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Role of surgery in the treatment of intrahepatic cholangiocarcinoma

A. RUZZENENTE, S. CONCI, A. VALDEGAMBERI, C. PEDRAZZANI, A. GUGLIELMI

Department of Surgery, Division of General and Hepato-biliary Surgery, University of Verona Medical School, Verona, Italy

Abstract. – Intrahepatic Cholangiocarcinoma (ICC) is the second most common primary liver cancer, accounting for 10% to 15% of primary hepatic malignancy, and its incidence is increasing in Western Countries.

Surgery with curative intent is the only treatment that offers a chance of long-term survival, with a reported 5-year overall survival rate ranging from 17% to 48%. In the most of recent series postoperative mortality is lower than 5% and morbidity varied from 6% to 66%. The macroscopic classification of ICC, proposed by Liver Cancer Study Group of Japan (LCSGJ), reflects different biologic behaviours, pattern of tumor growth and clinicopathological findings. The most important prognostic factors after resection are positive resection margins, lymph-node metastases, tumor size, presence of macrovascular invasion and intrahepatic metastases. Unfortunately, recurrence is still frequent and it is the leading cause of death. The treatment of the recurrence varied according to the location and extension of the disease.

Recently, expression of several genes found to be related with the carcinogenesis of ICC. These molecular findings are helpful to differentiate the biological behaviour and will provide evidence for the development of new target therapies.

Key Words:
Intrahepatic cholangiocarcinoma, Cholangiocarcinoma, Liver resection, Liver Surgery, Primary liver cancer.

Introduction

Cholangiocarcinoma (CCA) is a heterogeneous group of malignancies arising from the epithelial cells of biliary tree[1]. CCA can be classified in three different forms: Intrahepatic Cholangiocarcinoma (ICC), arising from intrahepatic bile ducts beyond the second order branches, Perihilar Cholangiocarcinoma (PCC), arising or involving first order biliary confluence and common bile duct, and Distal Cholangiocarcinoma (DCC), arising from the bile duct distal to the cystic duct origin[2-4].

Intrahepatic Cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma (HCC), accounting for 10% to 15% of all primary hepatic malignancy[5,6]. Nowadays, curative surgery still represents the most effective treatment for ICC with a reported 5-years survival rate of 20-40%[7-10].

This review summarizes the current principles and the results of the surgical treatment in patients with ICC.

Epidemiology and Risk Factors

ICC is a rare malignancy, accounting for 3% of gastrointestinal cancers and 10% of biliary tract cancers[11]. From 1970 to 2000 the age-adjusted worldwide incidence of ICC has tripled rising from 0.32 per 100,000 to 0.85 per 100,000[12]. The incidence of ICC varies according to the geographic distribution, ranging from 0.2 per 100,000 in Australia to 96 per 100,000 in Thailand[12,13]. In Italy the incidence of ICC has increased from 0.5 per 100,000 to 1.2 per 100,000 over a 30-year period, corresponding to an average 3% yearly increase[14].

ICC is uncommon before the fifth decade and the higher incidence is observed between the sixth and seventh decade, with a male:female ratio of 2:3[12].

The disorders of the biliary system when related to chronic biliary inflammation, cholestasis and chronic liver diseases are well-established risk factors for ICC. In particular, primary sclerosing cholangitits (PSC), congenital abnormalities of the bile ducts (fibrocystic liver disease, choledochal cysts, and Caroli's disease), intrahepatic lithiasis, parasite infestation (*Clonorchis sinensis* and *Opistorchis viverrini*), and exposures to some chemical carcinogen agent (thorium dioxide, dioxin, asbestos, and radon) are associated with an increased risk of developing ICC[15,16].

Corresponding Author: Andrea Ruzzenente, Ph.D; e-mail: ruzzenentea@gmail.com

More recently, liver diseases related with chronic viral hepatitis and metabolic syndrome have been recognized as significant risk factors for ICC in western countries[17,18]. An American multi-institutional study[18] based on the Surveillance, Epidemiology and End Results (SEER) Medicare database comparing 743 patients with ICC and 195,953 controls showed that chronic viral hepatitis infection (HBV and/or HCV) is significantly related with the occurrence of ICC. Similarly, an Italian case-control study reported in ICC patients a prevalence of HCV and HBV infection of 23.0% and 12.5% compared to 6.0% and 5.5% in the control group without ICC[19]. Welzel et al[18] showed that also metabolic syndrome is significantly more common in ICC patients compared to controls (29.7% versus 17.1%, $p < 0.01$).

Despite the well-established relationship between the above-mentioned risk factors and ICC, they can be recognized in only a minority of patients. In literature, Western and Eastern studies reported the presence of PSC in only 1% of patients with ICC, intrahepatic lithiasis in 3%, congenital abnormalities of bile ducts in 1%, and 8% had HCV or HBV[20].

Macroscopic Classification

The Liver Cancer Study Group of Japan (LCSGJ) proposed a macroscopic classification of ICC according to the gross appearance and the pattern of growth. According to this classification ICCs can be divided ICC into three different subtypes: mass forming (MF) type that is characterized by discrete firm mass into the liver parenchyma; periductal infiltrating (PI) type that is characterized by infiltrative growth of the tumor along the intrahepatic bile ducts; intraductal growth (IG) type that is characterized by tumor growth inside of the bile duct through the epithelial surface with low frequency of invasion of the bile duct wall[21]. The reported prevalence of each subtype of ICC in surgical series is 60-70% for MF type, 7-15% for PI type and 4-15% for IG type[22-24]. In up to 20% of cases mixed forms with both MF and PI type can be identified, more rarely the mixed form MF plus IG type. Furthermore, the pathogenesis of ICC might be different among the macroscopic gross type[25]. In particular, MF type shows a higher association with viral chronic liver diseases compared to other ICC type[26]. In contrast PSC, intrahepatic lithiasis and parasite infection are more frequently related with PI type[27,28].

The macroscopic gross type reflects different biologic behaviours and pattern of tumor growth[29]. In several surgical series lymph node metastases are significantly related to the gross type: the PI type and the MF+PI type showed an higher incidence of lymph node metastases compare to to MF or IG type, with a frequency of 60%, 16-50% and less of 5%, respectively[9,11,23,30,31].

Perineural invasion is also related to the gross type of ICC, as described by Hirohashi et al[32], who reported a significantly higher rate of perineural infiltration in MF+PI tumors (80%) compared to MF group (33%).

The clinical presentation can be different among the three types of ICC: patients with MF type usually have no symptoms with large liver mass at the time of presentation, otherwise obstructive jaundice can occur in patients with PI type due to the tumor invasion of hepatic hilum, cholangitis without jaundice is more frequent in IG type[22].

Staging Systems

The staging systems that are more frequently applied in ICC are the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification (7th edition)[33] and the Liver Cancer Study Group of Japan (LCSGJ) TNM classification[22].

UICC/AJCC TNM Classification (7th Edition)

The UICC/AJCC TNM classification (7th edition) was published in 2010, it revised the previous 6th edition in which ICC and HCC were described within the same staging system[33]. The differences in biological behavior and prognosis of ICC and HCC were described in several clinical studies and for these reasons the UICC/AJCC TNM 7th edition proposed a specific classification for ICC, including as major prognostic factors the vascular invasion, the tumor number, the invasion of adjacent strictures and the periductal infiltrating macroscopic type of growth described in 1997 by LCSGJ. Regional lymph-node involvement was classified as N1. The presence of metastases in celiac, periaortic and caval lymph-nodes are considered as distant metastasis (M1). The prognostic value of 7th edition of UICC/AJCC TNM classification was validated by a recent multicentric analysis of 434 patients submitted to curative resection for ICC[34].

LCSGJ TNM Classifications

The 1st edition of this classification was published in 1997 and it was reviewed in 2003[22]. According to the different macroscopic types the LCSGJ classification was created only for MF forms. A LCSGJ classification cannot be applied to periductal infiltrating (PI) and intraductal growth type (IG). The classification includes the local extent of disease (T), nodal diffusion (N) and distant metastases (M). The evaluation of the extent of neoplasm (T) is assessed by three different parameters: lesion size, number of nodes (single or multifocal), presence of vascular involvement (portal vein or hepatic vein) and/or serosal involvement. Unlike the first edition, in which left and right lobe ICC had two different lymph-node classifications, this English edition subdivides N-stage only in function of the presence or absence of lymph nodes involvement (N1 and N0). Finally, the evaluation of M-stage is based on the presence of metastases to other organs or non-regional lymph nodes. This staging system has been validated in a sample of 136 patient with a good prognostic value: 5-year survival for stage I was 100%, 70% for stage II, 40% for stage III and 10% for stage IV[22]. Other data in literature confirmed the performances of this staging system[35].

Surgical Results

Surgery is the only treatment that offers a chance of long-term survival in patients with ICC[7-10]. Unfortunately, the resectability rate is still low due to the presence of intrahepatic metastases, peritoneal carcinomatosis or extrahepatic metastases. In recent surgical series the resection rate varies from 30% to 60%[36,37]. The goal of surgical resection is to achieve the complete removal of the tumor with negative histological margins (R0 resection) and adequate remnant liver volume[38] (Figure 1).

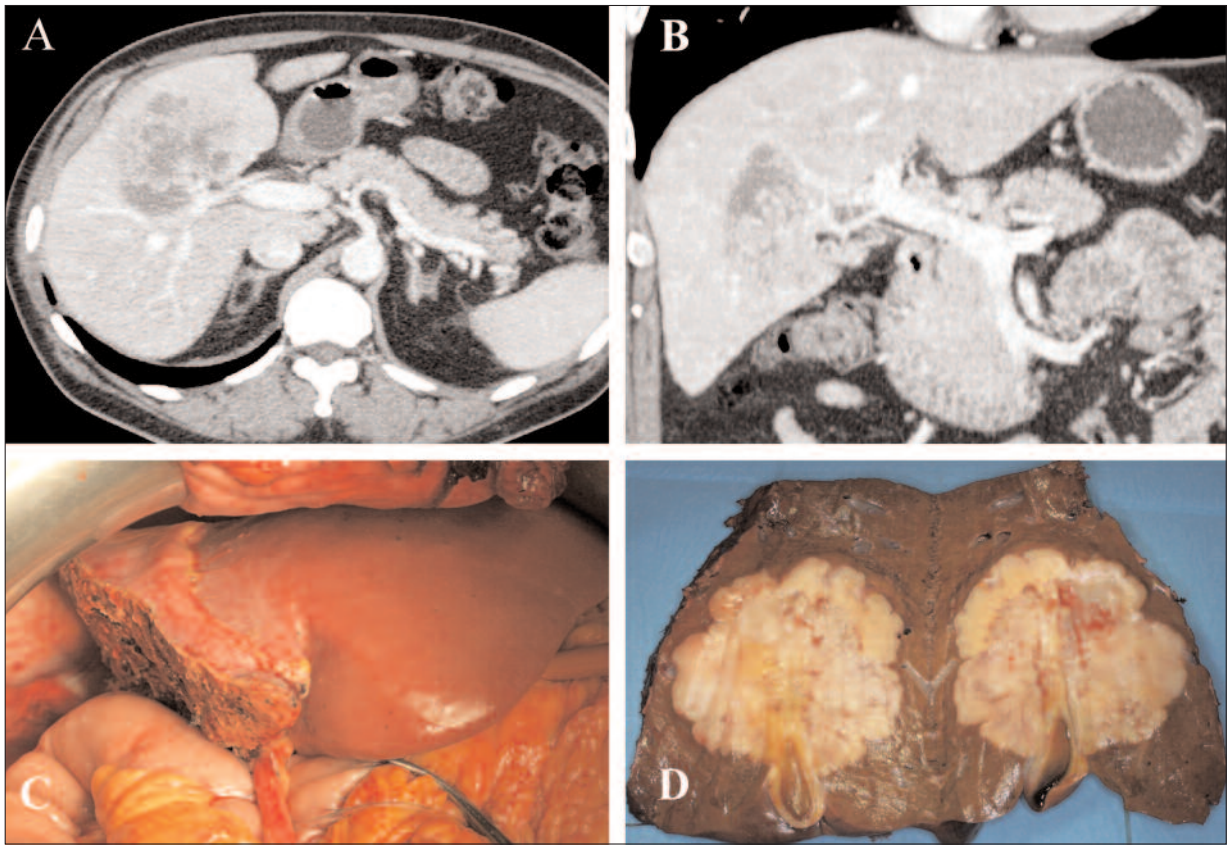

Figure 1. Intrahepatic cholangiocarcinoma of the right hepatic lobe. ***A, B,*** CT imaging showing 12 cm right liver mass with invasion of the right branch of the portal vein. ***C,*** Intraoperative image after right trisectionectomy. ***D,*** Surgical specimen showing mass-forming type intrahepatic cholangiocarcinoma.

Ribero et al[10], in a multi-institutional series of 434 resected patients, showed an R0 resection rate of 84.6% and major or extended hepatectomies were required in more than 70% of cases. Also in other Eastern and Western surgical series the rate of major or extended hepatectomies varied from 65% to 86%[9,31,39,40] with an R0 resection in more than 80% of cases[9,10,31,41-45].

Table I shows the results of surgery in patients with ICC in the main surgical series published after 2000.

Postoperative mortality was lower than 5% in the most of the series and morbidity varied from 6% to 66% (Table I). Guglielmi et al[45], in a recent study including 70 MF type ICC patients, reported a 0% of mortality and 23% of morbidity, with 60% of major hepatectomies and 90% of R0 resections.

The long-term survival of ICC is still low. The majority of the recent surgical series reported a 5-year overall survival rate after liver resection close to 30% (ranging from 17% to 48%) (Table I). Tumor recurrence is the leading cause of death after liver resection, and it occur in over 50% of the patients[37,46]. The most frequent site of recurrence is the remnant liver. The treatment of the recurrence includes surgical resection, chemotherapy or local ablative therapies. The surgical resection is feasible in less than 20% of the patients and when applied in an aggressive multimodal approach can offer good long term survival after intrahepatic recurrence[47,48].

Prognostic Factors

Several prognostic factors have been identified in literature. The most important factors are tumor size, tumor number, radical resection, lymph-node involvement, vascular invasion and direct invasion of other organs.

The size of the tumor is an important prognostic factor: the 5-year survival in patients with a tumor smaller than 5 cm is 53%, compared to 28% in patients with tumors larger than 5 cm[42]. Furthermore, a tumor size grater than 5 cm is re-

Table I. Surgical results in patients with intrahepatic cholangiocarcinoma,

Author	Year	No. of patients	R0 resection	Post-operative mortality	Post-operative morbidity	Disease free survival rate (3y/5y)	Median overall survival (months)	Overall survival rate (3y/5y)
Okabayashi T[49]	2001	60	45%	5%	na	na/na	19.6	35%/29%
Ohtsuka M[55]	2002	62	77%	8%	na	na/na	25.5	38%/23%
Lang H[36]	2005	50	32%	6%	36%	na/na	46.0 (R0)	55%/na
Nakagawa T[54]	2005	53	62%	6%	na	na/na	21.5	38%/26%
Shimada K[70]	2007	94	69%	1%	na	na/na	24.0	35%/31%
DeOlivera ML[11]	2007	44	45%	4%	66%	na/na	28.0	na/40%
Endo I[37]	2008	110	64%	1%	38%	na/na	36.0	na/na
Portolani N[71]	2008	67	76%	6%	41%	59%/51%	37.8	59%/48%
Paik KY[41]	2008	97	93%	2%	na	6%/2%	52.9	52%/31%
Nathan H[72]	2009	598	na	na	na	na	21.0	31%/18%
Shen WF[73]	2009	429	74%	1%	6%	na	12.4	22%/17%
Zhou XD[74]	2009	272	54%	3%	na	19%/13%	na	30%/26%
Choi SB[42]	2009	64	86%	2%	22%	35%/na	39.0	53%/39%
Guglielmi A[9]	2009	52	83%	4%	32%	na/na	40.0	50%/20%
Yedibela S[75]	2009	45	80%	4%	28%	na/30%	37.0	na/35%
Tamandl D[46]	2009	69	80%	na	na	21%/na	25.5	35%/na
Jonas S[8]	2009	195	71%	7%	41%	na/na	na	na/22%
Farges O[76]	2010	242	74%	na	na	na/na	36.0	50%/32%
Uchiyama K[31]	2011	341	85%	3%	34%	29%/25%	20.0	36%/29%
de Jong MC[43]	2011	449	81%	na	na	na/na	27.0	44%/31%
Li YY[40]	2011	113	72%	2%	35%	na/na	21.0	27%/17%
Farges O[39]	2011	212	76%	na	na	na/na	28.0	43%/28%
Ribero D[10]	2012	434	85%	5%	35%	na/na	33.0	47%/32%
Hyder O[44]	2013	301	81%	na	na	39%/32%	37.8	na/na
Wang Y[77]	2013	367	na	na	na	37%/33%	21.0	41%/35%
Guglielmi A[45]	2013	70	90%	0%	23%	na/na	36.0	52%/31%

lated with a shorter disease-free survival, with a hazard ratio of 2.3 (1.2-4.5)[37]. A statistical relationship between tumor size and lymph-node involvement have been identified: the frequency of lymph-node metastases is 24.4% for tumors smaller than 3 cm, 32.8% for tumors between 3-5 cm and 51.6% for patients with tumors larger than 10 cm. The presence of multiple tumors, vascular invasion and low differentiation grade are also related with the presence of lymph node metastases[10]. The presence of satellite nodules, reported in 20-30% of patients, is related with a 5-year survival of 14-20%[10,42]. Moreover, the presence of portal vein invasion is an important negative prognostic factor for ICC: with a 3-year survival of 46% and 0% for patients without or with vascular invasion, respectively[49].

Several biomarkers were investigated for possible prognostic value in patients with CCA[50,51]. Recently, serum level of MUC5AC showed a relationship with tumor burden and with long-term outcome, moreover combined assessment of serum and bile level of MUC5AC may offer a new interesting diagnostic tool[52,53].

Lymph Node Involvement

In literature, the presence of lymph-node metastases ranges from 7% to 73%. It is a major prognostic factor: the 5-year survival with positive lymph-nodes ranges between 0% and 30%[9,45,54]. The frequency of lymph-node involvement is related to the macroscopic type of growth: is lower than 20% in IG type, while in the mixed type MF + PI reaches 80%[55].

The prognostic value of lymph-nodes involvement has been demonstrated in literature and it overcomes the relative prognostic value of others factors such as the tumor number and vascular invasion[9,31,43,45]. The prognostic value of lymph node dissection and of the total number of lymph node retrieved is still debated in literature[42,43]. A recent paper[45] demonstrated that, in patients without lymph-node metastases, the number of total lymph-nodes retrieved was associated with longer survival in ICC patients. In patients without lymph-node metastases, patients with one to three retrieved lymph-nodes survived for 38 months, while those with more than three lymph-nodes retrieved survived for 69 months (p = 0.05). In patients with lymph-node metastases, the total number of positive lymph-nodes was related to survival; patients with less than three positive lymph-nodes had a median survival of 52 months compared to 12 months for those with three or more positive lymph-nodes (p = 0.02)[45]. By contrast, Tamandl et al[46] did not find different survival in patients with ICC with less than six or more than six lymph-nodes retrieved.

Furthermore, Tamandl et al[46] demonstrated that the lymph-node ratio (LNR) was a strong prognostic factor for ICC and reported a median survival times of 33.6, 31.2, and 10.4 months for patients with LNRs of 0, between 0 and 0.20, and more than 0.20, respectively. In our data, we confirmed these results: the median survival was significantly longer in patients with an LNR = 0 compared to those with an LNR > 0.25 (p < 0.01), even if survival was not significantly different between patients with an LNR = 0 and an LNR = 0-0.25 (p = 0.99)[45].

Recurrence After Surgical Treatment

Tumor recurrence is the leading cause of death after liver resection in patients with ICC[37, 46]. The reported recurrence rate varies from 46% to 68[56]. The location of recurrence is intrahepatic in 50-92% of cases[57]. High preoperative Ca 19-9, multiple liver tumors, tumor size and histological grading are the most significant factors related with recurrence[30,58-60]. Tamandl et al[46] and Saiura et al[60] showed that the tumor grading is a significant risk factor for recurrence in univariate and multivariate analysis, with an HR of 7.02 and 2.01, respectively. Also Shirabe et al[61] confirmed this finding in univariate and multivariate analysis, reporting a shorter 5-year recurrence-free survival in patients with poor tumor differentiation compared with patients with well or moderate tumor differentiation (57%, 52.7%, 23.2%, respectively).

The treatment of recurrent disease varies according to the location and extension of the tumor, unfortunately in about 50% of cases only palliative non-interventional treatment can be applied, due to the poor general conditions of patients, for the impaired liver function or for the extension of the disease[47,48]. Nevertheless, it has been reported that in selected cases surgical treatment including liver transplantation can achieved good long-term results[62]. The majority of studies available in literature reported case reports or small case series[63]. Interestingly, Ercolani et al[47], in a study including 38 patients affected by recurrence among 72 patients underwent surgical resection for ICC, reported 6 (17.6%) patients treated with liver resection and 8 (23.5%) patients treated with percutaneous radiofrequency ablation, with a 3-year survival

rate of 60% compared to 0% of untreated patients ($p = 0.001$).

Molecular Prognostic Factors

The molecular carcinogenesis of ICC have been recently investigated in literature; in particular the progression from pre-neoplastic lesions to ICC was related to the mutation different genes in particular of KRAS and over expression of p53[64]. The presence of different type of mutations seem to be related to the different risk factors, hepatolithiasis and fluke infection related ICC are associated with specific mutations in different genes[65]. Moreover, macroscopic and histopathological characteristics of ICC are related with specific type of mutation: Kras mutation is significantly more frequent with periductal infiltrating type compared to mass-forming type[66]. The molecular profiling of patients with ICC can identify different classes with different molecular alterations and prognosis. Sia et al[67] defined two different types, inflammatory and proliferative, and according to these two types the Authors observed different survival and recurrence rate. Recent studies[68,69] identified that different genes (BAP1, ARID1A, PBMR1, IDH1 & IDH2) are significantly mutated in ICC compared to normal tissue. Mutations of these genes are related with survival in patients who underwent to surgical resection.

All these preliminary studies should be confirmed in larger series in order to confirm the pathogenetic pathway of carcinogenesis of ICC and to help the development of new target therapies for tailored treatment strategies.

Conclusions

Recent improvements in surgical techniques and perioperative care have enhanced the feasibility and safety of liver resection with satisfactory long-term results patients with ICC. Prognostic factors after curative resection includes lymph-node status, macrovascular invasion and multifocality. Recently, important advances have been made in clarifying the molecular carcinogenesis and prognostic factors of ICC. In future, the molecular classification of ICC and the precise definition of categories with different prognosis will help clinician in selection of patients for surgical or non-surgical therapies.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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