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ORIGINAL SCIENTIFIC REPORT

Actual Long-Term Survival Outcome of 403 Consecutive Patients with Hilar Cholangiocarcinoma

Mee Joo Kang[1] · Jin-Young Jang[1] · Jihoon Chang[1] · Yong Chan Shin[1] · Dooho Lee[1] · Hong Beom Kim[1] · Sun-Whe Kim[1]

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Abstract

Background Despite aggressive surgical resection, prognosis of patients with hilar cholangiocarcinoma is still unsatisfactory. There were limited data about actual long-term survival outcome. This study was designed to explore actual long-term survival outcome of hilar cholangiocarcinoma after surgical treatment, and to investigate the characteristics of patients with actual long-term survival.

Methods The study cohort consisted of 403 consecutive patients with at least 5-year follow-up after surgical treatment for hilar cholangiocarcinoma at Seoul National University Hospital between 1991 and 2010. Prognostic factors were analyzed with Cox proportional hazard models, and the effect of adjuvant treatment was evaluated by propensity score analysis.

Results Of all patients, R0 resection rate was 41.2 and 63.8 % among intended curative resection. Adjuvant therapy was performed in 48.8 % after curative surgery. Actual 5-year overall survival (OS) rate was 18.9, and 30.1 % after R0 resection. Actual 5-year disease-free survival rate was 25.8 % after resection. Adjuvant treatment improved prognosis in patients with positive metastatic lymph nodes (median OS 21.9 vs. 11.5 months, $p = 0.003$). Overall recurrence rate was 55.0 %, and distant metastasis (39.7 %) was more frequent than loco-regional recurrence (20.8 %). Lymph node metastasis ($p = 0.021$) and poor histologic grade ($p < 0.001$) were independent prognostic factors after curative resection. Patients who survived more than 5 years had less lymph node metastasis ($p = 0.025$), poor histologic differentiation ($p = 0.010$), R2 resection ($p = 0.040$), and recurrence ($p < 0.001$).

Conclusion Actual 5-year OS rate after R0 resection of hilar cholangiocarcinoma is 30.1 %. Adjuvant treatment could be beneficial in patients with lymph node metastasis.

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✉ Sun-Whe Kim
sunkim@snu.ac.kr

[1] Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Chongno-gu, Seoul 110-744, South Korea

Introduction

Although radical surgical resection is the only treatment that offers the chance for cure and enhances long-term survival of perihilar cholangiocarcinoma [1–5], various factors can make curative resection difficult, including proximity of the tumor to major vessels, and the tendency of these tumors to infiltrate the intrahepatic biliary tree and liver [1, 5–8]. Thus, the R0 resection rate ranges from 19 to

75 % [1, 5–8] with a 5-year overall survival (OS) rate after surgical treatment of 10–44 %, paralleling the R0 resection rate [1, 5, 6, 8, 9]. Recent improvements in radiologic imaging, endoscopy, and surgical technology, however, have enhanced patient prognosis [4, 5].

Prognostic factors in patients with bile duct cancer include depth of tumor invasion, lymph node metastasis, perineural invasion, histologic differentiation, and resection margin status [2, 5, 9]. Since resection margin is a surgically manageable factor, more extensive surgery to achieve negative resection margins has been attempted [10, 11]. However, many patients have positive resection margins despite an aggressive surgical approach, with relatively little known about the clinical outcomes of those patients [12, 13]. The high rates of local recurrence and distant metastasis [14] suggest that postoperative treatment may improve long-term survival. Thus, studies have evaluated the effects of local control with postoperative radiation, with or without chemotherapy for systemic control, on long-term survival [15–17]. However, the absence of randomized controlled trials (RCT) has limited the ability to determine whether postoperative adjuvant treatment can benefit patients with perihilar cholangiocarcinoma, especially those with positive resection margins.

This study therefore analyzed the actual long-term outcomes of 403 consecutive patients with perihilar cholangiocarcinoma who were surgically treated at a single center. The authors especially assessed the effects of adjuvant treatment using propensity score (PS) analysis.

Materials and methods

This study was approved by our Institutional Review Board. The study cohort consisted of 403 consecutive patients with at least 5-year follow-up after surgical treatment for perihilar cholangiocarcinoma at Seoul National University Hospital between 1991 and 2010. Patients with cancers originating from the primary confluence of the bile duct to the secondary convergences were included, whereas patients with intrahepatic cholangiocarcinoma and distal extrahepatic cholangiocarcinoma were excluded. However, patients with cancers arising at the hilar bile duct and infiltrating into the distal bile duct were included. Prospectively collected clinicopathologic data were retrospectively analyzed. All patients were evaluated by imaging methods, including computed tomography, magnetic resonance cholangiography, and/or direct cholangiography, to determine the extent of the tumor and to formulate the treatment strategy.

Patients underwent surgery with curative intent if imaging analysis showed the absence of (1) distant metastases, (2) extensive proximal infiltration into the bilateral intrahepatic bile ducts, (3) bilateral portal vein invasion, or (4) invasion of the proper hepatic artery or branches to the contralateral hepatic lobe, or (5) if patients had a severe comorbidity. Types of surgery performed to achieve R0 resection included extended hepatic resection with extrahepatic bile duct resection (HBR), segmental bile duct resection (BDR), hilar resection plus pancreatoduodenectomy (PD), and hepatopancreatoduodenectomy (HPD). Patients with Bismuth type I or II tumors with extensive distal tumor spread underwent PD, and patients with diffuse bile duct cancer underwent HPD. Patients for whom radical resection was impossible, including those with intraoperatively diagnosed distant metastases or invasion of major vessels, underwent palliative surgery including bypass operations or open biopsy.

The aim of curative surgery was the achievement of microscopically negative resection margins. Resection margins with invasive cancer, carcinoma in situ, or high-grade dysplasia were classified as positive resection margins. Patients with high-grade dysplasia were included in the subgroup of those with carcinoma in situ because it was difficult or impossible to distinguish between them histologically [12]. Resection margins were evaluated for both bile duct and circumferential margins. If positive bile duct resection margins were detected, additional resection was attempted. Regional lymph nodes were removed as described [9]. Patients were followed up every 3 months for the 1st 6 months, then every 6 months for at least 5 years at the department of Surgery. Loco-regional recurrence was defined as recurrence in the primary tumor bed and regional lymphatic areas. Distant metastasis was defined as recurrence in a systemic organ, the peritoneum, or distant lymph nodes.

All patients were attempted to receive postoperative concurrent chemoradiotherapy (CCRT) or chemotherapy, except if they had early TNM stage (T1N0, T2N0) tumors with negative resection margins, or if they refused treatment. For 166 patients receiving CCRT, the total radiation dose of 40 Gy was delivered as a split course of 20 Gy in 10 fractions over 2 weeks with a 2-week break between courses. The planning target volume encompassed the tumor bed and regional lymph nodes including the porta hepatis and pericholedochal, lymph nodes according to the location of primary tumor. Typically, patients were treated using a 2 opposing field as described earlier [18, 19]. After radiotherapy, 113 patients received maintenance chemotherapy based on 5-FU (375 mg/m^2 D1 $\sim$5, every 4 weeks, 6 cycle, $n = 96$), gemcitabine (1000 mg/m^2, D1 $\sim$4, every 3 weeks, 6 cycle, $n = 12$), or others ($n = 5$). Twenty-three patients received adjuvant chemotherapy only, and 53 patients received postoperative radiation therapy only.

Statistical analysis

All statistical analyses were performed using IBM SPSS Version 19.0 (IBM Corp., Somers, NY, USA). Nominal variables were compared using the Chi-square test and continuous variables were compared using Wilcoxon's test. Survival was analyzed using the Kaplan–Meier method and compared by the log rank test. For survival analysis, only the patients who underwent curative intended operation were included. Multivariate analysis for prognostic factors was performed using a Cox proportional hazards method. Two-sided p values less than 0.05 were considered statistically significant, and p values less than 0.1 were considered marginally significant. A multivariable regression was carried out with variables whose P value was <0.1 in the univariable analyses, using a forward stepwise method.

To minimize biases related to the non-random allocation of adjuvant treatment, propensity score (PS) analysis was performed to assess the effects of adjuvant treatment on survival among patients with similar risk profiles [20]. To confirm the effects of adjuvant treatment, PS analysis was performed in patients who underwent curative surgery, excluding those who underwent palliative resection or bypass operation. The PS was defined as the probability that a patient would receive postoperative treatment, and was constructed using logistic regression to adjust for between-group differences in demographic and clinical variables, including patient age, operation period, American Joint Committee on Cancer seventh edition TNM stage, histologic grade, and age-adjusted Charlson comorbidity index (AACCI) [21]. Sensitivity analyses included PS matching, stratification, and adjustment, with these analyses compared using a standard multivariable Cox model, in which adjuvant treatment and all covariates were entered as independent variables. Differences in baseline covariates between adjuvant treated and untreated patients were determined using statistical significance testing and standardized differences. To estimate the adjusted hazard ratio (HR) between two groups, we used a weighted Cox hazard model with the robust standard error for stabilized Inverse probability weighting (IPTW) and a Cox hazard model with the robust standard error for propensity matched data [22]. Cox hazard models were estimated for stratification and propensity adjustment.

Results

Demographics and operative outcomes

The demographic and clinical characteristics of the 403 included patients are shown in Table 1. None of the patients had Child B or C cirrhosis. Preoperative portal vein embolization was performed in 15 patients. Patients underwent hepatobiliary resection (HBR, $n = 190$, 47.1 %; 106 extended right hemihepatectomy, 69 extended left hemihepatectomy, 5 right trisectionectomy, 10 hepatopancreatoduodenectomy), followed by bile duct resection (BDR, $n = 117$, 29.06 %) and pancreatoduodenectomy (PD, $n = 10$, 2.5 %). The combined portal vein resection rate was 6.4 %. None of the patients underwent arterial reconstruction. Intraoperative transfusion was done in 112 patients. The rate of intended curative resection in overall patients was 64.5 % and the R0 resection rate was 63.8 % of intended curative resection. R0 resection rate was not related with types of operation (HBR 65.8 % vs. BDR 60.0 vs. 50.0 %, $p = 0.466$).

One hundred (24.8 %) had lymph node metastases, and 40 (9.9 %) had unexpected distant metastases. Assessment of the histologic grade of differentiation showed that 73 patients (18.1 %) had papillary or well-differentiated tumors, 290 (72.0 %) had moderately differentiated tumors, and 40 (9.9 %) had poorly differentiated tumors.

The overall morbidity rate was 37.7 % ($n = 152$), and was highest in patients who underwent PD ($n = 14/20$, 70.0 %), followed by those who underwent HBR ($n = 92/180$, 51.1 %) and BDR ($n = 26/117$, 22.2 %). The 90-day mortality rate was 4.0 % ($n = 16$), and 9 of them underwent intended curative HBR.

Actual long-term survival outcome and prognostic factors

Actual 5-year OS rate of perihilar cholangiocarcinoma after surgical treatment was 18.9 % and median survival was 20.0 months. OS rate was higher after curative resection than palliative operation (actual 5-year OS rate 25.0 vs. 7.7 %, $p < 0.001$). Actual 5-year OS rate of each stage was as follows: Stage I 72.0 %, Stage II 29.0 %, Stage III 10.8 %, and Stage IV 9.6 % ($p < 0.001$). Among patients who achieved curative intended resection, patients with R0 resection had better prognosis than R1 resection (actual 5-year OS rate 30.1 vs. 16.0 %, $p = 0.090$, Fig. 1). Actual survival after R0 resection was 28.2 vs. 24.1 months ($p = 0.335$), and 21.2 vs. 22.0 months after R1 resection ($p = 0.467$) before and after year 2000. Among R1 resection, actual 5-year OS was longer for the patients who had high-grade dysplasia or carcinoma in situ at the bile duct resection margin ($n = 13$) than for those with invasive carcinoma at the resection margins ($n = 81$, actual 5-year OS rate 38.5 vs. 12.3 %, $p = 0.028$). OS rate was not different between types of operation [actual 5-year OS rate 24.2 % (HBR) vs. 30.0 % (BDR) vs. 10.0 % (PD), $p = 0.597$]. Survival rate was higher after palliative R2 resection than bypass operation or open and closure [actual

Table 1 Demographics and pathologic results

	$N = 403$	R0 resection ($n = 166$)	R1 resection ($n = 94$)	R2 resection, palliative operation ($n = 143$)	p value
Age (mean ± SD)	61.3 ± 10.1	60.3 ± 10.0	61.6 ± 10.4	62.3 ± 10.2	0.359
Sex (M:F)	288:115	126:40	64:30	98:45	0.255
Preoperative biliary drainage	327 (86.5 %)	136 (87.2 %)	71 (80.7 %)	120 (89.6 %)	0.159
Bismuth type					<0.001
Type I	37 (9.2 %)	19 (11.4 %)	11 (11.7 %)	7 (4.9 %)	
Type II	54 (13.4 %)	16 (9.6 %)	13 (13.8 %)	25 (17.5 %)	
Type IIIa	132 (32.8 %)	69 (41.6 %)	31 (33.0 %)	32 (22.4 %)	
Type IIIb	64 (15.9 %)	36 (21.7 %)	9 (9.6 %)	19 (13.3 %)	
Type IV	116 (28.8 %)	26 (15.7 %)	30 (31.9 %)	60 (42.0 %)	
Operation					
Curative intended resection	260 (64.5 %)				0.466
Hepatobiliary resection+HPD	190 (73.1 %)	125 (75.3 %)	65 (69.1 %)	0	
Bile duct resection	60 (23.1 %)	36 (21.7 %)	24 (25.5 %)	57 (39.9 %)	
Pancreatoduodenectomy	10 (3.8 %)	5 (3.0 %)	5 (5.3 %)	0	
Palliative operation*	143 (35.5 %)	0	0	86 (60.1 %)	
Combined portal vein resection	26 (6.4 %)	11 (6.6 %)	15 (16.9 %)	0	0.017
R0 resection	166 (41.2 %)				
Postoperative chemoradiation therapy	189 (48.8 %)	86 (54.4 %)	62 (68.1 %)	41 (29.7 %)	<0.001
Chemotherapy	136 (35.1 %)	65 (41.1 %)	42 (46.2 %)	29 (21.0 %)	<0.001
Radiation therapy	166 (42.9 %)	72 (45.6 %)	58 (63.7 %)	36 (26.1 %)	<0.001
Recurrence	149 (37.0 %)	95 (57.2 %)	48 (51.1 %)		0.337
Follow-up (median, months)	102.8 (range, 60.8–238.6)	109.5 (range, 61.1–237.2)	92.6 (range, 60.8–229.9)	105.1 (range, 71.0 = 238.6)	
Lymph node metastasis	100 (24.8 %)	44 (26.5 %)	28 (29.8 %)	28/65 (43.1 %)	0.176
AJCC 7th stage					<0.001
Stage 0	4 (1.0 %)	4 (2.4 %)	0	0	
Stage I	21 (5.2 %)	16 (9.6 %)	5 (5.3 %)	0	
Stage II	107 (26.6 %)	75 (45.2 %)	32 (34.0 %)	0	
Stage IIIA	35 (8.7 %)	27 (16.3 %)	8 (8.5 %)	0	
Stage IIIB	58 (14.4 %)	43 (25.9 %)	15 (16.0 %)	0	
Stage IVA	138 (34.2 %)	0	32 (34.0 %)	106 (74.1 %)	
Stage IVB	40 (9.9 %)	1 (0.6 %)	2 (2.1 %)	37 (25.9 %)	

* Bypass operation, open and closure

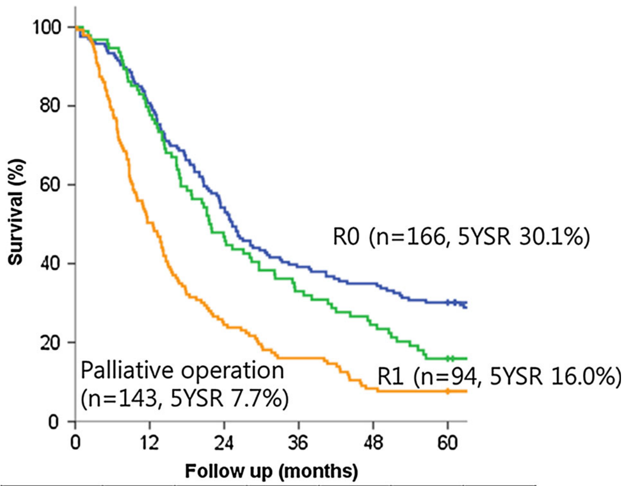
5-year OS rate 17.5 % (R2 resection) vs. 0 % (no resection), $p < 0.001$].

Multivariate Cox proportional hazards model analysis revealed that lymph node metastasis ($p = 0.021$) and histologic grade ($p < 0.001$) were independent prognostic factors for patient with actual OS (Table 2).

Number of disease-free survivors after 5 years were 67, being cure rate of 25.8 % after resection, and 16.6 % after overall surgical treatment (Fig. 2).

Recurrence

Of the 260 patients who underwent curative resection, 143 (55.0 %) developed recurrences, with 38 (14.6 %) developing loco-regional recurrence, 87 (33.5 %) developing distant metastases, and 16 (6.2 %) developing both. Recurrence rates were similar in patients who underwent HBR (55.3 %), BDR (55.0 %), and PD (50.0 %, $p = 0.948$). Of 166 R0 resection, 95 (57.2 %) developed



Number at risk	0m	12m	24m	36m	48m	60m
R0	166	134	90	65	58	50
R1	94	74	44	31	23	15
Palliative operation	143	72	35	23	12	11

Fig. 1 Actual overall survival outcome in relation to R status

recurrences, and 63 of them (66.3 %) had distant metastasis. After 94 R1 resection, 48 (51.1 %) developed recurrences, including 40 with distant metastases (83.3 %). The loco-regional recurrence rates were similar after R0 ($n = 34$, 20.5 %) and R1 ($n = 10$, 10.6 %) resection ($p = 0.142$). After R1 resection, distant metastasis rate was lower in patients undergoing adjuvant treatment but statistical significance was not achieved ($n = 24$, 38.7 % vs. $n = 16$, 50.0 %, $p = 0.294$).

Prognostic impact of adjuvant treatment

After intended curative resection, the adjuvant treatment rate was 48.8 %. Of the entire study cohort, adjuvant treatment did not have a significant impact on median OS (24.8 vs. 24.5 months, $p = 0.518$). PS matching was performed to evaluate the significance of adjuvant treatment after R0 and R1 resection (Supplement Table 1, 2). When patients were stratified according to R status, median OS was not affected by adjuvant treatment following R0 resection (24.8 vs. 28.2 months, $p = 0.633$) nor R1 resection (24.1 vs. 20.4 months, $p = 0.434$). Adjuvant treatment had no survival benefit in node-negative patients

Table 2 Prognostic factors for hilar cholangiocarcinoma after curative intended resection

Variables		No. of patients	Median survival (months)	*p* value	HR	95 % CI	*p* value
Operation type	HBR	190	24.5	0.597			
	BDR	60	23.4				
	PD	10	23.3				
T stage	T0, 1, 2	178	26.5	0.012	1.338	0.945–1.893	0.101
	T3, 4	82	20.4				
N stage	Negative	157	28.6	0.001	1.464	1.060–2.023	0.021
	Positive	72	20.4				
AJCC stage	0, I	25	193.2	<0.001			
	II	107	26.2				
	III	93	19.1				
	IV	35	23.9				
Histologic grade	Papillary and well differentiated	55	51.8	<0.001	1.765	1.173–2.657	<0.001
	Moderately differentiated	174	23.1		3.136	1.830–5.373	
	Poorly differentiated	31	14.4				
R status	R0	166	25.3	0.090	1.075	0.771–1.499	0.670
	R1	94	21.6				
Adjuvant treatment	No	101	24.5	0.518			
	Yes	148	24.8				
AACCI	0–2	218	24.1	0.995			
	3–5	41	25.9				
	>5	1	42.0				

HBR hepatobiliary resection, *BDR* bile duct resection, *PD* pancreatoduodenectomy

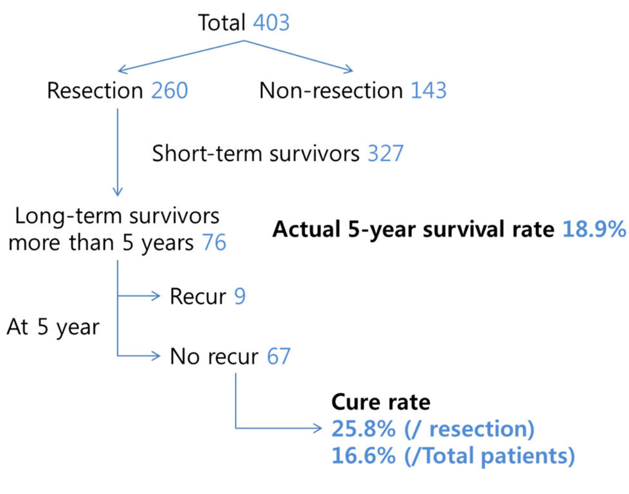
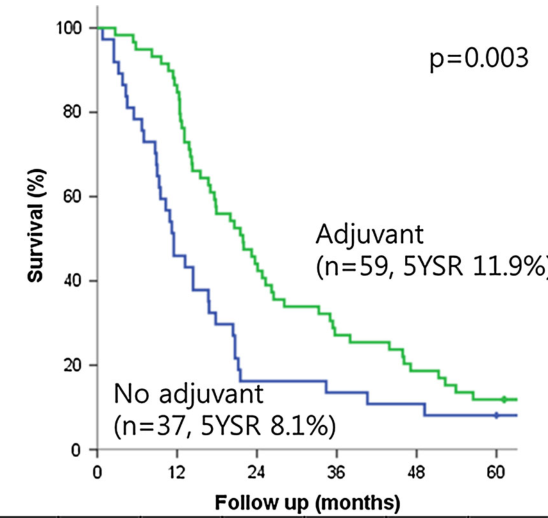


Fig. 2 Flow of patients who were followed up for more than 5 years after surgery



Number at risk	0m	12m	24m	36m	48m	60m
Adjuvant	59	51	26	16	11	7
No adjuvant	37	17	6	5	4	3

Fig. 3 Overall survival in relation to adjuvant treatment in patients with metastatic lymph nodes

(27.1 vs. 32.2 months, $p = 0.485$), but prognosis was improved in patients with positive metastatic lymph nodes with univariate analysis (21.9 vs. 11.5 months, $p = 0.003$, Fig. 3). Among patients with positive lymph node, distribution of histologic grade ($p = 0.162$) and rate of complication ($p = 0.385$) were not statistically different.

Characteristics of the patients with actual long-term survival

Of the 403 patients with follow-up for at least 5 years, 76 patients (18.9 %) survived more than 5 years after surgery. No patient with metastatic disease or AACCI index higher than 5 at presentation survived more than five years. When the 76 patients were compared with the 327 who survived less than 5 years, multivariate analysis revealed that node-negative disease, higher grade of histologic differentiation, and the absence of recurrence were independent factors for long-term survival (Table 3). Adjuvant treatment did not significantly affect long-term survival.

Eleven patients survived more than five years after palliative operation. Ten of them underwent palliative hilar resection, with none having poorly differentiated histology. Nine of these patients received adjuvant CCRT, with none showing recurrence.

Discussion

To our knowledge, the cohort in this study is the second largest group of patients surgically treated for perihilar cholangiocarcinoma reported to date. In our institute, the R0 resection rate was 41.2 % of all patients and the actual 5-year OS rate after R0 resection was 30.1 %. A 90-day mortality rate was 4.0 % which is comparable to those with previous reports [1, 5–9]. Cure rate was 25.8 % after resection, and 16.6 % of total patients. Our previous report suggested that tumor histology and lymph node metastasis were independent factors predicting long-term survival after surgery for extrahepatic bile duct cancer [9]. The present study re-confirmed that tumor histology and lymph node metastasis were independent factors for long-term survival.

In our center, hepatectomy is performed when R0 or R1 resection is achievable, but not when R2 resection is likely. In addition, if R0 resection can be achieved with bile duct resection, we do not perform major hepatectomy, especially in Bismuth type I and II patients. We found that recurrence rate and median OS were similar in patients who underwent HBR and BDR. Although hepatectomy has been reported necessary to achieve prolonged survival, even in patients with Bismuth type I and II tumors [23–26], those studies included only 3–26 patients per group. In contrast, the results of our relatively large-scale study suggest that hepatectomy is not necessary if BDR can achieve negative resection margins. Positive resection margins have been reported in 17 to 50 % of patients with perihilar cholangiocarcinoma who underwent intended curative resection [4, 13, 21–24] and in 36.2 % of our patients [2, 12, 27–30]. We found that the rates of margin positivity following hepatobiliary resection and bile duct

Table 3 Factors associated with actual long-term survival more than 5 years

Variables		Survival <5 years ($n = 327$)	Survival ≥5 years ($n = 76$)	p value	HR	95 %CI	p value
Age		61.6 ± 9.9	60.3 ± 11.0	0.315			
Sex	Male	235 (81.6 %)	53 (18.4 %)	0.711			
	Female	92 (80.0 %)	23 (20.0 %)				
Biliary drainage	No	35 (68.6 %)	16 (31.4 %)	0.022	1.757	0.693–4.453	0.235
	Yes	269 (82.3 %)	58 (17.7 %)				
T stage	T0, 1, 2	124 (69.7 %)	54 (30.3 %)	<0.001	2.482	0.996–6.187	0.051
	T3, 4	203 (90.2 %)	22 (9.8 %)				
N stage	Negative	137 (70.6 %)	57 (29.4 %)	<0.001	2.588	1.128–5.935	0.025
	Positive	90 (90.0 %)	10 (10.0 %)				
M stage	M0	288 (79.3 %)	75 (20.7 %)	0.005	<0.001		0.999
	M1	39 (97.5 %)	1 (2.5 %)				
Histologic grade	Pap. and W/D	43 (58.9 %)	30 (41.1 %)	<0.001	6.201	1.470–26.151	0.010
	M/D	247 (85.2 %)	43 (14.8 %)		2.319	0.591–9.104	0.013
	P/D	37 (92.5 %)	3 (7.5 %)				0.228
R status	R0	116 (69.9 %)	50 (30.1 %)	<0.001	3.180	0.975–10.368	0.040
	R1	79 (84.0 %)	15 (16.0 %)		1.174	0.364–3.788	0.055
	R2	132 (92.3 %)	11 (7.7 %)				0.789
Any adjuvant treatment	No	165 (83.3 %)	33 (16.7 %)	0.258			
	Yes	149 (78.8 %)	40 (21.2 %)				
AACCI	0–2	278 (81.5 %)	63 (18.5 %)	0.808			
	3–5	46 (78.0 %)	13 (22.0 %)				
	>5	3 (100 %)	0				
Recurrence	No	187 (73.6 %)	67 (26.4 %)	<0.001	10.772	4.595–25.248	<0.001
	Yes	140 (94.0 %)	9 (6.0 %)				

resection were similar, suggesting that a more aggressive surgical approach cannot increase the R0 resection rate.

Relatively little is currently known about adjuvant treatment for perihilar cholangiocarcinoma. The National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant CCRT in patients with positive margins or positive lymph nodes after resection for cholangiocarcinoma [31], but these recommendations are expert-opinion driven, without a high level of evidence. Neither radiation nor chemotherapy alone has been proved to prolong survival after resection in patients with perihilar cholangiocarcinoma. Only one RCT has compared adjuvant chemotherapy with surgery alone in patients with cholangiocarcinoma who underwent radical resection, but that trial failed to demonstrate significant between-group differences [32]. Several studies have reported that adjuvant chemotherapy has survival benefits in patients with resectable biliary tract cancer [17, 33], but these were not RCTs. A recent meta-analysis showed that any type of adjuvant therapy tended to improve survival, but not significantly, compared with surgery alone [15]. However, pooled analysis in this study showed that adjuvant radiation therapy had significant benefits in patients with margin-positive bile duct cancers [34–36].

Because relatively few patients are resectable at presentation, large-scale RCTs powered to show that adjuvant treatment improves OS in patients with perihilar cholangiocarcinoma are difficult to perform [15]. Therefore, we performed PS analysis to overcome the limitations of non-randomized retrospective analyses. In this study, PS analyses revealed that adjuvant treatment had no significant benefit in survival after R0 or R1 resection. However, prognosis was improved with adjuvant treatment in node-positive patients with univariate analysis.

Our results also suggested that resection margin status was not related to local recurrence rate, and that distant metastases were more common in patients with positive resection margins. Moreover, the overall recurrence rates did not differ in patients with positive and negative resection margins. Because distant metastasis were more frequent than loco-regional recurrences, systemic control of the disease is important. Therefore, not only achieving R0 resection but also performing proper adjuvant treatment to control systemic metastasis can enhance survival outcomes. In addition, radiation therapy could be beneficial in R1 patients as recent meta-analysis revealed [15]. However, more effective adjuvant treatment than current treatment regimen should be developed. Moreover, more attention should be paid to the patients who underwent palliative operation. In this study, only 28.8 % of the patients in palliative operation group received postoperative chemoradiotherapy, because more than half of the patients refused or were lost to follow-up because of pessimism.

In conclusion, R0 resection rate was 41.2 % among patients who underwent surgical treatment for perihilar cholangiocarcinoma. Actual 5-year OS rate of perihilar cholangiocarcinoma after surgery was 18.9 %, and 30.1 % after R0 resection. Lymph node metastasis, histologic grade, R status, and recurrence were independent predictors of long-term survival. Adjuvant treatment was beneficial in patients with metastatic lymph node with univariate analysis. Distant metastases occurred more frequently than loco-regional recurrence after surgical resection, even in patients with positive resection margins. Although achieving R0 resection is the most important predictor of prolonged OS, more effective adjuvant treatment is needed to improve survival outcome.

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Compliance with ethical standards

Competing interests The authors disclose no conflicts.

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