Original article

SURGICAL TREATMENT OF 144 CASES OF HILAR CHOLANGIOCARCINOMA WITHOUT LIVER-RELATED MORTALITY

N. Furusawa, A. Kobayashi, T. Yokoyama, A. Shimizu, H. Motoyama, H. Sakai, T. Arai, N. Kitagawa, T. Shirota and S. Miyagawa

Department of Surgery and Department of Internal Medicine, Division of Gastroenterology, Shinshu University School of Medicine

Asahi 3-1-1, Matsumoto 390-8621, Japan

Corresponding author: Akira Kobayashi

Address: Department of Surgery, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto 390-8621, Japan

Phone number: +81 263 37 2654 Fax number: +81 263 35 1282

Email address: kbys@hsp.md.shinshu-u.ac.jp

Abstract

Background

The present study evaluated whether the short- and long-term outcomes improved during our23 years of experience treating 144 consecutive patients with hilar cholangiocarcinoma.

Methods

Patients treated between 1990 and 2000 (period 1; n = 70) were retrospectively compared with those treated between 2001 and 2012 (period 2; n = 74). Mortality and major complications were defined as any death occurring within 90 days of surgery and a grade III–IV complication according to the Clavien classification, respectively.

Results

The mortality and major complication rates decreased from 1.2 and 34 % during period 1–0 and 24 % during period 2, respectively. Although the surgical procedure was comparable between the two periods, the median blood loss was significantly reduced from 1,020 mL during period 1–745 mL during period 2 (P = 0.003), and blood loss was the only significant predictor of postoperative morbidity in a multivariable analysis. The R0 resection rate (70 vs. 78 %, P = 0.250) and the 5-year survival rate (33 vs. 35 %, P = 0.529) were similar for the two periods. A multivariable analysis identified positive nodal involvement and R1–2 resection as independent prognostic factors for survival.

Conclusions

The perioperative outcomes after surgical treatment for hilar cholangiocarcinoma have steadily improved through the accumulation of experience and meticulous surgical techniques to reduce blood loss. Further improvement of the R0 resection rate could prolong patient survival.

Introduction

Surgical resection with negative margins has long been recognized as providing the only chance for a cure and long-term survival in patients with hilar cholangiocarcinoma [1–3]; however, the close proximity to hilar structures, such as the hepatic artery and portal vein, and the longitudinal extension of the tumor make curative resection difficult [4, 5]. Moreover, radical surgical treatment often necessitates an extensive hepatic resection concomitantly with a caudate lobectomy [6–9], considerably increasing the operative risks, especially in patients with a cholestasis induced impairment of liver function [7, 10, 11]. Since 1990, we have routinely adopted an aggressive and uniform surgical approach whenever possible; this approach typically includes a major hepatectomy (three or more Couinaud's segments) with a total caudate lobectomy, extrahepatic bile duct resection, and dissection of the regional lymph nodes in patients with hilar cholangiocarcinoma [9, 12]. As preoperative adjuncts, we have also applied portal vein embolization (PVE) [13] and biliary decompression [14] when indicated. The aim of the present study was to evaluate whether the short- and long-term outcomes after surgical treatment for hilar cholangiocarcinoma have improved during our 23 years of experience performing 144 consecutive resections.

Materials and methods

Between January 1990 and December 2012, a total of 253 patients were diagnosed as having hilar cholangiocarcinoma and were admitted to the First Department of Surgery, Shinshu University Hospital, Japan. Hilar cholangiocarcinoma was defined as a tumor originating in the upper common, right, or left hepatic duct. Among these patients, 144 patients who had undergone surgical resection were retrospectively enrolled in the present study (respectability rate 57 %). The patients were divided into two groups according to the period during which they underwent surgery:1990–2000 (period 1; n = 70) and 2001–2012 (period 2; n = 74). None of the patients in this series received chemotherapy and/or radiotherapy preoperatively.Our principle treatment protocol, which was consistent throughout both study periods, is described below [15].

Preoperative management

The location of the tumor was clarified using ultrasonography (US), computed tomography (CT), and/or magnetic resonance cholangiopancreatography (MRCP). Tumors with para-aortic lymph node involvement or hepatic or distant metastases were considered to be unresectable. The decision regarding whether a right- or left-sided hepatectomy should be performed was made according to the predominant site of the cancer: when the predominant site was the right hepatic duct or when both hepatic ducts were

involved equally, a right hemihepatectomy was considered to be indicated, whereas a left hemihepatectomy was selected for patients in whom the left hepatic duct was mainly involved. For patients with obstructive jaundice, we performed preoperative biliary decompression using either percutaneous transhepatic cholangiodrainage [14] or endoscopicretrograde biliary drainage. Our policy was to perform unilateral biliary decompression of the remnant hemiliver after the resection. Longitudinal tumor extension was assessed using direct opacification of the bile duct during MRCP and/or multidetector-row CT.

If the scheduled liver resection encompassed more than 60 % of the total liver parenchyma, as calculated from serial CT images, preoperative PVE was considered to be indicated to reduce the risk of postoperative liver insufficiency, once the serum total bilirubin level had decreased to $<$5 mg/dL [13]. The resectional surgery was planned for 2–3 weeks after the PVE, once hypertrophy of the future remnant liver (more than 40 % of the total liver volume) had been confirmed by successive CT scans and the serum total bilirubin level had decreased to $<$2 mg/dL. Tumor, node, metastasis (pTMN) staging was performed according to the staging manual of the American Joint Committee on Cancer (7th edition) [16].

Intraoperative management

The standard curative operation consisted of mainly a right or left hepatectomy, resection of the entire caudate lobe and extrahepatic bile duct, and dissection of the lymph nodes and connective tissues in the hepatoduodenal ligament, posterior to the upper portion of the pancreatic head, and around the common hepatic artery. Liver resection was performed using the clamp-crushing method and/or with an ultrasonic dissector under the routine application of the intermittent inflow occlusion technique [17]. A concomitant pancreaticoduodenectomy (PD) was indicated if the tumor's distal border was considered to be in the intrapancreatic bile duct and/or if peripancreatic head lymph node metastasis was suspected. A closed silicone drain was inserted along the cut surface of the liver and behind the bilioenteric anastomosis prior to the closure of the abdominal wound.

Adjuvant chemotherapy

Since 2008, a total of 22 patients with Stage II or more severe disease were treated with gemcitabine-based adjuvant chemotherapy. The reasons for failure to receive adjuvant chemotherapy included patient refusal (n = 3), early cancer recurrence (n = 1), and malnutrition (n = 1).

Definition of morbidity and mortality

Mortality was defined as any death occurring within 90 days of surgery. Major complications were defined as having a grade of III–IV according to the Clavien classification [18]. Posthepatectomy liver failure (PHLF) was defined according to the definition of the International Study Group of Liver Surgery [19].

Factors analyzed

The relationship of each clinical and pathological variable to postoperative morbidity and overall survival was investigated using univariable and multivariable regression analyses. The following factors were analyzed in relation to the overall morbidity after surgery: sex, age (above or below the median age), preoperative comorbidity (present vs. absent), diabetes mellitus (present vs. absent), biliary drainage (yes vs. no), preoperative cholangitis (present vs. absent), indocyanine green retention rate at 15 min (ICGR15, above or below the median value), preoperative serum bilirubin value (above or below the median value), major hepatectomy (yes vs. no), liver resection concomitant with PD (yes vs. no), liver resection concomitant with vascular resection (yes vs. no), operative time (above or below the median value), amount of bleeding (above or below the median value), intraoperative packed red blood cell transfusion (yes vs. no), and the pedicle clamping time (above or below the median value). The following factors, classified as patient-, cancer-, or surgery-related, were analyzed in relation to overall survival. The patient-related factors were sex, age, and ICGR15 value. The cancer-related factors included the AJCC tumor (T) classification (T1–2 vs. T3–4), G grade (G1 vs. G2–4), N grade (N0 vs. N1), invasion of the liver parenchyma (present vs. absent), microscopic lymphatic invasion (present vs. absent), microscopic vascular invasion (present vs. absent), and microscopic perineural invasion (present vs. absent). The surgery-related factors were as follows: period of operation (period 1 vs. 2), residual tumor (R0 vs. R1–2), liver resection concomitant with PD (yes vs. no), vascular resection (yes vs. no), amount of bleeding (above or below the median value), intraoperative packed red blood cell transfusion (yes vs. no), and adjuvant chemotherapy (yes vs. no).

Statistical analysis

Continuous data were expressed as the median (range), unless stated otherwise. Categorical and continuous data were compared between the two periods using the v2 test and the unpaired Student t test, respectively. The median values of the continuous data were chosen as the cutoff values. A multivariable stepwise logistic regression analysis (backward elimination method) was performed to identify variables that might be significantly associated with morbidity. The overall survival rate curves were constructed using the Kaplan–Meier method, with postoperative deaths included, and univariable analyses were performed using the log rank test. A multivariable regression analysis was performed using the Cox proportional hazard model. Variables to be entered into the regression analysis were chosen based on the results of the univariable analyses ($P \prec 0.050$). Significance was set at $P \prec 0.050$.

All the analyses were performed using PASW Statistics 18 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

The patient characteristics are summarized in Table 1. No significant differences were observed between the two periods.

Pre- and intraoperative outcomes

Details regarding the preoperative biliary drainage are summarized in Table 2. The approaches for biliary drainage were evenly distributed between PTBD (49.2 %) and ERBD (45.8 %) during period 1, whereas the latter was the dominant approach (85.7 %) during period 2. Unilateral biliary decompression of the future remnant liver was performed in 79.7 % of the cases during period 1 and 77.8 % of the cases during period 2, with no significant difference observed between the two periods (P = 0.828). Biliary drainage-related cholangitis was observed in 23.7 % of the cases during period 1, which was similar to the percentage observed during period 2 (30.2 %, P = 0.424). Although the surgical procedures that were used were similar between the two periods, the median operative blood loss (1,020 vs. 745 mL, P = 0.003) was significantly lower in period 2 than in period 1 (Table 1). The number of patients requiring perioperative red blood cell transfusion (18/70 vs. 2/74; P¥0.0001) and the amount of fresh frozen plasma that was transfused (1,280 vs. 480 mL; P¥0.0001) were significantly reduced in period 2 (Table 1).

Surgical radicality

The type of hepatectomy that was used and the surgical radicality were listed according to the Bismuth–Corlette classification (Table 3). Although the R0 resection rate was comparable between the two periods in patients with Bismuth–Corlette type I–III tumors, the rate improved from 60 % during period 1 to 80.6 % during period 2 among patients with Bismuth–Corlette type IV tumors (P = 0.097)

(Table 3). A positive proximal ductal margin was the predominant cause of the residual tumor.

Postoperative outcomes

A 71-year-old male patient died on postoperative day 31 in period 1 because of cerebral infarction 21 days after a left hepatectomy; the patient had showed no signs of liver failure. In period 2, zero mortality was achieved along with a significantly reduced morbidity rate (85.9 vs. 60.8 %, P = 0.001) and a lower major complication rate (34.3 vs. 24.3 %, P = 0.189) (Table 4). Among patients with cholangitis related to preoperative biliary drainage, the incidence of postoperative cholangitis was 28.6 % during period 1 and 10.5 % during period 2 (Table 2); these rates were comparable to those observed in patients without

preoperative biliary drainage (13.3 % during period 1, P = 0.227; and 20.5 % during period 2, P = 0.480). Figure 1 shows the postoperative outcomes stratified according to cotreatment with preoperative biliary drainage and/or PVE. Although the incidence of PHLF was higher among patients with both biliary drainage and PVE than among the other patients, the maximum postoperative serum bilirubin level was comparable irrespective of the use of biliary drainage or PVE. The postoperative maximum serum bilirubin values were weakly correlated with the resection ratio, calculated using the following equation: (1 - future liver remnant volume/total liver volume) 9 100 (r2 = 0.068, P = 0.003, Fig. 2). Univariable analyses identified a blood loss of more than 900 mL and an operative time of longer than 760 min as being significantly related to overall morbidity, and blood loss was selected as an independent risk factor for morbidity in a multivariable logistic regression analysis (Table 5). Univariable analyses failed to show any risk factors for major complications.

Long-term outcomes

The overall survival rate was similar between the two periods (Fig. 3). The 5-year survival rates were 32.5 % during period 1 and 34.8 % during period 2, respectively. Univariable analyses revealed the following factors to be significantly associated with poor survival: a higher AJCC T classification, a higher G grade, positive nodal involvement, microscopic lymphatic invasion, vascular invasion, perineural invasion, R1–2 resection, and packed red blood cell transfusion (Table 6). A multivariable analysis identified positive nodal involvement and an R1–2 resection as independent prognostic factors for survival (Table 6). Significant differences in the overall survival were observed between patients with and those without nodal involvement (Fig. 4a, P¥0.0001) and between those with a positive ductal margin and those with a negative (R0) resection margin (Fig. 4b, P = 0.003). No significant difference was observed in terms of the extent of nodal involvement (within vs. beyond the hepatoduodenal ligament, P = 0.702, Fig. 4c). Survival among patients with a positive margin with carcinoma in situ was poorer than

among those who underwent R0 resection, although the difference did not reach statistical significance

(P = 0.125). Patients with a positive margin with invasive carcinoma had a significantly poorer survival outcome than those undergoing R0 resection (P = 0.006) (Fig. 4d).

Discussion

Major liver resection for the treatment of hilar cholangiocarcinoma carries a substantial risk of mortality because the majority of patients have impaired liver function due to cholestasis [7, 10, 11]. With the recent refinement of surgical techniques and perioperative care [20, 21], an improvement in operative outcome has been reported. However, the mortality rate remains relatively high at around 10 %, even in recently published studies, as shown in Table 7 [22, 23]. In the present study, the mortality rate was 1.2 % during period 1, and we achieved a zero mortality rate in the most recent decade of the study, even though a major hepatectomy was performed in a high proportion of patients (90.0 % during period 1 and 97.3 % during period 2). Furthermore, it should be emphasized that the present series included patients who underwent a concomitant PD (19 % during period 1 vs. 12 % during period 2) and patients who required vascular resection (11 % during each time period). Importantly, no liver failure related deaths were observed during our 23 years of experience. The role of preoperative biliary drainage in cases of hilar cholangiocarcinoma has been a matter of debate. The routine application of biliary drainage has been extensively advocated by several Japanese centers [6, 9, 20, 21, 24] based on the results of both clinical and experimental studies [25–28], whereas the Blumgart group has consistently argued against its routine application [29] based on the findings of two retrospective studies [30, 31]. Recently, a multicenter study reported that the impact of biliary drainage depends on the type of surgery performed;namely, biliary drainage was associated with a decreased mortality rate after a right hepatectomy and, surprisingly, an increased mortality rate after a left hepatectomy [23]. In the present study, the mortality rate was far lower than that in previous reports, despite our routine application of biliary drainage for obstructive jaundice. In addition, biliary drainage was not related to an increased morbidity rate when examined using univariable analysis. It should be emphasized that, to date, zero mortality rates after liver resection for hilar cholangiocarcinoma have been achieved at Japanese centers only where biliary drainage is routinely applied [21, 24, 32]. According to the Clavien classification, the overall incidence of postoperative morbidity was extremely high during period 1 but decreased significantly to 60.8 % during period 2. Similarly, the major complication rate also decreased from 34.3 to 24.3 % for the respective periods,

but this difference was not significant. These figures for period 2 were similar to those reported in previous studies [23, 33]. Farges et al. [23] conducted a multicenter study evaluating the role of biliary drainage before a hepatectomy for hilar cholangiocarcinoma and showed that the overall morbidity and severe morbidity rates, defined as Clavien grades III to IV, were 68.6 and 27.6 %, respectively. The frequency of major complications in the present study was attributed largely to our policy of performing

thoracocentesis whenever possible. Indeed, among the 33 patients with grade IIIa complications, 28 (84.8 %) underwent a tap for pleural effusion. As described above, the overall morbidity and major complication rates have steadily decreased over the most recent decade; however, the incidence remains relatively high. Because a major hepatectomy with PD, especially for patients with impaired liver function [34], is reportedly associated with higher mortality and morbidity rates, our improved short-term outcomes during period 2 might reflect only the lower rate of the concomitant performance of PD. Indeed, patients who underwent concomitant PD had a higher morbidity rate than those without PD in the present study, although the difference did not reach statistical significance. Thus, we cannot fully deny the influence of the lower rate of PD on postoperative morbidity. Similarly, a hepatectomy with vascular resection and reconstruction [5, 7, 35–37] is known to influence the mortality and morbidity rates. However, because the vascular resection rate was comparable between the two periods, explaining the improvement in the short-term outcomes during period 2 based on the rate of vascular resection and reconstruction is difficult. Because the surgical treatment of hilar cholangiocarcinoma is technically demanding and challenging [32], the reported median blood loss is typically nearly 2 L, even in high-volume centers [32, 38]. The present study showed a marked reduction in the median blood loss from 1,020 to 745 mL by enhancing the meticulousness of the surgical procedure, namely, careful hemostasis, especially during parenchymal transection; this reduction was achieved without any increase in operative time despite the use of comparable surgical procedures between the two periods. Of note, the amount of blood lost was identified by multivariable analysis as an independent risk factor of postoperative morbidity, suggesting that the reduction in blood loss contributed to the reduction in the morbidity rate during period 2. Our results were in line with those of previous studies, which showed that intraoperative blood loss [39] and subsequent blood transfusion [40] increased the risk of postoperative mortality and morbidity after liver resection. In summary, although further improvement in perioperative outcomes remains possible, surgical treatment, specifically a major hepatectomy, for hilar cholangiocarcinoma, can be safely performed using our perioperative treatment policy and meticulous surgical techniques. While the short-term outcomes have improved steadily over the last decade, the long-term outcomes remained roughly the same between the two periods. The 5-year survival rates for each period were similar to those in previous reports, which ranged from 22 to 37 % [7, 8, 20, 22, 41, 42]. Complete tumor clearance is known to be a significant

predictor of long-term survival after surgical treatment for hilar cholangiocarcinoma. Indeed, among the several surgery-related variables that were analyzed in the present study, R0 resection was the only independent prognostic factor to be identified in multivariable analysis. The R0 resection rates in the present study were comparable to previously reported values [7, 8]. Because a positive proximal ductal margin was a predominant cause of the residual tumor in the present study, a further improvement of the R0 resection rate might be achieved by the aggressive application of a left or right trisectionectomy [43, 44]. However, since a trisectionectomy involves the removal of 65–80 % of the liver, the application of such an extensive procedure could heighten the risk of postoperative liver failure, especially in patients with cholestasis-induced impairments in liver function. Hence, the potential benefit of the procedure for obtaining a cancer-free ductal margin should be balanced against the accompanying risks. Although a positive ductal margin has been known to have a negative impact on the long-term outcome after

surgical resection of hilar cholangiocarcinoma [5, 7, 8, 20,45], previous reports have shown that the overall survival was comparable between patients with a negative ductal margin and those with positive margins with carcinoma in situ after surgical resection for extrahepatic cholangiocarcinoma [46–48]. In the present study, patients with a positive margin with carcinoma in situ had a poorer overall survival (although the difference did not reach statistical significance) than those who underwent R0 resection, showing a clear contrast to the results of previous studies. This difference can be explained by considering that the present study included only patients with hilar cholangiocarcinoma. The small number of patients with carcinoma in situ might also have affected the outcomes. Further studies are needed to confirm whether the details of a positive ductal margin status have an impact on long-term survival in patients with hilar cholangiocarcinoma. This study had several limitations including a small sample size, retrospective design, and long study period. However, our principal treatment protocol remained the same throughout the entire study period. Despite these limitations, we believe that our results are of interest, since only a few reports published in the English-language medical literature have achieved a zero mortality rate after the surgical treatment of hilar cholangiocarcinoma. In conclusion, while the perioperative outcomes after the surgical treatment of hilar cholangiocarcinoma have steadily improved based on the accumulation of experience and a meticulous surgical technique to reduce blood loss, the longterm outcomes remain unsatisfactory. Further improvement of the R0 resection rate could prolong patient survival.

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Conflict of interest None.

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Table 1 Patients characteristics and operative results

	Period 1 (1990-2000, *n* = 70)	Period 2 (2001-2012, *n* = 74)	*P*
Age (years)*	69 (39-84)	70 (42-82)	0.706
Male/female	50/20	52/22	0.879
ASA classification 1/2/3	37/25/8	27/41/6	0.231
ICGR15 (%)*	12.6 (4.9-29.5)	11.0 (4.0-30.0)	0.149
Preoperative total bilirubin value (μmol/L)*	17 (5-74)	15 (6-48)	0.823
Comorbidity			0.064
Diabetes mellitus	9 (12.9)	12 (16.2)	0.064
Hypertension	15 (21.4)	34 (45.9)	0.002
Cardiopulmonary	10 (14.3)	11 (14.9)	0.922
Biliary drainage	59 (84.3)	63 (85.1)	0.887
Bismuth-Corlette classification			0.777
I, II	15 (21.4)	17 (23.0)	
IIIa	13 (18.6)	15 (20.3)	
IIIb	12 (17.1)	11 (14.8)	
IV	30 (42.9)	31 (41.9)	
AJCC			
T grade			0.637
T1	9 (12.9)	10 (13.5)	
T2a	35 (50.0)	34 (46.0)	
T2b	12 (17.1)	19 (25.6)	
T3	8 (11.4)	9 (12.2)	
T4	6 (8.6)	2 (2.7)	

Table 1 Continued

N grade			0.752
N0	36 (51.4)	40 (54.1)	
N1	34 (48.6)	34 (45.9)	
G grade			0.355
G1	39 (55.7)	40 (54.1)	
G2	23 (32.9)	19 (25.7)	
G3	8 (11.4)	14 (18.9)	
G4	0 (0)	1 (1.3)	
AJCC pathologic staging			0.634
I	7 (10.0)	7 (9.4)	
II	26 (37.1)	29 (39.2)	
IIIA	2 (2.9)	3 (4.1)	
IIIB	29 (41.4)	33 (44.6)	
IVA	6 (8.6)	2 (2.7)	
IVB	0 (0)	0 (0)	
Type of resection			0.950
Right hepatectomy	47 (67.2)	44 (59.5)	
Left hepatectomy	14 (20.0)	22 (29.7)	
Left trisectionectomy	1 (1.4)	3 (4.1)	
Sg 4, 5, 8	1 (1.4)	3 (4.1)	
Minor hepatectomy†	6 (8.6)	2 (2.7)	
Bile duct resection	1 (1.4)	0	
With PD	13 (18.6)	9 (12.2)	0.285

Table 1 Continued

With vascular resection	8 (11.4)	8 (10.8)	0.906
PV	7	6	
HA	2	2	
PV+HA	1	0	
Operative time (min)*	793 (445-1305)	735 (497-1284)	0.067
Pedicle clamping time (min)*	60 (20-160)	60 (30-140)	0.300
Blood loss (mL)*	1020 (390-4040)	745 (130-1700)	0.003
Red blood cell transfusion	18 (25.7)	2 (2.7)	<0.001
Amount of FFP transfused (mL)*	1280 (400-2880)	480 (0-2880)	<0.001

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Minor hepatectomy was defined as resection of one or two Couinaud's segments. ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on Cancer. ICGR15; indocyanine green retention rate at 15 minutes; PVE, portal vein embolization; PD, pancreaticoduodenectomy; PV, portal vein; HA, hepatic artery; FFP, fresh frozen plasma

Table 2 Details regarding preoperative biliary drainage

	Period 1 (1990-2000, *n* = 70)	Period 2 (2001-2012, *n* = 74)	*P*
Biliary drainage	59 (84.3 %)	63 (85.1 %)	0.887
Type of drainage			
PTBD	29 (49.2 %)	4 (6.3 %)	<0.0001
ERBD	27 (45.8 %)	54 (85.7 %)	
Both	3 (5.0 %)	5 (8.0 %)	
Unilateral or bilateral drainage			
Unilateral	47 (79.7 %)	49 (77.8 %)	0.800
Bilateral	12 (20.3 %)	14 (22.2 %)	
Persistent jaundice	4 (6.8 %)	5 (7.9 %)	
Cholangitis	0	1 (1.6 %)	
Performed at a regional hospital	6 (10.2 %)	4 (6.3 %)	
Others	2 (3.4 %)	4 (6.3 %)	
Preoperative cholangitis related to biliary drainage	14 (23.7 %)	19 (30.2 %)	0.424
Postoperative cholangitis			
Yes	4 (28.6 %)	2 (10.5 %)	0.363
No	10 (71.4 %)	17 (89.5 %)	

PTBD percutaneous transhepatic biliary drainage, ERBD endoscopic retrograde biliary drainage

Table 3 Type of liver resection and surgical radicality according to the Bismuth- Corlette classification

Bismuth–Corlette classification	I–III			IV		
	Period 1	Period 2	*P*	Period 1	Period 2	*P*
Number of patients	40	43		30	31	
Type of hepatectomy						
Right hepatectomy	21 (52.5 %)	26 (60.5 %)	0.511 [a]	26 (86.7 %)	18 (58.1 %)	0.021 [a]
Left hepatectomy	12 (30.0 %)	14 (32.6 %)		2 (6.7 %)	8 (25.8 %)	
Left trisectionectomy	1 (2.5 %)	0		0	3 (9.7 %)	
Others	6 (15.0 %)	3 (6.9 %)		2 (6.6 %)	2 (6.4 %)	
Surgical radicality						
R0	31 (77.5 %)	33 (76.7 %)	0.935 [b]	18 (60.0 %)	25 (80.6 %)	0.097 [b]
R1	4 (10.0 %)	8 (18.6 %)		1 (3.3 %)	2 (6.5 %)	
Radial margin	1	0		1	1	
Ductal margin	3	8		0	1	
Carcinoma in situ	3	7		0	0	
Invasive carcinoma	0	1		0	1	
R2	5 (12.5 %)	2 (4.7 %)		11 (36.7 %)	4 (12.9 %)	
Radial margin	0	0		0	0	
Ductal margin	5	2		11	4	
Carcinoma in situ	0	0		0	0	
Invasive carcinoma	5	2		11	4	

[a] Right hepatectomy versus others

[b] R0 versus R1–2

Table 4 Postoperative outcomes

	Period 1 (1990–2000, n = 70)	Period 2 (2001–2012, n = 74)	P
30-day mortality	0	0	
90-day mortality	1 (1.4 %)	0	0.978
No. of complications	89	84	
Grade IVa [a]	1 (1.1 %)	0	
Cerebral infarction	1 (1.1 %)	0	
Grade IIIb	5 (5.6 %)	3 (3.6 %)	
Intra-abdominal abscess	2 (2.2 %)	0	
Jejunal perforation	1 (1.1 %)	0	
Hepatic artery rupture	2 (2.2 %)	0	
Intra-abdominal bleeding	0	2 (2.4 %)	
Biliary peritonitis	0	1 (1.2 %)	
Grade IIIa	21 (30.0 %)	18 (21.4 %)	
Pleural effusion	19 (21.3 %)	16 (19.0 %)	
Intra-abdominal abscess	1 (1.1 %)	1 (1.2 %)	
Bile leakage	1 (1.1 %)	1 (1.2 %)	
Grade II	46 (65.7 %)	43 (51.2 %)	
Grade I	16 (22.9 %)	20 (23.8 %)	
Patients with complications	60 (85.7 %)	45 (60.8 %)	0.001
Patients with major complications	24 (34.3 %)	18 (24.3 %)	0.189
Grade IVa [a]	1 (1.4 %)	0	
Grade IIIb	5 (7.1 %)	3 (4.1 %)	
Grade IIIa	18 (25.7 %)	15 (20.3 %)	
Postoperative hospital stay (days)	53 (23–319)	47 (17–287)	0.020

SSI surgical site infection

[a] According to Clavien-Dindo classification

[b] Values are median (range) unless indicated otherwise

Table 5 Univariable and multivariable analyses of factors associated with postoperative overall morbidity

Univariable				Multivariable	
Comparison	No. patients	Patients with complication	P [a]	Odds ratio (95% CI)	P[b]
Sex					
Male	102	75	0.796		
Female	42	30			
Age (years)					
≥ 70	69	52	0.526		
< 70	75	53			
Comorbidity					
Yes	50	33	0.173		
No	94	72			
Diabetes mellitus					
Yes	21	18	0.153		
No	123	87			
Biliary drainage					
Yes	122	92	0.113		
No	22	13			
Preoperative colangitis					
Yes	34	25	0.927		
No	110	80			

Table 5 continued

ICGR15					
> 12%	74	57	0.254		
≤ 12%	70	48			
Preoperative total bilirubin value					
> 17 μmol/L	63	45	0.723		
≤ 17 μmol/L	81	60			
Major hepatectomy					
Yes	131	94	0.320		
No	13	11			
With PD					
Yes	22	19	0.123		
No	122	86			
With vascular resection					
Yes	16	12	0.842		
No	128	93			
Operative time					
> 760 min	71	57	0.049	1.28 (0.55, 2.98)	0.605
≤ 760 min	73	48			
Amount of blood loss					
> 900 ml	65	57	0.0003	4.20 (1.66, 10.64)	0.003
≤ 900 ml	79	48			

Table 5 continued

Packed red blood cell transfusion			
Yes	20	18	0.064
No	124	87	
Pedicle clamping time			
> 60 min	57	41	0.829
≤ 60 min	87	64	

CI confidence interval, *ICGR15* indocyanine green retention rate at 15 min, *PD* pancreaticoduodenectomy

[a] χ^2 or Fisher's exact test

[b] Logistic regression analysis

Table 6 Univariate and multivariate analysis of prognostic variables for overall survival

Univariate				Multivariate	
Comparison	No. of patients	Length (monthes)	*P* [a]	Hazard ratio (95% CI)	*P* [b]
Host-related factors					
Sex					
Male	102	38	0.479		
Female	42	36			
Age					
≥ 70	69	35	0.525		
< 70	75	40			
ICGR15					
> 12%	74	40	0.150		
≤ 12%	70	32			
Cancer-related factors					
AJCC (7th ed.) T grade					
T1-2	119	39	0.001	1.11 (0.69, 1.78)	0.379
T3-4	25	16			
AJCC (7th ed.) G grade					
G1	79	42	0.041	1.13 (0.74, 1.72)	0.561
G2-4	65	23			

I

Table 6 Continued

AJCC (7th ed.) N grade					
N0	76	47	<0.0001	2.43 (1.63, 3.62)	<0.0001
N1	68	21			
Invasion of liver parenchyma					
Yes	70	35	0.811		
No	74	34			
Microscopic lymphatic involvement					
Yes	127	32	0.037	1.08 (0.45, 2.59)	0.864
No	17	55			
Microscopic vascular involvement					
Yes	110	32	0.004	1.38 (0.79, 2.40)	0.222
No	34	55			
Microscopic perineural invasion	127	30	0.008	2.09 (0.99, 4.39)	0.052
Yes	17	65			
No	79	42	0.041	1.13 (0.74, 1.72)	0.561
Surgery-related factors					
Period					
Period 1	70	35	0.393		
Period 2	74	39			

Table 6 Continued

Residual tumor					
R0	107	41	0.002	1.86 (1.22,2.85)	0.004
R1-2	37	15			
With PD					
Yes	22	33	0.244		
No	122	37			
With vascular resecton					
Yes	16	17	0.051		
No	128	37			
Amount of Blood loss (ml)					
> 900	65	32	0.104		
≤ 900	79	37			
Packed red blood cell transfusion					
Yes	20	24	0.020	1.49 (0.90, 2.47)	0.117
No	124	36			
Adjuvant chemotherapy					
Yes	22	36	0.223		
No	122	32			

CI confidence interval, *ICGR15* indocyanine green retention rate at 15 min, *PD* pancreaticoduodenectomy

[a] Log lank test [b] Cox multivariable regression analysis

Table 7 Mortality, morbidity, and 5-year survival rates after surgical treatment of hilar cholangiocarcinoma in previous reports

Author	Period	No. resections	Hepatectomy (%)	Mortality (%)	Morbidity (%)	Risk factors for morbidity	5-year survival (%)
Jarnagin et al. [6]	1991–2000	80	78	10.0	64	NA	27
Seyama et al. [24]	1989–2001	58	100	0	43	NA	40
Hemming et al. [49]	1997–2004	53	98	9.4	40	NA	35
Miyazaki et al. [37]	1981–2004	161	88	6.8	39	NA	NA
Sano et al. [32]	2000–2004	102	100	0	50	Preoperative cholangitis or cholecystitis	44
						B–C type IIIa[a]	
Dinant et al. [42]	1988–2003	99	38	15.2	66	Right hemihepatectomy[a]	27
						Portal vein resection[a]	
Lee et al. [50]	2001–2008	302	89	1.7	43	NA	33
Cannon et al. [51]	1992–2010	59	83	5.1[b]	39	NA	17.7[c]
Nuzzo et al. [22][d]	1992–2007	440	86	8.6	48	NA	26
Farges et al. [23][d]	1997–2008	366	100	10.7	69	NA	NA

Table 7 Continued

Nagino et al. [52]	1977–2010	386[e]	99[e]	2.0[e]	47[e]	NA	38[e]
Current series	1990–2000	70	99	1.4[f]	86	Blood loss >900 mL	33
	2001–2012	74	100	0[f]	61		35

NA not available, *B–C* Bismuth-Corlette classification

[a] Univariable analysis

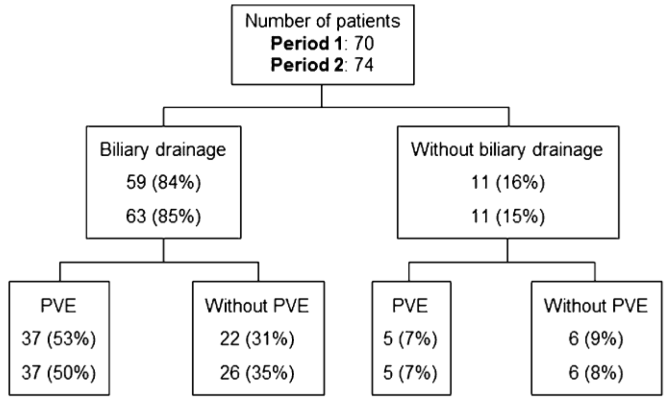
[b] 30-day mortality

[c] Including patients who did not undergo resection

[d] Multicenter study

[e] Between 2001 and 2010

[f] 90-day mortality



		PVE	Without PVE	PVE	Without PVE	
Hypertrophy ratio (%)	Period 1	130 ± 26	NA	127 ± 14	NA	*P* = 0.783 [b]
	Period 2	130 ± 22	NA	127 ± 24	NA	*P* = 0.808
Maximum serum bilirubin [a]	Period 1	44 ± 17	37 ± 13	40 ± 23	37 ± 28	*P* = 0.317 [b]
	Period 2	41 ± 15	39 ± 16	28 ± 11	36 ± 11	*P* = 0.469
PHLF, Grade A/B/C	Period 1	0/21/0	0/0/0	0/1/0	0/2/0	*P* = 0.0002 [c]
	Period 2	0/17/0	2/2/0	0/0/0	0/1/0	*P* = 0.010

[a] μmol/L, [b] Kruskal Wallis test, [c] chi-square test

Fig. 1 Postoperative outcomes stratified according to the period of operation, preoperative biliary drainage, and PVE. The hypertrophy ratio was defined as the ratio of the future liver remnant volumes measured after and before PVE. *PVE* portal vein embolization, *PHLF* posthepatectomy liver failure

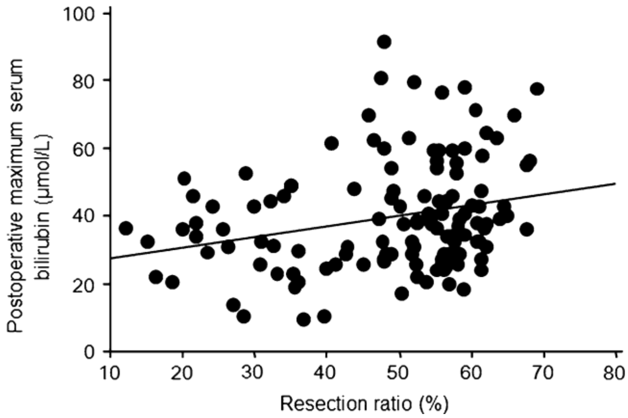
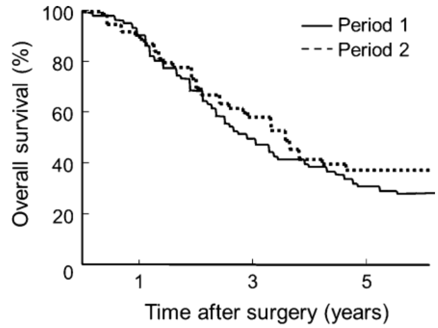


Fig. 2 Correlation between the postoperative maximum serum bilirubin value (ordinate) and the resection ratio (abscissa). Resection ratio was calculated as (1 − future liver remnant volume/total liver volume) ×100. Linear regression; maximum serum bilirubin value = 0.314 × resection ratio + 24.4, $r^2 = 0.068$, $P = 0.003$



No. at risk

Period 1	70	63	34	22
Period 2	74	56	29	16

Fig. 3 Overall survival rates stratified according to the time period during which the patients with hilar cholangiocarcinoma were treated; P = 0.393 (log rank test)

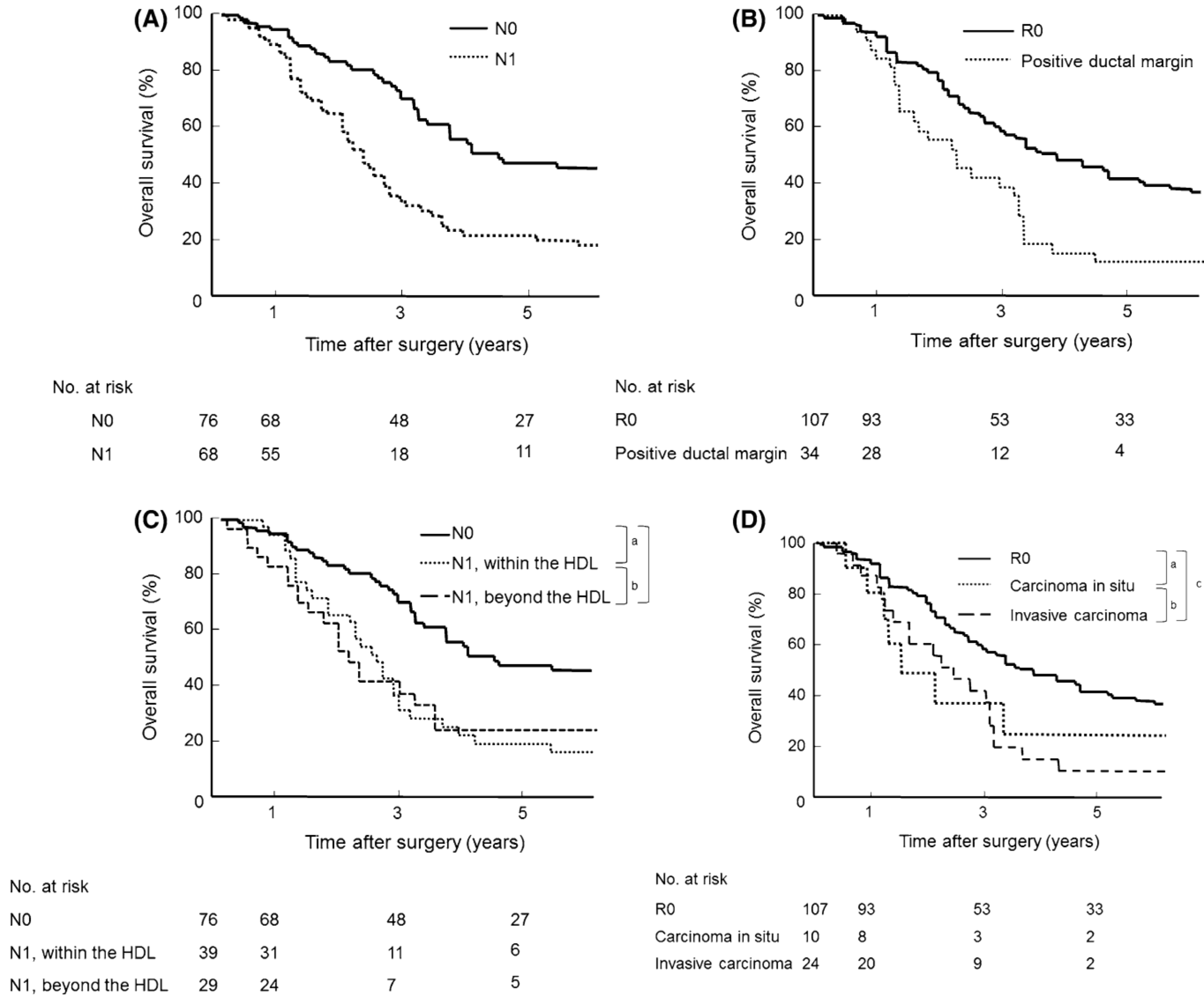


Fig. 4 Patient survival stratified according to the presence or absence of **a** the nodal involvement (N0 vs. N1, P <0.0001, log rank test) and **b** the residual tumor (R0 vs. positive ductal margin, P = 0.003). **c** Survival for patients with the prognostic factor stratified further according to the extent of nodal involvement, i.e., within vs. beyond the hepatoduodenal ligament; *a* P <0.0001, *b* P = 0.702, *c* P <0.0001. **d** The details of the positive ductal margin status: carcinoma in situ vs. invasive carcinoma; *a* P = 0.125, *b* P = 0.754, *c* P = 0.006