

Left Hepatectomy with Combined Resection and Reconstruction of Right Hepatic Artery for Bismuth Type I and II Perihilar Cholangiocarcinoma

Teiichi Sugiura¹ · Yukiyasu Okamura¹ · Takaaki Ito¹ · Yusuke Yamamoto¹ · Ryo Ashida¹ · Katsuhisa Ohgi¹ · Masahiro Nakagawa² · Katsuhiko Uesaka¹

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Abstract

Background Right hepatectomy with caudate lobectomy (RHx) is considered an appropriate procedure for Bismuth type I/II perihilar cholangiocarcinoma in terms of its anatomical and oncological aspect. However, validity of left hepatectomy with caudate lobectomy (LHx) concomitant with arterial resection and reconstruction (AR) is not fully evaluated.

Methods The patients who underwent surgical resection for Bismuth type I/II perihilar cholangiocarcinoma between 2002 and 2013 were studied. The standard procedure for Bismuth type I/II cholangiocarcinoma in the institute was RHx, while in patients who had insufficient functional reserve of the left liver, LHx was selected, irrespective of the necessity of AR. The clinicopathologic and perioperative outcomes after LHx + AR were compared with those after RHx.

Results The surgical procedures comprised LHx + AR in 12 and RHx in 24. The left liver volume and left liver functional reserve were significantly lower with LHx + AR than with RHx (left liver volume: 28.0 vs. 33.7%, $p = 0.026$; estimated indocyanine green clearance of the left liver: 0.036 vs. 0.046, $p < 0.001$). The rate of surgical morbidity was almost identical between the two procedures. No arterial reconstruction-related complications occurred. The overall 3- and 5-year survival rates and median survival time were 66.7%, 41.7% and 44 months for LHx + AR and 70.8%, 49.0% and 57 months for RHx ($p = 0.640$).

Conclusion LHx + AR for Bismuth type I/II perihilar cholangiocarcinoma is considered to be a valid alternative to RHx in patients with an insufficient left liver functional reserve.

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✉ Teiichi Sugiura
t.sugiura@scchr.jp

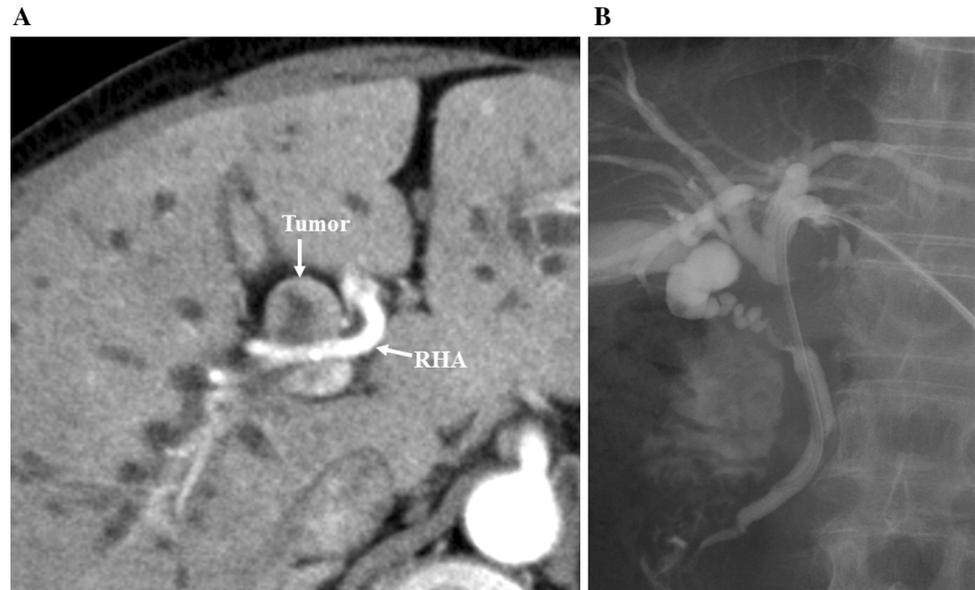
¹ Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, 1007 Shimo-Nagakubo, Sunto-Nagaizumi, Shizuoka 411-8777, Japan

² Division of Plastic Surgery, Shizuoka Cancer Center, Shizuoka, Japan

Introduction

Since its first review by Klatskin in 1965, perihilar cholangiocarcinoma still remains one of the most difficult malignancies for which to achieve R0 resection [1]. To obtain a favorable outcome, curative resection with no residual tumor has been considered as the only appropriate treatment for perihilar cholangiocarcinoma. Many types of resection have been performed, according to the horizontal tumor extension; from extrahepatic bile duct resection alone to major hepatectomy with and without pancreatoduodenectomy [2, 3], and the vertical tumor extension; a

Fig. 1 **a** Computed tomography strongly suggested cancer invasion of the right hepatic artery, based on the absence of a visible low-density plane between the right hepatic artery (RHA) and the adjacent tumor, **b** Cholangiography of Bismuth type I perihilar cholangiocarcinoma



combined resection of the hepatic artery and/or portal vein [4–7].

For Bismuth type I/II perihilar cholangiocarcinoma [8], historically, extrahepatic bile duct resection without hepatectomy has been attempted but has resulted in dismal outcomes with a high incidence of locoregional recurrence [9–14]. Nowadays, right hepatectomy and caudate lobectomy with bile duct resection (RHx) is deemed an acceptable procedure for Bismuth type I/II perihilar cholangiocarcinoma [15]. Perihilar cholangiocarcinoma often involves the right hepatic artery, which runs behind the common hepatic duct, making RHx a rational procedure [9–12, 15–18]. However, the right liver occupies generally 60–70% of the total liver volume [19–21]. As such, some patients with an extremely small left liver run the risk of postoperative liver failure despite portal vein embolization. For such patients, left hepatectomy, caudate lobectomy and bile duct resection (LHx) with concomitant resection and reconstruction of the right hepatic artery (AR) were attempted.

The aim of this study is to review the surgical strategy for Bismuth type I/II perihilar cholangiocarcinoma and to clarify the validity of LHx with AR.

Patients and methods

The patients who underwent surgical resection for Bismuth type I or II perihilar cholangiocarcinoma between 2002 and 2013 were included in this study.

The patients' characteristics were reviewed using the prospectively collected data base. The clinicopathologic and perioperative outcomes after LHx + AR were

compared with those after RHx. The postoperative complications were described in line with the Dindo–Clavien classification [22]. Posthepatectomy liver failure was defined and graded by the International Study Group of Liver Surgery (ISGLS) definition [23]. This study was approved by the Institutional Review Board of the Shizuoka Cancer Center.

Preoperative assessment and management

For the preoperative clinical evaluation, laboratory and imaging studies, including multidetector-row computed tomography (MDCT) [24–26], ultrasonography and cholangiography via either endoscopic retrograde or percutaneous transhepatic approach, were performed (Fig. 1). Other imaging examinations, such as magnetic resonance imaging (MRI) and positron emission tomography, were performed when needed.

The preoperative volumetric assessment of the liver was performed using computed tomography. The remnant liver function was assessed by the estimated indocyanine green (ICG) clearance of the future liver remnant [27, 28]. The cutoff value for deciding liver resection was set with ICG clearance of the future liver remnant of 0.05 [27].

Preoperative portal vein embolization was performed when RHx was intended. This procedure was performed through the percutaneous transhepatic approach approximately 2–3 weeks before surgery [27]. In cases of RHx, liver functional assessment was conducted before and after portal vein embolization.

Surgery

The standard surgical procedure for Bismuth type I/II perihilar cholangiocarcinoma in the authors' institute is RHx. In some patients who had small left liver volume, increase of the left liver function was not expected to reach to the lower limit of surgical tolerance, even if a 10% gain in the left liver volume would be obtained after right PVE [27]. Therefore, in these cases, RHx was abandoned, and LHx was alternatively selected, even though combined resection and reconstruction of the right hepatic artery is required (Fig. 2). Principally, concomitant resection of the hepatic artery or portal vein was performed in cases of intraoperative findings of macroscopic cancer invasion to these vessels. Hepatic arterial reconstruction was performed by plastic surgeons with an interrupted suture using 8–0 or 9–0 nylon under a surgical microscope. All anastomoses were carried out in an end-to-end fashion. Portal vein reconstruction was conducted by hepatobiliary surgeons with continuous sutures using 5-0 monofilament suture.

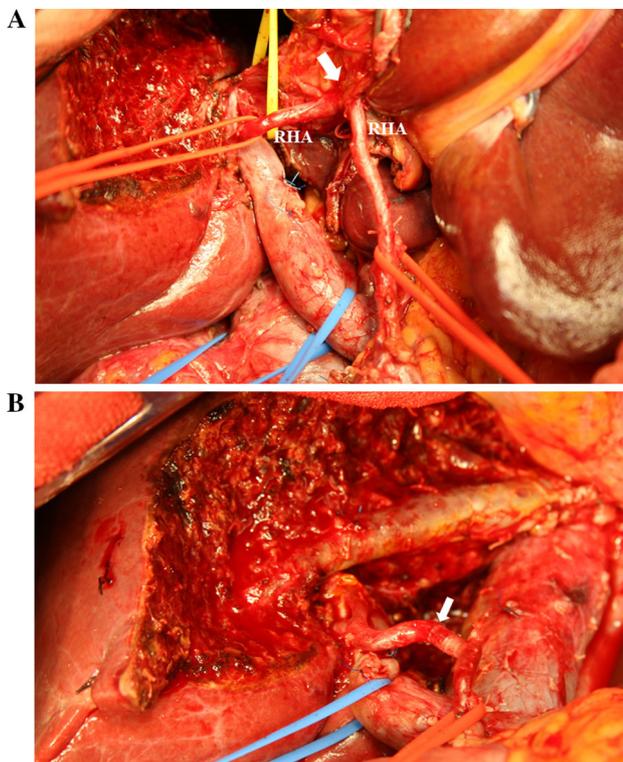


Fig. 2 An intraoperative photograph of combined hepatic artery resection and reconstruction. **a** The right hepatic artery (RHA) was involved by tumor (arrow). **b** Left hepatectomy was performed with en bloc resection of the right hepatic artery. The resected hepatic artery was reconstructed with end-to-end anastomosis (arrow)

Histopathologic evaluation

The surgical specimens were fixed in 10% formalin for several days and serially sliced at 5-mm intervals. The specimens were prepared in the usual manner for microscopic examinations with hematoxylin and eosin staining. The TNM Classification of Malignant Tumors by the International Union Against Cancer (7th edition, 2009) was used to describe the pathologic findings [29]. Microscopic invasion of the resected right hepatic artery was examined. In patients without microscopic tumor invasion, the distance between the tumor and the resected artery was measured.

Statistical analysis

All statistical analyses were performed using the SPSS® version 19.0 (IBM, Armonk, New York, USA). Continuous variables were expressed as medians with the range and compared using the Mann–Whitney U test. The Kaplan–Meier method was used to calculate the overall survival rates. These survival values were compared by the log-rank test. The Chi-square test or Fisher's exact test was performed for categorical variables where appropriate. A *p* value less than 0.05 was considered to be statistically significant.

Results

Among 162 patients with perihilar cholangiocarcinoma who underwent surgical resection, 36 patients with Bismuth I/II perihilar cholangiocarcinoma were reviewed. These patients comprised 29 men and 7 women with median age of 67 year. The surgical procedures were LHx + AR in 12 and RHx in 24.

Table 1 presents the demographics of the patients according to the surgical procedure. The ICG clearance was almost equal between the two groups.

The surgical outcomes and postoperative complications are listed in Table 2. Regarding arterial reconstruction in the LHx + AR patients, only the right hepatic artery was used for the distal part; however, several kinds of arteries were selected for the proximal part based on the suitable diameter for reconstruction.

The rates of postoperative complications were almost similar. Although there was no significant difference, posthepatectomy liver failure (PHLF) according to ISGLS grade B or refractory ascites tended to develop more frequently in the RHx group than in the LHx + AR group (PHLF, 0 vs. 21%; refractory ascites; 0 vs. 17%). No arterial resection or reconstruction-related complications,

Table 1 Patient characteristics according to surgical procedure

	LHx + AR (<i>n</i> = 12)	RHx (<i>n</i> = 24)	<i>p</i>
Age (years)*	65 (58–84)	68 (37–81)	0.545
Gender (M:F)	11:1	18:6	0.384
Bismuth type (I:II)	2:10	8:16	0.438
CA19-9 (U/ml)*	66 (8–630)	34 (2–1960)	0.322
Total liver volume (ml)*	1297 (675–1735)	1196 (635–1559)	0.169
ICG clearance*	0.133 (0.098–0.178)	0.140 (0.100–0.187)	0.168
Left liver volume (ml)*	331 (255–567)	380 (196–659)	0.591
Left liver volume ratio (%)*	28.0 (19.7–37.9)	33.7 (23.7–43.2)	0.026
ICG clearance of left liver*	0.036 (0.023–0.049)	0.046 (0.035–0.074)	<0.001
Future remnant liver volume (ml)*	902 (397–1249)	496 (272–659)	<0.001
Future remnant liver volume ratio (%)*	69.3 (58.8–78.0)	42.5 (32.7–51.4)	<0.001
ICG clearance of future remnant liver*	0.090 (0.064–0.127)	0.059 (0.045–0.083)	<0.001

LHx + AR, left hepatectomy, caudate lobectomy and bile duct resection concomitant resection and reconstruction of right hepatic artery; RHx, right hepatectomy and caudate lobectomy with bile duct resection; CA 19-9, carbohydrate antigen 19-9; ICG, indocyanine green

Future remnant liver means right liver in LHx + AR and left liver after portal vein embolization in RHx

*Median (ranges)

such as liver abscess or arterial occlusion, developed in any patients undergoing LHx + AR.

Table 3 shows the pathologic findings of each group. There were no significant differences in the pathologic findings between the two groups. Microscopic invasion of the right hepatic artery was observed in approximately one-third of patients in each group. Among the seven patients without microscopic arterial invasion in the LHx + AR group, the distance between the artery and cancer could be measured in five (prepared slides of two patients in the early period were lost); the median distance between the artery and cancer was 485 μm (110–1044 μm).

During this study period, 21 patients developed recurrence: 8 in the LHx + AR group and 13 in the RHx group (Table 4). The incidence across all recurrence sites was almost identical. However, while all patients were shown to have a negative dissection margin, two patients in the LHx + AR group and five in the RHx group developed local recurrence. All of these patients had massive perineural invasion of the tumor. Figure 3 shows the overall survival curve according to the surgical procedure. The overall 3- and 5-year survival rates and median survival time were 66.7%, 41.7% and 44 months for LHx + AR and 70.8%, 49.0% and 57 months for RHx. The difference was not significant between the LHx + AR and RHx groups ($p = 0.640$).

Discussion

In the present study, we evaluated a new surgical approach in patients with Bismuth type I/II perihilar cholangiocarcinoma. Many surgeons have reported that extrahepatic bile duct resection without major hepatectomy resulted in a dismal outcome, including a high R1 resection rate, frequent locoregional recurrence and few long-term survivors [9–14]. These results indicate that extrahepatic bile duct resection alone is inappropriate for Bismuth type I/II cholangiocarcinoma. The major cause of high R1 resection is the presence of anatomical complexity at the hepatic hilum. The right hepatic artery passes behind the common hepatic duct and is therefore often involved at this site. RHx with en bloc resection of the right hepatic artery without skeletonization maneuvers near the tumor is a reasonable way of achieving complete clearance of the tumor. Given the reported favorable outcomes and appropriate concept, RHx is considered the standard treatment of choice for Bismuth type I/II perihilar cholangiocarcinoma [12, 15–18, 30].

Combined arterial resection and reconstruction is technically demanding and can be performed in a limited institution. In the mid-2000s, Miyazaki et al. reported disappointing outcomes of 33% mortality and no 2-year survivors [5]. However, recent studies from Japanese high-volume centers have described suitable outcomes after major hepatectomy with concomitant arterial resection and reconstruction in select patients with perihilar cholangiocarcinoma [7, 31, 32]. In contrast, Peng et al. [33] reported left hepatectomy combined with hepatic artery resection but without reconstruction. However, in their 26 cases, 2

Table 2 Surgical outcomes and complications

	LHx + AR (<i>n</i> = 12)	RHx (<i>n</i> = 24)	<i>p</i>
Operation time (min)*	692 (469–971)	574 (365–763)	0.034
Blood loss (ml)*	1855 (815–4692)	1573 (578–2984)	0.365
Portal vein resection	0 (0%)	4 (17%)	0.278
Arterial reconstruction (proximal–distal)			
RHA–RHA	6 (50%)		
LHA–RHA	2 (17%)		
GDA–RHA	2 (17%)		
PHA–RHA	1 (8%)		
RGA–RHA	1 (8%)		
T.Bil max (mg/dL)*	1.1 (0.5–2.5)	1.1 (0.5–5.5)	0.893
Morbidity			
Dindo–Clavien classification grade			
≤2	6 (50%)	13 (54%)	0.515
3	6 (50%)	9 (38%)	
4	0	2 (8%)	
Liver failure			
ISGLS grade A–C	1 (8%)	6 (25%)	0.384
ISGLS grade B–C	0	5 (21%)	0.146
Refractory ascites	0	4 (17%)	0.278
Bile leakage	1 (8%)	3 (13%)	1
Pancreatic fistula	2 (17%)	4 (17%)	1
Bacteremia	1 (8%)	3 (13%)	1
Intraabdominal abscess	1 (8%)	1 (4%)	1
Bleeding	0	1 (4%)	1
Portal vein thrombus	0	1 (4%)	1
Hospital stay (days)*	25 (15–47)	28 (12–83)	0.431

LHx + AR, left hepatectomy, caudate lobectomy and bile duct resection concomitant resection and reconstruction of right hepatic artery; RHx, right hepatectomy and caudate lobectomy with bile duct resection; T.Bil max, maximum total bilirubin value; RHA, right hepatic artery; LHA, left hepatic artery; GDA, gastroduodenal artery; PHA, proper hepatic artery; RGA, right gastric artery; ISGLS, International Study Group of Liver Surgery

*Median (ranges)

patients developed liver abscess, and 3 developed liver failure. In that sense, arterial reconstruction should be performed when possible. In the current series, fortunately, no arterial resection or reconstruction-related complications occurred. Combined arterial resection and reconstruction was usually carried out in cases of left-sided hepatectomy (LHx or left trisectionectomy [LTx]) for perihilar cholangiocarcinoma [5–7]. Arterial resection and reconstruction in LTx is more difficult than LHx: First, the length of arterial invasion is longer, so complicated reconstruction is sometimes necessary; second, arterial involvement extends in a more peripheral direction, and the arterial caliber is smaller than with LHx; third, the anatomy of the right posterior hepatic artery is more complicated than with LHx [7, 34]. Arterial reconstruction in LHx is therefore relatively easy due to the short range involvement and wide caliber of the distal artery (right hepatic artery).

Regarding surgery of perihilar cholangiocarcinoma, we principally limited the operator to an experienced hepatobiliary surgeon (K.U and T.S) and plastic surgeon (M.N). Therefore, we never set any apparent limitations on vascular resection and reconstruction provided the peripheral part of the vessel was secured, even if double arterial resection of the anterior and posterior branches or simultaneous arterial and portal vein resection was needed. In addition, the rate of surgery-related morbidity, such as biliary leakage or pancreatic fistula, between the two procedures was almost identical.

In the current series, two-thirds of patients showed no histologic arterial invasion despite the intraoperative findings of macroscopic arterial invasion. However, in most cases without histologic arterial invasion, the distance between the cancer and hepatic artery was nearly <1 mm. Therefore, if combined arterial resection had not been

performed in LHx, the dissection margin would likely be positive. Should combined arterial resection be performed in all cases of LHx for Bismuth type I/II perihilar cholangiocarcinoma? A number of advances have been made in diagnostic modalities, especially MDCT, which is helpful for evaluating vascular invasion in cases of perihilar cholangiocarcinoma [24, 26]. Fukami et al. [26] reported that no macroscopic arterial invasion was detected in all of the 50 patients with the presence of low-density planes between the right hepatic artery and adjacent tumor, whereas 38 of 53 patients without visible low-density planes presented with macroscopic arterial invasion. These findings may help us to determine the optimal indications for combined AR.

Another reason for the preference of RHx for Bismuth type I/II perihilar cholangiocarcinoma is that surgeons believe that the right hepatic duct is longer than the left hepatic duct, suggesting a high chance to obtain a negative hepatic ductal margin [17]. However, the incidence of positive hepatic ductal margin was identical in both LHx + AR and RHx groups. Recently, Hirose et al. [35] clarified that the lengths of the resected bile ducts were comparable between RHx and LHx and stressed that the notion of the left hepatic duct being longer than the right hepatic duct was simply based on surgeons' biased views. They therefore recommended flexible procedure selection for various types of perihilar cholangiocarcinoma. From

the perspective of the length of the left and right hepatic ducts, the current surgical strategy for treating Bismuth type I/II perihilar cholangiocarcinoma seems rational.

The incidence of postoperative morbidities was almost identical between the LHx + AR and RHx groups. Although there was no significant difference, posthepatectomy liver failure (PHLF) or refractory ascites tended to occur more frequently in the RHx group, whereas no patients suffered from such a complication in the LHx + AR group. Most patients who underwent LHx + AR had a small left liver volume, which is the main reason for avoiding RHx. Conversely, if LHx is performed, the remnant liver volume would be large enough to ensure a good postoperative course. In that sense, LHx leads to a better postoperative course in certain patients than RHx.

This study has several limitations such as retrospective nature and small cohort size. A randomized controlled trial is ideal to confirm this surgical strategy. However, trial in a single center is almost impossible due to the extremely limited number of patients with this disease, and a multi-center trial seems difficult to conduct, because of quality control in the diagnosis and the surgery itself. A propensity score-matched analysis using retrospectively collected data from multiple centers will be needed to overcome this concern.

In this study period, standard strategy for treating Bismuth type I/II perihilar cholangiocarcinoma in the authors'

Table 3 Pathologic findings

	LHx + AR (n = 12)	RHx (n = 24)	p
Tumor size (mm)*	47 (25–98)	40 (19–148)	0.626
Histology			
Well	4 (33%)	12 (50%)	0.272
Moderate	7 (58%)	12 (50%)	
Poorly	1 (8%)	0	
Lymph node metastasis	4 (33%)	11 (46%)	0.721
Venous invasion	5 (42%)	5 (21%)	0.247
Perineural invasion	11 (92%)	20 (83%)	0.646
Arterial invasion	5 (42%)	8 (33%)	0.624
Portal vein invasion	0	4 (17%)	0.279
UICC stage			
I–II	5 (42%)	7 (29%)	0.479
III–IV	7 (58%)	17 (71%)	
Margin status			
Positive proximal margin	1 (8%)	2 (8%)	1
Positive distal margin	0	0	1
Positive dissected margin	0	0	1
R1 resection	1 (8%)	2 (8%)	1

LHx + AR, left hepatectomy, caudate lobectomy and bile duct resection concomitant resection and reconstruction of right hepatic artery; RHx, right hepatectomy and caudate lobectomy with bile duct resection

*Median (ranges)

Table 4 Site of recurrence*

	LHx + AR (n = 12)	RHx (n = 24)	p
All recurrence	8 (67%)	13 (54%)	0.721
Liver	4 (33%)	4 (17%)	0.397
Local	2 (17%)	5 (21%)	1
Lymph node	1 (8%)	3 (13%)	1
Peritoneum	2 (17%)	3 (13%)	1
Other distant	2 (17%)	1 (4%)	0.253

LHx + AR, left hepatectomy, caudate lobectomy and bile duct resection concomitant resection and reconstruction of right hepatic artery; RHx, right hepatectomy and caudate lobectomy with bile duct resection

*Number includes overlapping patients

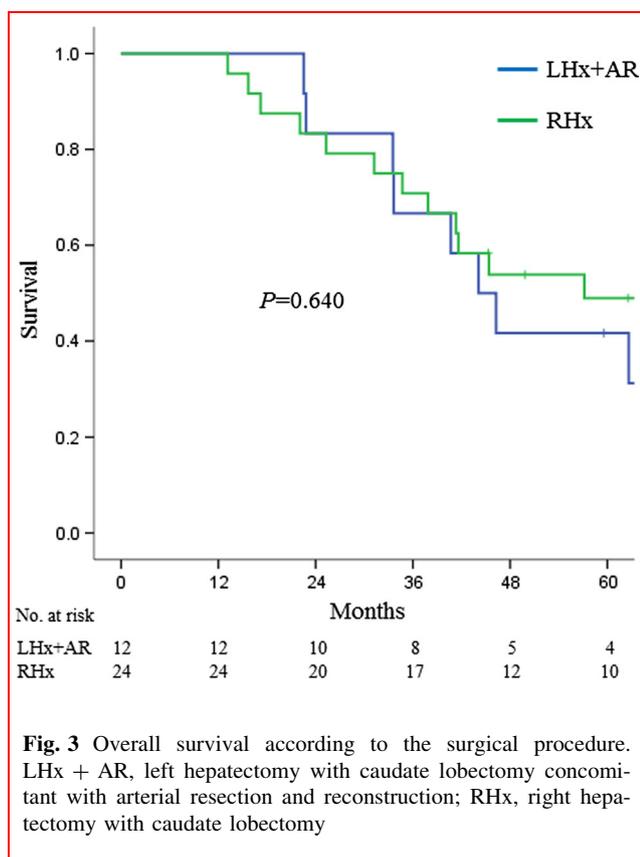


Fig. 3 Overall survival according to the surgical procedure. LHx + AR, left hepatectomy with caudate lobectomy concomitant with arterial resection and reconstruction; RHx, right hepatectomy with caudate lobectomy

institution was RHx, due to its technical simplicity. Therefore, LHx + AR was strictly indicated mainly for patients with insufficient left liver functional reserve as a desperate measure. However, reflecting on the current experience, expanding the surgical indications of LHx + AR for Bismuth type I/II perihilar cholangiocarcinoma seems to be worth considering. Further accumulation of experience is expected to clarify this concern.

In conclusion, LHx + AR for Bismuth type I/II perihilar cholangiocarcinoma is considered to be a valid alternative

to RHx in patients with an insufficient left liver functional reserve or a poor general condition.

Compliance with ethical standards

Conflict of interest The authors declare no financial or any other type of support.

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