Published in final edited form as:

Surg Oncol Clin N Am. 2014 April ; 23(2): 231–246. doi:10.1016/j.soc.2013.10.004.

Intrahepatic Cholangiocarcinoma

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Keywords

Intrahepatic cholangiocarcinoma; Peripheral cholangiocarcinoma; Cholangiocarcinoma; Bile duct neoplasms; Intrahepatic bile duct cancer

INTRODUCTION: NATURE OF THE PROBLEM

Epidemiology

Intrahepatic cholangiocarcinoma (ICC) is a subtype of a family of aggressive cholangiocarcinomas, tumors that arise from cholangiocytes of the biliary tree. There are several key epidemiologic considerations of ICC:

- ICCs are rare, accounting for 20% to 25% of all cholangiocarcinomas; perihilar (50%–60%) or distal common bile duct (20%–25%) tumors are more common (Fig. 1).¹ They are still the second most common primary liver malignancy, following hepatocellular carcinoma.²
- The incidence rate of ICCs for Americans has increased from 3.2 per 1,000,000 in 1975 to 1979 to 8.5 per 1,000,000 in 1995 to 1999,^{3,4} but this trend has stabilized over the last decade.⁵
- The reasons underlying this increasing incidence are unclear, but potential reasons include changes in the classification system⁶ or a recent increase in the incidence of Hepatitis C.⁷ This increased incidence does not seem to be related to increased tumor detection, as there has been no change in the proportion of early stage or smaller tumors detected over time.³
- Population-based data demonstrate that men are 1.5 times as likely to develop ICCs as women in the United States.

- The average age of diagnosis worldwide is 50 years old, and patients are rarely diagnosed younger than age 40.^{3,8}
- ICCs are lethal malignancies with more aggressive tumor biology than the more common liver malignancy, hepatocellular carcinoma.⁹ Overall 3-year and 5-year survival rates are a dismal 30% and 18%, respectively.¹⁰
- Mortality from ICCs has risen over the last several decades. Data from the World Health Organization database indicate that although mortality has improved for extrahepatic biliary tumors, mortality has actually increased worldwide for ICCs since the 1970s.¹¹ For the United States, age-adjusted mortality has risen from 0.7 per 1,000,000 in 1973 to 6.9 per 1,000,000 in 1997, paralleling the rising incidence of ICCs (Fig. 2).⁴

Risk Factors

Risk factors for ICC can range from established precursors such as choledochal cysts, cholangitis, and toxin exposure to potential associations such as smoking and diabetes.¹² Patients with chronic inflammatory processes such as primary sclerosing cholangitis and patients infected with the parasites *Opisthorchis viverrini* or *Clonorchis sinensis* are at particularly increased risk for ICC.¹³ Other risk factors are listed in Box 1. Although these factors are key considerations in the diagnosis of ICC, most of these cancers occur de novo in the absence of any underlying liver disease.^{7,14}

Box 1

Risk factors for cholangiocarcinoma

Established risk factors

Primary sclerosing cholangitis
 Choledochal cyst
 Parasitic infection (*Opisthorchis viverrini* or *Clonorchis sinensis*)
 Inflammatory bowel disease
 Drug or toxin exposure (thorotrast)
 Biliary cirrhosis
 Cholelithiasis
 Bile duct adenoma and biliary papillomatosis
 Alcoholic liver disease

Associated risk factors

Diabetes
 Thyrotoxicosis
 Chronic pancreatitis

Obesity
 Nonalcoholic liver disease
 Hepatitis B/C infection
 Typhoid
 Smoking

Subtypes

The Liver Cancer Study Group of Japan has distinguished 3 different histologic subtypes of ICCs: mass-forming, periductal infiltrating, and intraductal growth (Fig. 3).¹⁵

- Mass-forming ICCs are the most common and are characteristically solid nodules that are discrete from the surrounding liver parenchyma. Intrahepatic metastases are more commonly observed with this subtype.¹⁶
- Periductal infiltrating ICCs invade the liver parenchyma along portal structures and metastasize to hilar lymph nodes; this subtype rarely forms a discrete liver mass. A combined mass-forming–periductal-infiltrating tumor type is an aggressive subtype correlating with decreased survival in the Japanese series,^{17,18} but this finding has not been observed in Western populations.¹⁹
- Intraductal growth ICCs are the least common subtype and can be characterized by growth into the biliary tract lumen. These ICCs may represent less aggressive variants with a more favorable prognosis.²⁰

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

The clinical presentation of ICCs is usually nonspecific, and symptoms can include generalized abdominal pain, or less commonly, weight loss and jaundice.

- In a retrospective review of a 31-year experience at Johns Hopkins University, patients with ICC most commonly presented with abdominal pain and were less likely to experience jaundice or weight loss than patients with extrahepatic cholangiocarcinoma.²¹ This finding was confirmed in other studies.^{22,23}
- Because these tumors are discrete from the main bile ducts and rarely cause obstructive jaundice, clinical diagnoses are rare, and many patients initially present with advanced disease.^{13,24} In addition, incidental diagnoses of ICCs in asymptomatic patients are also relatively common, accounting for 12% to 30% of diagnoses in some series.^{14,25}
- A single-institution retrospective review at the Memorial Sloan Kettering Cancer Center demonstrated that 54% of these tumors are unresectable at presentation.²³

Diagnosis and Initial Evaluation

The nonspecific, aggressive presentation of ICC, coupled with its relatively rare incidence, makes the initial diagnosis challenging. ICCs are most commonly identified on cross-sectional imaging, which is also used for staging and determining tumor resectability. Determining the diagnosis before intervention has significant treatment implications given the unique tumor biology of these cancers relative to others (hepatocellular carcinoma, metastatic adenocarcinoma). Laboratory tests are rarely helpful, with occasional exceptions:

- CA 19-9 is the most widely used laboratory test, but it is nonspecific and may be elevated in any number of benign or malignant diseases.^{26,27} It may serve a role as an ancillary test in patients with PSC who present with a suspicious intrahepatic lesion. In these patients a value greater than 100 U/mL carries a sensitivity and specificity of 89% and 86%, respectively, for the diagnosis of cholangiocarcinoma.²⁸
- α -Fetoprotein is similarly controversial and has been suggested to play a role in differentiating ICCs from hepatocellular carcinoma.²⁹ In one study by Koh and colleagues⁹ these values were typically lower or normal in patients with ICCs compared with patients with hepatocellular carcinoma, but this finding was not statistically significant.
- On ultrasound there are no characteristic findings to differentiate these lesions from secondary metastases or hepatocellular carcinoma.^{30,31}
- Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) rarely identifies any pathognomonic features of ICC compared with other liver lesions. As a result, neither is superior to the other in the initial diagnosis of these tumors.³² However, there are findings on these studies that can aid in the diagnosis, particularly when the 2 modalities are used in conjunction.
- Characteristic findings of ICC on CT include the following:
 - Thin rimlike contrast enhancement on both arterial and portal venous phases;
 - Areas of low attenuation within the tumor with areas of high attenuation scattered throughout, also on both phases³³;
 - Delayed contrast enhancement, which may also correlate with poor prognosis. In a retrospective comparison of patients with tumors with delayed contrast enhancement versus those without enhancement, patients in the former group experienced worse overall survival.³⁴
- Characteristic findings of ICC on MRI include the following:
 - Hypointensity on T1-weighted imaging and hyperintensity on T2-weighted imaging;
 - Peripheral enhancement, progressive concentric filling, and contrast pooling on delayed images in contrast-enhanced MRI.²⁹

- The utility of PET-CT in the initial diagnosis and staging of suspected ICC is unclear. Studies have been mixed, with some finding a sensitivity and specificity greater than 85%,^{35,36} whereas others observed limited specificity in the presence of infectious or inflammatory processes.^{37,38}
- Patients who present with a hepatic lesion, biopsy-proven to be adenocarcinoma with an unknown primary lesion, represent special diagnostic cases. In these patients the aim is to discern primary ICC from secondary metastases, and patients should undergo a thorough evaluation to identify a potential primary lesion. These evaluations should include cross-sectional imaging of the chest, abdomen, and pelvis, upper and lower endoscopy, mammography, and gynecologic evaluation as indicated.

STAGING AND PROGNOSIS

7th Edition AJCC Staging

Previous iterations of the American Joint Committee on Cancer (AJCC) staging for ICCs had been based on data from patients with hepatocellular carcinoma. Findings from population-based studies⁵ and basic science literature^{39,40} have demonstrated that ICCs are pathologic entities with a more aggressive tumor biology and distinct phenotype than hepatocellular carcinoma. Recognizing this, Nathan and colleagues¹⁰ used Surveillance, Epidemiology, and End Results-Medicare data from 1988 to 2004 to (1) assess the validity of the 6th edition staging system and (2) identify prognostic findings from pathologically confirmed ICCs. The authors observed that tumor size as defined by the previous staging classification had no prognostic value, whereas vascular invasion, number of tumors, and extent of lymph node invasion had significant prognostic significance. Based on these findings, the AJCC revised the previous classification system to construct the 7th edition staging classification, the first novel staging system for patients with ICCs (Table 1).⁴¹

- In a multi-institutional study of 12 tertiary academic centers, the AFC-IHCC-2009 study group validated the AJCC 7th edition staging classification as a discriminatory system in which each TNM stage was associated with significantly varying survival outcomes (Fig. 4).⁴²
- Another single-institutional Japanese study recognized in a multivariate analysis that this system has some limitations and ignores or underestimates the influence of tumor histology and multiplicity while overemphasizing the influence of periductal invasion.⁴³
- Wang and colleagues⁴⁴ conducted a multivariate analysis to construct a prognostic nomogram for overall 3-year and 5-year survival. This study confirmed the prognostic implications of tumor multiplicity, vascular invasion, and lymphatic spread, all of which are included in the current AJCC staging system. However, in this retrospective review the addition of carcinoembryonic antigen (CEA) and CA 19-9 levels resulted in improved staging accuracy.

MANAGEMENT AND TREATMENT

Although there have been some developments in adjuvant therapies, surgical resection remains the only potentially curative treatment modality for patients with ICCs.^{21,45,46} This section deals with the considerations of operative resection, including the extent of resection, minimally invasive surgical techniques, and orthotopic liver transplantation (OLT). Finally, the role of other nonsurgical therapies is discussed.

Preoperative Preparation

The preoperative evaluation of a patient with suspected ICC should include high-quality cross-sectional imaging of the liver to determine tumor resectability but should also include a detailed evaluation to exclude metastatic or occult primary disease in the chest, abdomen, and pelvis. A discussion of all of the considerations involved in hepatic parenchymal resection is outside the scope of this article, but a few salient points are mentioned:

- Resectability in ICC is defined as the ability to resect tumor to negative margins while preserving adequate functioning liver with intact arterial, portal venous, and hepatic venous flow, and biliary-enteric drainage.
- Preservation of an adequate functioning liver is a central tenet in liver surgery but predicting the amount and function of viable future liver remnant is sometimes difficult. Most authors have suggested 20% to 25% of future liver remnant^{47–49} or 40% future liver remnant in patients with compromised liver function⁵⁰ as standard cutoff values.
- Preoperative portal venous embolization has been developed as a technique to stimulate hypertrophy in the future liver remnant by interrupting flow to tumor-bearing segments, thereby mitigating the risks of postoperative liver failure. The data on this technique in patients with ICCs are limited but studies in other populations have demonstrated that it is safe and can reduce the incidence of postoperative liver failure.^{50,51}

Staging Laparoscopy

Staging laparoscopy has been demonstrated to reduce unnecessary laparotomy for patients with hepatopancreaticobiliary malignancies. However, in the largest series of staging laparoscopy for ICC (53 patients), the sensitivity of staging laparoscopy was only 55%.⁵² A smaller study of 11 patients also demonstrated a high false-negative rate with laparoscopy for ICCs, but this finding is inconclusive given the small sample size.⁵³ Unresectability is often determined by local involvement of vascular supply or biliary drainage of the future liver remnant, which may not be evident on laparoscopic exploration, contributing to the low yield for laparoscopy. As a result, routine staging laparoscopy is not currently recommended in these patients.

Hepatic Resection

- Morbidity and mortality after hepatectomy have declined over the past several decades, owing to improved surgical technique, perioperative care, and advances in

hemostasis.⁵⁴ For ICCs, perioperative morbidity and mortality range from 1% to 14%^{21,23,25,52,55–59} and 6% to 43%,^{21,23,25,52,55–59} respectively. Studies of survival after resection and factors associated with survival are illustrated in Table 2.

- R0 resection (resection of both gross and microscopic disease) is the aim of curative intent surgery⁶⁰ and is associated with favorable outcomes,^{19,21,22,25,52,58,60,61} but is achieved in only 45% to 96% of attempted resections.^{19,21–23,25,52,55–57,60,61}
- R0 resection only improves survival in cases where regional lymphatic spread has not already occurred and has been confirmed in 2 multi-institutional studies.^{19,60}
- Five-year overall survivals after resection range from 17% to 44%, with median survivals of 12 to 43 months.^{19,21,23,25,55,57,59,62}

Lymphadenectomy

The lymphatic drainage of the liver is generally predictable, and the left lobe of the liver generally drains toward the lesser curve and cardia of the stomach, whereas the right lobe drains to the hepatoduodenal ligament.⁶³ However, for ICC there are some important considerations with regards to lymph node disease:

- In a study mapping the lymphatic drainage of patients with left-sided ICC, 46% of tumor deposits were identified in the hepatoduodenal ligament, where right-sided tumor metastases normally occur.⁶⁴
- Although lymphatic involvement is a clear prognostic factor, there is no evidence that routine lymphadenectomy confers any survival benefit.⁶⁵ Although this finding has been observed in only small single-institution studies, most large series demonstrate that routine lymphadenectomy is rarely performed in practice.^{19,23,52,57}
- Lymphadenectomy with surgical resection is recommended in patients with grossly positive lymphatic disease, but spread beyond the regional lymph node basins is a contraindication to resection.⁶⁶

Vascular Resection

- Because ICCs are locally invasive tumors, vascular invasion is a relatively common occurrence, and vascular resections are required in 9% to 14% of hepatectomies.^{23,25,52,55,57,58,61}
- Vascular resection is feasible in experienced centers. In a single-institution review by the Mayo Clinic, 12% of patients underwent major vascular resection.⁵⁵ There was no difference in achievable R0 resections in patients who required vascular resection compared with patients who did not require vascular resection. In addition, there were no differences in perioperative morbidity and mortality. As a result, overall 5-year survival did not differ between groups (44% in the vascular resection group vs 23% in the nonresected group, $P = .268$).

Minimally Invasive Surgery

Since the advent of minimally invasive surgical techniques for hepatic resection in the early 1990s, many of the initial questions of the feasibility of minimally invasive hepatic resection have been answered. Although there have been no randomized controlled trials comparing minimally invasive liver resection to open techniques, there are several observational studies that support the use of the minimally invasive approach.⁶⁷

- Minimally invasive hepatic resection is associated with decreased narcotic pain medication requirement, decreased hospital length of stay, and comparable morbidity and mortality when compared with open resection.^{68–71}
- In small case-control series of patients with hepatic malignancy, minimally invasive hepatectomy was not associated with margin positivity or decreased disease-free survival.^{70,72} However, the conclusions of these observational studies should be approached with caution as they are subject to selection bias. Prospective studies are needed to determine the true impact of minimally invasive techniques on the adequacy of hepatic resection for patients with cancer.
- Robotic resections of hepatic malignancies are currently being investigated with promising results,^{73–75} but long-term data are lacking and these resections should only be undertaken at high-volume centers with specialized expertise in robotic surgery.

Transplant

Given the locally aggressive nature of ICCs, OLT has been attempted as a treatment option. Potential indications for OLT in this population include locally advanced unresectable disease or the presence of advanced cirrhosis that would preclude partial hepatectomy.

- In one of the earliest experiences with OLT for ICC at the University of Pittsburgh, investigators observed similar tumor-free survival and recurrence rates in a small retrospective series (N =54) of patients who underwent hepatectomy versus OLT.⁷⁶
- However, similar patterns in disease-free survival have not been consistently reproduced. Other experiences with OLT have found dismally low disease-free survival rates of 40% at 1 year,⁷⁷ or high recurrence rates of 51% to 80%.^{78,79} The University of California, Los Angeles OLT experience for ICCs actually observed a trend toward improved recurrence-free survival with OLT compared with hepatectomy.⁸⁰
- In a retrospective review of United Network for Organ Sharing database from 1987 to 2005, 1-year and 5-year survival for 280 patients who underwent OLT for ICCs were 74% and 38%, respectively.⁸¹
- Nearly all of these studies included some form of adjuvant or neoadjuvant therapy in conjunction with OLT. Based on these mixed data and the potential likelihood for high tumor recurrence in patients with ICCs, OLT for ICC should only be considered in the context of clinical trials.

- Noteworthy, the Mayo Clinic team has reported excellent results with OLT for early-stage Klaskin cholangiocarcinoma tumors, typically in the setting of PSC, with 5-year OS rate of ~70%.⁸²

Medical Therapy

Nonsurgical therapies for ICCs have not been demonstrated to improve survival or decrease recurrence independently. Because of the relative rarity of ICCs, data on chemotherapy in the adjuvant setting are lacking, but chemotherapy may serve a role in select populations:

- For patients with unresectable ICCs, combination chemotherapy with cisplatin and gemcitabine may provide a survival benefit. In a prospective randomized controlled trial of unresectable biliary tract cancers, Valle and colleagues⁸³ observed a modest survival benefit (~3 months) with combined cisplatin-gemcitabine therapy compared with gemcitabine alone. In a subgroup analysis of patients with ICC, patients treated with combination therapy experienced a survival benefit (hazard ratio [HR] for mortality 0.57, 95% CI 0.34–0.94).
- Studies of other adjuvant therapies have been limited by small sample size or retrospective design.
- Radiation therapy in conjunction with surgery was suggested to improve survival when compared with resection alone in a retrospective population-based study,⁸⁴ but this observation is subject to unmeasured confounding and should be interpreted with caution.
- Transarterial chemoembolization (TACE) is a promising therapy with limited side effects⁸⁵ that may improve survival in patients with unresectable ICC.⁸⁶ In one nonrandomized study, treatment with gemcitabine-cisplatin combination TACE resulted in significantly longer survival (13.8 months) compared with TACE with gemcitabine alone (6.3 months).⁸⁷ TACE has had limited impact in the adjuvant setting.⁸⁸

SUMMARY

ICCs are aggressive malignancies that have been increasing in incidence and mortality over time. Few patients present with resectable disease at the time of presentation, and diagnosis is often difficult because of the occult nature and anatomic position of ICCs. Prognostic features, such as multifocality, vascular invasion, lymphatic spread, and histopathology, should be considered in the management and treatment of these patients. However, because of the relative rarity of ICCs, little is known of the optimal treatment strategy beyond surgical resection. Prospective data are needed to better characterize the efficacy of minimally invasive techniques, transplantation, chemotherapeutic regimens, and other adjuvant therapies on patients who present with this lethal disease.

Acknowledgments

Funding: Supported by grants from the UTMB Clinical and Translational Science Award no. UL1TR000071 and NIH T-32 Grant no. 5T32DK007639.

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KEY POINTS

- Intrahepatic cholangiocarcinomas (ICCs) are aggressive, locally invasive tumors with limited 5-year survival. Multifocality, vascular invasion, lymphatic spread, and tumor histology are all determinants of staging and prognosis.
- Both the incidence and the mortality of ICCs have risen over the past several decades.
- Surgical resection is the only viable treatment option for patients who present with ICCs. Minimally invasive hepatectomy is increasingly becoming a valid option in select cases.

Fig. 1.

Anatomic distribution of cholangiocarcinomas. Intrahepatic lesions such as the lesion in the right lobe of the liver shown in this image are many times asymptomatic and as a result present at a later stage. dCCA, distal cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

Fig. 2.

Age-adjusted mortality for ICC, 1973–1997. (From Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* 2001;33(6):1354; with permission.)

Fig. 3.

Histologic subtypes of ICC. Mass-forming types (A) are the most common type, typically presenting as a mass lesion. Periductal infiltrating (B) are the next most common and infiltrate the hepatic parenchyma along portal structures. Intraductal growth types (C) carry the best prognosis but are the least common. Mass-forming periductal infiltrating mixed type (D) have been suggested to be the most aggressive of these subtypes.

Fig. 4.

Kaplan-Meier survival curve of patients with cholangiocarcinoma. (From Nathan H, Pawlik TM. Staging of intrahepatic cholangiocarcinoma. *Curr Opin Gastroenterol* 2010;26(3):271; with permission.)

Table 1

Staging classification for intrahepatic cholangiocarcinoma

Classification	Description
T1	Solitary tumor without vascular invasion ^a
T2a	Solitary tumor with vascular invasion ^a
T2b	Multiple tumors, with or without vascular invasion ^a
T3	Tumor perforating visceral peritoneum or involving local extrahepatic structures by direct invasion
T4	Tumor with periductal invasion ^b
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis ^c
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, any T N1 M0
Stage IVB	Any T, any N M1

^aIncludes major vascular invasion (portal vein or hepatic vein) and microvascular invasion.

^bIncludes tumors with periductal-infiltrating or mixed mass-forming and periductal-infiltrating growth pattern.

^cNodal involvement of the celiac, periaortic, or caval lymph nodes is considered to be distant metastasis (M1).

Adapted from Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th edition. New York: Springer; 2010; with permission.

Table 2

Factors associated with disease-free survival and overall survival after resection for ICC

First Author/Year	N	R0 Resection	LN Positivity	Tumor Size	Multifocality	Vascular Invasion	Median Survival (mo)	1-y OS (%)	5-y OS (%)
Madariaga et al., ⁵⁸ 1998	34	Yes-OS	No	No	Yes	No	19	67	35
Weber et al., ⁵² 2001	33	Yes	No	Yes-DFS	No	Yes-OS	37	—	31
Nakagawa et al., ⁶¹ 2005	44	Yes-OS	Yes-OS	No	Yes-OS	No	22	66	26
DeOliveira et al., ²¹ 2007	44	Yes	Yes	No	No	No	28	—	40
Paik et al., ²² 2008	97	Yes-DFS	Yes-DFS	Yes-DFS	Yes-DFS	No	53	75	31
Endo et al., ²³ 2008	77	No	Yes-RFS	Yes	Yes-RFS	No	36 (DSS)	—	—
Guglielmi et al., ⁵⁶ 2009	62	Yes	Yes	No	N/A	Yes	41	—	26
Lang et al., ⁵⁹ 2009	83	Yes	No	No	No	No	26	71	21
Nathan et al., ¹⁰ 2009	598	N/A	Yes	No	Yes	Yes	21	—	18
Shen et al., ²⁵ 2009	429	Yes-OS	Yes-OS	Yes-OS	No	No	12	51	17
de Jong et al., ¹⁹ 2011	449	Yes-OS	Yes-OS	No	Yes	Yes	27	78	31
Farges et al., ^{42,60} 2011	212	Yes-OS in N0	No	No	Yes-OS	No	28	77	28

Abbreviations: DSS, disease-specific survival; OS, overall survival.