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REVIEW

Current status of intrahepatic cholangiocarcinoma

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Abstract

Intrahepatic cholangiocarcinoma (ICC) is a rare primary liver cancer with a global increasing trend in recent years. Symptoms tend to be vague and insidious in development, often are diagnosed at an advanced stage when only palliative approaches can be used with a median survival rate of months. Comparing with HCC, ICC tends to spread to lymph nodes early, and is rarely limited to the regional lymph nodes, with a frequent postoperative recurrence. Surgery is the only choice of curative therapy for ICC, but recently no consensus has been established for operation. Thus, more data from multiple centers and more cases are needed. Generally speaking, current adjunctive therapy cannot clearly improve survival. Further research is needed to find more effective radio- and chemotherapeutic regimens.

Key words: Intrahepatic cholangiocarcinoma; Lymph node metastasis; Liver transplantation; Adjunctive therapy

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EPIDEMIOLOGY

Intrahepatic cholangiocarcinoma (ICC) is a rare malignant tumor which arises from the epithelial cells of intrahepatic bile ducts (beyond the second order bile ducts). The incidence of ICC is reported to be only about 10% of primary liver cancers. But, recent studies from several countries have indicated that the incidence of ICC is increasing which cannot be solely explained by reclassification and improved detection[1-10]. The rate of ICC for males is greater than that for females; but ICC is less distinct than hepatocellular carcinoma and usually occurs after the sixth decade of life[1-10]. A recent study reported that in addition to the established risk factors such choledochal cysts, chronic cholangitis, inflammatory bowel disease, primary sclerosing cholangitis (PSC) parasitic infections, drug or toxin exposure, and genetic risks, other conditions such as biliary cirrhosis, cholelithiasis, alcoholic liver disease, nonspecific cirrhosis, are significantly associated with ICC[11]. The incidence of diabetes, thyrotoxicosis, chronic pancreatitis, obesity, chronic nonalcoholic liver disease, HCV/HBV infection, chronic typhoid carrier state and smoking, is increasing, suggesting that these conditions might partly explain the trends of ICC in incidence[12]. However, many tumors arise in the absence of any known predisposition[13-17]. Despite the global increase, regional, racial, ethnic, gender and age variations occur. Moreover, it was reported that the incidence of ICC has decreased in Denmark[18,19]. ICC has the worst prognosis of any tumor arising in the liver; its 5-year survival is poor, and accompanied by a high recurrence rate. The overall 5-year survival rate ranges 13%-42%[20-22]. Chu *et al*[23] showed that the median survival after conservative therapy and hepatic resection is 1.8 mo and 12.2 mo, respectively.

DIAGNOSIS

Recent advances have been made in diagnosis of ICC with MRCP combined MRI, CT, positron-emission tomography scanning (PET) with [F-18] fluorodeoxyglucose (FDG), virtual three-dimensional images and optical coherence tomography (OCT), a high-resolution imaging technique that produces cross-sectional images *in vivo*[24,25], endoscopic retrograde cholangiography (ERCP) with brush cytology and biopsy, endoscopic ultrasound with guided fine-needle aspiration, advanced cytological tests including fluorescent *in situ* hybridization or

digital image analysis (DIA), cholangioscopy (peroral cholangioscopy, percutaneous cholangioscopy, transpapillary cholangioscopy)[26,27]. Sandwich enzyme-linked immunosorbent assay can show a 71% sensitivity and 90% specificity for new tumor markers in serum and bile including genomic and proteomic markers [such as CA199, CEA and mucin5, subtypes A and C (MUC5AC)][28]. On the other hand, most patients present too late to be diagnosed at an advanced stage when only palliative approaches can be used with a median survival of months.

Macroscopic aspect

ICC is defined as a kind of tumor originating from the second branch (segmental branch) or the proximal branch of bile duct[29] and further classified into hilar type and peripheral type. The former arises from the large intrahepatic biliary epithelium (segmental branches) having histological features of a papillary epithelial component or a large tubular component. The latter arises from small biliary epithelium (smaller than segmental branches) with histological features of small-sized glands in a fibrotic background, closely packed, somewhat distorted small ducts, and cordlike structure, but lacking large glands, and Shinichi Aishima, *etc*. It was recently reported that ICC is associated with different predispositions when arising from different levels of the biliary tree and likely to show an aggressive course even in cases of a small tumor arising from the large biliary duct[30,31].

Histological aspect

ICC, arising from cholangiocytes, is a moderately- to well-differentiated tubular adenocarcinoma. Papillary adenocarcinoma, signet-ring carcinoma, squamous cell or muco-epidermoid carcinoma and lymphoepithelioma-like forms are rare histological variants. The most outstanding histological feature is the presence of abundant desmoplastic stroma in ICC compared with HCC, leading to a low diagnostic yield of random biopsies. Desmoplasia may also cause capsular retraction. According to the degree of stromal desmoplasia in the tumor and Kajiyama, Kiyoshi, *etc*, ICC is microscopically categorized into scirrhous-type (SICC) and nonscirrhous-type (NSICC). The frequencies of lymphatic permeation, perineural invasion and the proliferative activity measured by MIB-1 immunostaining, monoclonal antibody specific for Ki-67 [a nuclear antigen expressed throughout the cell cycle (G_1, S-G_2 and M), but absent in quiescent cells (G_0)], were significantly higher in SICC than in NSICC, and serosal invasion, vascular invasion, lymph nodes metastases also tend to be more frequent in SICC and are closely related to the prognosis[32].

Classification

Three types of ICC have been established using the TNM staging system and the classification system established by the Liver Cancer Study Group of Japan: mass-forming type (MF), periductal-infiltration type (PI) and intraductal growth type (IG). MF type forms a definite round-shaped mass with an expansive growth pattern, but without fibrous capsule, and locates in the liver parenchyma. The border between cancerous and non-cancerous portions is distinct, and this type of ICC does not invade the major branch of the portal triad. PI type is defined as a mass extending longitudinally along the bile duct, occasionally involves the surrounding blood vessels and/or hepatic parenchyma, often resulting in dilatation of the peripheral bile duct. IG type proliferates towards the lumen of bile duct papillary or like a tumor thrombus, occasionally involving superficial extension. This type of ICC is usually detected in a thick bile duct[29].

Table 1 Staging system for ICC proposed by Liver Cancer Study Group of Japan

T1: Meet requirements (single nodule, tumor 2 cm or less and no portal vein, hepatic vein and serous membrane invasion)			
T2: Meet two of the three requirements			
T3: Meet one of the three requirements			
T4: Meet none of the three requirements			
N1: No metastasis to lymph node			
N2: Metastasis to any lymph nodes			
M0: No distant metastasis			
M1: Positive distant metastasis			
Stage Ⅰ	T1	N0	M0
Stage Ⅱ	T2	N0	M0
Stage Ⅲ	T3	N0	M0
Stage ⅣA	T4	N0	M0
	Or any T	N1	M0
Stage ⅣB	Any T	Any N	M1

Staging system

ICC is a rare type of primary liver cancer, accounting only for 5%-10% of all liver cancers, and has a low resectability rate. So the International Union against Cancer (UICC) defined the TNM staging system solely from clinical experience in treating HCC[33]. Based on the distinct difference in the mechanism and biologic behavior between HCC and ICC, the Liver Cancer Study Group of Japan has proposed a new TNM staging system for the MF type of ICC (Table 1)[34]. Serosal invasion is not a T-factor component in the UICC tumor staging system. Uenishi *et al*[35] retrospectively analyzed sixty-three patients who underwent hepatic resection for mass-forming intrahepatic cholangiocarcinoma between January 1983 and December 2003, and found that that serosal invasion has no impact on survival of patients after hepatic resection for MF type of ICC. Another staging system used for MF type of ICC, defined a solitary tumor without vascular invasion as stage Ⅰ, a solitary tumor with vascular invasion as stage Ⅱ, multiple tumor with or without vascular invasion as stage ⅢA, tumor with regional lymph node metastasis as stage ⅢB, tumor with distant metastases as stage Ⅳ. In this system, tumor size is excluded from T factor. It is likely that the influence of tumor size on its prognosis cannot be evaluated because the number of small tumors is too small[36].

Table 2 Lymph node groups by tumor location

	N1	N2	N3
Right lobe	Hepatoduodenal ligament	Along left gastric artery Along common hepatic artery Along celiac artery Posterior surface of pancreas head	Distant
Left lobe	Right cardiac region	Along left gastric artery	
	Lesser curvature of stomach	Along common hepatic artery	
		Along celiac artery	Distant
	Hepatoduodenal ligament	Posterior surface of pancreas head	

N3 distant: Abdominal aorta, root of the mesentery, inferior vena cava, *etc.*

Spreading mode

The spreading modes of ICC, such as sinusoidal invasion, spreading along duct walls and periductal tissue, growth replacing the biliary epithelium or intraductal growth, spreading along Glisson's sheath (lymphatic involvement, perineural or intraneural invasion, permeation of the portal connective tissue and vascular involvement) have been reported[37-40]. Nakajima *et al*[37] reported that sinusoidal invasion and portal vein invasion are the most frequent mode of intrahepatic spread. Different macroscopic types of ICC have different modes of spread. The MF type of ICC tends to invade the liver *via* the portal vein system and Glisson's sheath when the tumor increases in size with a frequent remnant hepatic recurrence. The PI type of ICC has a tendency to infiltrate making it difficult to get clear margins during hepatectomy, and to spread along Glisson's sheath *via* lymphatic vessels, thus invading connective tissue and major vessels at the hilum and hepatoduodenal ligament. The IG type of ICC has an extremely favorable prognosis after surgical resection compared with the other two types. Moreover, this type of ICC has a lower rate of lymphatic or intrahepatic metastasis and recurrence after curative surgical resection[37-39]. Yamamoto *et al*[40] suggested that anatomic and extensive hepatectomy is a rational procedure for MF type of ICC, and hepatectomy with extrahepatic duct excision and hilar lymph node resection is a rational procedure for IP and MF types of ICC with biliary invasion. The Liver Cancer Study Group of Japan has proposed a criterion for the invasion degrees of ICC: (1) no tumor invasion of the portal vein, hepatic vein, or bile duct; (2) tumor invasion distal to the second branch of the portal vein or bile duct and/or invasion of a branch of the hepatic vein; (3) tumor invasion of the second branch of the portal vein or the bile duct, the major hepatic veins and/or the short hepatic veins; (4) tumor invasion of the first branch of the portal vein or of the bile duct and tumor invasion of the inferior vena cava[29].

Lymph node metastasis

The most outstanding pattern of ICC compared with HCC is early lymphatic spread. The findings in the majority recent literature indicate that lymph node status is an important prognostic factor for patients undergoing hepatic resection[41-47]. Yet nodal status does not affect survival after aggressive surgical treatment in patients with ICC[48], and some long-term survivors with positive lymph nodes have also been reported[49-51]. It was reported that the rate of metastasis for ICC to hilar lymph nodes is about 50%[41,42,52]. Nakagawa *et al*[43] reported that the positive rate of lymph nodes in patients with lymph node dissection is 47%, 33%, 17%, 13%, 10%, 3%, respectively. Regarding the pattern of lymph node spread, the Liver Cancer Study Group of Japan has proposed a classification of regional lymph nodes in liver cancer (Table 2) and three major routes of lymphatic spread of ICC: hepatoduodenal route, cardiac route (through the lesser omentum to the cardiac portion of the stomach and the gastric lesser curvature), and diaphragmatic route[48]. Hepatoduodenal ligament is the most common site of nodal metastasis in ICC patients irrespective of the tumor location. Almost all patients are involved in positive lymph nodes of the hepatoduodenal ligament or along the common hepatic artery, lymph nodes are also found in about half of the patients involving the left lobe of liver[43,44,53-56]. Nozaki *et al*[57] reported that extensive lymph node metastasis was observed in most patients, only 3 (20%) of 15 patients with lymph node metastasis had regional lymph node metastasis. Shimada *et al*[47] has reported the similar observations, suggesting that lymph node metastasis of ICC is rarely limited to the regional lymph nodes.

Surgical treatment

Surgery is the only choice of curative therapy for ICC. However, only a few patients are suitable for surgery. Good results depend on comprehensive preoperative evaluation, patient selection and discreet operation.

EVALUATION

Assessment of resectability

Tumors that are medically fit for hepatic resection must be completely resected with negative histological margins, no evidence of metastases, disseminated disease, and extensive lymphadenopathy. The following factors must be considered. (1) Biliary tract invasion: bilateral involvement of hepatic ducts to the level of the secondary biliary radicals, atrophy of one liver lobe with contralateral secondary biliary radical involvement is a contraindication to resection. (2) Lymph node metastasis: Inoue *et al*[46] reported that the outcome of 16 patients with lymph node metastasis, accounting for 31.4% of all patients, was quite poor. Their median survival time was 14.1 mo and none of them survived 5 years except for one patient with the IG type of ICC, suggesting that the presence of lymph node metastasis in the MF type of ICC is a sign of non-curability. However, a longer survival time (over 5 years) in ICC patients with lymph node metastasis has been described[54,58]. (3) Vessel invasion: Based on some

centers' support for resection of ICC with vascular reconstruction *en bloc*, involvement of the main hepatic artery or portal vein is the relative contraindication to resection[40,59]. (4) Intrahepatic metastasis: Intrahepatic metastasis in the remaining liver is considered unfit for hepatic resection, and disseminated disease should not undergo hepatectomy. (5) Hepatic functional reserve: It is important to accurately estimate liver reserve function before hepatectomy to avoid postoperative liver failure. Methods to evaluate liver function, including routine examinations of aminotransferase, bilirubin, albumin, prothrombin time, Child-Pugh classification, and hepatic imaging providing volumetric information, indocyanine green (ICG) test. The indocyanine green retention rate at 15 min [ICG (R15)] has recently been considered a sensitive marker for liver reserve function. Nevertheless, it remains imperfect. Moreover, how to evaluate the maximal hepatic resection volume according to liver reserve function remains controversial. Trimethadione (TMO) tolerance test can show the Child-Pugh score in evaluation of cirrhosis. Hepatic 99mTc-diethylenetriamine pentaacetic acid-galactosyl-human serum albumin (99mTc-GSA) clearance test can show postoperative hepatic function and liver stiffness assessed quantitatively with a tactile sensor. The combination of Child-Pugh score, presence of ascites, serum bilirubin levels, indocyanine green retention (ICG R15) value, and remnant liver CT volumetry as well as age, diabetes, cardiopulmonary function, and general performance need to be taken into consideration preoperatively. Other factors affecting respectability include the size and extent of the tumor[60].

Evaluation modalities

Ultrasound can diagnose biliary dilatation and suspected cholangiocarcinoma by localizing the site of obstruction and excluding gallstones. Color Doppler can detect tumor-induced compression/thrombosis of the portal vein or hepatic artery. However, ultrasound is non-specific, often misses small perihilar, extrahepatic, and periampullary tumors, and is not good at defining the extent of tumor.

CT can detect biliary dilatation, intrahepatic cholangiocarcinoma greater than 1 cm in diameter, small liver metastases, lymphadenopathy, biliary obstruction, suspected perihilar tumor or tumor involving the portal venous/arterial system. However, CT can only establish the resectability in 60% of cases[61], and cannot usually define the extent of cholangiocar-cinoma because of the sclerosis and fibrosis of surrounding tissue. In addition, CT cannot accurately differentiate ICC from PSC[62].

MRI along with MRCP can detect ICC and assess preoperative ICC patients by investigating all involved structures, such as the bile ducts, vessels, and hepatic parenchyma, which are important factors for prognosis. Some new tissue-specific MR contrast agents with hepatobiliary and reticuloendothelial cell affinity, such as gadobenate, and ultra-small iron-oxide (USPIO) particles contrast agents with lymph node specificity can be used to detect and assess tumor invasion[63-65]. MRCP may have some potential advantages over CT in identifying intrahepatic mass lesions, and can provide a three-dimensional computerized reconstruction of the biliary tree allowing assessment of bile ducts both above and below a stricture. The non-invasively acquired cholangiographic images obtained by MRCP are comparable with invasive cholangiographies (ERCP and PTC), high positive and negative predictive values for detecting the level and features of biliary obstructions[61,66-68]. Owing to its intrinsically high tissue contrast and multiplanar capability, MRCP is superior to ERCP for defining the anatomy of tumor and assessing its respectability. However, the tendency of MRCP to understage the extent of cholangiocarcinoma has been reported[69]. MRI is not superior to CT in identifying lymph node metastasis.

PET scanning with the focal accumulation of nucleotide tracer 18-fluorodeoxyglucose (FDG) is an emerging staging technique for many cancers. This technique can detect nodular cholangiocarcinoma as small as 1 cm in diameter, but is less sensitive to infiltrating tumors[70]. FDG-PET has a higher specificity for lymphadenopathy than CT, although there is no difference in sensitivity between them[71,72]. In a retrospective study, 21 patients with ICC underwent CT, MRI and PET for lymph node metastasis, which were concordant in 16 patients and discordant in 5 patients (positive FDG-PET in three, positive CT and MRI in two). Moreover, PET may has some superiority over CT and MRI in detecting distant metastases[71].

The above non-invasive techniques may be complementary and sometimes are all necessary as part of surgical assessment depending on the clinical situation. Furthermore, invasive modalities are also needed sometimes to assess the resectability and predict the prognosis. In most cases, ERCP/PTC is replaced by MRCP, but ERCP with OCT can provide more information for surgical plan[21]. Another advantage of these techniques over MRCP is that washing, brushing and intraductal biopsies can be obtained for cytopathologic analysis, adding some new cytological tests, such as DIA, fluorescent *in situ* hybridization, so that the sensitivity increases, especially to patients with PSC or apparent biliary obstruction[73,74]. But, negative cytology from brushings does not exclude malignancy. Preoperative (percutaneous choledochoscope) and intraoperative vholedochoscope with biopsy can help to make an early diagnosis. Blood vessel involvement is an important prognosis factor. As a means of evaluating vascular invasion, hypovascular or hypervascular lesion, concomitant vascular resection and reconstruction, angiography should be reserved in some cases. Percutaneous transhepatic portography (PTP) and retrograde selective hepatic venography should be selected. Virtual 3D is a new kind of technique for constructing three-dimensional virtual images of the portal vein, hepatic artery, and bile ducts. On account of it, accurate knowledge of partial anatomy can be gotten. Preoperative planning for complex biliary

surgery especially lesions invading the hepatic hilum may be improved[75]. ICC in patients with lymphadenopathy is often missed on preoperative imaging. Endoscopic ultrasound can be useful in identifying local lymph node enlargement and allows a good view of distal extrahepatic biliary tree and vasculature[26]. The sensitivity of fine needle aspiration of the tumor mass or its surrounding lymph nodes and endoscopic ultrasound is greater than ERCP with brushings in detecting malignancy[26,27,76]. Endoscopic ultrasound-guided regional lymph node sampling can be performed in early disease to assess the respectability or eligibility for transplantation[77]. However, endoscopic aspiration of hilar masses is not recommended because of the potential of tumor seeding. Laparoscopy is gradually replaced by ultrasonography and other imaging studies, but has identified a third case of peritoneal and superficial liver metastases[51,78,79].

OPERATION

Hepatectomy

It was recently reported that aggressive surgical strategies in the treatment of ICC can significantly increase the survival of ICC patients[14,80,81]. Yamamoto *et al*[82] and Ohashi *et al*[83] suggested that anatomic and extensive hepatectomy is the rational procedure for mass-forming ICC, while hepatectomy with extrahepatic duct excision, and hilar lymph nodal resection is the rational procedure for infiltrating ICC. The 3- and 5-year survival rates of ICC patients after curative resection (n = 56, 53% and 50%, respectively) were significantly higher than those of patients after non-curative resection (n = 67, 7% and 2% respectively, $P < 0.0001$). In 54 patients followed-up after curative resection, the rate of recurrence after surgery was 46%. The rate of recurrence was significantly higher in patients with various mass-forming ICC tumors ($P = 0.039$) than in those with other types of tumors or tumors > 3 cm in diameter than in those with tumors > 3 cm or < less 3 cm ($P = 0.006$)[84]. Kim *et al*[85] reported that the median survival time after non-curative resection is 3.0 mo. Chu *et al*[22] showed the the median survival time is 1.8 mo and 2.9 mo, respectively, after conservative management and palliative operations. Only a curative resection can prolong survival. ICC has no characteristic symptoms at its early stage and is often at its advanced stage when it is diagnosed. Consequently, the resectability rate is usually low, extended hepatectomy possibly in combination with resection of other structures (e.g. extrahepatic bile duct, portal vein and inferior vena cava) is generally required. Wu *et al*[86] described a case of initially unresectable, locally advanced intrahepatic cholangiocarcinoma that showed a remarkable regression after transcatheter arterial chemoembolization with degradable starch microspheres, allowing for subsequent successful curative resection. In a retrospectively study, Yamamoto *et al*[40] allocated 83 patients who had undergone resection to a standard surgery group (n = 56), in which the patients underwent hepatectomy alone or hepatectomy with bile duct resection, and an extended surgery group (n = 27), in which the patients underwent the standard operation combined with vessel resection and/or pancreatectomy. The 5-year survival rate was significantly higher in the standard surgery group (30%) than in the extended surgery group (10%, $P = 0.0061$). So they concluded that extended surgery does not improve the curative resection rate or the surgical outcome of ICC[40].

Lymphadenectomy

ICC frequently demonstrates lymphatic spread. Lymph node metastasis is a significant prognostic factor for IHCC. Whether lymph nodes are dissected, and what is the extent of dissection remain the two important questions to be solved. No consensus has been reached concerning the indications and value of lymph node dissection for ICC. Hepatectomy with extensive lymph node dissection is the standard operation for intrahepatic cholangiocarcinoma in Japan. However, lymph node dissection may not always be effective in reducing tumor recurrence. Chu *et al*[22] and Shimada *et al*[47] that lymph node dissection alone is not likely to improve the prognosis without further control of liver metastases. However, there are reported cases of long-term survival after extended surgical resection of intrahepatic cholangiocarcinoma with extensive lymph node metastasis[56,87].

Transplantation

Pichlmayr *et al*[88] reported that the median survival time of 18 patients with IHCC after liver transplantation was 5.0 mo, and the 1-year survival rate was 13.9%. Casavilla *et al*[89] performed liver transplantation for patients with unresectable tumor (n = 12) or advanced cirrhosis (n = 8) and found that the mortality within 30 d was 7.4%. Overall, the tumor-free survival rates were 64% and 57%, respectively at 1 year, 34% and 34%, respectively at 3 years, and 26% and 27%, respectively at 5 years after operation. About 59.3% patients experienced tumor recurrence. When patients with positive margins, multiple tumors, and lymph node involvement were excluded, the patient survival rate was 74%, 64% and 62%, at 1, 3, and 5 years, respectively after operation. A Mayo Clinic group[90] used preoperative irradiation and chemotherapy for patients with unresectable cholangiocarcinoma above the cystic duct without intrahepatic or extrahepatic metastases. Patients initially received external-beam irradiation plus bolus fluorouracil (5-FU), followed by brachytherapy with iridium and concomitant protracted venous infusion of 5-FU. 5-FU was then administered continuously through an ambulatory infusion pump until OLT. After irradiation, patients underwent an exploratory laparotomy to exclude metastatic disease. The patients have a median follow-up time of 44 mo (range 17-83 mo, 7 of 9 patients > 36 mo). Only 1 patient developed tumor relapse. The group concluded that OLT in combination with preoperative irradiation and chemotherapy is associated with prolonged disease-free, and overall survival in highly selected patients with early-stage cholangiocarcinoma[90]. A comparison of recent series is shown in Table 3.

Table 3 Comparison of recent series

Authors	Yr	Countries	Procedure (patients)	Prognosis (%)				Tumor recurrence (%)
				Median (mo)	1 yr	3 yr	5 yr	
Pichlmayr *et al*[88]	1995	Germany	Hepatic resection (32)	12.8				
			Liver transplantation (18)	5.0				
Casavilla *et al*[89]	1997	America	Hepatic resection (34)		60	37	31	56
			Liver transplantation (20)		70	29	18	55
Chu *et al*[22]	1997	Hong Kong, China	Conservative management (15)	1.8				
			Palliative operation (23)	2.9				
			Hepatic resection (39)	12.2	57.3	23.9	15.9	
Madariaga *et al*[98]	1998	Japan	Hepatic resection (34)	19	67	40	35	
Meyer *et al*[99]	2000	America	Liver transplantation (207)		72	48 (2 yr)	23	51
Kawarada *et al*[100]	2001	Japan	hepatic resection (37)	31.5	54.1	34	23.9	
Fu *et al*[101]	2004	China	Palliative or curative operation (79)	11.9	49.4	17.3	9.6	
Robles *et al*[102]	2004	Spain	Liver transplantation (23)		77	65	42	35
Lang *et al*[80]	2005	Germany	R0-resection (complete tumor removal) (16)	46	94	82		37.5
			R1-resection (microscopic tumor at the cutting margin) (11)	5	22	0		
Ghali *et al*[103]	2005	Canada	Liver transplantation (10)		90	80	20	80
Urahashi *et al*[104]	2007	Japan	HPD (hepatectomy with pancreatoduodenectomy) (12)		42	33	33	75
De Oliveira *et al*[105]	2007	America	Hepatic resection (R0-resection)	80			63	
			Hepatic resection (overall)	28			40	
Becker *et al*[106]	2008	America	Liver transplantation (280)		74		38	

Adjunctive therapy

Recurrence of ICC is due to failure in surgery, warranting consideration of adjuvant treatments. Neither adjuvant nor neoadjuvant therapy, however, has been shown to improve survival. Roayaie *et al*[91] performed chemo-radiation therapy for postoperative patients with positive resection margins or nodal invasion and did not find any difference in the actuarial disease-free survival between the patients with or without adjuvant chemo-radiation. Sanz-Altamira *et al*[92] used 5-fluorouracil, leucovorin, and carboplatin in patients with unresectable biliary tree carcinoma and found that 21% of the patients had significant responses. Ando *et al*[93] treated an IHCC patient with postoperative recurrence of multiple liver metastases, and a complete response was noted 1 year after the patient underwent 4 courses of hepatic arterial infusion therapy *via* a subcutaneously implanted injection port and received cisplatin. The research of Furuse *et al*[94] showed that, of the twenty-four patients not amenable to surgery, three had a response rate of 12.5%, thirteen had a stable disease, seven had a progressive disease, and one was not evaluated. Lee *et al*[95] treated 24 patients immunohistochemically proven cholangiocarcinoma patients with gemcitabine and cisplatin. Of these 24 patients, 5 had a partial response, 12 had a stable disease, and 7 had a progressive disease during treatment. These patients had a median survival time of 9.30 mo. In a study by Feisthammel *et al*[96], the response rate was 10% for patients with inoperable intrahepatic cholangiocarcinoma (n = 17) or gallbladder cancer (n = 13) after treatment with irinotecan followed by folinic acid and 5-FU, and an additional 10% of patients had a stable disease. The median overall survival time of was 166 d and 273 d, respectively and median progression-free survival time of intrahepatic cholangiocarcinoma and gallbladder cancer patients was 166-273 d, and 84-159 d, respectively. These results suggest that the present therapy is a useful option for advanced IHCC. Rai *et al*[97] reported a 59-year old lady who underwent orthotopic liver transplantation (OLT) for intrahepatic cholangiocarcinoma recurrence 13 mo after transplantation in spite of adjuvant chemotherapy. She survived 18 mo after her recurrent tumor was treated with radiofrequency ablation, suggesting that radiofrequency ablation can be used in treatment of recurrent tumor after liver transplantation.

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