ORIGINAL ARTICLE

Surgical treatment of intrahepatic cholangiocarcinoma: a retrospective study of 104 cases

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ABSTRACT

Objective: To explore the clinicopathological features, surgical treatment techniques, and prognostic risk factors of intrahepatic cholangiocarcinoma (ICC).

Methods: A total of 104 ICC cases were collected from January 2008 to December 2013 at Tianjin Medical University Cancer Institute and Hospital and divided into the hepatic hilum lymphadenectomy (HLL, 21 cases), extended hepatic hilum lymphadenectomy (EHLL, 12 cases), and non-lymphadenectomy (NL, 71 cases) groups. The clinical data of the patients were retrospectively analyzed, and the prognostic differences were compared among different groups.

Results: The 1-, 2-, and 3-year overall survival (OS) rates of all cases were 72.1%, 56.1%, and 43.7%, respectively. The median survival duration was 34 months. The 1-, 2-, and 3-year OS rates of the HLL group (42.9%, 28.6%, and 28.6%, respectively) were significantly lower than those of the NL group (78.9%, 62.5%, and 47.8%, respectively). Meanwhile, the 1-, 2-, and 3-year OS rates of the EHLL group (75.0%, 56.1%, and 33.3%, respectively) were not significantly different from those of the other two groups. Univariate analysis showed that age, gender, American Joint Committee on Cancer (AJCC) stage, differentiation, ferritin (Fer), carbohydrate antigen19-9 (CA19-9) and carcinoembryonicantigen (CEA) levels, lymph node metastasis (LNM), and lymph node dissection (LND) were prognostic factors for the long-term survival of ICC. Meanwhile, multivariate analysis revealed that age, AJCC stage, differentiation, Fer levels, and LNM were independent risk factors for survival.

Conclusions: ICC patients will not benefit from lymphadenectomy in the absence of LNM. However, systematic lymphadenectomy may improve ICC outcomes if the location of lymphatic metastasis is known. Age, AJCC stage, differentiation, Fer level, and LNM are independent risk factors for survival in ICC.

KEYWORDS   Intrahepatic cholangiocarcinoma; surgical treatment; lymph node dissection; prognosis

Introduction

Intrahepatic cholangiocarcinoma (ICC), a primary liver cancer, initially presents in the intrahepatic biliary tree and is the second most common liver malignancy after hepatocellular carcinoma, accounting for 10% of all primary liver cancers[1]. Surgical resection is currently the most effective treatment for ICC, but has several intrinsic limitations and disadvantages, such as poor curative effect, high recurrence rate, and low survival rate. The liver is the most common target organ for ICC metastasis, whereas lymph node metastasis (LNM) has been reported in

30%–70% of cases. Therefore, controlling LNM is the most important consideration for ICC treatment. For lymph node dissection (LND), there are various questions and controversies regarding the following aspects: when to perform LND, the extent of LND, and whether prophylactic LND should be performed. This study retrospectively analyzed the clinical data of 104 ICC cases collected from January 2008 to December 2013 at Tianjin Medical University Cancer Institute and Hospital. The clinical treatment strategies and prognostic factors for ICC were then explored.

Materials and methods

General clinical data

A total of 148 ICC cases were admitted to our hospital from January 2008 to December 2013. We ruled out 44 cases,

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including 4 cases diagnosed as hepatocellular carcinoma (HCC), 13 cases without surgical and interventional therapy, and 27 cases that were not followed up. The final 104 cases were investigated and divided into the hepatic hilum lymphadenectomy (HLL; 21 cases, 20.19%), extended hepatic hilum lymphadenectomy (EHLL; 12 cases, 11.54%), and the non-lymphadenectomy (NL; 71 cases, 68.27%) groups. **Table 1** shows the clinical features of the case groups.

Therapeutic modalities

The tumor diameters of the 104 cases ranged from 1 cm to 15 cm. All the cases that underwent liver resection were pathologically confirmed as R0 resections. The excision areas of the HLL group included the gallbladder neck and any single or several lymph node areas in zones 12 (12A, 12B, and 12P), 5, 7, 8, and 9. The EHLL group further underwent extraction of any single or several areas of zone 13, peritoneal lymph nodes, and intestinal region, in addition to the excision areas of the HLL group. No case in the NL group underwent lymph node removal. Additionally, 43 cases underwent regular hepatic resection (monosegmentectomy), 22 cases underwent left hemihepatectomy, 24 cases underwent right hemihepatectomy, 5 cases underwent extended left hemihepatectomy, 6 cases underwent extended right hemihepatectomy, and 4 cases underwent liver wedge resection.

Follow up

The follow-up was performed via telephone conversations. The median follow-up duration was 41 months (1–92 months). The overall survival (OS) time was defined as the time from surgery to death or end of follow-up. The follow-up data of the 104 cases were completed.

Statistical analysis

Statistical analysis was conducted by SPSS 19.0 statistical software. Survival analysis was performed by the Kaplan-Meier method, and the prognostic factors were compared by the log-rank test. Independent ICC prognostic factors were analyzed by the Cox regression model. Clinical parameters included gender, age, hepatitis B status, cirrhosis, tumor number, American Joint Committee on Cancer (AJCC) stage, differentiation, maximum tumor diameter, tumor marker levels [ferritin (Fer), alpha fetoprotein, CEA, and CA19-9], vascular invasion, LNM, and lymph node excision. $P < 0.05$ was considered as statistically significant.

Table 1 Summary of clinicopathological features of ICC, n (%)

Characteristics	HLL	EHLL	NL
Gender			
Female	12 (57.1)	8 (66.7)	27 (38.0)
Male	9 (42.9)	4 (33.3)	44 (62.0)
Age, years			
≤60	15 (71.4)	6 (50.0)	41 (57.7)
>60	6 (28.6)	6 (50.0)	30 (42.3)
Tumor number			
Solitary	12 (57.1)	9 (75.0)	41 (57.7)
Multiple	9 (42.9)	3 (25.0)	30 (42.3)
Tumor diameter, cm			
≤5	6 (28.6)	4 (33.3)	40 (56.3)
>5	15 (71.4)	8 (66.7)	31 (43.7)
Hepatitis B			
Negative	11 (52.4)	10 (83.3)	38 (53.5%)
Positive	10 (47.6)	2 (16.7)	33 (46.5)
Cirrhosis			
Negative	16 (76.2)	12 (100.0)	39 (54.9)
Positive	5 (23.8)	0 (0.0)	32 (45.1)
Fer			
Normal	6 (28.6)	6 (50.0)	41 (57.7)
Higher	15 (71.4)	6 (50.0)	30 (42.3)
CEA			
Normal	13 (61.9)	8 (66.7)	62 (87.3)
Higher	8 (38.1)	4 (33.3)	9 (12.7)
CA19-9			
Normal	5 (23.8)	2 (16.7)	48 (67.6)
Higher	16 (76.2)	10 (83.3)	23 (32.4)
AFP			
Normal	20 (95.2)	11 (91.7)	50 (70.4)
Higher	1 (4.8)	1 (8.3)	21 (29.6)
AJCC stage			
I/II	10 (47.6)	9 (75.0)	49 (69.0)
III/IVa/IVb	11 (52.4)	3 (25.0)	22 (31.0)
Differentiation			
Poor	7 (33.3)	7 (58.3)	40 (56.3)
Well or moderate	14 (66.7)	5 (41.7)	31 (43.7)
Vascular invasion			
Negative	13 (61.9)	8 (66.7)	48 (67.6)
Positive	8 (38.1)	4 (33.3)	23 (32.4)
LNM			
Negative	15 (71.4)	7 (58.3)	71 (100.0)
Positive	6 (28.6)	5 (41.7)	0 (0.0)

Results

Survival rate

The 1-, 2-, and 3-year OS rates of the 104 cases were 72.1%, 56.1%, and 43.7%, respectively. The median survival time was 34 months. The 1-, 2-, and 3-year OS rates of HLL were 42.9%, 28.6%, and 28.6%, respectively. The 1-, 2-, and 3-year OS rates of EHLL were 75.0%, 66.7%, and 33.3%, respectively. The 1-, 2-, and 3-year OS rates of NL were 78.9%, 62.5%, and 47.8%, respectively. The overall differences among the three groups were statistically significant. The 1-, 2-, and 3-year OS were significantly higher in the NL group than in the HLL group ($P < 0.05$, **Table 2**).

Prognostic factors

Univariate analysis (**Table 3**) revealed that age, gender, AJCC stage, differentiation, tumor marker levels, LNM, and LND significantly affected the prognosis of ICC patients. Meanwhile, multivariate analysis (**Table 4**) showed that age, AJCC stage, differentiation, Fer, and LNM were independent risk factors for survival. Furthermore, 62 of the 104 cases once received adjuvant therapy before or after surgery, including 37, 10, and 15 cases that received transcatheter arterial chemoembolization, radiofrequency ablation, and chemotherapy, respectively. After further analysis, we found that the 1-, 2-, and 3-year OS did not significantly differ between the adjuvant therapy (71.7%, 51.0%, and 38.6%, respectively) and non-adjuvant therapy groups (72.7%, 63.5%, and 51.2%, respectively). Therefore, the effects of adjuvant therapy can be excluded.

Discussion

Currently, there are many controversies on the application of LND in ICC patients. According to the AJCC guidelines on ICC, ICC and combined hepatocellular intrahepatic cholangiocarcinoma (cHCC-ICC) are not partitioned. Tumor diameter has been reported to be closely related to LNM and vascular invasion[4]. This study set the boundary value of the maximum tumor diameter at 5 cm. According to

Table 2 Comparison of the OS according to the LND

LND	HLL		EHLL		NL	
	Chi-square	P	Chi-square	P	Chi-square	P
HLL	-	-	2.855	0.091	6.345	0.012
EHLL	2.855	0.091	-	-	0.002	0.969
NL	6.345	0.012	0.002	0.969	-	-

Table 3 Results of univariate analysis

Characteristic	n	Survival rate (%)			P
		1 year	2 years	3 years	
Gender					0.028
Female	47	68.1	44.0	31.1	
Male	57	75.4	66.0	53.2	
Age, years					0.041
≤60	62	75.8	62.4	54.3	
>60	42	66.7	46.7	27.6	
Tumor number					0.503
Solitary	62	75.8	58.8	44.0	
Multiple	42	66.7	52.4	43.7	
Tumor diameter, cm					0.059
≤5	50	76.0	60.9	53.7	
>5	54	68.5	48.9	32.4	
Hepatitis B					0.896
Negative	59	74.6	56.8	44.1	
Positive	45	68.9	52.4	43.0	
Liver cirrhosis					0.649
Negative	67	71.6	56.2	44.7	
Positive	37	73.0	52.6	41.4	
Fer					0.010
Normal	53	83.0	67.2	55.9	
Higher	51	60.8	42.0	31.5	
CEA					0.042
Normal	83	75.9	60.6	46.5	
Higher	21	57.1	38.1	31.7	
CA-199					0.038
Normal	55	80.0	62.4	52.5	
Higher	49	63.3	46.2	34.6	
AFP					0.632
Normal	81	70.4	54.8	43.7	
Higher	23	78.3	60.6	44.2	
AJCC stage					0.000
I/II	68	82.4	71.1	54.0	
III/IVa/IVb	36	52.8	27.8	23.8	
Differentiation					0.009
Poor	54	68.5	48.7	28.4	
Well or moderate	50	76.0	63.6	59.9	
Vascular invasion					0.689
Negative	69	71.0	55.9	42.5	
Positive	35	74.3	56.1	46.8	
LNM					0.003
Negative	93	76.3	59.5	47.8	
Positive	11	36.4	27.3	0	
LND					0.032
HLL	21	47.6	28.6	28.6	
EHLL	12	75.0	66.7	33.3	
NL	71	78.9	62.5	47.8	

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Table 4 Results of multivariate analysis

Clinical features	B	Wald	P	Exp (B)	Exp (B) 95% CI
Age	− 0.607	4.841	< 0.05	0.545	(0.317, 0.936)
AJCC stage	− 0.948	11.510	< 0.05	0.388	(0.224, 0.670)
Differentiation	0.602	4.494	< 0.05	1.825	(1.046, 3.182)
Fer	0.674	5.530	< 0.05	1.962	(1.119, 3.439)
LNM	1.072	7.307	< 0.05	2.921	(1.343, 6.353)

some ICC guidelines, surgical excision is suitable for patients in AJCC stages I and II, whereas conservative treatment is suitable for patients in stages III and IV (IVa and IVb)[5]. Therefore, the stage I and II cases were classified into one group, and stage III and IV cases were classified into another group. The effect of surgical resection on the prognosis of ICC was then investigated. Univariate analysis showed that age, gender, AJCC stage, differentiation, Fer, CA19-9, and CEA levels, LNM, and LND significantly affected the prognosis of ICC patients. Multivariate analysis revealed that age, AJCC stage, differentiation, Fer, and LNM were independent risk factors of survival. This study found that hepatitis B was not an independent risk factor for the prognosis of ICC patients, which is consistent with the view of some researchers[5]. No study had reported that Fer is an independent risk factor for the survival of ICC patients. However, plasma Fer concentrations were reported to be closely related to the occurrence and development of HCC, breast cancer, and gastrointestinal tumors[7-9]. Additionally, some researchers posited that in male patients, excessively high or low preoperative Fer concentrations are an independent risk factor for hepatitis C in HCC[7]. In this study, only Fer had statistically significant effects on survival rate whereas Fer, gender, and hepatitis B were covariates, which varied from the results reported by some studies performed in China[10]. In this study, we found that the risk of death was 1.7 times higher for patients with high preoperative Fer concentrations than for patients with normal Fer levels.

This study analyzed the application of LND in ICC, although the results of multivariate analysis showed that LND was not an independent risk factor for ICC survival. A total of 104 cases were divided into the HLL, EHLL, and NL groups. Univariate analysis showed that LND significantly affected the prognosis of ICC patients ($P < 0.05$). This finding coincides with a previous perspective that ICC patients without LNM do not benefit from routine LND[11]. Furthermore, this study observed some differences among groups. The EHLL group had considerably improved prognosis compared with the HLL group, as noted from the OS, although the difference between groups was not statistically significant. Moreover, 5 cases in the EHLL group (5/12) and 6 cases in the HLL group (6/21) exhibited lymph metastases. LNM had been confirmed to be rarely confined to the first lymph node, and has an apparent tendency for skip metastasis[11]. Therefore, we suspected that ICC patients will not benefit from lymphadenectomy when LNM is absent. However, systematic lymphadenectomy may improve the outcomes of ICC if we identify the location of lymphatic metastasis[13]. Some researchers recommend that ICC patients without LNM should not undergo routine LND, and extended systemic LND is not recommended for ICC patients with LNM[14]. Therefore, this study analyzed LND and LNM as covariates. The results showed that only the effects of LNM on the prognosis were significantly different. LND did not significantly improve the prognosis of some ICC patients. Therefore, establishing a comprehensive, clear, and standardized LND system for ICC is critical. Multivariate analysis revealed that LNM was an independent factor for ICC prognosis, which is consistent with most research perspectives[15,16]. Li et al.[11] found that the ligamentum hepatoduodenale is the most common LNM site in ICC. In this study, 11 cases exhibited ICC in LNM, including 5 cases in zone 12, 5 cases in zone 8, 2 cases in zone 13, and 1 case in the retroperitoneum. Hence, the results suggested that zones 12 and 8 are the most common LNM sites.

Some shortcomings of this study must be acknowledged. First, the study performed retrospective analyses, and some clinical data may not be reliable. Several reports showed that vascular invasion and tumor number are independent prognostic factors[16], which contradict our results. This discrepancy possibly resulted from the inaccuracy of some clinical information, selective bias of the treatment, or insufficient sample size. Some previous studies identified CEA and CA19-9 as prognostic factors for ICC, a conclusion not verified by this study[15,16]. This incongruity might have resulted from the insufficient sample size, such that individual differences may have affected the result.

Moreover, this study collected cases that were in relatively early stages of ICC progression, and the majority of the AJCC stage I and II cases have increased in recent years. Therefore, the median survival time (34 months) in our study was
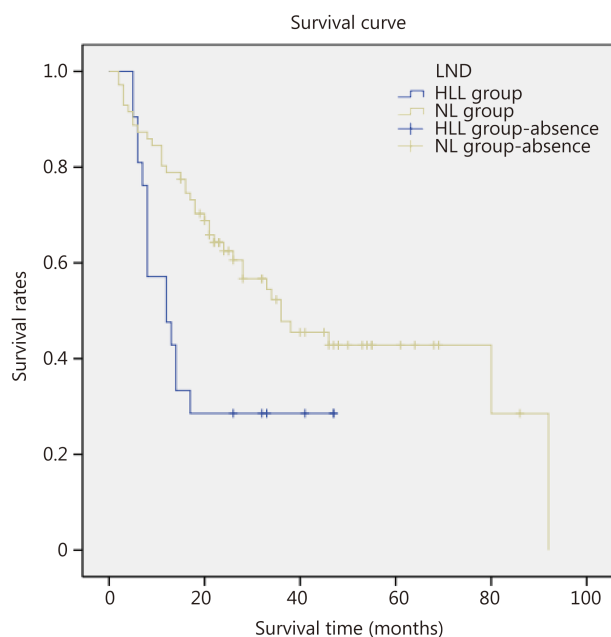
Figure 1   Survival curves of patients in the HLL group and NL group.

higher than in some reports[17,18]. In conclusion, we recommend that ICC patients without or with uncertain LNM should not undergo routine LND, but that ICC patients with LNM should undergo LND. A comprehensive, clear, and standardized LND system for early-stage ICC must be established.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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