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WORD COUNT

3090

TIME SUBMITTED

26-FEB-2022 02:03PM

PAPER ID

83023620

Name of Journal: *World Journal of Gastrointestinal Surgery*

Manuscript NO: 71691

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Analysis of prognostic impact factors of patients with mass-forming intrahepatic cholangiocarcinoma: a case series of 68 patients

Clinical outcomes of mass-forming intrahepatic cholangiocarcinoma

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Abstract

BACKGROUND

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer in humans after hepatocellular carcinoma (HCC), is a rare epithelial malignancy that results in poor prognosis. According to Liver Cancer Study Group of Japan (LCSGJ) classification, ICC can be divided into three types: mass-forming (MF) type, periductal-infiltrating (PI) type and intraductal- growth (IG) type. The MF type is the most common, accounting for 57.1-83.6% of ICC. Nevertheless, little is known about the epidemiology and treatments of MF ICC.

AIM

This study aims to examine the prognostic factors of patients with mass-forming intrahepatic cholangiocarcinoma (MF ICC).

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.

RESULTS

The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively. Univariate analyses revealed that surgical resection ($P < 0.001$), nodal metastasis ($P < 0.001$), tumor location ($P = 0.039$), vascular invasion ($P < 0.001$), ascites ($P < 0.001$) and differentiation ($P = 0.009$) were significantly associated with the prognosis and survival of MF ICC. Multivariate analysis revealed 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, $P = 0.045$) may be used as independent risk factors for MF ICC. The pooled 1-, 3-, and 5-year survival rates in the 19 patients of exploration group were 5.3%, 5.3%, and 0,

respectively. Among the 49 patients who underwent surgical resection, the pooled 1-, 3-, and 5-year survival rates were 93.5%, 49.7%, and 14.4%, respectively. univariate and multivariate analyses revealed that 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, $P = 0.008$) may be used as independent prognostic risk factors for surgical resection patients.

CONCLUSION

The prognosis of MF ICC is dismal, especially with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affected the efficacy of surgical resection.

Key Words: Intrahepatic cholangiocarcinoma; mass-forming; treatment; prognosis

Feng J, Liang B, Zhang HY, Liu Z, Jiang K, Zhao XQ. Analysis of prognostic impact factors of patients with mass-forming intrahepatic cholangiocarcinoma: a case series of 68 patients. *World J Gastrointest Surg* 2021; In press

Core Tip: This is a single-center, large-scale retrospective study on mass-forming intrahepatic cholangiocarcinoma (MF ICC). To examine the prognostic factors of MF ICC and improve the outcomes, we carried out this study. The study found the patients with MF ICC with ascites and vascular invasion have a poor prognosis. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and patients with vascular invasion and lymph node metastasis have poor surgical results.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) refers to a malignant tumor originating from the branching epithelial cells of the intrahepatic secondary bile duct and above, with a poor prognosis [1-2]. It has been reported that both the morbidity and mortality have gradually increased in recent years [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, periductal-infiltrating (PI) type and intraductal- growth (IG) type [11]. Among them, 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 analyze prognostic factors of patients with MF ICC.

MATERIALS AND METHODS

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.

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.

Data collection

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

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.

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 \pm 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.

RESULTS

Characteristics of the patients

Among the 68 patients, 50 were male and 18 female, ranging from 24 to 74 years with a median age of 54. 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). Twenty-eight (41.2%) patients had elevated CA 19-9 levels, 5 of whom had 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).

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 pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively. (Table 2). Univariate analyses revealed that surgical resection ($P < 0.001$), nodal metastasis ($P < 0.001$), tumor location ($P = 0.039$), vascular invasion ($P < 0.001$), ascites ($P < 0.001$) and differentiation ($P = 0.009$) were significantly associated with the prognosis and survival of MF ICC (Table 3). Multivariate analysis revealed 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, $P = 0.045$) may be used as independent risk factors for MF ICC. (Table 3).

Subgroup analyses

The pooled 1-, 3-, and 5-year survival rates in the 19 patients of exploration group were 5.3%, 5.3%, and 0, respectively. Correspondingly, the pooled 1-, 3-, and 5-year

survival rates in the 49 patients of surgical resection group were 93.5%, 49.7%, and 14.4%, respectively. The survival rates of resection group was significantly better than that of exploration group ($P < 0.001$) (Figure). Table 4 presents the univariate and multivariate analyses of the factors associated with survival in the surgery group. Unlike the whole group of patients, univariate and multivariate analyses revealed that **1** 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, $P = 0.008$) may be used as independent prognostic risk factors for surgical resection patients.

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. The results showed that the prognosis of MF ICC is dismal, especially with ascites or vascular invasion. Resectable patients have a better prognosis, and vascular invasion and lymph node 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* [23] 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%). Ahn *et al* [24] reported that HBV infection itself was not regarded as an independent prognostic factor. Tao *et al*[25] described that 1-, 3-, and 5-year cumulative survival rates of HBsAg-positive ICC patients are significantly lower than HBV-negative ICC patients. 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* [13] deemed that patients with positive margins had a poor prognosis. Tang *et al* [16] reported that the prognosis in patients with margins >1 cm was better than that of patients with margins ≤1 cm, while Bartsch *et al* [10] showed that the margin width was not related to prognosis. 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 matter 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* [13] 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%. In the present study, the 5-year survival rates in patients of the resection group and 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 multicentric 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.

CONCLUSION

The prognosis of MF ICC is dismal, especially with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affected the efficacy of surgical resection.

ARTICLE HIGHLIGHTS

Research background

The MF type is the most common intrahepatic cholangiocarcinoma (ICC), accounting for 57.1-83.6% of ICC. Nevertheless, little is known about the epidemiology and treatments of MF ICC.

Research motivation

Improve the outcomes of ICC.

Research objectives

To examine the prognostic factors of patients with MF ICC.

Research methods

We carried out a retrospective analysis of consecutive patients with MF ICC. The patients were divided into the resection group and exploration group.

Research results

The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively. Univariate analyses revealed that surgical resection ($P < 0.001$), nodal metastasis ($P < 0.001$), tumor location ($P = 0.039$), vascular invasion ($P < 0.001$), ascites ($P < 0.001$) and differentiation ($P = 0.009$) were significantly associated with the prognosis and survival of MF ICC. Multivariate analysis revealed 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, $P = 0.045$) may be used as independent risk factors for MF ICC. The pooled 1-, 3-, and 5-year survival rates in the 19 patients of exploration group were 5.3%, 5.3%, and 0%, respectively. Among the 49 patients who underwent surgical resection, the pooled 1-, 3-, and 5-year survival rates were 93.5%, 49.7%, and 14.4%, respectively. Univariate and multivariate analyses revealed that 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, $P = 0.008$) may be used as independent prognostic risk factors for surgical resection patients.

Research conclusions

The prognosis of MF ICC is dismal, especially with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affected the efficacy of surgical resection.

Research perspectives

Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affected the efficacy of surgical resection.

ACKNOWLEDGEMENTS

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