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ORIGINAL ARTICLE

Prognostic impacts of postoperative complications in patients with intrahepatic cholangiocarcinoma after curative operations

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Abstract
Background The postoperative complication is one of an indicator of poor prognosis in patients with several gastroenterological cancers after curative operations. We, herein, examined prognostic impacts of postoperative complications in patients with intrahepatic cholangiocarcinoma after curative operations.
Methods We retrospectively analyzed 60 patients with intrahepatic cholangiocarcinoma who underwent primary curative operations from June 2002 to February 2016. Prognostic impacts of postoperative complications were analyzed using log-rank test and Cox proportional hazard model.
Results Postoperative complications (Clavien-Dindo classification grade 3 or more) occurred in 13 patients (21.7%). Overall survival of patients without postoperative complications was significantly better than that of patients with postoperative complications ($p = 0.025$). Postoperative complications are independent prognostic factor of overall survival (hazard ratio 3.02; $p = 0.030$). In addition, bile duct resection and reconstruction (Odds ratio 59.1; $p = 0.002$) and hepatitis C virus antibody positive (Odds ratio 7.14; $p= 0.022$), and lymph node dissection (Odds ratio 6.28; $p = 0.040$) were independent predictors of postoperative complications.
Conclusion Postoperative complications may be an independent predictor of poorer survival in patients with intrahepatic cholangiocarcinoma after curative operations. Lymph node dissection and bile duct resection and reconstruction were risk factors for postoperative complications, therefore we should pay attentions to perform lymph node dissections, bile duct resection and reconstruction in patients with intrahepatic cholangiocarcinoma.

Keywords ICC · Postoperative complication · Prognosis · Lymph node dissection

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic tumor after hepatocellular carcinoma and accounts for nearly 3% of all gastrointestinal cancers diagnosed worldwide [1, 2]. Although their incidence is increasing worldwide, ICC still have a poorer prognosis than other cancers such as 5-years survival rate as 5–50% [3–5]. It is considered a highly malignant neoplasm because it is frequently associated with lymph node (LN) involvement, intrahepatic metastasis, and peritoneal dissemination [6]. In additions, many ICC have a feature of the chemotherapy resistance, therefore effective chemotherapies including adjuvant therapy, are few in ICC. In this point, curative resection is a only potent therapy for ICC.

Postoperative complications are reported to be one of the poor prognosis factors in several cancers such as colorectal liver metastasis, pancreatic cancer, and esophageal cancer [7–9]. It is said that postoperative complications may cause to systemic inflammation and this decrease the immunoresponse for the cancer [10]. Therefore, we surgeons should perform safe operations without postoperative complications and to prevent its occurrence to improve patient's prognosis. A few studies reported about prognostic impacts of postoperative complications

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in patients with ICC. In addition, major hepatectomy and intraoperative transfusion were independent predictors of severe morbidity [11]. However, there is few study in only Asian population about prognostic impacts of postoperative complications in patients with ICC after curative operations. Therefore, we would evaluate prognostic impacts of postoperative complications in patients with ICC after curative operations and identify predictors of postoperative complications.

Materials and methods

Patients

We performed a retrospective analysis of consecutive patients at Kumamoto University Hospital (KUH, Kumamoto, Japan) to examine the surgical outcomes of patients with ICC who underwent curative operations. Between June 2002 and February 2016, 78 patients underwent laparotomy for ICC at KUH. The diagnosis of ICC was confirmed by pathological examinations. Of 78 patients, 60 patients, without preoperative chemotherapy, underwent primary curative operations, which resulted in pathological curative resection (R0). Of 18 excluded patients, 10 patients were operations for recurrence, 4 were non-curative operations (including R1 cases), 2 patients were performed preoperative chemotherapy, and 2 were died within 90 days of surgery. Therefore, we analyzed 60 patients to examine the prognostic impacts of postoperative complications in patients with ICC. The median follow-up time for censored patients was 2.6 years. The institutional review board approved this study.

The definition of postoperative complication

Postoperative complications related to the operation were graded according to the Clavien-Dindo classification [12]. Any complications that required invasive or radiological intervention were classified as grade 3. Life-threatening complications requiring intensive care unit stay were classified as grade 4, and perioperative mortality as grade 5. Perioperative complications were recorded during the initial hospital stay—from day of surgery to discharge. Complications resulting in patients being readmitted within 30 days of surgery were also assessed. Perioperative mortality was defined including death within 90 days of surgery or during post-surgery hospitalization. In this report, we defined postoperative complications as 3 or more in Clavien-Dindo classification.

The indications for lymph node dissection

We performed lymph node dissection for the patients who were suspected to have LN metastasis in preoperative computed tomography scan or positron emission tomography or macroscopic findings during the operations [13]. We suspected LN metastasis if LN size was 10 mm or larger in preoperative imaging or hard texture was noted during the operation. In such cases, we mainly performed lymph node dissection at #8, #12 and occasionally added on some LN such as #1, #3, #7 and #13. Sampling of LN for rapid pathological diagnosis or staging during operations was not included in lymph node dissection.

Statistical analysis

Comparison between two groups was examined by the Student t test and Mann–Whitney U test where appropriate in continuous variables, and χ^2 tests and Fisher's exact test where appropriate in categorical variables. Continuous variables are presented as mean ± standard deviation. Independent predictors of postoperative complication were identified by means of a multiple logistic regression model. Factors included in this model were chosen by the result of univariate analysis in clinicopathological characteristics ($p < 0.10$). The cut off value of operating time was median in 60 patients. The overall survival (OS) rate was calculated using the Kaplan–Meier method from the date of surgery, and comparisons of survival curves were made by the log-rank test. In addition, significant variables in univariate analysis were included in a Cox proportional hazard model in order to identify independent prognostic predictors. The variables from pre-, intra-, and postoperative factors that might influence the prognosis were selected such as positive LN metastasis [6, 11, 14], age, tumor size, multiple tumors, and vascular invasion [11, 14]. Gender, ICGR15, blood loss, transfusion, operative time, major hepatectomy, bile duct resection and reconstruction, lymph node dissection, postoperative complications were also selected. The cut off value of blood loss was median in 60 patients (525 ml). All results with 2 tailed values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using JMP software (Version 12; SAS Institute, Cary, NC, USA).

Results

Details of complications

Twenty-one patients (35.0%) had unremarkable postoperative courses. Grade 1 complications occurred in 2 patients (3.3%), grade 2 in 6 patients (10%), grade 3 in 13 patients

(21.7%), and grade 4 in none. As mentioned before, in this study, grade 1 and grade 2 complications were not defined as postoperative complications that did not result in a change in the postoperative course. Details of postoperative complications were presented in Table 1. There were 6 cases of bile leakage, 5 of surgical site infection, 4 of pleural or abdominal effusion, 2 of delayed gastric emptying and 1 of anastomosis leakage, stomach ulcer bleeding, ileus, and elevation of liver enzyme. Table 2 shows comparisons of clinicopathological characteristics, tumor-related factors and perioperative outcomes between the complication (+) group and the complication (−) group. Bile duct resection and reconstruction ($p = 0.006$) and lymph node dissection ($p = 0.015$) were more frequently performed in the postoperative complications (+) group.

Predictors for complications

Table 3 shows the independent predictors of postoperative complications in patients with ICC. Factors with $p < 0.1$ in Table 2 were applied to multiple logistic regression model, and bile duct resection and reconstruction (Odds ratio 59.1, $p = 0.002$), HCV antibody positive (Odds ratio 7.14, $p = 0.022$), and lymph node dissection (Odds ratio 6.28, $p = 0.040$) were identified as independent risk factors for postoperative complications.

Postoperative complications in relation to patient's prognosis

During the follow-up of 60 patients, there were 22 deaths (36.7%). According to log-rank test, the overall survival rate of patients with postoperative complications ($n = 13$) was significantly worse than that of those without postoperative complications (Log-rank $p = 0.025$). Kaplan–Meier curves were shown in Fig. 1. Cox regression analysis identified independent poor prognostic factors as pN1 (HR 3.31, $p = 0.042$) and postoperative complications (HR 3.02, $p = 0.030$) (Table 4). On the other hands, as shown in Fig. 2, there was no significant difference in recurrence free survival between the two groups ($p = 0.230$). Although patients with postoperative complications had more recurrence ($n = 8$, 61.5%) than patients without postoperative complications ($n = 24$, 51.1%), there was no significant difference in recurrence ($p = 0.728$). In addition, the recurrence pattern (intrahepatic vs. extrahepatic) was 3 vs. 5 patients in patients with postoperative complications and 11 vs. 13 patients in patients without postoperative complications. There was no significant difference between the two groups ($p = 0.681$).

Discussion

This study examined the prognostic impacts of postoperative complications in 60 patients who had undergone curative operations of ICC. We found that postoperative complications have negative impacts in patient's OS. In addition, we also found lymph node dissection may be a risk factor for postoperative complications.

In our study, postoperative complications (grade 3 or more) occurred in 13 (21.7%) patients. Total patients with postoperative complications, which include grade 1 or 2, were 21 (35.0%) patients. Our results are almost similar to other reports. Spolverato et al. reported the major morbidity (grade 3 or more) rate was 15.6% and these were found to be independent predictors of worse long-term outcomes in patients with ICC [15]. Doussort et al. reported the major morbidity (grade 3 or more) rate was 21.6%, and reported major hepatectomy and intraoperative transfusion were independent predictors of postoperative complications [11]. However, these two factors were not identified as risk factors for postoperative complications in our own study. On the other hand, lymph node dissection and bile

Table 1 Detail of postoperative complication (*n*)

Complications	Clavien-Dindo classification					Total
	0	I	II	III	IV	
None	39					39
Bile leakage			1	5		6
Surgical site infection		2		3		5
Pleural or abdominal effusion			1	3		4
Delayed gastric emptying			2			2
Anastomosis leakage				1		1
Ulcer bleeding				1		1
Ileus			1			1
Elevation of liver enzyme			1			1
Total	39	2	6	13	0	60

Table 2 Comparisons of clinicopathological characteristics, tumor-related factors,and perioperative factors between patients with and without postoperative complications

Variables	Postoperative complications		*p* value
	(−), $n = 47$	(+), $n = 13$	
Clinicopathological characteristics			
Age (years)	66.0 ± 1.5	65.1 ± 2.9	0.769
Gender (M/F)	11/36	3/10	0.980
BMI (kg/m^2)	23.1 ± 0.41	21.8 ± 0.79	0.118
HBs-Ag (+)	6/41	1/12	0.614
HCV-Ab (+)	7/40	5/8	0.060
AST (U/L)	36.9 ± 4.0	32.2 ± 7.6	0.592
ALT (U/L)	42.4 ± 7.6	30.7 ± 14.7	0.484
T-bil (mg/dL)	0.75 ± 0.047	0.80 ± 0.09	0.620
Alb (g/dL)	4.10 ± 0.068	3.87 ± 0.13	0.133
PT (%)	96.1 ± 3.2	105 ± 5.5	0.148
ICG R15 (%)	9.36 ± 0.81	10.1 ± 1.5	0.640
Liver damage (A/B)	45/1	13/0	0.592
CEA (ng/mL)	48.1 ± 39.1	2.3 ± 75.6	0.594
CA19-9 (U/mL)	1359 ± 1002	70 ± 1937	0.558
Tumor-related factors			
Gross type			0.205
Mass-forming	39	9	
Periductal infiltrating	3	3	
Mass-forming ± periductal infiltrating	5	1	
Tumor size (mm)	41.6 ± 3.4	40.0 ± 6.8	0.794
Tumor number (single/multiple)	39/8	11/2	0.889
Vascular invasion (yes/no)	23/24	5/8	0.503
pN positive (yes/no)	6/41	1/12	0.614
UICC pStage (I/II/III/IV)	15/22/1/9	3/5/0/5	0.507
Perioperative factors			
Hepatectomy (major/minor)	29/18	10/3	0.512
Bile duct resection and reconstruction (yes/no)	1/46	4/9	0.006
Blood loss (mL)	616 ± 84	535 ± 139	0.605
Blood transfusion (yes/no)	6/39	3/9	0.325
Operative time (min)	428 ± 15	490 ± 29	0.062
Type of hepatectomy (minor/major)	18/29	3/10	0.309
Lymph node dissection (yes/no)	15/32	9/4	0.015

BMI body mass index, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *T-bil* total bilirubin, *Alb* albumin, *PT* prothrombin time, *ICG R15* indocyanine green retention at 15 min, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9

Table 3 Predictors of postoperative complications

Predictors	Multivariate analysis		
	Odds ratio	95% CI	*p* value
HCV-Ab (+)	7.14	1.3–45	0.022
Bile duct resection and reconstruction	59.1	3.92–2663	0.002
Operative time ≧ 445 min	6.48	0.73–152	0.097
Lymph node dissection	6.28	1.1–45	0.040

HCV-Ab hepatitis C virus antibody, *CI* confidence interval

duct resection and reconstruction were risk factors for postoperative complications in our study. Sharma et al. also reported lymph node dissection can be associated with significant postoperative complications and patient morbidity in patients with penile cancer [16]. As for lymph node dissection, it may improve the prognosis of the patients with several cancers [17, 18], and also contribute to certify the cancer stage which determine the appropriate treatment such as postoperative chemotherapy [19–21]. However, its clinical benefit is controversial in ICC. Some reports showed lymph node dissection for ICC does not contribute

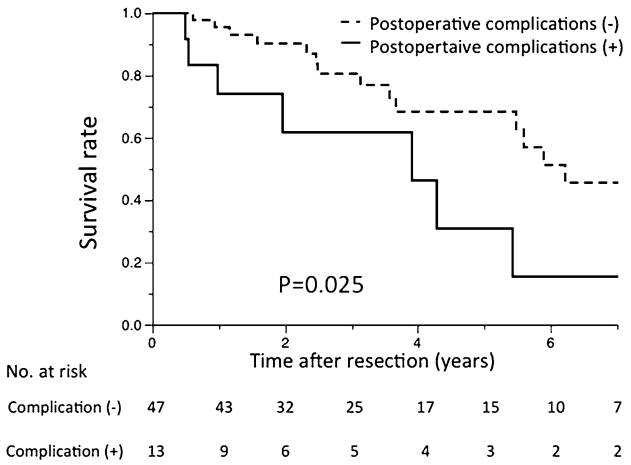

Fig. 1 The patients with postoperative complications were significantly worse prognosis in overall survival ($p = 0.025$)

to patient's prognosis [6, 22]. Others reports showed that regional lymph node dissection should be considered as a standard procedure in resections of ICC [23]. Lymph node dissection was a possible cause of postoperative complications, therefore all patients with ICC had not better undergo lymph node dissection routinely, in other words, only limited patients, who are suspected to have LN metastasis before or during surgery with perihilar type of ICC [24], may be good indications for lymph node dissection. In our study, 9 patients with lymph node dissection had postoperative complications. Of 9 patients, 3 were bile leakage, 3 were pleural or abdominal effusion, 2 were deep surgical site infection, and 1 was anastomosis leakage. On the other hand, 4 patients without lymph node dissection had postoperative complications. Of 4 patients, 2 patients were bile leakage, 1 was ulcer bleeding and 1 was peritonitis. Comparison between patients with and without lymph node dissection, pleural or abdominal effusion was likely to occur in patients with lymph node dissection.

In other cancers, it is considered that postoperative complications are one of the poor prognosis factors, for example, in colorectal liver metastasis [7], hepatocellular carcinoma [25–27], pancreas cancer [8] and esophageal cancer [9]. Although the relationship between postoperative complications and poor prognosis is unclear, there are several possible explanations. First, in addition to the general systematic inflammatory response of surgery itself, complications may further exacerbate systemic inflammation. The systematic inflammatory response is a result of elevated some cytokine and CRP, which contributes to tumor angiogenesis, proliferation, growth, and metastases [28]. Next, severe systematic inflammation caused by postoperative complications, results in immunosuppress condition, which can lead to a modulation of the decrease of tumor surveillance, and possibly increases the risk of tumor metastasis and disease-specific death [10, 29, 30]. Therefore, postoperative complications, especially severe complications which increase systemic inflammation, may significantly adversely impacts the long-term oncological outcome.

This study has some limitations including its retrospective design and that it was a single-center study. Nonetheless, we utilized a database from a single institution built by relatively standardized surgical techniques and postoperative managements, thus avoiding some of the limitations of multicenter, population-based, or nationwide studies.

Table 4 Univariate and multivariate cox regression for overall survival

Variables	Univariate analysis		Multivariate analysis		
	HR	*p* value	HR	95% CI	*p* value
Age ≧ 65	1.39	0.453			
Gender (male vs female)	1.38	0.475			
ICG R15 ≧ 10%	1.62	0.294			
Blood loss ≧ 525 mL	1.25	0.607			
Blood transfusion present (vs absent)	1.49	0.453			
Operative time ≧ 445 min	1.50	0.351			
Major hepatectomy yes (vs no)	1.39	0.502			
Bile duct resection and reconstruction yes (vs. no)	1.92	0.275			
Lymph node dissection yes (vs. no)	1.55	0.304			
Multiple tumors (vs. single)	1.69	0.331			
Tumor size	1.01	0.467			
Vascular invasion present (vs. absent)	1.37	0.456			
pN1 (vs. pNX and pN0)	2.92	0.061	3.31	1.1–8.8	0.042
Postoperative complications yes (vs. no)	2.74	0.044	3.02	1.1–7.4	0.030

ICG R15 indocyanine green retention rate at 15 min, *HR* hazard ratio, *CI* confidence interval

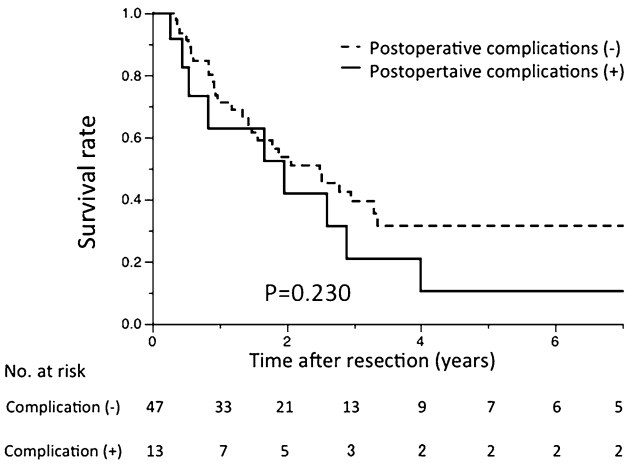

Fig. 2 There was no significant difference in recurrence free survival between the patients with postoperative complications and the patients without postoperative complications ($p = 0.230$)

However we need larger and prospective studies to examine the prognostic impacts of preventing postoperative complications in patients with ICC.

In conclusion, postoperative complications would have poor prognostic impacts in patients with ICC after curative operations. Lymph node dissection and bile duct resection and reconstruction were independent predictive factors for postoperative complications, therefore we should pay attentions to perform lymph node dissections, bile duct resection and reconstruction in patients with ICC.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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