114106 Version 1.0

BilIN with varying degrees of cytologic atypia, ranging in severity from BilIN1 t



(A) BilIN1: Flat or micropapillary architecture with basally located and relatively uniform nuclei (arrows).

(B) BilIN2: Pseudopapillary or micropapillary architecture with nuclear pseudostratification reaching the lum demonstrate dysplastic nuclear changes, including enlargement, hyperchromasia, and irregular nuclear me sizes and shapes are seen (arrowheads).

(C) BilIN3: Pseudopapillary lesion, cytologically resembling carcinoma, but invasion through the basement m polarity resulting in cellular piling at luminal surface (arrows) and "budding off" of small clusters of cells in tl cytologically malignant features with hyperchromasia, nuclear membrane irregularities, and large nuclei (da

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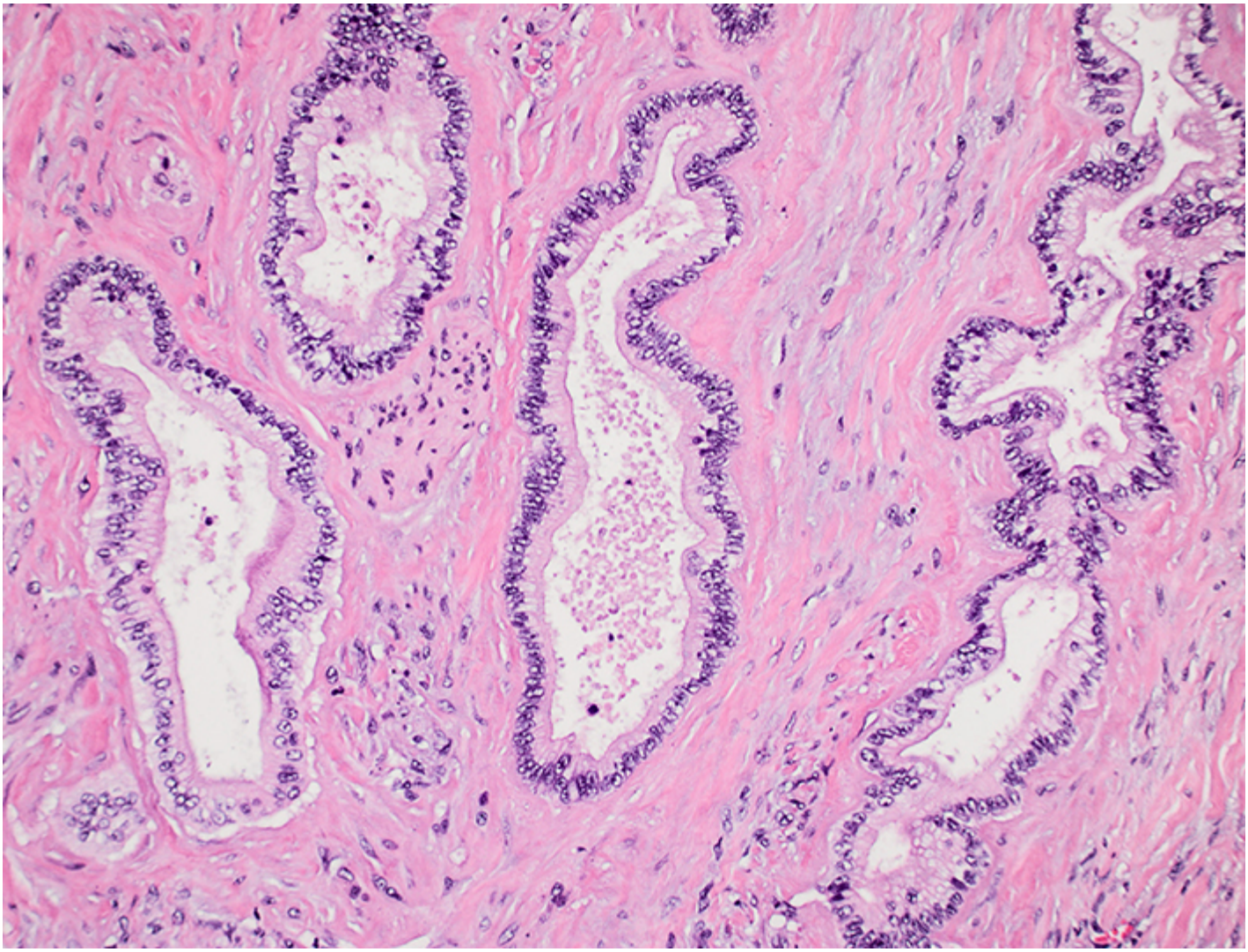
BilIN: biliary intraepithelial neoplasia.

Graphic 98058 Version 1.0

Histology of intrahepatic cholangiocarcinoma, large duct type

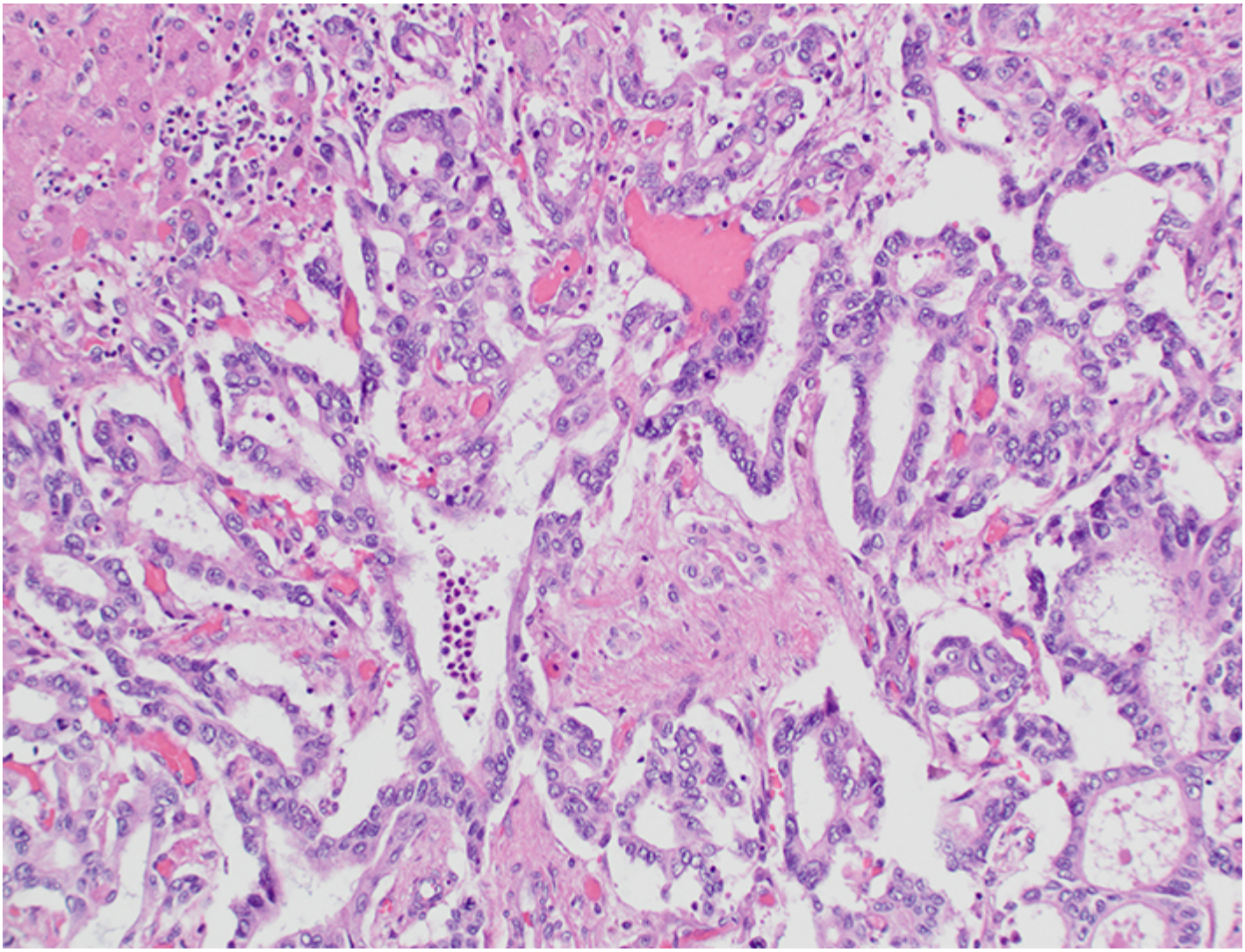


The large duct type of intrahepatic cholangiocarcinoma is characterized by large, neoplastic, ductular structures with a columnar cell lining and apical mucin in the background of densely hyalinized desmoplastic stroma.

Courtesy of Arief Suriawinata, MD.

Graphic 122187 Version 1.0

Histology of intrahepatic cholangiocarcinoma, small duct type



The small duct type of intrahepatic cholangiocarcinoma is characterized by mucin-poor, small, ductular structures with cuboidal neoplastic cells.

Courtesy of Arief Suriawinata, MD.

Graphic 122188 Version 1.0

Differential diagnosis of unknown primary cancers based upon immunostaining for cytokeratin (CK) 7 and 20

CK7+ CK20+	CK7+ CK20-	CK7- CK20+	CK7- CK20-
Urothelial tumors	Non-small cell lung cancer	Colorectal cancer	Hepatocellular cancer
Mucinous ovarian cancer	Small cell lung cancer	Merkel cell cancer	Renal cell cancer
Pancreatic or biliary cancer	Breast cancer		Prostate cancer
	Endometrial cancer		Squamous cell lung cancer
	Nonmucinous ovarian cancer		Head and neck cancer
	Mesothelioma		
	Squamous cancer of cervix		
	Pancreatic or biliary cancer		

CK: cytokeratin; +: positive; -: negative.

Modified from: Dabbs D. Diagnostic Immunohistochemistry, 2nd ed, Churchill Livingstone, Philadelphia, PA 2006.

Graphic 58475 Version 4.0

Contributor Disclosures

Robert C Lowe, MD Consultant/Advisory Boards: GI Reviewers [IBD clinical trials]. All of the relevant financial relationships listed have been mitigated. **Christopher D Anderson, MD, FACS** No relevant financial relationship(s) with ineligible companies to disclose. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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