Clinical Outcomes of Mass-Forming Intrahepatic Cholangiocarcinoma: A Case Series of 68 Patients

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Citation:

Zhao X. Clinical Outcomes of Mass-Forming Intrahepatic Cholangiocarcinoma: A Case Series of 68 Patients. Japanese Journal of Gstroenterology and Hepatology. 2020; V5(5): 1-7.

Abbreviations:

MF: mass-forming; ICC: intrahepatic cholangiocarcinoma; PLA: People's Liberation Army; PI: periductal-infiltrating; IG: Intraductal-growth; CA19-9: Carbohydrate antigen 19-9; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HBSAg: Hepatitis B surface antigen; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transpeptadase; TBIL: Total bilirubin; AR: Anatomic resection; NAR: Non-anatomical resection

1. Abstract

1.1 Background: This study aims to examine the prognostic factors of patients with MF ICC in order to improve the outcomes of ICC.

1.2. Methods: We carried out a retrospective analysis of consecutive patients with MF ICC treated at the Faculty of Hepato-Pancreato-Biliary Surgery of Chinese PLA General Hospital between January 2008 and December 2018. The patients were divided into the resection group and exploration group.

1.3. Results: The 1-, 3-, and 5-year survival rates of the 68 cases in this study were 66.5%, 36.3%, and 9.3%, respectively. Univariate analyses revealed that the survival rates were significantly different according to nodal metastasis (P<0.001), vascular invasion (P<0.001), ascites (P<0.001), group (P<0.001), differentiation (P=0.009), and tumor location (P=0.032). Multivariate analysis demonstrated that ascites (HR=5.6, 95%CI: 1.6-18.9, P=0.006) and vascular invasion (HR=2.5, 95%CI: 1.0-6.1, P=0.045) were independent risk factors affecting the prognosis of the patients. Among patients who underwent surgical resection, the 1-, 3-, and 5-year survival rates of the 49 cases were 93.5%, 49.7%, and 14.4%, respectively. Univariate analyses showed that vascular invasion (P<0.001), nodal metastasis (P=0.001), and tumor size (P=0.044) were associated with survival. While vascular invasion (HR=3.1, 95% CI: 1.2-8.5, P=0.024) and nodal metastasis (HR=3.2, 95% CI: 1.4-7.6, P=0.008) were independently associated with survival. The 1-, 3-, and 5-year survival rates of the 19 cases in exploration group were 5.3%, 5.3%, and 0.0%, respectively.

1.4. Conclusions: The prognosis of MF ICC was poor for patients with ascites or vascular invasion. Surgical resection is a key factor in improving survival. Vascular invasion and nodal metastasis affected the efficacy of surgical resection of MF ICC.

2. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer in humans, after hepatocellular carcinoma (HCC) [1] is a rare epithelial malignancy that results in poor prognosis [2]. Recent data suggests that both the incidence and mortality

rate of ICC has increased over the last few decades [1-4].

Surgical resection is currently the only potentially curative treatment for ICC [3-5], but the cure rates and survival of patients with ICC remain very low because of the high aggressiveness of the disease [6-7]. It has been reported that many factors influence the prognosis of surgical resection [8-11].

According to Liver Cancer Study Group of Japan(LCSGJ) classification, ICC can be divided into three types: mass-forming (MF) type, characterized by the presence of a spherical mass with a distinct border in the liver parenchyma; periductal-infiltrating (PI) type, characterized by tumor infiltration along the bile duct, occasionally involving the surrounding blood vessels and/or hepatic parenchyma; intraductal- growth (IG) type, characterized by papillary or granular growth into the bile duct lumen, occasionally showing superficial extension [11]. The MF type is the most common, accounting for 57.1-83.6% of ICC [12-14].

Nevertheless, little is known about the epidemiology and treatments of MF ICC. Therefore, the aim of the present retrospective study was to examine the prognostic factors of patients with MF ICC in order to improve the outcomes of ICC.

3. Materials and Methods

3.1. Study Design

This was a retrospective analysis of consecutive patients with MF ICC treated at the Faculty of Hepato-Pancreato-Biliary Surgery of Chinese PLA General Hospital between January 2008 and December 2018. The study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital.

3.2. Patients

The inclusion criteria were: 1) ≥18 years of age; 2) hospitalized patients; 3) confirmed as MF ICC by histopathological examination; and 4) no prior history of any malignancy. The exclusion criteria were: 1) incomplete data; 2) metastasis; 3) hilar cholangiocarcinoma; 4) cystadenocarcinoma; 5) PI ICC; or 6) IG ICC. The patients were divided into the resection group and exploration group according to the received treatments.

Treatments

All cases were discussed in tumor boards before any treatment. The indications for radical hepatectomy were: 1) no distant metastases preoperatively; 2) preoperative imaging suggesting that the tumors could be completely resected, including eventual satellite lesions; 3) Child grade A or B; and 4) good cardiopulmonary function and no surgical or anesthetic contraindications.

The surgical principle was to achieve R0 resection. The pattern of hepatectomy was based on residual liver function, tumour size and tumour–vessel relationship. Anatomic resection(AR) was the priority if feasible, while non-anatomical resection(NAR) was more frequently applied if the tumour was adjacent to major vascular structure. surgical exploration was only performed in patients with extensive metastases in the liver, abdominal wall, and omentum. Lymph node dissection of the hepatoduodenal ligament was performed for patients with lymphadenectasis found by imaging or intraoperatively. Tumor and lymph node biopsy were performed in patients undergoing surgical exploration.

3.3. Data Collection

General data and results of auxiliary examinations were recorded, including CA19-9, HBV, ALT, AST, ALP, GGT, and TBIL tests.

3.4. Follow-up

All patients were followed up after surgery. Follow-up visits were performed once every 3 months during the first year, re-examined once every 6 months during the second and third years, and re-examined once a year later. Items checked during the follow-up visits included routine laboratory tests, tumor markers, chest roentgenogram, abdominal ultrasound, CT, and/or MRI examinations. The follow-up deadline was 31 December 2019, and the follow-up duration ranged from 1 to 82 months, with a median duration of 13 months.

4. Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co, Armonk, NY, USA). Continuous data meeting the normal distribution were presented using mean ± standard deviation. Differences between the two groups were determined using independent sample t test. Continuous data not meeting the non-normal distribution were presented using median (range). The non-parametric Mann-Whitney U test was used to determine the differences between the two groups. The chi-square test or the Fisher's exact test was used for categorical data. Univariate Cox proportional hazard regression model analysis was used for survival data. The variables with $P<0.05$ in univariate analyses were included in the multivariate Cox proportional hazard regression model. Kaplan-Meier analysis was used to calculate the survival rate. Log-Rank method was used for group-wise comparison. Two-sided P-values <0.05 were considered statistically significant.

5. Results

5.1. Characteristics of the Patients

Of these 68 patients, the majority was male (73.5%) and the median age was 54 years (range: 24–74 years). There were 40 patients with tumors in the right lobe of the liver and 28 with tumors in the left lobe of the liver. The median tumor diameter was 7.0 cm (range, 2.2–14.0). Elevated CA 19-9 levels were observed in 28 (41.2%) patients at presentation with five patients presenting with CA 19-9 >1000 U/ml. Sixteen and four had concomitant hepatitis B and C viral infections, respectively. 14 cases were accompanied with ascites. The characteristics were similar between the two groups, except that the exploration group had higher levels of ALT(P=0.031), higher frequencies of ascites (P<0.001), nodal metastasis (P<0.001) and vascular invasion (P<0.001), and the tumors were mostly located in the left lobe (P<0.001) (Table 1).

Table 1: Baseline characteristics of the patients

Variables	All n= 68	Surgery n= 49	Exploration n= 19	P value
Age (years)	54.3±1.4	52.6±1.7	58.6±2.2	0.435
Gender, Male	50 (73.5%)	34 (69.4%)	16 (84.2%)	0.924
HBV infection	16 (23.5%)	13(26.5%)	3 (15.8%)	0.997
HCV infection	4 (5.9%)	2 (4.1%)	2 (10.5%)	0.314
Ascites	14 (20.6%)	1 (2.0%)	13(68.4%)	<0.001
Tumor size(cm)	6.9±0.3	6.8±0.4	7.63±0.5	0.495
ALT (IU/L)(median)	1.8-92.1 (26)	1.8-92.1 (24.9)	23-76.3 (32.1)	0.031
AST (IU/L) (median)	9.6-74.2 (29)	9.6-74.2 (27.3)	18.2-61.9 (31)	0.142
ALP (U/L) (median)	13.4-280.5 (82.8)	13.4-280.5 (81.4)	45.3-109.9 (85.4)	0.149
GGT (U/L) (median)	11-325.6 (42.4)	11-325.6 (41.1)	28.9-104.7 (45.8)	0.512
TBIL (mg/dL) (median)	4.2-140.0 (18)	4.2-140 (18.1)	4.2-42.6 (17.8)	0.707
CA19-9 (U/mL) (median)	21-2000 (34.5)	21-1891 (36)	22-2000 (30)	0.104
Differentiation				0.536
Poor	30 (44.1%)	20 (40.8%)	10 (40.052.6	
Poor-moderate	24 (35.3%)	19 (38.8%)	5 (26.3%)	
Moderate	14 (20.6%)	10(20.4%)	4 (21.1%)	
Nodal metastasis	33 (48.5%)	14 (28.6%)	19 (100.0%)	<0.001
Tumor Location				<0.001
Left lobe	28 (41.2%)	11 (22.4%)	17 (89.5%)	
Right lobe	40 (58.8%)	38 (77.6%)	2 (10.5%)	
Vascular invasion	31 (45.6%)	13 (26.5%)	19 (100.0%)	<0.001

5.2. Survival

All patients were discharged successfully from the hospital. During follow-up, 48 patients died and 20 survived. Survival time ranged from 1 to 82 months (median, 24 months). The 1-, 3-, and 5-year survival rates of the 68 cases in this study were 66.5%, 36.3%, and 9.3%, respectively (Table 2). Univariate analyses revealed that the survival rates were significantly different according to group (P<0.001), nodal metastasis (P<0.001), tumor location (P=0.039), vascular invasion (P<0.001), ascites (P<0.001), and differentiation (P=0.009) (Table 3). Multivariate analysis demonstrated that ascites (HR=5.6, 95% CI: 1.6-18.9, P=0.006) and vascular invasion (HR=2.5, 95% CI: 1.0-6.1, P=0.045) were independent risk factors affecting the prognosis of the patients (Table 3).

Table 2: Overall survival of the patients with MF ICC.

	All n= 68	Resection n= 49	Exploration n= 19	P value
Follow-up (months)	1-82	3-82	1-57	
Survival				<0.001
1 year	66.50%	93.50%	5.30%	
3 years	36.30%	49.70%	5.30%	
5 years	9.30%	14.40%	0.00%	

Table 3: Univariate and multivariate analysis of the clinical and pathological factors for overall survival of 68 patients with MF ICC.

Variables	No. of patients	1 Year (%)	3 Year (%)	5 Year (%)	P Value	HR	95% CI	P Value
Age(years)					0.278			
≤54	35	71.8	39.8	13.5				
>54	33	61.4	32.7	6.1				
Gender					0.292			
Male	50	62.2	34.2	9.7				
Female	18	79.6	43	10.8				
HBV infection					0.327			
Yes	16	74	24.7	0				
No	52	64	40	13.3				
Ascites					<0.001	5.553	1.628-18.941	0.006
Present	14	0	0	0				

	n	1-year	3-year	5-year	P	HR	95%CI	P
Absent	54	84	45.8	11.8				
Tumor size (cm)					0.23			
≤7	41	64,3	49	10.1				
> 7	27	70.2	12.5	6.3				
CA 19–9 (IU/mL)					0.881			
≤27	40	62.7	36.6	7.8				
>27	28	72.3	34.8	15.5				
Differentiation					0.009	0.769	0.466-1.270	0.305
Poor	30	56.4	21.7	0				
Poor-moderate	24	78.5	62.4	12.8				
Moderate	14	66.1	23.6	23.6				
Nodal metastasis					<0.001	2.294	0.983-5.353	0.055
Yes	35	97	64	21.7				
No	33	37.8	9.1	0				
Tumor location					0.032	2.186	0.801-5.965	0.127
Left lobe	28	40.9	28.6	0				
Right lobe	40	86.8	43.9	12.4				
Vascular invasion					<0.001	2.501	1.020-6.131	0.045
Yes	31	35.5	9.7	0				
No	37	97.1	66.3	22.2				
Group					<0.001	1.619	0.351-7.469	0.537
Resection	49	93.5	49.7	14.4				
Exploration	19	5.3	5.3	0				

5.3. Subgroup Analyses

The 1-, 3-, and 5-year survival rates of the 19 cases in exploration group were 5.3%, 5.3%, and 0.0%. Among patients who underwent surgical resection, the 1-, 3-, and 5-year survival rates of the 49 cases were 93.5%, 49.7%, and 14.4%, respectively. The survival rates of resection group were significantly better than that of exploration group (P<0.001) (Figure 1).

(Table 4) presents the univariate and multivariate analyses of the factors associated with survival in the surgery group. In this group, univariate analyses showed that nodal metastasis (P=0.001), vascular invasion (P<0.001) and tumor size (P=0.044) were associated with survival, while vascular invasion (HR=3.1, 95% CI: 1.2-8.5, P=0.024) and nodal metastasis (HR=3.2, 95%CI: 1.4-7.6, P=0.008) were independently associated with survival.

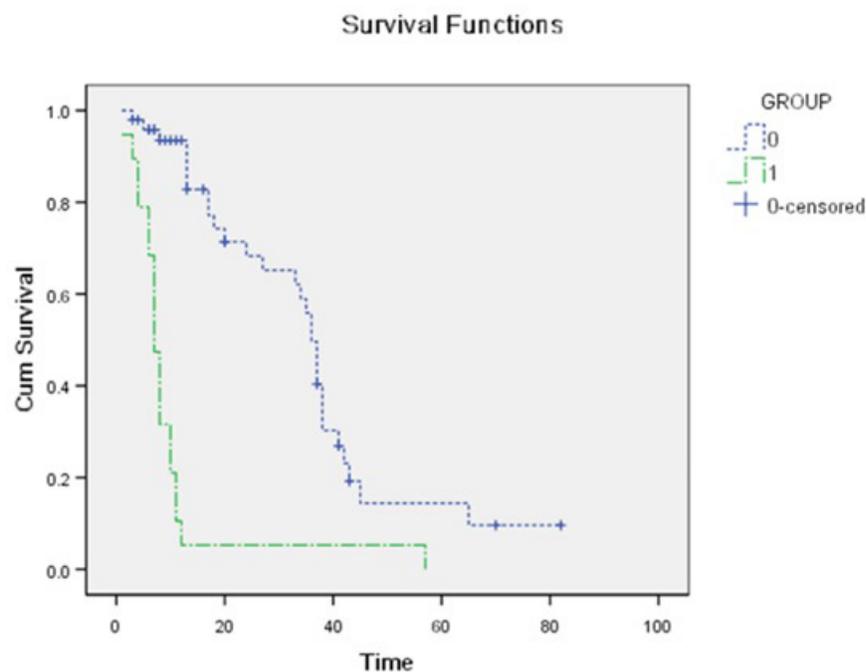**Figure 1:** The resection group (blue line) vs. the exploration group (green dashed line) (P<0.001).

Table 4: Univariate and multivariate analysis of the clinical and pathological factors for overall survival of patients in the surgery group

Variables	No. of patients	1 Year (%)	3 Year (%)	5 Year (%)	P Value	HR	95% CI	P Value
Age(years)					0.633			
≤54	27	92.3	48.6	21.2				
>54	22	95	50.7	9.5				
Gender					0.441			
Male	34	90.9	48.2	18.1				
Female	15	100	54	13.5				
HBV infection					0.063			
Yes	13	92.3	30.8	0				
No	36	94	57.1	22.5				
Ascites					0.836			
Present	1	0	0	0				
Absent	48	93.4	49.6	14.4				
Tumor size (cm)					0.044	1.273	0.485-3.339	0.624
≤7	28	92.9	69.6	16.9				
> 7	21	94.1	33.6	8.4				
CA 19–9 (IU/mL)					0.571			
≤27	26	96	53.9	12.9				
>27	23	90.6	43.7	19.4				
Differentiation					0.061			
Poor	20	89.7	34.5	0				
Poor-moderate	19	94.7	73.9	23.9				
Moderate	10	100	35.7	35.7				
Nodal metastasis					0.001	3.221	1.364-7.610	0.008
Yes	35	97	64	21.7				
No	14	85.7	11.9	0				
Tumor location					0.545			
Left lobe	11	100	66.7	33.3				
Right lobe	38	91.4	46.3	13				
Vascular invasion					<0.001	3.148	1.160-8.544	0.024
Yes	12	83.3	16.7	0				
No	37	97.1	66.3	22.2				
Pattern of liver resection					0.773			
AR resection	23	96	50.6	11.4				
NAR resection	25	95.5	51.7	9.7				
Resection margin(cm)					0.361			
≤1	21	95.2	40.3	16.1				
>1	27	96	57.3	14.6				

6. Discussion

Little is known about the epidemiology and treatments of MF ICC. Therefore, this study aimed to examine the prognostic factors of patients with MF ICC in order to improve the outcomes of ICC. The results showed that the prognosis of MF ICC was poor for patients with ascites or vascular invasion. Vascular invasion and nodal metastasis affected the efficacy of surgical resection.

It is reported that the morbidity of ICC in male is 40-63.5% [14, 16-18], and the age at diagnosis is mainly in the 6th decade of life, but ranges from 21 to 86years [17-20]. Among the 68 cases in the current study, 50 were males accounting for 73.5% of the patients, which was higher than that reported in the literature. The age of onset was 24-74 years with the median age of 54 years, which was consistent with literature reports but could still be a little younger than in the literature. This discrepancy could be due to a number of reasons including genetics, environment, and methods of detection.

Many previous studies showed that HBV and HCV infections were associated with the occurrence of ICC. It has been reported that the rate of HBV infection ranges from 3.9% to 28.8% in ICC patients, and the rate of HCV infection ranges from 0.6% to 16.5% [20-22]. In the present study, the infection rate of HBV and HCV were 23.5% and 5.9%, respectively, which were similar to those reported in the literature. Currently, the relationship between HBV and ICC prognosis is still controversial. Pan et al. reported that the 1-, 3-year overall survival rates of patients with HBV infection was higher than that of patients without HBV infection (67.6%, 47.2% vs. 43.8%,18.4%) [23]. Ahn et al. reported that HBV infection itself was not regarded as an independent prognostic factor [24]. Tao et al. described that 1-, 3-, and 5-year cumulative survival rates of HBsAg-positive ICC patients are significantly lower than HBV-negative ICC patients (27.3%, 0%, and 0% vs. 87.5%, 66.7%, and 50.0%, P <0.001) [25]. The present study found that there was no significant difference in survival between patients with HBV infection and patients without HBV infection. Nevertheless, among the 68 patients, the 5-year survival was 0 in patients with HBV infection, while it was 13.3% in those without HBV infection. In the surgery group, the 5-year survival was 0 in patients with HBV infection, while it was 22.5% in patients without

HBV infection. These rates raise the question of the impact of HBV infection on the survival to ICC and further study is needed to investigate this point.

Surgical resection is the most important factor for long-term survival of ICC patients. In this study, the 5-year survival rate was 14.4% for patients in the resection group, while it was 0% for patients in the exploration group. The surgical approach required tumor-free surgical margins, i.e. R0 resection. The literature has reported that the R0 resection rate of ICC ranges from 24.1% to 92.8% [10, 26], but the relationship between margins and survival is still controversial in patients with ICC. Bagante et al. deemed that patients with positive margins had a poor prognosis [13]. Tang et al. reported that the prognosis in patients with margins >1 cm was better than that of patients with margins ≤1 cm [16], while Bartsch et al. showed that the margin width was not related to prognosis [10]. Other studies reported that no significant difference in survival was observed between patients with R0 resection and patients with R1 resection [7, 27, 28]. In the present study, the resection rate was 72.1% (49/68), and all resections were R0. Whether the margins were >1 cm or not was not related to survival. Furthermore, there was no significant difference in 1, 3, and 5-year survival rates between AR and NAR resection (96.0%, 50.6%,11.4% vs 95.5%, 51.7%, 9.7%). These results suggest that the objective is achieving R0 no mater using AR or NAR resection. A number of studies have indicated that patients with positive lymph nodes have a poor prognosis [11, 13, 17-18]. Bagante et al. showed that the 5-year survival rates in patients with positive lymph nodes was 9.4%, while in patients with negative lymph node was 45.5% [13]. In the present study, the 5-year survival rates in patients of the resection group with positive lymph nodes was 0%, compared with 21.7%, in patients with negative lymph nodes. Lymph node metastasis could be an important prognostic factor for ICC. Nevertheless, there is still no definite conclusion as to whether resection of positive lymph nodes can extend survival or not [17-18, 29-30].

Previous studies showed that vascular invasion was an important factor affecting the prognosis of ICC [27, 31-32]. Our results revealed that the 3- and 5-year survival rates in resection group with vascular invasion were 16.7% and 0%, respectively, compared with 66.3% and 22.2%, respectively, in patients without vascular invasion. The survival rate in patients without vascular invasion was higher than that of patients with vascular invasion. The multivariate analysis revealed that vascular invasion was an independent prognostic factor in patients with ICC.

In the present study, there was no significant difference in survival for left and right lobe tumors in the resection group. However, in the whole group of 68 patients, the resection rate of tumor in the right lobe was 95.0% (38/40), and that in the left lobe was 39.3% (11/28), indicating that the resection rate of tumors in the left lobe was low. Survival analysis also suggested that the survival rate was low for patients with tumors in the left lobe, which may be because tumors in the left lobe are more prone to metastasis through the ligament of the liver and stomach. In addition, we also noted that tumors in the left lobe could metastasize from the round ligament of the liver and sickle ligament of the liver to the abdominal wall. Nevertheless, further study is necessary for confirmation.

Data revealed that 25-40% of the tumors with metastasis could not be dissected by surgical exploration for ICC patients whose tumors are considered to be removable before surgery. Therefore, laparoscopic examination should be performed before operation for patients with multi centric lesions, high CA19-9, suspected vascular infiltration, or peritoneal carcinomatosis [4]. In the present study, 19 patients (27.9%) underwent surgical exploration. Among the 40 cases with tumors in the right lobe of the liver, 5% (n=2) underwent surgical exploration, while 60.7% (n=17) underwent surgical exploration among the 28 patients with tumors in the left lobe of the liver, suggesting that the exploration rate was high for tumors in the left lobe of the liver. Among the 14 cases with preoperative ascites, there were 13 cases with abdominal metastasis and peritoneal metastasis. Therefore, we believe that routine laparoscopic exploration should be performed before operation for patients with tumors in the left lobe of the liver or with ascites in order to avoid meaningless laparotomy.

The present study is not without limitations, this was a retrospective, single-center study with a small sample size. In addition, it was limited to Chinese patients. Thus, the results should be validated using multicenter studies.

7. Conclusion

The prognosis of MF ICC was poor for patients with ascites present or vascular invasion. Surgical resection is a key factor in improving survival. The width of surgical margins was not associated with the survival of patients with R0 resection. Vascular invasion and nodal metastasis affected the efficacy of surgical resection of MF ICC. Laparoscopic examination should be performed before the operation for patients with MF ICC in the left lobe or patients with ascites.

References

1. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol. 2014; 60: 1268-89.

2. Moeini A, Sia D, Bardeesy N, Mazzaferro V, Llovet JM. Molecular Pathogenesis and Targeted Therapies for Intrahepatic Cholangiocarcinoma. Clin Cancer Res. 2016; 22: 291-300.

3. Ransome E, Tong L, Espinosa J, Chou J, Somnay V, Munene G et al. Trends in surgery and disparities in receipt of surgery for intrahepatic cholangiocarcinoma in the US: 2005-2014. J Gastrointest Oncol. 2019; 10: 339-47.

4. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM et al. Intrahepatic cholangiocarcinoma: expert consensus statement. HPB (Oxford). 2015; 17: 669-680.

5. Cillo U, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt

HJ et al. Surgery for cholangiocarcinoma. Liver Int. 2019; 39: 143-155.

6. Bartsch F, Hahn F, Muller L, Baumgart J, Hoppe-Lotichius M, Kloeckner R et al. Relevance of suspicious lymph nodes in preoperative imaging for resectability, recurrence and survival of intrahepatic cholangiocarcinoma. BMC Surg. 2020; 20: 75.

7. Luvira V, Eurboonyanun Ch, Bhudhisawasdi V, Pugkhem A, Pairojkul Ch, Luvira V et al. Patterns of Recurrence after Resection of Mass-Forming Type Intrahepatic Cholangiocarcinomas. Asian Pac J Cancer Prev. 2016; 17: 4735-9.

8. Buettner S, Galjart B, van Vugt JLA, Bagante F, Alexandrescu S, Marques HP et al. Performance of prognostic scores and staging systems in predicting long-term survival outcomes after surgery for intrahepatic cholangiocarcinoma. J Surg Oncol. 2017; 116: 1085-95.

9. Conci S, Ruzzenente A, Vigano L, Ercolani G, Fontana A, Bagante F et al. Patterns of Distribution of Hepatic Nodules (Single, Satellites or Multifocal) in Intrahepatic Cholangiocarcinoma: Prognostic Impact After Surgery. Ann Surg Oncol. 2018; 25: 3719-27.

10. Bartsch F, Baumgart J, Hoppe-Lotichius M, Straub BK, Heinrich S, Lang H et al. Intrahepatic cholangiocarcinoma - influence of resection margin and tumor distance to the liver capsule on survival. BMC Surg. 2020; 20: 61.

11. Ma CH, Hwang DW, Song KB, Kim SC, Shin SH, Lee JH et al. Prognostic factors predicting survival rate over 10 years of patients with intrahepatic cholangiocarcinoma after hepatic resection. Ann Surg Treat Res. 2020; 98: 116-123.

12. Uno M, Shimada K, Yamamoto Y, Nara S, Esaki M, Sakamoto Y et al. Periductal infiltrating type of intrahepatic cholangiocarcinoma: a rare macroscopic type without any apparent mass. Surg Today. 2012; 42: 1189-94.

13. Bagante F, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, Maithel SK et al. Long-term outcomes of patients with intraductal growth sub-type of intrahepatic cholangiocarcinoma. HPB (Oxford). 2018; 20: 1189-97.

14. Dover LL, Jacob R, Wang TN, Richardson JH, Redden DT, Li P et al. Improved Postoperative Survival for Intraductal-Growth Subtype of Intrahepatic Cholangiocarcinoma. Am Surg. 2016; 82: 1133-9.

15. Ohira M, Yoshizumi T, Yugawa K, Kosai-Fujimoto Y, Inokuchi S, Motomura T et al. Association of inflammatory biomarkers with long-term outcomes after curative surgery for mass-forming intrahepatic cholangiocarcinoma. Surg Today. 2020; 50: 379-388.

16. Tang H, Lu W, Li B, Meng X, Dong J. Influence of surgical margins on overall survival after resection of intrahepatic cholangiocarcinoma: A meta-analysis. Medicine (Baltimore). 2016; 95: e4621.

17. Navarro JG, Lee JH, Kang I, Rho SY, Choi GH, Han DH et al. Prognostic significance of and risk prediction model for lymph node metastasis in resectable intrahepatic cholangiocarcinoma: do all require lymph node dissection? HPB (Oxford). 2020; 22: 1411-9.

18. Asaoka T, Kobayashi S, Hanaki T, Iwagami Y, Tomimaru Y et al. Clinical significance of preoperative CA19-9 and lymph node metastasis in intrahepatic cholangiocarcinoma. Surg Today. 2020; 50: 1176-86.

19. Li Y, Wang H, Li D, Hu J, Wang H, Zhou D et al. Occult hepatitis B virus infection in Chinese cryptogenic intrahepatic cholangiocarcinoma patient population. J Clin Gastroenterol. 2014; 48: 878-82.

20. De Rose AM, Cucchetti A, Clemente G, Ardito F, Giovannini I, Ercolani G Et al. Prognostic significance of tumor doubling time in mass-forming type cholangiocarcinoma. J Gastrointest Surg. 2013; 17: 739-47.

21. Reddy SK, Hyder O, Marsh JW, Sotiropoulos GC, Paul A, Alexandrescu S et al. Prevalence of nonalcoholic steatohepatitis among patients with resectable intrahepatic cholangiocarcinoma. J Gastrointest Surg. 2013; 17: 748-755.

22. Wang JJ, Li H, Li JX, Xu L, Wu H, Zeng Y. Preoperative gamma-glutamyl transferase to lymphocyte ratio predicts long-term outcomes in intrahepatic cholangiocarcinoma patients following hepatic resection. World J Gastroenterol. 2020; 26: 1501-12.

23. Pan QX, Su ZJ, Zhang JH, Wang CR, Ke SY. Glasgow Prognostic Score predicts prognosis of intrahepatic cholangiocarcinoma. Mol Clin Oncol. 2017; 6: 566-574.

24. Ahn CS, Hwang S, Lee YJ, Kim KH, Moon DB, Ha TY et al. Prognostic impact of hepatitis B virus infection in patients with intrahepatic cholangiocarcinoma. ANZ J Surg. 2018; 88: 212-7.

25. Tao LY, He XD, Xiu DR. Hepatitis B virus is associated with the clinical features and survival rate of patients with intrahepatic cholangiocarcinoma. Clin Res Hepatol Gastroenterol. 2016; 40: 682-87.

26. Li MX, Bi XY, Li ZY, Huang Z, Han Y, Zhao JJ et al. Impaction of surgical margin status on the survival outcome after surgical resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis. J Surg Res. 2016; 203: 163-173.

27. Kinoshita M, Kanazawa A, Takemura S, Tanaka S, Kodai S, Shinkawa H et al. Indications for laparoscopic liver resection of mass-forming intrahepatic cholangiocarcinoma. Asian J Endosc Surg. 2020; 13: 46-58.

28. Bektas H, Yeyrek C, Kleine M, Vondran FW, Timrott K, Schweitzer N et al. Surgical treatment for intrahepatic cholangiocarcinoma in Europe: a single center experience. J Hepatobiliary Pancreat Sci. 2015; 22: 131-7.

29. Morine Y, Shimada M. The value of systematic lymph node dissection for intrahepatic cholangiocarcinoma from the viewpoint of liver lymphatics. J Gastroenterol. 2015; 50: 913-27.

30. Zhou R, Lu D, Li W, Tan W, Zhu S, Chen X et al. Is lymph node dissection necessary for resectable intrahepatic cholangiocarcinoma? A systematic review and meta-analysis. HPB (Oxford). 2019; 21: 784-92.

31. Chan KM, Tsai CY, Yeh CN, Yeh TS, Lee WC, Jan YY et al. Characterization of intrahepatic cholangiocarcinoma after curative resection: outcome, prognostic factor, and recurrence. BMC Gastroenterol. 2018; 18: 180.

32. Lin ZY, Liang ZX, Zhuang PL, Chen JW, Cao Y, Yan LX et al. Intrahepatic cholangiocarcinoma prognostic determination using pre-operative serum C-reactive protein levels. BMC Cancer. 2016; 16: 792.