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ORIGINAL ARTICLE

Major postoperative complications compromise oncological outcomes of patients with intrahepatic cholangiocarcinoma after curative resection — A 13-year cohort in a tertiary center

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KEYWORDS
Intrahepatic cholangiocarcinoma;
Hepatectomy;
Post-operative complication;
Oncological outcomes

Summary *Background/Objective:* Hepatectomy is the mainstay of curative treatment for intrahepatic cholangiocarcinoma (ICC). The relationship between postoperative complication and oncological outcome has not been defined. We aimed to elucidate the effect of postoperative complication on long-term survival of ICC patients after curative resection.
Methods: Data of consecutive patients who had curative resection for ICC at our hospital from 1991 to 2013 were reviewed. Patients with cholangiohepatocellular carcinoma, metastatic adenocarcinoma or Klaskin tumor were excluded. Clinicopathological data and postoperative events were extracted from database for survival analysis.
Results: There were 107 patients in our series. Their median age was 61 years. The median follow-up time was 24 months. The median tumor size was 6 cm. Major hepatectomy was required in 52.3% of them. The median operation time and blood loss was 439 minutes and 0.9L respectively. R0 resection was achieved in 88.8% of them. The median length of stay was 11 days. The 30-day and 90-day mortality was 2.5% and 6.8% respectively. Major complications were found in 20.6% of them. Patients with postoperative complications had significantly inferior survival than patients without (3-yr DFS 38% vs. 27%, $P = 0.001$; 3-yr overall: 51% vs. 27%, $P < 0.001$). Multivariable analysis showed that postoperative complication was

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an independent factor associated with disease-free survival (OR 1.9 95% C.I. 1.10—3.24, P = 0.021) and overall survival (OR 2.1, 95% C.I. 1.13—3.93, P = 0.018).
Conclusion: Postoperative complication has a significant impact on ICC patients' long-term survival. Extra measures such as adjuvant chemotherapy should be considered for patients who develop major complications after surgery.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer, following hepatocellular carcinoma (HCC). It contributes to 10% of all primary liver cancer and 25% of all cholangiocarcinomas.[1,2] Pathologically, it can be sub-classified into mass-forming, intra-ductal growth and peri-ductal infiltrative types,[3] with the last one being the least common but most aggressive.[4] Complete resection represents the only hope of cure. Despite the advances in surgical and perioperative intensive care, prognosis of ICC patients remains poor. The 5-year survival of patients with ICC after resection ranged from 21% to 39% according to various series.[5—8] A number of clinical and pathological factors, such as tumor size, number of tumor, presence of metastatic lymph node, microvascular permeation, resection margin status and role of PET scan had been associated to influence long-term survival.[5,7,9—20] Data concerning the influence of postoperative complication on long-term survival was scarce.[21] Such relationship had been established in colorectal cancer,[22,23] pancreatic cancer,[24] colorectal liver metastasis[25] and hepatocellular carcinoma.[26] We aimed to further elucidate the effect of postoperative complication on long-term survival of ICC patients who had undergone a curative resection.

2. Patients and methods

2.1. Patient selection

This is a retrospective cohort of consecutive 107 patients who had undergone curative resection for ICC in Queen Mary Hospital, the University of Hong Kong, from 1991 to 2013. Clinical and pathological data were extracted from a prospectively maintained database. Patients who had mixed hepatocholangiocarcinoma, metastatic adenocarcinoma, Klaskin tumor or macroscopic residual disease (i.e. R2 resection) were excluded from the study. Diagnosis of ICC in all patients were confirmed with microscopic assessment by dedicated pathologists; Immunohistochemical staining such as cytokeratin-7, cytokeratin-20 and TTF-1 were performed whenever necessary.

2.2. Preoperative assessments and operative techniques

Apart from routine chest radiography and baseline biochemical tests, indocyanine green (ICG) clearance and volumetric study was performed for all patients who undergo major liver surgery in our center. The cut-off level for ICG retention at 15 min was 18% and 22% for minor and major hepatectomy respectively. While the minimum acceptable future liver remnant volume to estimated liver volume was 25% for non-cirrhotic livers.[27,28] Details of the operative techniques had been described elsewhere.[27] In brief, the operations started with a right subcostal incision with midline extension, midline incision or bilateral rooftop with midline extension depending on tumor location and anticipated complexity of the operation. Intra-operative ultrasound was performed to look for addition tumor and outline major vascular structures. Transection of liver parenchyma was performed with Cavitron ultrasonic aspirator (CUSA) after ischemic demarcation by individual inflow ligation. Drain was not inserted unless collection anticipated. Patients were discharged to intensive care unit, high dependence unit or general ward according to patient's hemodynamic and anesthesiologist's advice. Patients were allowed to resume normal diet on day 3 to day 4 and discharged home on day 7. Outpatient follow-up was arranged in two weeks after discharge and then every 3-monthly for the first year, and half-yearly for the second year onwards.

2.3. Definition and follow-up surveillance

Nomenclature on the type of liver resection was in accordance with the IHBPA (Brisbane 2000) consensus statement.[29] Clear resection referred to the distance between

Table 1 Clavien—Dindo classification.

Grade	Definition
I	Any deviation from normal postoperative course without the need of pharmaceutical, endoscopic, radiological and surgical intervention
II	Need of antibiotics, blood product or parenteral nutrition as treatment
III	Need of endoscopic, radiological or surgical intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication requiring intensive care and organ support
IVa	Single organ support
IVb	Multi-organ support
V	Death of a patient

tumor cell and resection margin more than 1 mm (i.e. R0 resection). R1 resection was also regarded as a curative resection in this study, referred to the distance between tumor cell and resection margin less than 1 mm. Surveillance of postoperative complications were performed by designated fellows. Classification of postoperative complication followed that of the Clavien-Dindo description (Table 1).[30] Only major postoperative complications, as defined by grade IIIa or above, were analyzed in the present study. UICC/TNM 7th edition[31] was used to standardize pathological staging for our patients. Tumor markers and cross-sectional contrasted imaging (i.e. Computed tomography (CT) or Magnetic Resonance Imaging (MRI)) were performed in three to six months interval after the second follow-up as surveillance of recurrence. 18-FDG Positron Emitted Tomography (PET) was performed in selected cases with suspicious clinical features. Radiological surrogate of disease recurrence was defined as CT,[32,33] MRI[34] or PET[35] evidence of new liver lesion demonstrating typical characteristics of ICC or presence of metastatic disease.[35,36]

2.4. Statistics

Continuous variable were presented as median. Categorical variables were analyzed using Chi-square test or Fisher's exact test where appropriate. Parametric variables were analyzed using Mann–Whitney U test or t-test where appropriate. Disease-free and overall survivals were calculated using Kaplan–Meier method. Survivals between

Table 2 Baseline and perioperative characteristics of the whole population and patient subgroup.

Basic characteristics	(*n* = 107)	Without Cx (n = 85)	With Cx (n = 22)	P-value
Median age (year) (range)	61 (25–79)	61 (25–78)	61 (29–79)	0.78
Male sex	58 (54.2%)	51%	49%	0.23
Body weight (kg)	55.6 (36–85.6)	56 (36–86)	53 (37–84)	0.75
Body height (cm)	162 (142–185)	162 (144–185)	155 (142–172)	0.12
Smoker	36 (33.6%)	29 (34.1%)	7 (31.8%)	0.07
Drinker	26 (24.5%)	20 (23.8%)	6 (27.2%)	0.36
Co-morbidity (overall)	51 (47.7%)	41 (48.2%)	10 (45.5%)	1.00
Cardiovascular	43 (40.2%)	33 (38.8%)	10 (45.5%)	0.63
Respiratory	12 (11.2%)	12 (14.1%)	0 (0%)	0.12
Renal	2 (1.9%)	1 (1.2%)	1 (4.5%)	0.37
Diabetes	18 (16.8%)	15 (17.6%)	3 (13.6%)	0.76
Hepatitis B carrier	28 (26.2%)	24 (28.2%)	4 (18.2%)	0.42
Preoperative biochemistry				
Hemoglobin (g/dl)	12.8 (8.2–16.7)	13 (8.2–16.7)	11.1 (10–15)	0.10
White cell count ($\times 10^9$/l)	6.9 (1.3–31.8)	6.6 (2.8–17)	7.9 (1.3–31.8)	0.11
Platelet count ($\times 10^9$/l)	206 (47–527)	204 (57–527)	217 (41–428)	0.87
creatinine (umol/l)	77 (37–167)	77 (37–167)	77.5 (43–147)	0.91
Albumin (g/l)	41 (25–51)	41 (27–49)	40 (25–51)	0.18
Bilirubin (umol/l)	10 (3–94)	10 (3–94)	10 (4–86)	0.05
ALP (U/l)	99 (38–830)	91 (38–830)	146 (65–541)	0.20
Prothrombin time (s)	11.6 (9.6–17.8)	11.5 (9.6–15)	11.7 (10–17.8)	0.54
CEA (ng/ml)	2.4 (0.3–151)	2.3 (0.3–151)	3.7 (0.7–149)	0.79
ICG retention at 15 min (%)	9.8% (0.8–82.5)	9,7% (3.4–40.5)	11% (0.8–82.5)	0.39
Follow-up time (month)	24.38 (3.19–276.2)	35.7	13	0.01
Hospital stay (day)	11 (4–281)	9 (4–115)	26.5 (8–281)	<0.01
Median blood loss (L) (range)	0.9 (0.1–26.6)	0.8 (0.1–9)	1.4 (0.3–26.6)	0.03
Operation time (minutes)	439 (100–1305)	399 (100–969)	600 (298–1305)	<0.01
30-day mortality (%)	3 (2.8%)	–	–	–
90-day mortality (%)	7 (6.5%)	–	–	
Coexisting RPC	17 (15.9%)	13 (15.3%)	4 (18.2%)	0.75
Size of primary tumor (cm)	6 (1–17)	6 (1–15)	7.8 (2.5–17)	0.01
Tumor differentiation				0.46
Well differentiated	11 (10.3%)	10 (12.3%)	1 (4.5%)	
Moderately differentiated	46 (43%)	38 (46.9%)	8 (36.4%)	
Poorly differentiated	26 (24.3%)	19 (23.5%)	7 (31.8%)	
Micro-vascular invasion (yes, %)	51 (47.7%)	38 (48.5%)	13 (59.1%)	0.34
TNM staging (UICC7)				0.18
I	46 (43%)	39 (45.9%)	7 (31.8%)	
II	24 (22.4%)	20 (23.5%)	4 (18.2%)	
III	25 (23.4%)	18 (21.2%)	7 (31.8%)	
IVA	12 (11.2%)	8 (9.4%)	4 (18.2%)	

groups were compared using Log-rank test. Variables associated with survival with p-value 0.05 or less in univariate analysis were put into the multivariate analysis. SPSS version 20 was used for all statistical analysis.

2.5. Ethics and declarations

This study does not require ethics board review according to local guidelines. All patient identities and clinical information were kept confidential. The authors declare no known benefit from this article.

3. Results

3.1. Patient characteristics

There were 107 consecutive patients recruited in the study period, 59 of them were male and the median age of the population was 61 year-old (25—79). The median follow-up time was 24 months (3.19—276.27). Hepatitis B carrier state was detected in 26.2% of our patients and about 16% of the patients had ICC developed in the background of recurrent pyogenic cholangitis. About half of the patients had one or more medical comorbidities before the operation, with cardiovascular problems i.e. hypertension, ischemic heart disease, being the most common. The median preoperative hemoglobin and albumin level was 12.8 g/dl (8.2—16.7) and 41 g/l (25—51) respectively (Table 2). The median preoperative carcino-embryonic antigen (CEA) was 2.4 ng/ml (0.3—151). The median tumor size was 6 cm (1—17) and majority of the tumors were of moderate differentiation. Microvascular invasion was identified in 51 patients (47.7%). Majority of the patients had early tumor stage, TNM stage I or II disease were found in 65.4% of the patients. Adjuvant chemotherapy was documented in 5 patients only in the study period.

3.2. Operative procedure and short-term outcome

Majority of the patients (52.3%) required major hepatectomy (resection of more than 3 Couinaud segments) and right trisectionectomy (15%) was the most commonly performed procedure (Table 3). Additional vasculo-biliary resection and reconstruction was required in 19.5% of the patients. R0 resection was achieved in 95 patients (88.8%) and none of our patients in the present series had R2 resection. The median operation time was 439 min (100—1305) and the median blood loss was 0.9 L (0.1—26.6). The median hospital length of stay was eleven days and the 30-day and 90-day mortality was 2.5% and 6.8% respectively. After excluding grade I, II and V complications, major postoperative complications were documented in 20.6% of the patients (Tables 4a & 4b) and 8 of patient had serious postoperative complications resulted in mortality.

3.3. Univariate and multivariate analysis for factors affecting survival

In order to find out the factors that can influence survival of ICC patients after curative resection, a number of clinical/

Table 3 Type and frequency of procedure performed.

Details of hepatectomy	No. (%)
Right hepatectomy	13 (12.1%)
Extended right hepatectomy	5 (4.7%)
Left hepatectomy	11 (10.3%)
Extended left hepatectomy	7 (6.5%)
Left lateral sectionectomy	10 (9.3%)
Right trisectionectomy	16 (15%)
Left trisectionectomy	2 (1.9%)
Segmentectomy	16 (15%)
Subsegmentectomy	6 (5.6%)
Others[a]	21 (19.5%)
Additional procedures[b]	21 (19.5%)

[a] Others include central bisectionectomy, central bisectionectomy + caudate resection, isolated segment + caudate lobe resection.

[b] Additional procedures include 15 bile duct resection, 4 portal vein resection & reconstruction, 1 hepatic artery or inferior vena cava resection & reconstruction and 1 radiofrequency ablation.

Table 4a Grade and frequency of postoperative complications.

Clavien-Dino grade	
IIIA	12 (11.2%)
IIIB	7 (6.5%)
IVA	3 (2.9%)
IVB	0 (0.0%)
V	8 (7.5%)

Table 4b Frequency of each documented complication (grade I to 5).

Overall post operation complication	35 (32.7%)
Chest infection	9 (8.4%)
Pleural effusion (tapping required)	12 (11.2%)
Pleural effusion (tapping not required)	5 (4.7%)
Wound infection	5 (4.7%)
Wound dehiscence	1 (0.9%)
Sub-phrenic abscess	6 (5.6%)
Intra-abdominal bleeding	2 (1.9%)
Variceal bleeding	1 (0.9%)
Peptic ulcer bleeding	3 (2.8%)
Urinary tract infection	1 (0.9%)
Cardiac arrhythmia	1 (0.9%)
Heart failure	2 (1.9%)
Biliary fistula	5 (4.7%)
Infected ascites	2 (1.9%)
Intestinal obstruction	4 (3.7%)
Liver failure	7 (6.5%)
Renal failure	7 (6.5%)
Massive liver necrosis	1 (0.9%)
Respiratory failure	1 (0.9%)
Sepsis	1 (0.9%)

pathological parameters were analyzed with univariate and multivariate model (Table 5). It was found that six factors were associated with disease free survival of the patients, namely primary tumor size (P = 0.026), postoperative complication (P = 0.002), multiple tumor nodule (P < 0.0001), micro-vascular invasion (P < 0.001), width of resection margin (P = 0.015) and TNM staging (P = 0.003).

Table 5 Univariate and multivariate analysis for factors associated with disease free survival.

Factors	Disease free survival	
	Univariate	Multivariate
Age	0.68 (NS)	NS
Sex	0.24 (NS)	NS
Presence of comorbidities	0.36 (NS)	NS
Intra-op blood loss	NS	NS
Bile duct resection	0.9 (NS)	NS
Vascular resection	0.079	NS
Tumor size	0.026	NS
Post-op complication	0.006	OR 1.9 95% C.I. 1.10—3.24, P = 0.021
Multi-focality	<0.0001	NS
Micro-vascular invasion	<0.0001	NS
Width of resection margin	0.015	OR 0.70 95% C.I. 0.51—0.96, P = 0.05
TNM staging (7th edition)	0.003	OR 1.35, 95% C.I. 1.17—1.55, P < 0.001

When these associated factors were put into multivariate analysis, only width of resection margin (OR 0.70 95% C.I. 0.51—0.96, P = 0.05), TNM staging (OR 1.35, 95% C.I. 1.17—1.55, P < 0.001) and postoperative complications (OR 1.9 95% C.I. 1.10—3.24, P = 0.021) were independent factors for disease free survival. The disease free survivals between patients with and without postoperative complication were compared with log-rank test. Patients without postoperative complication had significantly between 3-year disease free survivals (38% vs. 27%, P = 0.001) (Fig. 1). Concerning the overall survival, intraoperative blood loss (P = 0.014), postoperative complication (P < 0.001), and multiple tumor nodule (P < 0.001), micro-vascular invasion (P = 0.001), width of resection margin (P = 0.014), and TNM staging (P = 0.044) were factors associated with overall survival. After these factors were put into multivariate analysis, resection margin width (OR 0.64, 95% C.I. 0.43—0.96, P = 0.032), postoperative complication (OR 2.1, 95% C.I. 1.13—3.93, P = 0.018) and TNM staging (OR 1.45, 95% C.I. 1.23—1.72, P ≤ 0.001) were the independent factors for overall survival (Table 6). The 3-year overalls survival was also significantly better in patients without postoperative complications as compared to those who developed postoperative complication (51% vs. 27%, P < 0.001) (Fig. 2).

4. Discussion

This study illustrated that, ICC is an uncommon primary hepatic malignancy with poor long-term survival; Avoidance of major post-operative complication could result in at least 3 times improvement in the 5-year disease free and overall survival of patients with resectable ICC.[37]

There has been an increasing trend in the incidence of ICC in recent decades.[38,39] while the cause of such rise

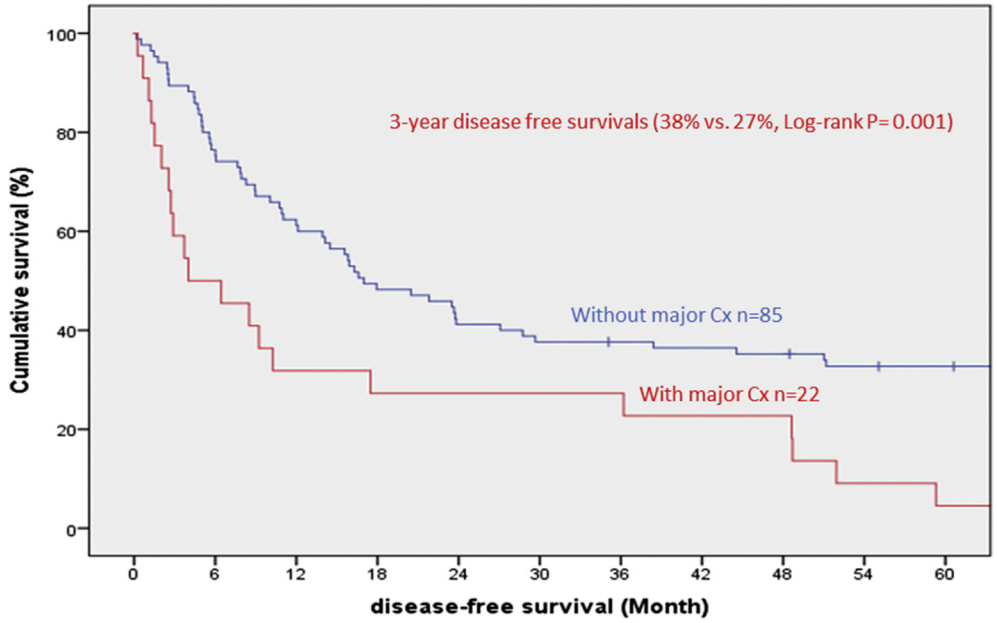

Figure 1 Disease free survival between patients with and without postoperative complication.

Table 6 Univariate and multivariate analysis for factors associated with overall survival.

Factors	Overall Survival	
	Univariate	Multivariate
Age	0.86 (NS)	NS
Sex	0.38 (NS)	NS
Presence of comorbidities	0.5 (NS)	NS
Hemoglobin	0.083	NS
Intra-op blood loss	0.014	NS
Bile duct resection	0.502	NS
Vascular resection	0.218	NS
Tumor size	NS	NS
Post-op complication	<0.001	OR 2.1, 95% C.I. 1.13–3.93, P = 0.018
Multi-focality	<0.001	NS
Micro-vascular invasion	0.001	NS
Width of resection margin	0.014	OR 0.64, 95% C.I. 0.43–0.96, P = 0.032
TNM staging (7th edition)	0.044	OR 1.45, 95% C.I. 1.23–1.72, P≤0.001

remains unclear, surgical resection is regarded as the only chance of cure for this lethal disease. In view of the poor long-term survival even after curative surgery, studies had been focusing on how to identify high-risk group and individualize management so as to improve the survival outcomes of ICC patients. Clinical pathological factors such as cancer antigen (CA) 19.9, resection margin, vascular invasion and lymph node status had been investigated, but majority of these factors were not modifiable preoperatively. There has been a growing research interest in the influence of patient-specific factors like performance status, medical co-morbidity and immune status to the long-term survival outcomes.[40,41] However, the role of post-operative complication in relation to oncological outcome was not defined. It had been postulated that, occurrence of postoperative complication could result in a change to the systemic immunological environments; imbalance of various cytokine/chemokine networks leads to an immunosuppressed state and predisposes the patient to tumor recurrence.[42–44] Spolverato et al recently published a multicenter cohort containing 583 patients recruited from 12 centers in 14 years time. That was the first study suggesting that postoperative complication is an independent factor for long-term survival of ICC patients after operation.[21] In that study, patients who developed postoperative complications had the median disease free and overall survival of 7.8 and 19.3 months compared to 12.3 and 34.5 months for patient who did not have postoperative complication respectively. These results were concurred by the findings in our present study.

In this studies, postoperative complication grade I and II were not analyzed, as there could be a substantial inter-observer variability in the grading of minor postoperative complications. Diagnosis of post-operative complication grade III and above was more clear-cut and comparable.

There were some limitations in this study; Firstly, selection bias and missing data are inherent problems for retrospective study, and these had been minimized by consecutive patient recruitment, specific definition of complication and a well-maintained database; secondly, some potential confounders such as CA 19.9, lymph node

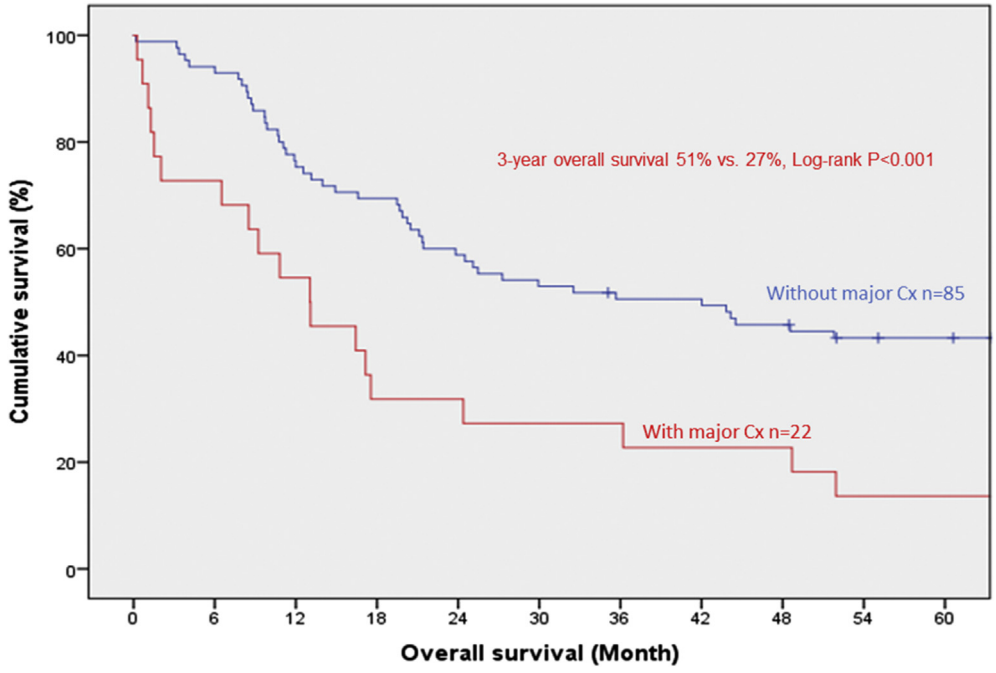

Figure 2 Overall survival between patients with and without postoperative complication.

status and adjuvant chemotherapy were not presented. Ca 19.9 was not regularly checked for ICC patients until recent decade; due to conflicting evidence on the survival benefit of routine lymphadenectomy and adjuvant chemotherapy, they were offered only in selected cases in our series, incomplete data in these factors precluded them from analysis; moreover, small sample size has been a common weakness for studies of rare diseases. Nonetheless, the results of this study highlighted the oncological implications of major post-operative complication in resectable ICC. This adverse event should be minimized by taking extra precautions preoperatively; For example, ICC patients should be stratified into different risk groups before the operation. We have previously published a predictive scoring system which helps to quantify the likelihood of developing major postoperative complication,[45] preemptive measures such as prehabilitation program[46] could be offered to optimize physiological conditions preoperatively.

5. Conclusion

Postoperative complication is associated with inferior disease-free and overall survival in ICC patients after resection. Preoperative optimization and prehabilitation program should be arranged for high-risk patients. Adjuvant treatment could be considered in patients who had developed major complication after the operation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.01.004.

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