# Intrahepatic Cholangiocarcinoma: Management Options and Emerging Therapies

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Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC), accounting for 10% to 15% of primary liver cancers.[1] Despite this, ICC remains a relatively rare cancer, with most series in the literature reporting only small numbers of patients who have undergone surgical resection. In fact, most studies include only a limited number of patients, usually from a single center. More recently, multi-institutional studies and reports using the Surveillance, Epidemiology and End Results (SEER) Medicare database have attempted to identify larger cohorts of patients to investigate outcomes for patients with ICC.[2-5] The emerging importance of ICC has been recognized by the American Joint Committee on Cancer (AJCC); a new, separate staging system for ICC has been included in the most recent 7th edition of the AJCC staging manual.[6] We review here the epidemiology, presentation, and surgical and general oncologic management of patients with ICC.

## EPIDEMIOLOGY AND RISK FACTORS

Intrahepatic cholangiocarcinoma is rare, accounting for 3% of gastrointestinal malignancies. Despite its relative rarity, the age-adjusted worldwide incidence of ICC has increased from 0.32 per 100,000 to 0.85 per 100,000 over a 30-year period—an increase of 165%.[5] Using the SEER Medicare database from 1973 to 1997, Patel[7] reported an increase in incidence of 9.1% in the United States (Fig. 1). The incidence of ICC varies significantly depending on geographic location. In the United States, the incidence of ICC has increased to 0.95 per 100,000; the incidence ranges from 0.2 per 100,000 in Australia vs 96 per 100,000 in Thailand.[5,8-10] The increased incidence of ICC is believed to be attributable to a true increase in the disease, rather than improvements in diagnostic accuracy or changes in pathologic reporting.[2,7,11,12]

The peak incidence for ICC is between ages 55 and 75 years; ICC is rare before the age of 45, with this age group accounting for less than 10% of cases. Unlike HCC, which is 5 to 6 times more prevalent in men, ICC appears to have only a slight male predominance, with a male:female ratio of 2:3.[5] Other established risk factors for ICC include disorders of the biliary system that produce chronic biliary inflammation, bile stasis, and cirrhosis. Specifically, primary sclerosing cholangitits (PSC), congenital abnormalities of the bile ducts, intrahepatic lithiasis, parasite infection, and thorocontrast (thorium dioxide) exposure have all been associated with an increased risk of ICC. Patients who have PSC and develop ICC usually present at a younger age (30 to 50 years old) and often present with advanced disease that is not amenable to resection. In one Swedish trial, 8% of patients with PSC developed cholangiocarcinoma, with a mean follow-up of 5 years.[13] Although two-thirds of patients with PSC will have inflammatory bowel disease (IBD), there is no association between severity of IBD and risk of developing ICC.[13,14] Another risk factor for ICC is congenital abnormalities of the biliary system, which carry a 15% risk of malignant transformation after the second decade of life. Common abnormalities include fibrocystic liver disease, choledochal cysts, and Caroli's disease.

Parasite infections with *Clonorchis sinensis* and *Opistorchis viverrini* are also well-established risk factors for ICC. These parasites are endemic in Japan and Southeast Asia and it is estimated that 8% to 10% of people with chronic parasitic infection may develop cholangiocarcinoma. In Thailand, where an estimated 7 million people are infected with opithorchiasis, the incidence of cholangiocarcinoma is 80 to 100 per 100,000. This region of Thailand also has a nitrosamine-rich diet, which is suspected to be an additional cofactor for development of ICC. Intrahepatic biliary stones are rare in the West, but are common in Asia. In Taiwan, up to 70% of patients with resected cholangiocarcinoma have

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**Abbreviations and Acronyms**

AJCC = American Joint Committee on Cancer
EGFR = epidermal growth factor receptor
HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
IBD = inflammatory bowel disease
ICC = intrahepatic cholangiocarcinoma
LN = lymph node
PSC = primary sclerosing cholangitits
VEGF = vascular endothelial growth factor

concomitant hepatolithiasis; in Japan the rate is 6% to 18%.[15,16] Thorocontrast (thorium dioxide), which was commonly used between 1928 and 1950, holds a 300-fold increased risk of cholangiocarcinoma. Other chemical carcinogen exposures with increased risk of ICC include dioxin, asbestos, and radon.

Recently, chronic hepatitis infection has increasingly been recognized as a risk factor for ICC.[17] In a small series of 11 patients, Perumal and colleagues[18] reported that hepatitis C virus (HCV) and hepatitis B virus (HBV) nucleic acids were present in ICC. A Korean study reported the prevalence of HCV and HBV to be 12.5 % and 13.8%, respectively, among patients with ICC vs only 3.5% and 2.3% among control non-ICC patients.[19] In a separate case-control study from China, Zhou and associates[20] noted that, compared with controls, ICC patients had a higher prevalence of HBV.[20] Similarly, an Italian study reported that patients with ICC had HCV and HBV prevalence of 23.0% and 12.5%, respectively, vs 6.0% and 5.5%, respectively, for control patients.[21] Examining populations in the United States, Shaib and coworkers[22] used SEER-Medicare data to compare 625 ICC cases with 90,834 controls. In this study, the authors noted that in addition to diabetes mellitus, IBD, and smoking, cirrhosis and hepatitis exposure were also risk factors for ICC. Interestingly, Shaib and associates found that although HCV infection was associated with an increased risk of ICC, there was no association noted for HBV infection. In another study using the SEER-Medicare database, 535 patients with ICC and 549 patients with extrahepatic cholangiocarcinoma were compared with 102,782 cancer-free controls to investigate which risk factors may be associated with cholangiocarcinoma.[17] In this study, Welzel and colleagues[17] found that the only factors associated with ICC included smoking, obesity, chronic nonalcoholic liver disease, and HCV. The authors postulated that the rising incidence of these factors may help explain the rising incidence of ICC (Table 1).

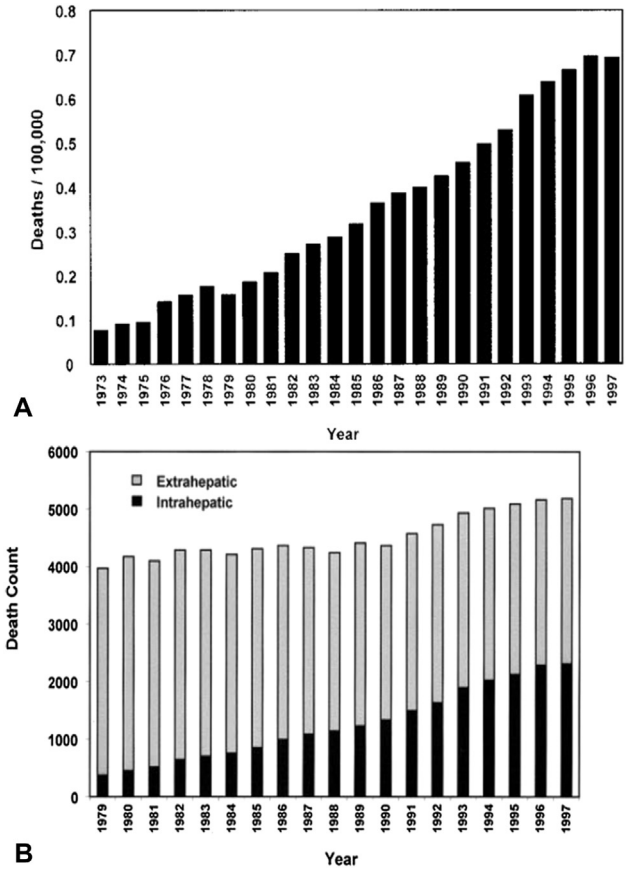


**Figure 1.** Intrahepatic cholangiocarcinoma, age-adjusted incidence (A) and mortality (B). Adapted from: Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353–1357, with permission.

Despite the well-established association of the aforementioned risk factors with ICC, it is important to note that only a minority of patients with ICC will present with an identifiable risk factor. Among patients with ICC reported in Western and Eastern experiences, only 1% of patients had PSC, 3% had intrahepatic lithiasis, 1% had congenital malformations, and only 8% had HCV or HBV.[23] As such, the overwhelming majority of patients with ICC will present with no identifiable risk factor.

## Presentation and diagnostic work-up

Intrahepatic cholangiocarcinoma often remains asymptomatic until an advanced stage. In contrast to extrahepatic cholangiocarcinoma, ICC does not typically present with symptoms of biliary obstruction. It commonly presents as an incidental liver mass found on imaging undertaken for other reasons or occasionally during the work-up of abnormal liver function tests. Symptoms, when present, include vague abdominal complaints and constitutional symptoms (eg, malaise, generalized weakness, night sweats, and nausea). In several surgical series, one-third

**Table 1.** Comparison of Pre-existing Medical Conditions among Patients with Extrahepatic Cholangiocarcinoma, Intrahepatic Cholangiocarcinoma, and Controls

| | ECC (n = 549) | | | ICC (n = 535) | | | Controls (n = 102,782) | |
|---|---|---|---|---|---|---|---|---|
| **Condition** | **n** | **%** | **p Value*** | **n** | **%** | **p Value*** | **n** | **%** |
| Biliary tract conditions/operations | | | | | | | | |
| Choledochal cysts | 27 | 4.9 | <0.001 | 21 | 3.9 | <0.001 | 108 | 0.1 |
| Cholangitis | 50 | 9.1 | <0.001 | 67 | 12.5 | <0.001 | 201 | 0.2 |
| Biliary cirrhosis | <5 | <0.9 | 0.003 | 5 | 0.9 | <0.001 | 53 | 0.1 |
| Cholelithiasis | 202 | 36.8 | <0.001 | 172 | 32.1 | <0.001 | 4273 | 4.2 |
| Choledocholithiasis | 87 | 15.8 | <0.001 | 59 | 11 | <0.001 | 543 | 0.5 |
| Cholecystitis | 42 | 7.7 | <0.001 | 29 | 5.4 | <0.001 | 973 | 0.9 |
| Cholecystectomy | 87 | 15.8 | <0.001 | 41 | 7.7 | <0.001 | 1649 | 1.6 |
| Chronic liver diseases | | | | | | | | |
| Alcoholic liver disease | 8 | 1.5 | <0.001 | 5 | 0.9 | 0.008 | 310 | 0.3 |
| Nonspecific cirrhosis | 10 | 1.8 | <0.001 | 17 | 3.2 | <0.001 | 359 | 0.3 |
| Hemochromatosis | <5 | <0.9 | 0.25 | <5 | <0.9 | 0.05 | 282 | 0.3 |
| Chronic nonalcoholic liver disease | <5 | <0.9 | 0.08 | 5 | 0.9 | 0.03 | 353 | 0.3 |
| HCV infection | <5 | <0.9 | 0.36 | <5 | <0.9 | 0.03 | 142 | 0.1 |
| Endocrine disorders | | | | | | | | |
| Diabetes mellitus type II | 165 | 30.1 | <0.001 | 177 | 33.1 | <0.001 | 22,764 | 22.1 |
| Thyrotoxicosis | 30 | 5.5 | 0.04 | 27 | 5 | 0.12 | 3864 | 3.8 |
| Digestive disorders | | | | | | | | |
| IBD | 10 | 1.8 | 0.03 | 18 | 3.4 | <0.001 | 936 | 0.9 |
| Crohn's disease | 6 | 1.1 | 0.02 | 5 | 0.9 | 0.06 | 419 | 0.4 |
| Ulcerative colitis | 5 | 0.9 | 0.11 | 13 | 2.4 | <0.001 | 595 | 0.6 |
| Duodenal ulcer | 20 | 3.6 | 0.001 | 34 | 6.4 | <0.001 | 1836 | 1.8 |
| Chronic pancreatitis | 13 | 2.4 | <0.001 | 8 | 1.5 | <0.001 | 272 | 0.3 |
| Miscellaneous conditions | | | | | | | | |
| Smoking | 12 | 2.2 | 0.03 | 12 | 2.2 | 0.02 | 1212 | 1.2 |
| Obesity | 16 | 2.9 | 0.79 | 23 | 4.3 | 0.12 | 3201 | 3.1 |

*Fisher exact test used to compute p value when n < 5.
ECC, extrahepatic cholangiocarcinoma; HCV, hepatitis C virus; IBD, inflammatory bowel disease; ICC, intrahepatic cholangiocarcinoma.
Reprinted from: Welzel TM, Graubard BI, El-Serag HB, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1221−1128, with permission.

of patients were asymptomatic, even with tumors as large as 5 to 7 cm.[24,25] A minority of patients (10% to 15%) have jaundice due to occlusion of the bile duct lumen by tumor thrombus, tumor extension along segmental or sectional bile ducts, and/or compression of the common bile duct by metastatic lymph nodes or the ICC mass itself. Rarely, patients can present with a liver mass, high fevers, and elevated white blood cell count, and the clinician needs to be sure to include ICC in the differential diagnosis.

Intrahepatic cholangiocarcinoma has traditionally been difficult to diagnosis on pathologic tissue biopsy because only over the last couple of decades has immunohistochemistry been better able to differentiate biliary tract adenocarcinomas from other metastatic adenocarcinomas. Currently, the report of an "adenocarcinoma consistent with a hepato-pancreato-biliary primary" by an experienced pathologist should raise the suspicion of an ICC in the setting of no obvious primary tumor. Although ICC is often a diagnosis of exclusion and no immunohistochemistry panel is pathonomonic, certain patterns may be suggestive of ICC (negative: TTF1, CDX2, DPC4 and positive: AE1/AE3, CK7+, CK20- in the presence of biliary dysplasia).

When a biopsy of a liver mass revealing "adenocarcinoma" is obtained, the diagnostic work-up should include a search for potential primary tumors, typically colon, lung, pancreas, and stomach, as well as urologic and gynecologic sites. Commonly, the work-up will include cross-sectional imaging with a CT of the chest, abdomen, and pelvis, as well as colonoscopy and upper endoscopy to rule out a gastrointestinal primary. Women should also have a routine mammogram and gynecologic screening. It is important to note that liver biopsy is not

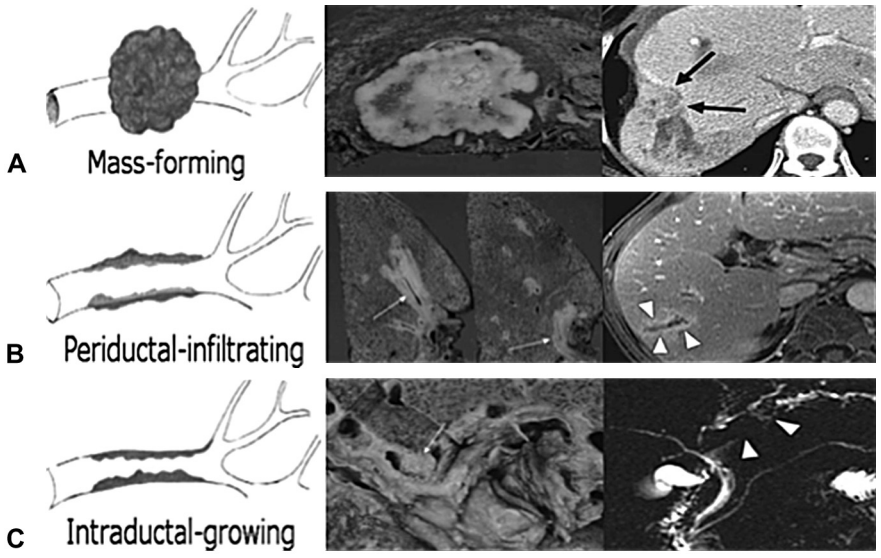


**Figure 2.** (A) Mass-forming intrahepatic cholangiocarcinoma: gross photograph and contrast enhanced CT showing a large, low-attenuation mass (arrows and arrowheads) with surrounding parenchyma atrophy, capsular retraction, and bile duct dilation. (B) Periductal-infiltrating intrahepatic cholangiocarcinoma: gross specimen and T1-weighted MRI showing periductal enhancement of tumor around irregularly dilated intrahepatic duct (arrowheads and arrows). (C) Intraductal-growth intrahepatic cholangiocarcinoma, gross specimen shows innumerable polyploidy lesions (tubular carcinomas) and dilated bile ducts and T2 magnetic resonance cholangiopancreatography showing mildly dilated duct with irregularities mimicking impacted stones (arrowheads). Illustrations adapted from: Hammill CW, Wong LL. Intrahepatic cholangiocarcinoma: a malignancy of increasing importance. J Am Coll Surg 2008;207:594–603, with permission; gross images adapted from Poultsides GA, Zhu AX, Choti MA, Pawlik TM. Intrahepatic cholangiocarcinoma. Surg Clin North Am 2010;90:817–837, with permission; and radiographs adapted from Nakanuma Y, Sato Y, Harada K, et al. Pathologic classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol 2010;2:419–427, with permission.

routinely recommended or necessary. If a patient presents with a liver mass suspicious for ICC and has a work-up that fails to reveal any primary tumor site, the surgeon can proceed to resection of the mass.

Currently available tumor markers lack sensitivity and specificity for ICC. Levels of CA19-9 can be elevated by hyperbilirubinemia, chronic hepatitis, bacterial cholangitis, hepatolithiasis, and chronic biliary parasites, as well as other malignancies. However, 30% of patients with ICC have a CA19-9 level greater than 1,000 U/mL, and another 25% have a level between 100 and 1,000 U/mL. In one study, the cut-off value for serum CA19-9 in patients with PSC was 20 U/mL, which provided a sensitivity of 78%, a specificity of 67%, a positive predictive value of 23%, and a negative predictive value of 96%.[26] In another study examining patients with PSC, CA19-9 levels above 100 U/mL had a sensitivity and specificity of 89% and 86%, respectively; in patients without PSC, the sensitivity and specificity of CA19-9 fell to 53% and 75%, respectively.[27] Nichols and colleagues[27] also found that unresectable ICC was associated with higher CA19-9 levels. Furthermore, Tamandl and associates[28] found that preoperative CA19-9 levels >100 U/mL were independently associated with recurrence risk after surgical resection. Other tumor markers such as CEA, alpha-fetoprotein (AFP), and cancer antigen-125 (CA-125) are less useful. For example, CEA levels are elevated >20 ng/mL in only 15% of patients and >100 ng/mL in 5% of patients with ICC.[29] Similarly, alpha-fetoprotein, which is often elevated in HCC, is <200 ng/mL in 95% of patients with ICC.[29]

The Liver Cancer Study Group of Japan (LCSGJ) proposed 3 macroscopic categories to describe the appearance of ICC: mass-forming, periductal infiltrating, and intraductal growth types with mixed forms (Fig. 2).[10,30,31] The mass-forming type represents 60% to 80% of ICC and includes nodular and exophytic ICC morphologies. Periductal infiltrating ICCs represent 15% to 35% of ICC and demonstrate diffuse infiltration along the biliary tree and portal tracts, resulting in biliary stricture with dilation of peripheral bile ducts. The intraductal growth type represents 8% to 29% of ICC and

often demonstrates papillary, polypoid, or grandular growth, with superficial spread along the bile duct. The morphologic subtypes of ICC can often be distinguished by ultrasound, CT, and magnetic resonance imaging, which are all commonly used to image ICC.

On CT, ICC often appears as a malignant-appearing, irregular, heterogeneous mass with peripheral biliary dilatation and can demonstrate rim-like contrast enhancement at the periphery of the tumor with areas of delayed contrast enhancement within the tumor. These characteristics are due to the fibrotic nature of ICC, which, in turn, results in delayed enhancement. When comparing ICC with other hepatic tumors, both ICC and metastatic colorectal tumors more commonly have areas of central hypointensity, which is a much less frequent finding for other hepatic tumors.[32] Another feature to help differentiate ICC on imaging from other hepatic tumors is its frequent association with peritumoral biliary dilatation. In one study, the authors noted that 54% of patients with ICC exhibited intrahepatic biliary dilation compared with only 3% of patients with metastatic colorectal cancer.[32]

On cross-sectional imaging, different ICC subtypes may have unique features. The mass-forming type of ICC often demonstrates a low attenuation mass with capsular retraction and parenchymal atrophy. Occasionally satellite nodules are present at the periphery of the tumor or there is encasement of vascular and biliary structures. It is important to look for invasion of the hepatic and portal veins and enlarged lymph nodes in the hepatic pedicle on cross-sectional imaging. Although portal lymph nodes can be enlarged secondary to chronic hepatitis C infection in the absence of metastatic disease, enlarged lymph nodes should be considered suspicious. Characteristic features of ICC on MRI include a hypointense lesion relative to normal liver on T1-weighted images and a heterogenous mass with a hyperintense periphery and hypointense center on T2-weighted images. Approximately half of patients with ICC on T2 imaging will have central areas of hypointensity compared with the tumor edge; the area of central lower intensity usually correlates with fibrosis on pathology. On T1-weighted images, periductal infiltrating-type ICC demonstrates periductal enhancement around irregularly dilated intrahepatic ducts. The intraductal growth type may show dilated ducts with intraductal irregularities, mimicking impacted stones; on pathologic examination this often correlates with numerous intraductal polypoid lesions (tubular carcinomas). In addition to the different appearances that each ICC subtype can have on cross-sectional imaging, patient prognosis can also be different based on ICC morphologic subtype. Specifically, the periductal infiltrating and intraductal growth subtypes can be associated with a worse and better prognosis, respectively, when compared with the more common mass-forming subtype.[33-37]

Positron-emission tomography (PET) scan has also been advocated as a helpful imaging modality for patients with ICC. The accuracy of PET, however, seems to vary based on ICC morphologic subtype. For example, some investigators have reported an 85% sensitivity for mass-forming ICC, but only an 18% sensitivity for the intraductal growth subtype of ICC.[38] Kim and associates[39] found no benefit of PET in detecting regional lymph node metastasis; PET did, however, identify occult distant metastasis that were not previously seen on CT or MRI in a subset of patients, thereby changing the management in up to 30% of patients.[39] In another study comparing PET-CT vs CT alone, Petrowsky and coworkers[40] reported no difference in sensitivity for detecting primary ICC or in identifying regional lymph node metastases. The use of PET did again, however, result in better detection of occult distant metastasis compared with CT alone, thereby changing management in up to 20% of patients.[40] Although the data on PET are somewhat limited, taken together, its use in the setting of ICC should be considered because additional PET finds may change the management strategy in a subset of patients.

## Management of intrahepatic cholangiocarcinoma

### *Surgical resection*

In addition to preoperative evaluation for assessment of resectability, thorough work-up of medical comorbidities and remnant liver function should be performed. The degree of portal hypertension should be gauged. Generally, ICC is unresectable if there are intrahepatic metastases, encasement or involvement of major vessels, extensive regional lymphadenopathy, or distant metastases. Although staging laparoscopy has insufficient data to justify its routine use, some studies have shown that perhaps up to 30% of ICC is found to be unresectable due to laparoscopic detection of peritoneal or intrahepatic metastasis. One study by Goere and colleagues,[41] of 39 potentially resectable patients with biliary malignancy, found that 36% (4 of 11) of patients with ICC were found to be unresectable by staging laparoscopy. In another study, 6 of 22 patients with potentially resectable disease were found to be unresectable with laparoscopy (4 had peritoneal metastasis and 2 had additional intrahepatic tumors).[42]

Surgery is the only effective treatment to achieve possible cure in ICC. Without surgery the prognosis of ICC is very poor, with nearly no survivors at 3 years; those who undergo resection have a 3-year survival of

40% to 50%.[7,27,32,41,43,44] Compared with some other liver malignancies, ICC portends a shorter survival, with lower resectability and curability rates. The main goal of resection is complete tumor excision with negative histologic margins and adequate liver remnant, and relief of any possible symptoms relating to biliary obstruction. Though resection has been shown to significantly improve survival, barriers still exist to providing surgery to patients with potentially resectable disease. Tan and colleagues,[3] using SEER Medicare data, identified 3,756 patients with ICC, and only 12% underwent cancer-directed surgery. In this study, 248 patients were identified with localized, potentially resectable disease (single, unilobar tumor without evidence of vascular invasion); however, only 91(37%) of these patients underwent cancer-directed surgery. Patients with localized disease who underwent cancer-directed surgery had significantly improved median survival (44 months vs 8 months; $p < 0.01$).[3]

The impact of resection margin status on survival remains controversial. Multiple studies on multivariate analysis report it to be an independent predictor of survival;[24,25,42,45-49] Other groups report that margin status was not an independent predictor of survival.[4,28,50-56] In a study of 74 patients with ICC, Tamandl and associates[28] found 80% had R0 resection and 20% of these patients had a margin >10 mm. There was no difference between R0 and R1 resection on disease-free or overall survival. Tamandl and associates[28] found a recurrence rate of 70%, with no difference between a close margin (1 to 10 mm) or a positive margin compared with a wide margin (>10 mm) with respect to recurrence or location, and they postulated that these findings may be due to the use of vaporizing ultrasonic dissection, which has been reported to ablate up to 5 mm from the surface of resection. The goal of resection remains negative margin, but the width of the negative margin may not matter. In a German study of R0 vs R1 resection, Lang and coworkers[24] studied 50 patients with locally advanced ICC who underwent surgical exploration. Resection was performed in 54% of patients and often required extended hepatectomy and major vascular and biliary reconstruction. R0 resection was achieved in 16 patients and R1 resection in 11 patients. At a median follow-up of 28 months, 13 of the 16 R0 patients were alive, with 1- and 3-year survival rates of 94% and 82%, respectively. In contrast, after R1 resection, 8 of 11 patients died within 1 year. Although on multivariate analysis, margin status was not associated with outcomes, the authors concluded that this was likely due to tumor-related factors and recommended that an aggressive surgical approach, including resection of vascular and biliary structures, is justified to achieve an R0 resection.[24] Ribero and colleagues[57] reported an R0 rate of 84.6%, with 70% of patients requiring major or extended hepatectomy, 9.2% requiring portal vein resection, and 5.3% requiring inferior vena cava resection. In this study, lymph node status was the most significant independent factor associated with survival, and therefore, the authors supported lymphadenectomy as a standard approach.

High rates of recurrence are reported after resection of ICC, between 46% and 65%. Strong risk factors for recurrence are multiple tumors and lymph node metastasis. Endo and coworkers[50] reported greater than 50% recurrence and a median disease-free survival of 36 months at a median follow-up of 26 months. In this study, the liver was the most common site of recurrence (63%).[50] Poor recurrence-free survival was associated with multiple hepatic tumors ($p < 0.001$), regional nodal involvement ($p = 0.012$), and large tumor size (≥5 cm; $p = 0.016$). Similarly, Yamamato and associates[58] reported high recurrence rates of 46%. Sites of recurrence were most commonly the liver (56%), peritoneum (24%), and lymph nodes (20%). Choi and colleagues[53] reported even higher overall recurrence rates of 65%. Solitary tumor recurrence was 47%, yet with multiple tumors or lymph node metastasis the recurrence rate was 93%. In this study, the most common sites of recurrence were the liver (56%), portal lymph nodes (31%), and peritoneum (22%). Hyder and associates,[59] in an international, multi-institutional study of 301 patients undergoing surgery for ICC, found a median recurrence-free survival of 20.2 months and a 5-year actuarial disease-free survival of 32.1%. The highest risk of recurrence occurred 24 to 32 months postresection, and the most common site of recurrence was intrahepatic, in 60.9%. Only 20% presented with extrahepatic recurrence only. In this study, risk factors associated with recurrence included macrovascular invasion, nodal metastasis, and tumor size ≥5 cm.[59]

The reported 5-year survival rate varies from 21% to 63% in surgical series, accounting for differences in margin status, number of tumors, and stage (Appendix 1, online only).[4,24,25,28,46-55,60,61] Endo and coauthors[50] compared the incidence and survival of ICC vs hilar cholangiocarcinoma, and found that the overall incidence of ICC was increasing along with the overall survival. They found that 115 of 270 patients (73.7%) had unresectable disease. They compared 2 periods, 1990 to 2000 and 2001 to 2006, and found improved overall survival (22 vs 12 months, $p = 0.002$). In this study, the median survival for those with ICC was 19 months: 36 months for those with resectable disease, and 9 months for those with unresectable disease.[50]

Nathan and colleagues,[2] using the SEER Medicare database, identified 591 patients with ICC who had undergone some form of cancer-directed surgery. They found improvement in survival after resection by 34%. The overall survival over 2 periods, 1973 to 1992 (n =171) and 1993 to 2002 (n = 420), increased from 16.5% to 22.9% (p = 0.003). The authors attributed increased survival from 1993 to 2002 to improvements in patient selection with better imaging, and the more widespread use of hepatic resection.[2]

### *Liver transplantation*

Results of liver transplantation have previously been poor, and many consider ICC a contraindication for transplantation.[62,63] Less than 1% of liver transplantations in North America and Europe are for cholangiocarcinoma. At most centers, ICC is a contraindication to liver transplantation. The 5-year survival after transplantation for cholangiocarcinoma is approximately 30%. Many believe that the poor survival after liver transplantation for ICC does not justify the use of limited organ resources. A multicenter Canadian study by Ghali and associates[43] investigated the outcome of incidental finding of ICC in PSC explanted livers and reported a 3-year survival of 30% and a median survival of 26 months. The following groups have reported 5-year survival rates: Cincinnati transplant tumor registry (28%),[62] Spanish liver transplant (30%),[64] and a Scandinavian series (30%).[65] Other studies have shown long-term survival in incidentally discovered cholangiocarcinoma in explanted livers of patients with PSC.[13,66] Currently, transplantation is not an established indication for ICC and should be considered only in the setting of a protocol.

## Prognostic features

The following factors have been studied for their effect on outcomes: solitary vs multiple tumors, lymph node status, margin status, vascular invasion, tumor size, bilobar tumors, capsular invasion, histologic subtype, mucobilia, and CA19-9 levels. The presence of multifocal disease has been shown to be an independent predictor of poor outcome and is believed to represent intrahepatic metastasis. Endo and associates[50] found solitary vs multifocal disease to be an independent predictor of disease-specific and disease-free survival, with a median survival of 87 months vs 19 months ($p < 0.0001$), respectively. Furthermore, the median survival of resected multifocal disease was similar to that of nonoperatively managed liver-only disease. Nakagohri and associates[51] found that survival after resected multifocal disease was less than 10 months. Multifocal disease may be a relative contraindication to surgical resection and some surgeons have advocated for systemic therapy or hepatic intra-arterial therapy for multifocal disease.[25,51]

Lymph node (LN) status is the second most commonly reported prognostic factor. Presence of portal LN metastasis is a poor prognostic factor and a sign of advanced disease.[45,48,50,67] In the Western world, routine lymphadenectomy is not performed, and there is no consensus on staging or therapeutic value of routine portal lymphadenectomy. In one study using SEER-Medicare data, 55% of patients had LN sampling performed, with a median survival of 7 months in patients with node-positive disease compared with 16 months in those with node-negative disease (p = 0.012).[50] Another study, by de Jong and coworkers,[68] using SEER data, found that 248 of 449 patients underwent lymphadenectomy, and 30% of these had LN metastasis. From this large population-based study, these authors empirically established the incidence of LN metastasis ranges between 20% and 30%. They found N1 status negatively affected overall survival and influenced the relative effect of tumor number and vascular invasion on prognosis (Fig. 3). They concluded that lymphadenectomy should be performed for ICC. Several studies suggested that the number of positive LNs may provide additional prognostic information.[4,69-71] Nakagawa and colleagues[69] reported that 3 or more positive LNs had a worse 3-year survival than 1 or 2 positive LNs (0% vs 50%, respectively). Suzuki and associates[70] reported 5-year survival with 1 positive LN as 33%; however, in those with 2 or more positive LNs, there were no survivors at 5 years. Similarly, Tamandl and associates[71] noted that recurrence-free and overall survival were associated with increased ratio of lymph node metatasis to examined lymph nodes.

In addition to prognostic value, some groups have suggested that lymphadenectomy may have therapeutic benefit. In a Japanese study, 145 patients underwent curative hepatic resection and portal lymphadenectomy (hepatoduodenal ligament, hepatic, celiac, left gastric arteries, and para-aortic LNs); the authors found that solitary node-negative disease had the best survival; multifocal, node-negative, and solitary node-positive disease had similar intermediate survival, while multifocal, node positive disease had the worst survival.[47] Two Japanese groups, Nakagawa and colleagues[69] and Suzuki and colleagues,[70] argued a therapeutic benefit to LN dissection when there is a solitary hepatic tumor and 1 or 2 positive lymph nodes. Weber and associates[42] reported 3 of 20 recurrences in the hilar LNs and suggested that lymphadenectomy may have prevented these recurrences. In a retrospective Japanese study, 41 of 49 patients underwent portal lymphadenectomy, and 24 of these patients had positive lymph node metastasis. In this series, 23

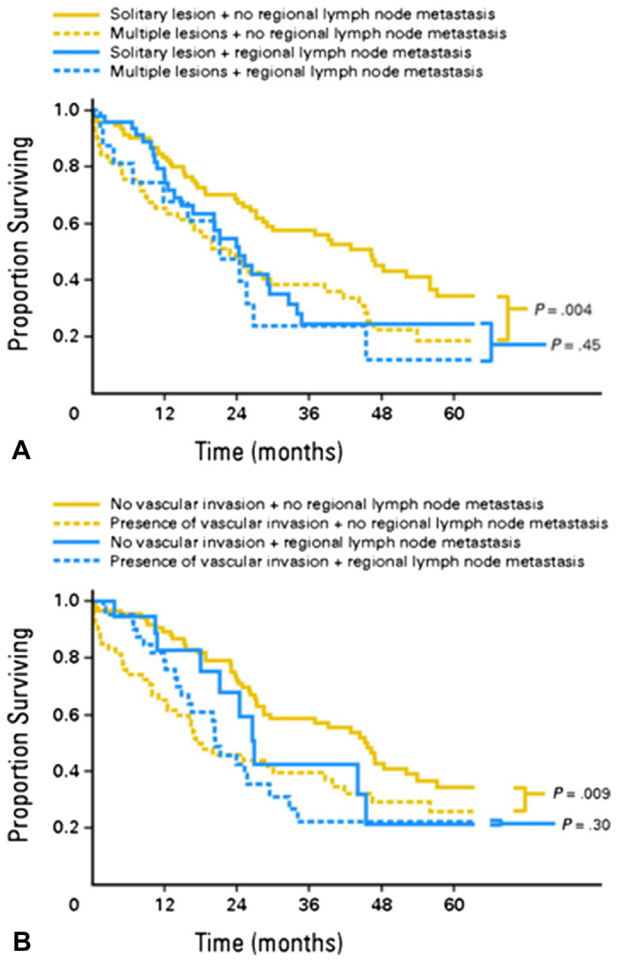


**Figure 3.** Lymph node metastasis influences overall survival and the relative effects of tumor number and vascular invasion. (A) Tumor number predicted survival in patients with N0 disease ($p = 0.004$), but not N1 disease ($p = 0.45$). (B) A similar effect was seen with vascular invasion; vascular invasion predicted survival in patients with N0 disease ($p = 0.009$), but failed to act as prognostic marker among patients with lymph node metastasis ($p = 0.30$). Reprinted from: de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 2011;29:3140-3145, with permission.



patients had recurrences, but none had portal LN recurrences. The authors concluded that lymphadenectomy should not be routinely performed and instead, adopted selective portal lymphadenectomy for suspicion on imaging or intraoperative assessment.[67] Farges and coworkers[72] found that the new 7th edition of the AJCC staging manual accurately predicted survival and could be applicable worldwide should lymphadenectomy be routinely performed. In sum, the data strongly suggest that lymphadenectomy should be performed at the time of surgery for staging purposes due to its strong prognostic ability, and it may lower the risk of locoregional recurrence.

## Staging of intrahepatic cholangiocarcinoma

Several staging systems have been used to stage ICC, including the Liver Cancer Study Group of Japan (LCSG) and the AJCC/Union Internationale Contre le Cancer (AJCC/UICC). In the previous 6th edition of the AJCC/UICC manual, ICC was staged identically to HCC due to the paucity of prognostic data for ICC. Using the same exact staging system for ICC and HCC, however, is problematic because of significant differences in the behavior of these tumors. In turn, as more prognostic data became available for ICC, apparent differences in T and N staging were recognized. For example, in HCC, one-third of patients present as T1 (<2 cm), corresponding to 70% 5-year survival after curative resection, yet ICC rarely presents <2 cm. A study from Tokyo never observed an ICC <2 cm in a series of 60 patients.[73] Another study, from Berlin, found only 2% of 195 patients presented with tumors <2 cm.[74] Others have reported rates as high as 5% to 10% of patients presenting with ICC <2 cm; however, these were likely periductal or intraductal variants and not the classical mass-forming ICC.[23,29] Other groups also demonstrated that size was not an independent prognostic factor in multivariate analysis.[24,50,74-77] Significant differences in HCC and ICC exist also with N status. The incidence of positive LNs in HCC ranges from 5% to 10%; in ICC, surgical series suggest a range from 30% to 40%.[78] Due to the differences in presentation, N status was demonstrated to be of more prognostic value than size in ICC.

The 7th edition of the AJCC staging manual was based on the work of Nathan and colleagues[4] from a retrospective review of 598 patients who underwent surgery from ICC between 1988 and 2004. The authors proposed a system that omits size due to lack of prognostic discrimination, instead using the following independent predictors of survival derived from the SEER database: number of tumors, vascular invasion, lymph node status, and presence of metastatic disease. Another significant finding of this retrospective study was that multiple tumors and vascular invasion had similar effects on prognosis. The AJCC 7th edition now has a separate, unique staging system for ICC, distinct from HCC and extrahepatic bile duct malignancies. The rare combined HCC and cholangiocarcinoma, or mixed hepatocholangiocarcinomas, are included in intrahepatic bile duct cancer. T status is based on 3 major prognostic factors: tumor number, vascular invasion, and direct extrahepatic extension (Table 2). N status is binary, given the presence or

**Table 2.** American Joint Committee on Cancer Seventh Edition Staging for Intrahepatic Cholangiocarcinoma

| TNM Classification | Description |
|---|---|
| Primary tumor (T) | |
| T1 | Solitary tumor without vascular invasion* |
| T2a | Solitary tumor with vascular invasion* |
| T2b | Multiple tumors, with or without vascular invasion* |
| T3 | Tumor perforating the visceral peritoneum or involving local extrahepatic structures by direct invasion |
| T4 | Tumor with periductal invasion† |
| Regional lymph nodes (N) | |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis‡ |
| Distant metastasis (M) | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| Stage groupings | |
| Stage I | T1 N0 M0 |
| Stage II | T2 N0 M0 |
| Stage III | T3 N0 M0 |
| Stage IVA | T4 N0 M0 |
| Stage IVB | Any T N1 M0, Any T Any N M1 |

*Includes major vascular (portal or hepatic vein) and microvascular invasion.
†Includes tumors with periductal-infiltrating or mixed mass-forming and periductal growth pattern.
‡Nodal involvement of the celiac, periaortic, or caval lymph nodes is considered to be distant metastasis (M1).

absence of regional LN involvement. The following are considered regional LNs: for left-sided ICC, common bile duct, hepatic artery, portal vein, and cystic duct LNs; and for right-sided ICC, hilar, periduodenal, and peripancreatic LNs. In general, during a lymphadenectomy, all aforementioned basins would be cleared. Celiac, periaortic, and caval LNs are considered distant metastases. As discussed, most Western centers do not routinely perform lymphadenectomy and for accurate staging, the new addition requires all patients with ICC to undergo lymphadenectomy. In the TNM staging system, M status is classified as a binary variable based on the presence or absence of distant metastasis. It is also recommended that CA19-9 be measured before treatment. The 7th edition has been validated by de Jong and colleagues[68] and Farges and associates,[72] who demonstrated that the T categories show discrete step-wise stratification. Modifications to 7th edition staging of ICC have been proposed by Igami and colleagues,[79] in which the authors recommended that periductal invasion be removed as T4 and replaced by multiple tumors. The authors also proposed that gastrohepatic lymph node metastasis as distant metastasis. In the future, revisions will be necessary as additional survival data becomes available. If portal lymphadenectomy becomes routine, the number of lymph nodes may be added as prognostic factors.

## Cytotoxic systemic therapy

The majority of patients with ICC are unresectable at presentation. Left untreated, survival is only 5 to 8 months.[80] Management for these patients includes systemic chemotherapy, regional chemotherapy, hepatic intra-arterial therapy, external beam radiation, and thermal ablation. There are no phase III randomized controlled trials evaluating chemotherapy in intrahepatic cholangiocarcinoma, and only in 2010 were phase III trials conducted for advanced biliary tract cancer. The majority of phase II studies comprise small patient numbers and a mix of biliary tract cancers. Overall, there has been an improvement in chemotherapy effectiveness from 5FU to gemcitabine-based regimens, with response rates increasing from 10% to 30% to 20% to 50%, respectively (Appendix 2, online only). In a phase II trial of 5FU as a single agent, the overall response rate was only 5%.[81] Combination regimens of 5FU with doxorubicin, epirubicin, cisplatin, lomustine, mitomycin C, or paclitaxel demonstrated a moderate improvement in response rate, up to 10% to 30%.[82-84] As a single agent, gemcitabine was shown to elicit a partial response in 30% of patients.[85] Further promise was shown when gemcitabine was combined with cisplatin, oxaliplatin, docetaxel, mitomycin C, or 5-FU/leucovorin, with response rates ranging from 36% to 60% and median survival between 10 and 15 months.[86-90] Eckel and Schmid[91] analyzed all published chemotherapy trials from 1985 to 2006 among patients with biliary tract cancer. In advanced cholangiocarcinoma, the authors noted that gemcitabine combined with platinum compounds (cisplatin or oxaliplatin) had the highest response rates.

After finding improved survival in a phase II trial (ABC-01) of cisplatin and gemcitabine, Valle and coworkers[92] conducted the first phase III trial for advanced biliary tract cancer. This study, the UK ABC-02 trial, compared gemcitabine alone vs in combination with cisplatin and included 410 locally advanced (25%) or metastatic (75%) bilary tract cancers (bile duct, 59%; gallbladder, 36%; ampulla, 5%). Combination therapy significantly improved progression-free survival (8.4 vs 6.5 months; $p = 0.003$) and overall survival (median 11.7 vs 8.3 months; $p = 0.002$). A follow-up to the UK ABC-02 trial to determine efficacy and safety of combined therapy by Okusaka and colleagues[93] found combination therapy to be effective and well tolerated. The most common grade 3 or 4 toxicities of combined

vs monontherapy were neutropenia (56.1% vs 38.1%), thrombocytopenia (39.0% vs 7.1%), leukopenia (29.3% vs 19.0%), decrease in hemoglobin (36.6% vs 16.7%), and increase in gamma-GTP (29.3% vs 35.7%).[93] Collectively, these results support that the ABC-02 trial was a well conducted phase III trial in a rare tumor type, and it establishes combination gemcitabine and cisplatin as a standard chemotherapy regimen for unresectable cholangiocarcinoma.

Although recurrence is high after resection of ICC, the role of adjuvant therapy is poorly defined in the literature. There are no prospective trials that have examined the role of adjuvant chemotherapy for ICC. As such, a standard chemotherapeutic regimen after the resection of ICC does not exist. Murakami and associates[94] used combined gemcitabine and S-1 in a mixed population of patients with biliary tract cancers including 11 patients with ICC. Based on the ABC-02 data, combination gemcitabine and cisplatin seem to be the most appropriate adjuvant therapy. Criteria for the selection of patients to receive chemotherapy in the adjuvant setting also do not exist. So far, chemotherapy is not routinely used for patients with R0 resection or LN-negative disease. However, adjuvant chemotherapy should be strongly considered for patients with LN metastasis, as well as those with perineural, or vascular invasion.[30,95]

## Molecular targeted therapies

The majority of ICC have P53 mutations; other oncogenic mutations identified in this disease include Her-2/neu, C-met, hepatocyte growth factor (HGF)/met, interleukin-6/gp130, c-myc, K-ras, c-neu, c-erbB2, and bcl-2.[96] The pathogenesis of ICC starts with the chronic presence of proinflammatory cytokines, which stimulate inducible nitric oxide synthase (iNOS) and cyclo-oxygenase (COX)2. This causes DNA damage and mutations to key genes including p53, p16INK4, p21/WAF1, and DPC4/Smad4. Transforming growth factor (TGF)-a activates epidermal growth factor receptor (EGFR) and stimulates RAS, RAF, and MAPK activity. This results in cyclo-oxygenase (COX)2 transcription and prostaglandin E (PGE)2 synthesis and STAT3 translocation. STAT3 induces anti-apoptotic genes (Bcl2 and BclXL) and angiogenesis (via vascular endothelial growth factor [VEGF], interleukin 8, EFGR, and its own inhibitor SOCS). The cytokine interleukin 6 also causes dimerization and translocation of STAT3.

Several of these steps have been the target of directed therapies including VEGF, EGFR, RAF kinase, and Her2/neu (Appendix 2, online only). Inhibitors of angiogenesis that have been studied for ICC include VEGF inhibitors: sunitinib, sorafenib, and bevacizumab.[97,98] Early results for VEGF inhibitors suggest only modest clinical efficacy with high toxicity. Inhibitors of EGFR include cetuximab, erlotinib, lapatinib, and gefitinib. Cetuximab combined with gemcitabine and oxaliplatin (GEMOX) showed promise in a small phase II trial of 30 patients with biliary tract cancers.[99] In this study, 63% of patients had an overall response: 3 patients had a complete response and 16 had a partial response. Nine of the responders became eligible for possibly curative resection. A phase III trial of gemcitabine and oxaliplatin alone or in combination with erlotinib in biliary tract cancers resulted in no difference in overall survival, but a modest improvement in progression-free survival in cholangiocarcinoma.[100] Lapatinib, an inhibitor of EGFR1, ErbB2 and HER-2 did not show efficacy in a phase II trial incorporating biliary tract cancer and HCC.[101] Future studies will need to be better define the role of targeted therapy for use among patients with advanced disease, as well as those in the adjuvant setting.

## External beam radiation

Overall, the use of adjuvant radiation therapy is poorly defined in ICC, given that most studies are small and involve other biliary tract cancers. In general, radiation therapy elicits response rates of 40% to 45% in biliary tract cancers.[102-104] Shinohara and colleagues,[104] using the SEER Medicare registry, reported on 3,839 patients with ICC only. The authors found improved survival in patients receiving radiation after surgery vs surgery alone, as well as radiation vs no treatment. The authors concluded that radiation therapy should be strongly considered for those undergoing R1 vs R0 resection. As such, radiation should be considered in the adjuvant setting for those patients with an R1 surgical margin. In another case control study of 45 patients with unresectable ICC, 22 patients underwent external beam radiation therapy (EBRT).[102] An objective response was observed in 36% of patients and pain was relieved in 90% of patients. The 1- and 2-year survival rates between treated and untreated groups were 36% and 19% vs 5.1% and 4.7%, respectively ($p = 0.021$). Chen and associates[103] evaluated palliative external beam radiation therapy in 84 patients with unresectable ICC and found improved survival and relief of symptoms. The complete and partial response rates were 8.6% and 28.5%, respectively. Of the 19 patients with jaundice, complete and partial relief rates were 36.8% and 31.6%, respectively. Median, 1-year, and 2-year survivals between external beam radiation therapy and non-external beam radiation therapy patients were 9.5 vs 5.1 months ($p = 0.003$), 38.5% vs 16.4%, and 9.6% vs 4.9%, respectively.

### Ablation

Radiofrequency ablation, cryotherapy, and microwave ablation are well established in the treatment of HCC, yet are rarely used in ICC. In HCC, ablation is offered to patients who are not candidates for resection due to poor liver function or comorbidities. However, ICC usually develops in the background of relatively healthy liver, and these patients typically can tolerate surgery. In addition, these therapies are often prohibited by the nature of ICC, due to its large size or central location, because effective ablation typically requires tumors to be small (eg, less than 3 to 5 cm). Central tumors near the hilum/pedicle are also at increased risk of severe biliary complications after these therapies. A small study of 13 patients with unresectable ICC (cirrhosis, n = 9; extrahepatic extension, n = 2; left lobe atrophy, n = 1; comorbidities, n = 1) underwent 17 radiofrequency ablations.[105] Treatment failure occurred in 2 patients with large tumors (7 and 8 cm). The median progression-free survival was 19.5 months and median overall survival was 38.5 months. The 1- and 5-year survivals were 85% and 15%, respectively. A more recent study by Fu and colleagues[106] showed that radiofrequency ablation could be an effective and safe treatment for unresectable/recurrent ICC, with a complication rate of 3.6%. In this study of 17 patients, 10 of whom had recurrence after resection, overall survival was 33 months and 1- and 5-year survival rates were 84.6% and 28.9%, respectively.

### Hepatic intra-arterial therapy

There are no randomized trials for hepatic intra-arterial therapy in ICC. In comparison with HCC, ICC is noted to be less responsive to intra-arterial therapy, perhaps due to its more fibrotic and less vascular nature. Small retrospective trials exist and often include other biliary tract cancers. Gusani and associates[107] reported 42 patients with unresectable ICC, 88% located centrally and 12% peripherally. Patients were treated, on average, with 3.5 treatments of gemcitabine-based chemoembolization (TACE). Median survival from first chemoembolization treatment was 9.1 months. There were no periprocedural deaths and limited grade 3 or 4 toxicities. The authors also found that intra-arterial administration of combined gemcitabine-cisplatin improved survival compared with gemcitabine alone (13.8 vs 6.3 months, respectively; p = 0.0005). In another study of chemoembolization and unresectable cholangiocarcinoma, 2 of 17 patients were down-staged and underwent successful resection. In a study by the Liver Cancer Study Group of Japan, only 4% of patients received chemoembolization with no or minor response among the majority of patients.[29] Hepatic artery infusion pumps have a reported response rate between 40% and 64% using various agents including floxuridine,[108] mitomycin C,[109] epirubicin with cisplatin,[110] and 5FU.[111] In one study, Jarnagin and coworkers[108] demonstrated that the infusion of floxuridine and dexamethasone via hepatic intra-arterial therapy infusional pumps resulted in higher response rates in patients with ICC (53.8%) compared with patients with HCC (25%). Increased response with doxorubicin drug-eluting beads[112] and yttrium-90 microspheres[113] have also been reported. Hoffmann and associates[114] demonstrated radioembolization with yttrium-90 microspheres to be safe. Among 13 treated patients, 12 patients had a partial response and 17 patients had stable disease. The median overall survival was 22 months post-treatment and 43.7 months postdiagnosis.

## CONCLUSIONS

Intrahepatic cholangiocarcinoma is the second most common type of primary liver tumor behind HCC. Although the majority of ICCs are sporadic, chronic inflammatory states of biliary epithelium increase the risk of ICC development. Epidemiologic studies indicate that the incidence and mortality of ICC is increasing while those of extrahepatic cholangiocarcinoma are decreasing. Resection remains the best option for long-term survival in ICC, and despite advances in surgical management including extended resections and vascular reconstruction, barriers remain to potentially resectable patients. For those who undergo resection, recurrence is high and is predicted by multifocal disease, lymphatic spread, vascular invasion, and R1 resection. As such, adjuvant therapy should be strongly considered for these patients. Although the overall prognosis of unresectable ICC remains dismal, combination chemotherapy with gemcitabine and cisplatin has shown promise and is now the standard of care. As the molecular pathology of ICC is elucidated, targeted therapies such as the EGFR inhibitor cetuximab, combined with standard therapy, may allow for possible increased response. The pathogenesis and treatment of ICC demands further study and elucidation if we are to improve the guarded prognosis associated with this disease.

### Author Contributions

Study conception and design: Dodson, Weiss, Cosgrove, Herman, Kamel, Anders, Geschwind, Pawlik

Acquisition of data: Dodson, Weiss, Cosgrove, Pawlik

Analysis and interpretation of data: Dodson, Weiss, Cosgrove, Herman, Kamel, Anders, Geschwind, Pawlik

Drafting of manuscript: Dodson, Weiss, Cosgrove, Pawlik

Critical revision: Dodson, Weiss, Cosgrove, Herman, Kamel, Anders, Geschwind, Pawlik

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**Appendix 1.** Comparison of Recent Surgical Series in Patients with Intrahepatic Cholangiocarcinoma

| First author | Year | Study period | n | No. resected | Resectability rate, % | 3–y Survival, % | 5–y Survival, % | Multiple tumors, % | Size >5 cm | N1 | VI | R1 | Negative prognostic factors (multivariate analyses) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Harrison[115] | 1998 | 1992–2000 | 32 | 32 | NR | NR | 42 | 40.6 | – | 12.5 | 31.2 | 18.7 | VI, Multiple tumors |
| Valverde[60] | 1999 | 1990–1997 | 42 | 30 | 71 | 22 | 10 | 43 | 83 | 27 | NR | 63 | Multiple lesions, N1 |
| Weimann[55] | 2000 | 1978–1996 | 162 | 95 | 59 | 31 | 21 | 47 | – | 25 | 25 | 0 | N1, M1, jaundice, AJCC stage |
| Inoue[46] | 2000 | 1980–1998 | 52 | 52 | – | NR | 36 | – | – | 40 | 63 | 31 | R1, N1, VI |
| Weber[42] | 2001 | 1992–2000 | 53 | 33 | 62 | 55 | 33 | 30.3 | – | 15.2 | 30.3 | 12.1 | VI, multiple tumors, R1 |
| Ohtsuka[54] | 2002 | 1984–2001 | 62 | 48 | 77 | 38 | 23 | – | – | – | – | – | Multiple tumors, CA19–9 >1,000 U/mL |
| Nakagawa[69] | 2005 | 1983–2004 | 53 | 44 | 83 | 38 | 26 | 13 | 41 | 29 | 32 | 11 | Multiple tumors, R1 |
| Jan[49] | 2005 | 1977–1997 | 373 | 135 | 36 | 9.2 | 4.1 | – | – | – | – | – | No mucobilia, no resection, no adj. chemo, nonpapillary |
| Lang[24] | 2005 | 1998–2003 | 50 | 27 | 54 | 82 (R0) | NR | 59.2 | – | 29.6 | 55.6 | 40.7 | R1, VI |
| Paik[25] | 2008 | 1994–2005 | 97 | 97 | – | 52 | 31 | 14 | 42 | 24 | – | 7 | R1 |
| DeOliveira[48] | 2007 | 1973–2004 | 44 | 29 | 66 | NR | 63 (R0) | – | – | 29 | – | 55 | R1, N1 |
| Nathan[2] | 2007 | 1988–2004 | 591 | 591 | – | NR | 17 | – | – | – | – | – | Age, regional and distant disease |
| Konstadoulakis[61] | 2008 | 1991–2005 | 72 | 54 | 71 | 49 | 25 | – | – | – | – | 22 | None significant |
| Nakagohri[51] | 2008 | 1992–2007 | 56 | 56 | – | NR | 32 | 18 | – | 37 | 68 | 25 | Multiple tumors |
| Tamandl[28] | 2008 | 1994–2007 | 74 | 74 | – | 45 | 28 | 28 | 54 | 31 | 26 | 19 | Size, multiple tumors, CA19–9 >100, UICC stage |
| Endo[50] | 2008 | 1990–2006 | 238 | 77 | 32 | NR | NR | 29 | 65 | 9 | 26 | 15 | Multiple tumors, N1, tumor size >5cm |
| Uenishi[47] | 2008 | 1985–2004 | 133 | 133 | – | 36 | 29 | 44 | – | 47 | 60 | 17 | Multiple tumors, N1, R1 |
| Nathan[4] | 2009 | 1988–2004 | 598 | 598 | – | 31 | 18 | 28 | 49 | 27 | 34 | – | Multiple tumors, VI, N1 |
| Lang[116] | 2009 | 1998–2006 | 158 | 83 | 52 | 38, 50 (R0) | 21, 30 (R0) | 53 | 84 | 34 | 41 | 36 | Male, R1, AJCC stage |
| Guglielmi[56] | 2009 | 1990–2007 | 81 | 52 | 64 | 50 | 20 | 21 | – | 27 | – | 17 | N1,VI |
| Choi[53] | 2009 | 2000–2007 | 64 | 64 | – | 52.7 | 39 | 11 | 56 | 27 | 58 | 14 | N1 |
| Shimada[52] | 2009 | 1990–2004 | 104 | 104 | – | NR | 34 | 40 | – | 32 | 27 | 26 | Multiple tumors, N1 |
| Shen[117] | 2009 | 1993–2003 | 429 | 395 | 92 | 22.2 | 17.4 | 34 | 66 | 20.5 | – | 18 | N1, R1, size, CA19–9 |
| Cho[118] | 2010 | 2001–2007 | 63 | 63 | – | 50 | 32.8 | 6 | 57 | 30 | 47 | 6.4 | N1, R1, CA19–9, Age |
| Ercolani[119] | 2010 | 1988–2008 | 103 | 80 | 77 | 62 | 48 | 12.5 | 55.5 | 29 | 33 | 16.6 | Year of operation |
| Saxena[120] | 2010 | 1990–2009 | 57 | 40 | 70 | 48 | 28 | 35 | – | 28 | – | 30 | N1, CA19–9, UICC stage, grade |
| Ellis[121] | 2011 | 1998–2009 | 31 | 31 | – | 31 | NR | 6 | – | – | – | 48 | R1 |
| Ribero[57] | 2012 | 1990–2008 | 434 | 434 | – | 47.1 | 32.9 | 32.3 | 90.2 | 36.9 | 48.6 | 15.4 | N1, multiple tumors, elevated CA19–9 |
| Ali[122] | 2012 | 1997–2011 | 121 | 121 | – | 46 | 25 | NR | – | 28 | – | 4 | N1, R1 |

AJCC, American Joint Committee on Cancer; N1, nodal metastasis; NR, not reported; R1, positive surgical margin; UICC, Union Internationale Contre le Cancer; VI, vascular invasion.

**Appendix 2.** Chemotherapy and its Efficacy in Clinical Studies

| First author | Year | Regimen | Total, n | BD | GB | ICC | DCR, % | ORR, % | Toxicity† | Median overall survival, mo* ICC |
|---|---|---|---|---|---|---|---|---|---|---|
| Ellis[123] | 1995 | 5FU + cisplatin + epirubicin | 25 | 14 | 11 | | 65 | 40 | + | 11 |
| Ducreux[82] | 1998 | 5FU + cisplatin | 25 | 14 | 11 | 6 | 72 | 24 | +/++ | 10 |
| Choi[124] | 2000 | 5FU + FA | 28 | 19 | 9 | | 53.6 | 32.1 | + | 6 |
| Taieb[125] | 2002 | 5FU + cisplatin | 29 | 19 | 10 | 13 | 72 | 34 | ++ | 9.5 |
| Patt[126] | 2001 | PIAF (cisplatin+IFNa-2B, adriamycin, 5FU) | 41 | 22 | 19 | | 49.1 | 21.1 | +++ | 14 |
| Nehls[127] | 2002 | 5FU-oxaliplatin-FA | 16 | 9 | 7 | 7 | 56.6 | 19 | + | 9.5 |
| Rao[128] | 2005 | 5FU-Epirubicin-cisplatin | 23 | 13 | 14 | | 65 | 19 | ++ | 9.2 |
| | | 5FU-etoposide-FA | 23 | 15 | 12 | | 60 | 16 | +++ | 12 |
| Papakostas[129] | 2001 | Docetaxal | 25 | 9 | 16 | | 44 | 20 | ++ | 8 |
| Patt[130] | 2004 | CAP | 26 | 18 | 8 | | 46 | 19 | + | 9 |
| Nehls[131] | 2008 | CAP-oxaliplatin | 66 | 38 | 27 | 18 | 65, 33* | 20, 0* | ++ | 9.5, 5.2* |
| Raderer[84] | 1999 | 5FU+FA+MMC | 20 | 10 | 7 | 10 | 70 | 20 | + | 9.5 |
| | | Gemcitabine | 19 | 14 | 5 | 8 | 37 | 16 | + | 6.5 |
| Kubicka[85] | 2001 | Gemcitabine | 23 | 23 | 0 | | - | 30 | + | NR |
| Gebbia[132] | 2001 | Gemcitabine | 18 | 6 | 12 | | 50 | 22 | + | 8 |
| | | Gemcitabine + 5FU | 22 | 12 | 10 | | 59 | 36 | ++ | 11 |
| Kuhn[133] | 2002 | Gemcitabine-docetaxel | 43 | 17 | 26 | | 67 | 9 | +++ | 11 |
| Hsu[134] | 2004 | Gemcitabine-5FU-FA | 30 | 25 | 5 | 16 | 67.8 | 21.4 | +++ | 4.7 |
| Kornek[135] | 2004 | gemcitabine-MMC | 25 | 18 | 7 | | 56 | 20 | +/++ | 6.7 |
| | | CAP-MMC | 26 | 19 | 7 | | 65 | 31 | +/++ | 9.3 |
| Cho[136] | 2005 | Gemcitabine-CAP | 44 | 37 | 7 | 14 | 66 | 32 | + | 14 |
| Kiba[86] | 2006 | Gemcitabine | 22 | 22 | 0 | 6 | 63, 50* | 5, 0* | + | 8.3 |
| Lee[88] | 2006 | Gemcitapine-cisplatin | 24 | 24 | | | 70 | 20 | + | 9.3 |
| Park[137] | 2005 | Gemcitabine | 23 | 15 | 8 | 9 | 61 | 26 | + | 13.1 |
| Andre[90] | 2004 | Gemcitabine-oxaliplatin | 56 | 37 | 19 | 29 | 58 | 33 | +/++ | 15.4 |
| Knox[89] | 2005 | Gemcitabine-CAP | 45 | 23 | 22 | | 73 | 31 | + | 14 |
| Thongprasert[138] | 2005 | Gemcitabine-CAP | 40 | 39 | 1 | | 60 | 27.5 | + | 9 |
| Riechelmann[139] | 2007 | Gemcitabine-CAP | 75 | 48 | 27 | | 78 | 29 | + | 12.7 |
| Koeberle[140] | 2008 | Gemcitabine-CAP | 44 | 36 | 8 | | | 25 | + | 13.2 |
| Sasaki[141] | 2009 | gemcitabine-S-1 | 35 | 21 | 14 | 14 | 83 | 34 | ++ | 11.6 |
| Okusaka[93] | 2010 | Gemcitabine | 42 | 25 | 17 | 14 | 50 | 11.9 | + | 7.7 |
| | | Gemcitabine-cisplatin | 41 | 22 | 15 | 14 | 68 | 19.5 | ++ | 11.2 |
| Valle[92] | 2010 | Gemcitabine | 200 | 114 | 76 | | 72 | 15 | + | 8.1 |
| | | Gemcitabine-cisplatin | 202 | 122 | 73 | | 81 | 30 | ++ | 11.7 |
| Safran[142] | 2008 | Lapatinib+ gemox or gemcitabine | 7 | | | | | 28 | ++ | |

(Continued)

**Appendix 2.** Continued

| First author | Year | Regimen | Total, n | BD | GB | ICC | DCR, % | ORR, % | Toxicity† | Median overall survival, mo* ICC |
|---|---|---|---|---|---|---|---|---|---|---|
| Ramanathan[101] | 2009 | lapatinib | 17 | 12 | 5 | | 26 | 0 | + | 5.2 |
| Peck[143] | 2012 | Lapatinib-gemox | 8 | | | | 50 | 0 | + | 5.1 |
| Bengala[97] | 2010 | sorafenib | 46 | 32 | 14 | 27 | 33 | 22 | + | 4.4 |
| Gruenberger[99] | 2010 | Cetuximab- gemox | 30 | 27 | 3 | 18 | 80 | 63 | ++/+++ | 13 |
| Paule[144] | 2007 | Cetuximab-gemox | 9 | 9 | - | 6 | 33 | 22 | + | 7 |
| Yi[145] | 2012 | Sunitinib | 56 | 41 | 15 | 35 | 50 | 8.9 | ++ | 5.9 |
| Philip[146] | 2006 | Erlotinib | 42 | 24 | 16 | 15 | 51 | 8 | ++ | 7.5 |
| Lee[100] | 2012 | Gemox | 133 | 86 | 47 | | 67 | 16 | ++ | 9.5 |
| | | Erlotinib-gemox | 135 | 100 | 35 | | 66 | 30 | ++ | 9.5 |
| Zhu[98] | 2010 | Bevacizumab-gemox | 35 | 25 | 10 | 22 | 69 | 40 | + | 12.7 |
| Lubner[147] | 2010 | Bevacizumab-erlotinib | 53 | 43 | 10 | 35 | 69 | 18 | + | 9.9 |
| Jensen[148] | 2012 | Panitumumab-gemox- CAP | 46 | 46 | - | 10 | 85 | 33 | ++ | 10 |

*Denotes ICC subset.
†Toxicity: reported > grade 3 nonhematologic or significant hematologic toxicity: +: mild, 20%; ++: moderate, 20% to 40%; +++, severe, >40%.
BD, bile duct; CAP, capecitabine; DCR, disease control rate; FA, folinic acid; FU, fluorouracil; GB, gall bladder; ICC, intrahepatic cholangiocarcinoma; MMC, mitomycin; NR, not reported; ORR, overall response rate.

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