(Full title)

Pathological Confirmation of Para-Aortic Lymph Node Status as a Potential Criterion for the Selection of Intrahepatic Cholangiocarcinoma Patients for Radical Resection with Regional Lymph Node Dissection

(A short title)

The prognosis after curative resection for intrahepatic cholangiocarcinoma without para-aortic lymph node metastasis

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Abstract

Background Para-aortic lymph node (PAN) metastasis has been traditionally defined as distant metastasis. Many studies suggest that lymph node metastasis in intrahepatic cholangiocarcinoma (ICC) is one of the strongest prognostic factors for patient survival; however, the PAN status was not examined separately from regional lymph node metastasis in these reports. Here, we investigated whether regional lymph node metastasis without PAN metastasis in ICC can be classified as resectable disease and whether curative resection can have a prognostic impact.

Methods Between 1998 and 2010, 47 ICC patients underwent hepatic resection and systematic lymphadenectomy with curative intent. We routinely performed the dissection of PANs, with frozen-section pathological examinations performed intraoperatively. If PAN metastases were identified, curative resection was abandoned. We retrospectively investigated the prognostic factors for patients survival after curative resection for ICC without PAN metastases, with particular attention on the prognostic impact of lymphadenectomy.

Results Univariate analysis identified concomitant portal vein resection, concomitant hepatic artery resection, intraoperative blood loss, intraoperative transfusion, and residual tumor as significant negative prognostic factors. However, lymph node status was not identified as a significant prognostic factor. The 14 patients with node-positive cancer had a survival rate of 20% at 5 years. Based on a multivariate analysis, intraoperative transfusion was an independent prognostic factor associated with a poor prognosis (Risk ratio, 4.161; $P = 0.0056$).

Conclusions Regional lymph node metastasis in ICC should be classified as resectable disease, because the survival rate after surgical intervention was acceptable when PAN metastasis was pathologically negative.

Introduction

Intrahepatic cholangiocarcinoma (ICC) arising from the intrahepatic bile ducts is the second most common hepatic malignancy after hepatocellular carcinoma, accounting for 5–20% of all primary liver cancers [1-4]. The incidence of ICC has increased over recent years, and the prognosis of patients with ICC is generally poor in comparison to that of patients with hepatocellular carcinoma. Currently, surgical resection is the only established therapeutic strategy for ICC; however, the reported 5-year survival rates and the median survival following curative resection ranges only from 8% to 29% and 19 to 31 months, respectively [5-10].

Previous reports have suggested that lymph node metastases have a strong negative impact on postoperative survival in ICC [11-16]; however, para-aortic lymph node (PAN) status has not been examined separately from regional lymph node metastases in these reports. In other cancers, PAN metastases are representative of systemic disease spread and are associated with a minimal benefit from radical surgery [17-19]. Meanwhile, regional lymphadenectomy has been recognized as necessary for biliary tract cancer with nodal disease [20,21]. Hence, an important question is

whether regional lymph node metastases and PAN metastases should be examined separately in terms of survival rate. Here, the study aim was to evaluate whether regional lymph node metastasis in ICC without PAN is a resectable disease.

Materials and methods

Between September 1998 and August 2010, 77 consecutive patients underwent surgery for ICC at the Division of Surgery, Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine. ICC was defined as adenocarcinoma arising from the second or more peripheral branches of the intrahepatic bile ducts. Patients with combined hepatocellular carcinoma and cholangiocarcinoma were excluded from this study. Of the 77 consecutive patients, 25 were not considered candidates for radical surgery because of PAN metastases diagnosed by intraoperative frozen-section diagnosis (n = 12), multiple liver lesions (n = 6), peritoneal metastases (n=4), and locally advanced tumors (n = 3). Postoperatively, PAN status had turn out to be positive by permanent-section examinations in two patients, and three patients received adjuvant chemotherapy during the study period. Therefore, totally 30 patients were excluded from the study. Hence, 47 patients (18 female, 29 male) with a median age of 66 years (range, 40–80 years) who underwent hepatic resection and systematic lymphadenectomy for ICC were included in this study. Complete lymphadenectomy was performed as follows:

Systematic resection of PAN and frozen-section pathological examination were performed during laparotomy prior to curative resection. The para-aortic connective tissue between the levels of the celiac artery and inferior mesenteric artery was resected as PAN (Fig.1). If PAN metastases were identified, curative resection was not performed. If PAN metastases were absent, we performed radical hepatic resection and systematic regional lymphadenectomy. The diagnoses of PAN metastasis were confirmed by permanent section after the surgery. The dissected regional lymph nodes included the lymph node of the hepatoduodenal ligament and those around the common hepatic artery, the portal vein, the common bile duct, and the head of pancreas. We performed lymph node sampling in the right cardiac portion and along the lesser curvature of the stomach only in cases in which the tumor was located within the left hepatic lobe. If sampled nodes were positive, additional lymph node dissection was conducted in the relevant areas.

Preoperatively, all patients underwent three-phase abdominal computed tomography (CT), chest CT, abdominal magnetic resonance imaging (MRI), and liver ultrasonography for preoperative assessment of liver and extrahepatic metastasis. No patients had been administered postoperative adjuvant chemotherapy . None of the patients who underwent curative liver resection were lost to follow-up. At the final assessment (August 2011), 23 patients remained alive, and 24 patients had died. The minimum follow-up period was 12 months or until death, with an overall median follow-up of 54 months (range, 12–155 months).

Tumor stage was defined using the pathological tumor node metastasis (TNM) classification system proposed by the Union Internacional Contra la Cancrum (UICC) 7th edition [22]. The

macroscopic tumor gross type was classified into the following categories according to the system proposed by the *Liver Cancer Study Group of Japan*: mass forming type, periductal infiltrating type, intraductal growth type, and other [23]. We analyzed the following clinicopathologic factors likely to influence survival after surgical resection: gender, age, preoperative jaundice, hepatitis virus, preoperative indocyanine green retention rate after 15 minutes, preoperative serum carcinoembryonic antigen level, preoperative serum carbohydrate antigen 19-9 level, concomitant resection of the portal vein, concomitant resection of the hepatic artery, operation time, blood loss, intrahepatic transfusion, macroscopic gross type, tumor number and size, macroscopic gross pattern, lymph node metastases, liver capsular invasion, microscopic vessel (vascular or lymphatic) invasion, perineural invasion, p stage (UICC), and resection margin.

Univariate analysis of overall survival rate was performed using the Kaplan-Meier method and the log-rank test, and multivariate analysis was conducted using a Cox proportional hazard regression model using StatView statistical software (version 5.0; SAS Institute Inc., Cary, NC). Values of $P < 0.05$ were considered significant.

Results

Paraaortic lymphnodes status

A median number of 10.5 PANs were resected per patient. 12 patients were not considered candidates for radical surgery because of PAN metastases by intraoperative frozen-section diagnosis.

In 2 patients, permanent-section examinations revealed positive PAN after surgery, despite negative results from the examination of the intraoperative frozen sections. Therefore, theses 2 patients were excluded from this study.

Surgical Procedures and Complications

The operative data are summarized in Table 1. Hemihepatectomy or trisectionectomy was performed in 43 (92%) of the 47 patients; 28 left hemihepatectomies (segments II–IV ± I), 8 right hemihepatectomies (segments V–VIII ± I), 5 left trisectionectomies (segments I–V + VIII), and 2 right trisectionectomies (segments I + IV–VIII). We also performed extrahepatic bile duct resection in 37 patients (79%). Concomitant vascular resections were performed in 18 patients, including resection and reconstruction of the hepatic artery (n = 5), the portal vein (n = 8), and the hepatic vein or inferior vena cava (n = 10). Partial resection of the diaphragm was necessary in 3 patients due to direct invasion of the tumor. Two patients died in the hospital because of liver failure, resulting in an in-hospital mortality rate of 4%. One of these patients had undergone right hemihepatectomy with concomitant extrahepatic bile duct resection and septicemia, whereas the other patient had undergone left trisectionectomy with concomitant inferior vena cava resection.

Postoperative complications occurred in 27 (57%) patients. The most common complication was biliary fistula (n = 7).

No complication associated with PAN dissection such as postoperative chylous ascites, bleeding, or thrombosis was encountered.

Clinicopathologic Characteristics

The tumor diameter ranged from 1.0 to 11.0 cm (median, 4.5 cm). Eight patients had multiple tumors. Overall, 43 (86%) R0 resections and 6 R1 resections (1 case demonstrated microscopic involvement of the bile duct stump, while 5 cases had exfoliated stumps) were performed.

Survival after Surgery and Univariate/Multivariate Analysis for Prognostic Factors

The overall survival rate for all 47 patients who underwent hepatic resection was 51% at 3 years and 28% at 5 years; the median duration of survival was 38 months. Univariate analysis identified 5 significant prognostic factors for survival after surgery; concomitant portal vein resection (P = 0.0139), concomitant hepatic artery resection (P = 0.0011), blood loss (P = 0.0181), intraoperative transfusion (P = 0.0006), and residual tumor (P = 0.0062) (Table 2). Lymph node status was not a significant prognostic factor (P = 0.0886) in univariate analysis. The 14 patients with lymph node metastases had a survival rate of 20% at 5 years, while the survival rate in the absence of lymph

node metastasis was 31% at 5 years (Fig. 2). In multivariate analysis, intraoperative transfusion was an independent prognostic factor associated with poor prognosis (risk ratio, 4.161; $P = 0.0056$) (Table 3).

Discussion

In our series of 47 patients without PAN metastases, intraoperative transfusion was identified as an independent prognostic factor. The 3- and 5-year overall survival for the 14 patients with positive lymph node metastases was 40% and 20%, respectively. By contrast, the absence or presence of lymph node metastases had no prognostic significance.

However, the benefit of lymph node dissection after curative resection for ICC is controversial. Some studies have purported that the 5-year survival rate after surgery is 0% in the presence of lymph node metastases and that lymph node dissection was not beneficial [10,24,25]. In contrast, other studies found no significant difference between patients with and without lymph node metastases in terms of survival rates, and suggested that lymphadenectomy may be necessary to improve the prognosis of patients with ICC [6,11,26]. In the previous reports [10,24,25] suggesting a negative prognosis for node-positive patients, systematic regional lymphadenectomy was not completed in all patients and the presence or absence of PAN metastases was not described in detail. In the reports by Uenishi et al. [7] and Shirai et al. [27], all patients received regional

lymphadenectomy. A conclusion of these studies was that lymph node metastasis was an independent prognostic factor associated with a poor prognosis. However, in both series, systematic PAN dissection and pathological examination were performed in only approximately half of the total cases, so that the PAN status could not be clearly defined. PAN metastases is generally accepted as equivalent to distant metastasis and thus to represent a systemic disease [17-19]. Therefore, in the present study, we attempted to identify prognostic factors for survivorship in ICC patients without PAN and to evaluate the efficacy of lymphadenectomy in these patients by excluding patients with PAN metastases, as determined by pathological confirmation. Our results showed that lymph node status was not an independent prognostic factor, and indicate that curative liver resection with systematic regional lymphadenectomy improves the prognosis after surgery for node-positive patients without PAN metastases.

Our results are entirely the opposite of those of previous retrospective reports, and the ultimate difference from past studies was the elimination of PAN metastases. However, our study results do not represent conclusive evidence, because the number of patients was small and the study design was not a prospective. Hence, future large-scale studies will be needed to confirm our findings.

In the present study, the evaluation for PAN metastases was performed by intraoperative pathological examination, since preoperative diagnostic imaging techniques, including CT, MRI, and 18F-fluorodexyglucose positron-emission tomography, have difficulty in accurately detecting lymph node metastases preoperatively [28,29]. Although initially negative according to intraoperative frozen-section examinations, the PAN status was overturned by permanent-section

examinations in 2 patients in the current study. Regardless of these 2 false negative findings, the pathological examination remained the most useful diagnostic method available for excluding PAN metastasis. Other problems of intraoperative PAN dissection are time consumption and related morbidities. As the required time for PAN dissection depends on the numbers of dissected nodes, an accustomed surgeon could obtain results of pathological diagnosis 30-45 minutes after beginning of the PAN dissection. Although intractable ascites retention including chylous ascites is a common complication following paraaortic lymhadenectomy, it may be prevented by complete seal or ligation of the dissected stump of the retropeitoneum and surrounding tissues.

In our study, intraoperative transfusion was differentiated as an independent prognostic factor. Many authors have reported transfusion as a significant prognostic indicator after surgery for a number of malignancies, including gastric cancer [30,31], hepatocellular cancer [32,33], colorectal cancer [34], and pancreatic cancer [35]. However previous studies have not reported intraoperative transfusion an important prognostic factor for survival in patients with ICC. Evaluating the various possible associations between transfusion and prognosis after surgery is difficult; however, the immunosuppressive effect of transfusion may be more apparent after resection, as suggested by the resuls of animal studies [36]. Moreover, Clark et al. [37] commented that the requirements for intraoperative transfusion may reflect the technical difficulty involved in a larger or more advanced tumor, which would be associated with poor prognosis.

In conclusion, regional lymph node metastasis was not a significant prognostic factor for ICC in the absence of PAN metastases diagnosed by pathological confirmation. ICC with positive regional

lymph nodes and negative para-aortic lymph nodes should be a resectable disease.

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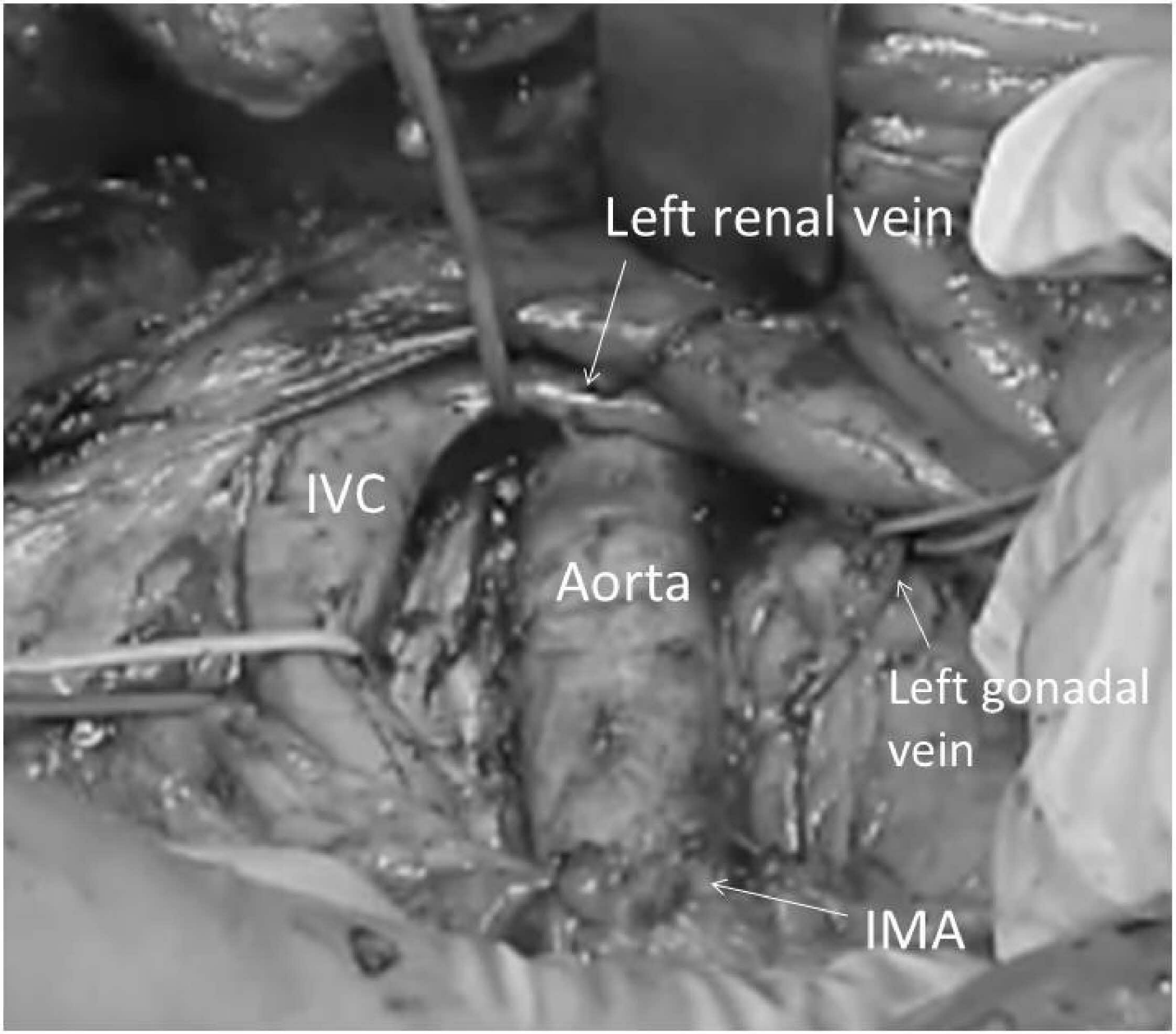
Figure caption

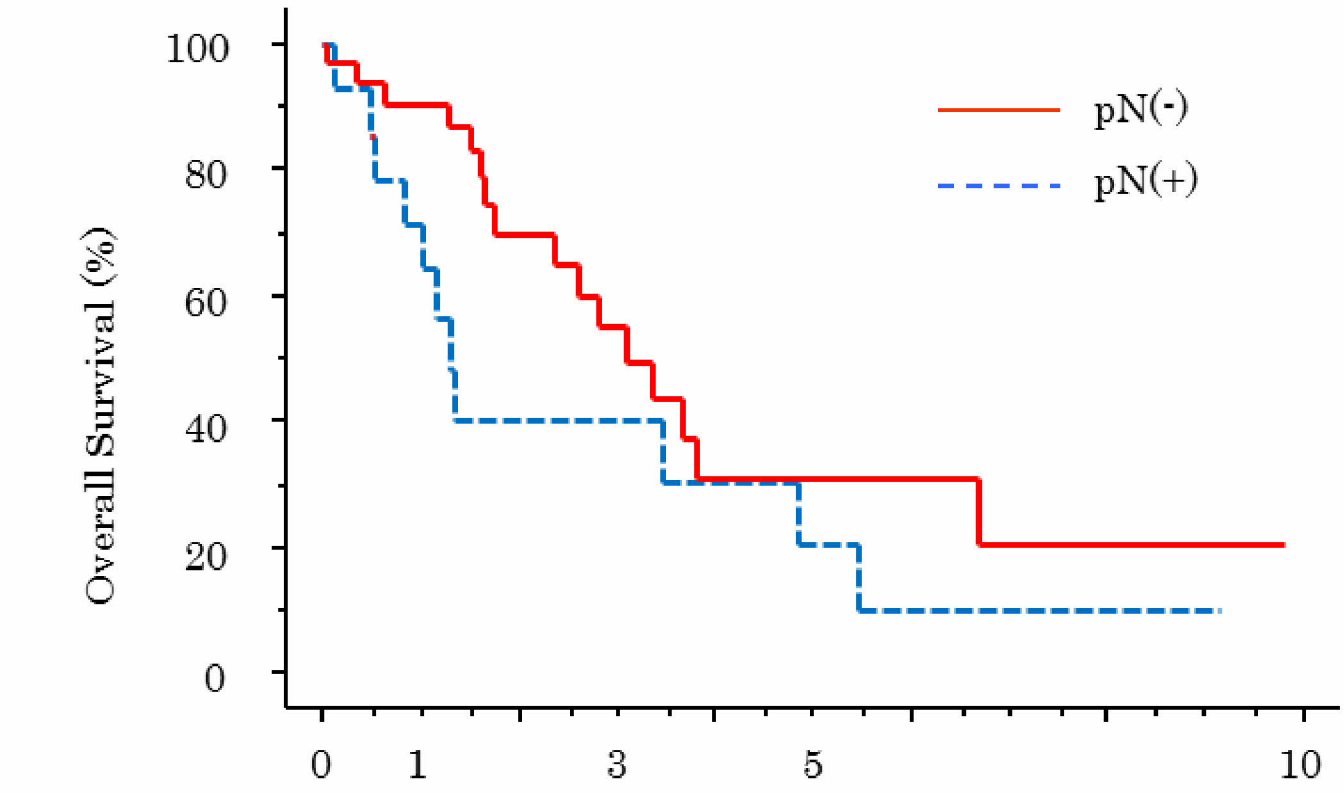
Fig. 1

After *En bloc* resection of PANs. The resected connective tissue containing PANs were located between the levels of the celiac artery and inferior mesenteric Artery, and on the area between the aorta and the inferior vena cava. *IMA* inferior mesenteric artery; *IVC* inferior vena cava

Fig. 2

Overall survival in case of lymph node positive and negative. Survival rate of 14 patients with lymph node metastasis is 20% at 5 years, while survival rate without lymph node metastasis is 31 % at 5 years. $P = 0.0886$ (log rank test)


Left renal vein
IVC
Aorta
Left gonadal vein
IMA



No. at risk				
pN(-)	33	29	10	5
pN(+)	14	10	4	2

Table 1 Surgical procedures and additional resection in the 47 patiets with ICC

Procedure	Number	%
Segmentectomy	0	0
Bisegmentectomy (segments III,IV)	1	2
Left lateral sectionectomy (segments II,III)	1	2
Right anterial sectionectomy (segments V,VIII)	2	4
Hemihepatectomy		
Right hemihepatectomy (Segments V–VIII)	3	6
Right hemihepatectomy and caudate lobe resection (Segments I,V–VIII)	5	11
Left hemihepatectomy (Segments II–IV)	1	2
Left hemihepatectomy and caudate lobe resection (Segments I–IV)	27	58
Trisectionectomy		
Right trisectionectomy and caudate lobe resection (Segments I,IV–VIII)	2	4
Left trisectionectomy and caudate lobe resection (Segments I–V,VIII)	5	11
Total	47	100

Table 2 Univariate analysis of prognostic factors in 47 patients with ICC

Factors	No. of patients	Actual survival numbers (and overall survival rate) 3y- (%)	5y- (%)	Median survival time (months)	Log rank test *P*-value
Total	47	14 (51)	7 (28)	37.5	
Gender					
Male	29	8 (44)	4 (22)	31.9	0.6243
Female	18	6 (67)	3 (40)	44.5	
Age(years)					
65＞	22	7 (44)	2 (15)	31.9	0.1340
65≦	25	7 (59)	5 (42)	59.1	
Preoperative jaundice					
(+)	11	3 (55)	3 (55)	66.4	0.4075
(-)	36	11 (49)	4 (20)	33.9	
Hepatitis virus					
(+)	5	3 (60)	2 (40)	46.4	0.7599
(-)	42	11 (48)	5 (24)	33.9	
ICG15R					
11＞	25	8 (53)	3 (23)	37.5	0.4702
11≦	22	6 (49)	4 (33)	21.2	
Preoperative CEA level					
6.5＞	36	11 (51)	6 (31)	37.5	0.1431
6.5≦	11	3 (55)	1 (18)	44.5	
Preoperative CA19-9 level					
37＞	16	5 (79)	2 (43)	40.8	0.2719
37≦	31	9 (40)	5 (22)	28.7	
Concomitant portal vein resection					
(+)	8	1 (17)	1 (17)	12.3	0.0139
(-)	39	13 (58)	6 (29)	40.8	
Concomitant hepatic artery resection					
(+)	5	0 (0)	0 (0)	9.9	0.0011
(-)	42	14 (58)	7 (32)	40.8	
Operation time					
630min＞	25	10 (63)	4 (28)	42.2	0.1097
630min≦	22	4 (36)	3 (27)	19.8	
Blood loss					
1800cc＞	25	11 (66)	6 (36)	44.5	0.0181
1800cc≦	22	3 (31)	1 (20)	18.4	
Intraperative Trunsfusion					
(+)	20	2 (24)	1 (24)	15.5	0.0006

(-)	27	12 (70)	6 (35)	44.5	
Macroscopic gross type					
MF	18	3 (32)	1 (11)	21.2	0.2061*
MF+PI	17	7 (63)	4 (36)	42.2	
MF+IG	3	1 (100)	0 (0)	44.5	
IG	5	2 (80)	1 (80)	—	
PI	4	1 (25)	1 (25)	28.7	
Tumor size					
50mm＞	25	7 (49)	4 (28)	33.9	0.8652
50mm≦	22	7 (52)	3 (27)	37.5	
Macroscopic growth pattern					
eg	17	6 (60)	2 (25)	37.5	0.9613
ig	30	8 (46)	5 (29)	33.9	
Tumor number					
St	39	12 (50)	7 (32)	40.8	0.3735
Mt	8	2 (55)	0 (0)	37.5	
Lymph node metastases					
(+)	14	4 (40)	2 (20)	15.9	0.0886
(-)	33	10 (55)	5 (31)	34.1	
Liver capsular invasion					
(+)	12	4 (48)	1 (12)	33.9	0.3732
(-)	35	10 (53)	6 (35)	40.8	
Microscopic vessel invasion					
(+)	34	9 (42)	4 (19)	31.9	0.1350
(-)	13	5 (74)	3 (56)	81.1	
Perineural invasion					
(+)	29	8 (41)	4 (20)	31.9	0.1860
(-)	18	6 (69)	3 (42)	46.4	
pStage(UICC)					
I,II,III	21	5 (52)	2 (28)	37.5	0.7415
IVA, IVB	26	9 (49)	5 (27)	31.9	
Resection margin					
(+)	6	0 (0)	0 (0)	15.5	0.0062
(-)	41	14 (58)	7 (32)	40.8	

ICG15R indocyanin green retention rate after 15 minutes; *CEA* carcinoembryonic antigen; *CA19-9* carbohydrate antigen 19-9; *MF type* mass forming type; *PI type* periductal infiltrating type; *IG type* intraductal growth type

*; Calculated between the MF type vs MF+PI type.

Table 3 Multivariate analysis of prognostic factors after hepatic resection for ICC

Prognostic factor	Risk ratio (95% CI)	*P*-value
Intraoperative transfusion	4.161 (1.517, 11.416)	0.0056
Blood loss (1800cc<)	1.657 (0.595, 4.613)	0.3338
Resection margin (positive)	1.122 (0.242, 5.200)	0.8828
concomitant portal vein resection	2.212 (0.647, 7.559)	0.2053
concomitant hepatic artery resection	2.896 (0.536, 15.632)	0.2164
lymph node metastases (positive)	1.799 (0.719, 4.496)	0.2092

CI; confidence interval.