Epidemiology and surgical management of intrahepatic cholangiocarcinoma

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Practice points

- Intrahepatic cholangiocarcinomas (ICCs) are rare malignancies with increasing incidence globally.
- Various forms of biliary inflammations, as well as chronic liver disease, may predispose the patients to develop ICCs.
- Surgical resection provides the only cure for ICC.
- Margin-negative resection can be achieved in a very limited number of patients.
- The role of liver transplantation for ICC is still controversial.

Intrahepatic cholangiocarcinoma (ICC) is a rare hepatobiliary malignancy arising from the epithelial cells of the intrahepatic bile ducts. The increased incidence of ICC worldwide may reflect both a true increase and the earlier detection of the disease. Despite the advances in modern surgical care, the curative chance for ICC remained suboptimal: tumor-free margins are hard to achieve due to tumor locations, and technical challenges and recurrence, either local or distant, may hamper the resectability in a large number of patients. Lymph node involvement and vascular invasions are considered negative predictive factors for survival of ICC patients. This review discusses the epidemiology, risk factors and surgical management of ICCs, and mainly focuses on outcomes and factors associated with surgical treatment.

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Intrahepatic cholangiocarcinoma (ICC) is one of the hepatobiliary malignancies arising from the epithelial cells of the intrahepatic bile ducts, either small intrahepatic ductules or large intrahepatic ducts proximal to the bifurcation of the hepatic ducts. It is the least common form of cholangiocarcinomas, compared with those located in the upper one-third of the biliary tract [1] and the two-thirds involving the bifurcation of the common hepatic duct (Klatskin tumors). Morphologically, ICCs could be divided into three distinct subtypes (mass-forming, periductal-infiltrating and intraductal-growth), each with different growth pattern and cross-sectional imaging characteristics [2]. Despite its rarity, it tends to be advanced or even lethal upon diagnosis due to the challengeable detection and treatment.

Epidemiology

In the USA about 35,660 primary liver and intrahepatic bile duct cancers are diagnosed each year [3], of which approximately 15% are ICCs, with an overall incidence rate of 0.95 cases per 100,000 adults, suggested by the National Cancer Institute Surveillance, Epidemiology and End Results

KEYWORDS

- epidemiology
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(SEER) program data [4,5]. The incidence of ICC worldwide, such as Europe, North America, Asia, Japan and Australia has been rising over the past 2 decades [5–7], with the highest incidence of 96 per 100,000 men reported in Thailand [8]. Some of these changes are attributable to alterations in disease classification [9], supported by the concurrent drop in extrahepatic cholangiocarcinoma incidence. Some also suggested that part of the increase in ICC may be attributable to more advanced diagnostic modalities that could identify early lesions and biliary malignancies that are undiagnosed previously [10]. However, the increasing incidence was found to be independent of the increased proportion of ICCs with early stage or smaller size and unstaged diseases [5]. Some suggested that the rising incidence of ICC might be associated with a rise in certain newly recognized risk factors such as viral hepatitis and nonviral chronic liver diseases [11]. Of the three morphological subtypes, the mass-forming type is the most common, which is found in over 85% of patients with ICC [2]. As other types of biliary tract cancers, the incidence of ICC increases with age; a typical patient would be at his or her 50 and 70 years of age, with a peak incidence between ages 55 and 75 years. The incidence of cholangiocarcinoma is slightly higher in males than females [5].

Risk factors

A number of pathologies affecting the biliary system that produce chronic biliary inflammation, bile stasis and cirrhosis would all predispose the patients to the development of biliary malignancies such as ICC. Specifically, intrahepatic lithiasis, primary sclerosing cholangitis (PSC), congenital abnormalities of the bile ducts, parasite infection and toxic exposures have all been associated with an increased risk of ICC. It is also worth noting that chronic liver disease (viral infection and cirrhosis) is now recognized as a risk factor for cholangiocarcinoma, especially ICC.

• Intrahepatic lithiasis

Intrahepatic stone disease, in other words, hepatolithiasis or recurrent pyogenic cholangitis is a strong risk factor for cholangiocarcinomas [12,13]. Stone disease affecting only the intrahepatic bile ducts is rare in the West but is endemic in many areas of Southeast Asia. In Taiwan, for instance, an estimated 50 to 70% of patients undergoing resection for cholangiocarcinoma have concomitant hepatolithiasis [14]. The etiology of

hepatolithiasis is not known, but diet, congenital ductal abnormalities, chronic inflammation from bacterial or parasitic infections have all been implicated. The calculi are usually brown pigment stones composed of calcium bilirubinate. Consequent bile stasis caused by the stones would predispose the patient to recurrent bacterial infections and chronic inflammation.

• Primary sclerosing cholangitis

There is a proven association between PSC and cholangiocarcinoma, especially perihilar disease. The annual incidence of cholangiocarcinoma in patients with PSC is approximately 0.6 to 1.5% per year [15,16]. ICCs 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 [17]. 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 [18]. Alcohol consumption has been suggested to be a risk factor for the development of cholangiocarcinoma in patients with PSC [18]. Certain genetic polymorphisms, such as natural killer cell receptor G2D (NKG2D), have been implicated as risk factors for cholangiocarcinoma in PSC [19].

• Congenital abnormalities

Congenital abnormalities of the biliary tree (Caroli's syndrome, congenital hepatic fibrosis, choledochal cysts) carry an approximately 15% risk of malignant change in the adult years (average age at diagnosis 34) [20]. The overall incidence of cholangiocarcinoma in patients with untreated cysts is as high as 28% [21].

• Parasitic infection

In some areas in Asia (particularly Thailand), infection with liver *Clonorchis sinensis* and *Opisthorchis viverrini* is associated with ICC [22]. Patients are infected by having undercooked fish and ingesting the adult worms inhabiting and laying eggs in the biliary system. The organisms induce a chronic inflammatory state in the proximal biliary tree and may lead to malignant transformation of the lining epithelium.

• Toxic exposures

Strong evidence has proved that exposure to the radiologic contrast agent Thorotrast and subsequent cholangiocarcinoma malignancy usually

develops in 30 to 35 years after exposure [23]. An increased incidence of cholangiocarcinoma has been less strongly associated with several occupations, including the auto, rubber and chemical industries. On the other side, studies on the association between smoking and alcohol exposure and ICC had reached controversial findings [24,25]. Some occupational exposures (e.g., printing companies) are also found to be associated with cholangiocarcinoma, either intrahepatic or hilar ones [76].

• Chronic liver disease

Hepatitis B virus and hepatitis C virus (HCV), as well as liver cirrhosis regardless of etiology, are proved to be potential risk factors for ICC [24,26–27]. The association between HCV infection and cholangiocarcinoma was first reported in 1991 [28], followed by several studies suggesting a high rate of HCV-related cirrhosis in patients with ICC, although it is less common than hepatocellular cancer [5,24]. A prospective case control study reported that a risk of developing cholangiocarcinoma in patients with HCV-related cirrhosis was 3.5% at 10 years [27]. More specifically, a large cohort study in the USA found a significant association between ICC and hepatitis C after adjustment for potential confounders [29]. An association between Hepatitis B virus infection and cholangiocarcinoma has also been reported, although the evidence is relatively weaker than for HCV [30,31]. Chronic liver disease of nonviral causes would also contribute to an increased risk for ICC. Frequently reported risk factors for patients with ICC included nonspecific cirrhosis (adjusted OR 27.2) and alcoholic liver disease (adjusted OR 7.4) [11]. A cohort study enrolling 11,605 persons with cirrhosis of any cause found a tenfold increase in risk for ICC after following up for over 6 years among these patients compared with the general population [32].

Diagnosis

• Symptoms & signs

Unlike cholangiocarcinoma of other sites, patients with ICC are less likely to have a history of jaundice. Instead, they usually present with dull right upper quadrant pain, weight loss and elevated alkaline phosphatase level, or rarely fever [32]. While a considerable number of patients are asymptomatic, with the lesions detected incidentally during radiologic examinations due to suspicion of other diseases [33]. Paraneoplastic syndromes are rare findings of

patients with ICC, which may present with cutaneous findings such as Sweet syndrome [34] and *Acanthosis nigricans* [35].

• Laboratory tests

Patients with ICC usually have elevated levels of alkaline phosphatase, whereas serum bilirubin levels are usually normal or only slightly elevated [36]. Elevated levels of gamma-glutamyl transpeptidase and 5'-nucleotidase may be supportive to the diagnosis of hepatobiliary disease. ICC usually appears as a mass lesion on imaging studies, and signs of metastatic disease may also be evident: The most common sites for metastatic ICCs are the peritoneum, the lungs and pleura. Tumor markers such as CEA, CA 19–9 and AFP should be checked in all patients with suspected ICC. Although the findings are insufficient in specificity, for instance CA 19–9 can be elevated in biliary ductal obstruction alone, multiple elevated tumor markers may aid in the setting of differential diagnosis, such as an elevated AFP would suggest hepatocellular carcinoma (HCC) instead of ICC. Some investigators also found the association of CA19–9 levels and postoperative outcomes. They found significantly higher CA19–9 levels in patients with unresectable cholangiocarcinomas [37], and that high CA19–9 levels (over 100 U/ml) were associated with worse recurrence-free survival after resection [38].

• Imaginary tests

ICCs usually present as a malignant-appearing mass lesion in a noncirrhotic liver. Cross-sectional imagings, such as enhanced CT scan and MRI, can be used to differentiate between ICC and HCC if intrahepatic metastatic diseases are ruled out. Typical radiographic features of ICC include a hypodense hepatic lesion without a capsule, with distal biliary dilatation (Figure 1). Capsular retraction may be seen in a small part of patients due to fibrotic nature of the tumor. Rim enhancement would be seen in both arterial and venous phases after contrast administration [39]. Some ICCs small in size can have similar enhancement patterns to HCC, which hyperenhances during the arterial phase and undergoes washout during the delayed venous phase [40]. CT scan is useful for detecting intrahepatic tumors, clarifying the level of biliary obstruction and detecting the presence of liver atrophy. Multiphasic contrast-enhanced multidetector-row CT can also help distinguish benign from malignant lesions in the setting of

intrahepatic bile duct strictures [39]. In addition, multidetector-row CT may aid with tumor staging and evaluation of resectability for ICC. On MRI, ICCs appear as hypointense lesions on T1-weighted images and are heterogeneously hyperintense on T2-weighted images [41]. After gadoteric acid enhancement, the tumor may present as a lobulated shape, weak rim and a target-shaped mass. Positron emission tomography with fluorodeoxyglucose scanning may also play an important role in perioperative evaluation for detecting occult distant metastatic disease [42], which may be a potential contraindication for surgical managements. Similarly, Doppler ultrasound can be useful in preoperative assessment for its ability to identify vascular invasions of the tumor to the portal vein and the hepatic artery with high sensitivity and specificity [43], which is comparable to angiography and CT arteriogram.

Tumor staging

In general, the staging starts with CT scan of the abdomen and pelvis. If distant metastatic disease, extraregional lymph node involvement or invasion of critical adjacent structures is not evident, a positron emission tomography (PET) scan could be ordered to look for occult metastases. If the PET scan is normal and the patient is a good candidate, surgical management should be considered. Unlike the past when ICC and HCC were regarded together as 'primary liver cancer,' the latest AJCC/UICCA staging system (7th) separately assessed predictive factors for ICCs alone. One of the updates is that the 7th edition no longer regards tumor size as a prognostic factor, instead, the number of lesions, vascular invasion, intrahepatic metastasis and invasion of adjacent tissues were some important factors affecting the T stage of ICCs [44]. Lymph node sampling (ordinarily 3 or more lymph nodes sampling) is necessary for staging according to the Union for International Cancer Control guidelines.

Surgical management

Compared with some other hepatobiliary malignancies, ICC is generally associated with lower resectability and curability, as well as poorer survival. Surgery provides the only possibility for a cure, but only a minority of patients is considered candidates for curative resections. The potential barriers for successful resections are the stage and size of the tumor, which bring challenges to surgical approach and the possibility to achieve margin-negative (R0) resections.

• Preoperative imaging

Imaging examinations are useful in the diagnosis and staging of the tumor, including abdominal CT and many forms of cholangiopancreatography, such as magnetic resonance, endoscopic or transhepatic. PET scan may be done to detect possible occult metastases.

• Staging laparoscopy

The role of staging laparoscopy has not been determined, but may be useful in ruling out small peritoneal implants before proceeding with a laparotomy incision. Studies have shown that approximately 36% of ICC is found to be unresectable due to laparoscopic detection of peritoneal or intrahepatic metastasis [45].

• Preoperative portal vein embolization (PVE)

PVE is a frequently used method to increase the safety for hepatic resection in patients with limited liver functions for the goal of achieving a histologically negative resection margin [46,47]. The aim of PVE is to induce lobar hypertrophy in patients who are predicted to have insufficient liver remnant after resection preoperative PVE may permit a margin-negative resection by increasing the future remnant liver volume. Despite some reports on hilar cholangiocarcinomas [48,49], evaluations of safety and efficacy of PVE in ICC are pending.

• Surgical resection

When contraindications are precluded, ICC is usually treated by radical hepatic resection with the goal to achieve negative resection margins [50]. Therefore, large-volume liver resections, such as hemi-hepatectomy or an extended hepatic resection, as well as resections and reconstruction of extrahepatic bile duct system may be needed in a considerable proportion of patients (over 70% for hemi-hepatectomy or extended hepatic resection [51] and over 20% for biliary resection and reconstruction [52]). The Nagoya group had demonstrated good outcomes in aggressive surgical treatment for hilar cholangiocarcinoma with overall survival at 5, 10 and 15 years of 22, 13 and 10%, respectively and acceptable mortality [51]. However, with considerable difficulties in surgical approach, curative resection with tumor negative margins can only be achieved in less than 30% of patients, even in selected candidates who tend to be younger in age and have early stage localized lesions [53].

Figure 1. Typical images of Intrahepatic cholangiocarcinoma in T1- and T2-weighted MRI scans. Left: T1-weighted image; right: T2-weighted image.

Margin-free resections are very challenging in patients with locally advanced tumors or tumors large in size [51]. Nevertheless, resection should not be attempted in patients with unresectable disease based on staging studies. ICC is considered unresectable if intrahepatic or distant metastases, invasion or encasement of major vessels, or extensive regional lymph node are present.

Few study has reported the benefits of lymphadenectomy during surgical resection for ICC [54]. Despite the fact that lymph node involvement is an important predictive factor for poorer prognosis, evidence of the therapeutic benefit from lymphadenectomy does not seem strong enough, and there is a lack of consensus about whether or not it should be routinely performed [52,55]. The risk of performing portal lymph node dissection such as common bile duct devascularization should be weighed against the perceived benefit. However, the presence of grossly positive porta hepatis lymph nodes is strongly associated with a poor prognosis so that portal lymphadenectomy should be considered in selected patients [52]. For resected ICCs, lymph node metastases and hepatic venous invasion are also negative prognostic factors. In addition, patients who develop ICC on the base of primary sclerosing cholangitis are associated with poorer outcomes. After curative surgical resection, local recurrence is the most common pattern [56], other patterns such as intrahepatic, nodal or extrahepatic distant (intra-peritoneal) recurrences were also reported [57]. Demonstrated risk factors for recurrence include

histologically-positive margins and lymph node involvement.

Long-term outcomes vary among patients who receive curative resection for cholangiocarcinoma, which is dependent to the location and extent of the primary lesion, margin status of the surgery and potential complications. Some had reported an improved survival over time for the past few years, however, they pointed out that this change might be attributed to improved nonsurgical therapy or more careful selection of candidates for surgical resection [58]. Outcomes of ICC depend on disease stage (especially the presence or absence lymph node involvements and vascular invasion) rather than size, as well as the status of surgical negative margins [55,59]. Postoperative 5-year overall survival is generally up to 40% [60,61], but better survival can be achieved in patients with negative margins (R0 resections) and negative lymph node involvement, among which the 5-year survival could be as high as 63% [62–64]. Stage-stratified 5-year survivals according to the 7th edition of the AJCC staging system in a French study of 163 patients undergoing potentially curative surgery were reported as 32% for all patients enrolled, 62% for Stage I (T1N0), 27% for Stage II (T2N0) and 14% for Stage III (T3N0, T1–3, N1) [65]. A nomogram is a good way to predict survival after resection. One nomogram has been developed for ICC that includes tumor (T) and nodal (N) classifications, tumor size, the number of tumor nodules, preoperative serum tumor marker levels and vascular invasion [66].

• Liver transplantation (LT)

LT is not recommended as a routine procedure for ICCs due to the lack of standard indications and highly controversial outcomes [66]. In fact, due to unsatisfactory long-term survival and high recurrence rates, many centers are no longer conducting LT for ICC. Without concomitant anticancer chemotherapies, the 3-year survival of patients with ICC who underwent LT ranges between 50 and 65% [67,68]. Meanwhile, patients undergoing systematic adjuvant or neoadjuvant therapy achieved better long-term survival [69]. Commonly reported adverse prognostic factors for LT were perineural invasion, multifocality, infiltrative tumor growth pattern, lymphovascular invasion and history of PSC. Meanwhile, recent studies [70,71] found that certain ICC patients, particularly those population with small solitary tumors, enjoyed more favorable long-term survival after liver transplantation, despite the limited number of participants who underwent LT. In summary, LT is not completely ineffective, but its controversial indications and cost-effectiveness may limit its use in the treatment of ICC, meanwhile, neoadjuvant and adjuvant therapy would be potential strategies to improve the long-term survival in patients with locally advanced ICC.

• Adjuvant therapy & prognosis

Both local and distant metastases following complete surgical resection are common, which provide the rationale for exploring adjuvant systemic chemotherapies either before or after resection. All high-risk (positive margin, vascular invasion or lymph node metastasis) patients with ICC should be encouraged to receive adjuvant therapy after surgery, if available. Neoadjuvant therapy should also be recommended for unresectable patients. 5-FU was the first chemotherapeutic drug as a single agent for unresectable ICC, which had only a 10% response rate [72], followed by fluoropyrimidine-based chemotherapy regimens and gemcitabine alone or gemcitabine-based combination therapies. A recent study [73] comprising 410 patients with advanced biliary tract cancer compared gemcitabine alone versus the combination of gemcitabine and cisplatin and demonstrated significantly higher OS in

the combination group (11.7 vs 8.3 months; HR: 0.70; 95% CI: 0.54–0.89; $p = 0.002$). In another study on 40 patients receiving adjuvant gemcitabine after resection for biliary tract cancer, OS in ICC patients was significantly elevated (HR: 0.09; 95% CI: 0.01–0.67) [74].

Given the negative results of the two randomized trials testing the value of chemotherapy alone, we suggest chemoradiotherapy plus chemotherapy rather than chemotherapy alone following either a margin-positive or node-positive resection, although this is a controversial area and others would suggest chemotherapy alone, particularly for patients with resected intrahepatic cholangiocarcinoma [75].

Conclusion

ICC is the second most common hepatic malignancy with increasing incidence and multiple infectious, environmental and metabolic risk factors. Surgical resection provides the only cure in selected patients while other treatment modalities, such as locoregional or systemic therapies, may be beneficial as adjuvant for curative surgery.

Future perspective

More precise histopathologic features and markers need to be discovered to enable more specific diagnosis and stratification. Large randomized controlled studies are needed as to better select the patients for surgical resection as well as determining the selection criteria for patients receiving adjuvant or neoadjuvant therapies. Overall, ICC remains to be a complicated clinical challenge requiring multidisciplinary approaches.

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Executive summary

- Patients with chronic liver disease are at risk for the development of hepatocellular carcinoma.
- Patients at risk should undergo surveillance for hepatocellular carcinoma.
- Guidelines from professional societies are based large scale epidemiological studies and cost efficacy modeling.
- Populations identified by the guidelines are too broad. More sophisticated assessments of risk are possible.
- Because different risk scores have been developed in different populations care must be taken to apply the appropriate risk score to patients.

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