Evolution of Surgical Treatment for Perihilar Cholangiocarcinoma

A Single-Center 34-Year Review of 574 Consecutive Resections

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Objective: To review our 34-year experience with 574 consecutive resections for perihilar cholangiocarcinoma and to evaluate the progress made in surgical treatment of this disease.

Background: Few studies have reported improved surgical outcomes for perihilar cholangiocarcinoma; therefore, it is still unclear whether surgical treatment of this intractable disease has progressed.

Methods: Between April 1977 and December 2010, a total of 754 consecutive patients with perihilar cholangiocarcinoma were treated, of whom 574 (76.1%) underwent resection. The medical records of these resected patients were retrospectively reviewed.

Results: The incidence of major hepatectomies has increased, and limited resections, including central hepatectomies and bile duct resections, were rarely performed. Combined vascular resection was being used more often. Operative time has become shorter, and intraoperative blood loss has also decreased significantly. Because of refinements in surgical techniques and perioperative management, morbidity decreased significantly but was still high, with a rate of 43.1% in the last 5 years. Mortality rate has also decreased significantly ($P < 0.001$) from 11.1% (8/72) before 1990 to 1.4% (3/218) in the last 5 years. The ratio of advanced disease defined as pStage IVA and IVB has increased significantly from 49.4% before 2000 to 61.4% after 2001. The disease-specific survival for the 574 study patients (including all deaths) was 44.3% at year 3, 32.5% at year 5, and 19.9% at year 10. The survival was significantly better in the later period of 2001 to 2010 than in the earlier period of 1977 to 2000 (38.1% vs 23.1% at year 5, $P < 0.001$). For pM0, R0, and pN0 patients ($n = 243$), the survival in the later period was good with 67.1% at year 5, which was significantly better than that of the earlier period ($P < 0.001$). For pM0, R0, and pN1 patients ($n = 142$), however, the survival in the later period was similar to that of the earlier period (22.1% vs 14.6% at year 5, $P = 0.647$). Multivariate analysis revealed that lymph node metastasis was the strongest prognostic indicator.

Conclusions: Surgical treatment of perihilar cholangiocarcinoma has been evolving steadily, with expanded surgical indication, decreased mortality, and increased survival. Survival for R0 and pN0 patients was satisfactory, whereas survival for pN1 patients was still poor, suggesting that establishment of effective adjuvant chemotherapy is needed.

Keywords: perihilar cholangiocarcinoma, surgical treatment, survival

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Perihilar cholangiocarcinoma[1,2] is a devastating disease that still remains the most difficult challenge for hepatobiliary surgeons. In the past 2 decades, many surgeons have reported outcome and survival rates after resection for this disease, with varying degrees of success.[3–20] Recently, the synergy of endoscopists, radiologists, oncologists, and surgeons has been reported to be quite promising.[17]

In April 1977, the first surgery for perihilar cholangiocarcinoma was performed in our department: the procedure was an extrahepatic bile duct resection without hepatectomy, which resulted in R2 resection. Thereafter, we have made a consistent effort to approach this intractable disease with aggressive surgical strategies.[21–32] Recently, we have used technically demanding procedures including left or right hepatic trisectionectomy,[27,31] combined portal vein and/or hepatic artery resection,[22,26,30] and hepatopancreatoduodenectomy.[23,32] As we have been performing these procedures for more than a decade, it is time to verify our strategy. To our knowledge, few studies[14,18] have reported improved surgical outcomes for perihilar cholangiocarcinoma, and those published have had limited numbers of resected patients. Therefore, it is still unclear whether surgical treatment for this intractable disease has really made progress. The aim of this study was to review in detail our 34-year experience with 574 consecutive resections for perihilar cholangiocarcinoma and to evaluate the progress made with regard to surgical treatment.

PATIENTS AND METHODS

Patients

Between April 1977 and December 2010, a total of 754 consecutive patients with perihilar cholangiocarcinoma[1,2] were treated at the First Department of Surgery, Nagoya University Hospital. Of these, 115 patients (15.3%) were deemed inoperable as a result of advanced disease with or without distant metastasis, poor general condition, and/or poor hepatic function. The remaining 639 patients underwent laparotomy: 65 patients (8.6%) underwent laparotomy alone or palliative bypass surgery due to distant metastasis or unexpected local extension of cancer, and the remaining 574 patients (76.1%) underwent resection (Fig. 1). These 574 resected patients, including 381 men and 193 women with a mean age of 64 ± 10 years (range, 24–83 years), were analyzed for this study.

Preoperative Management

Before 2005, we primarily chose to utilize percutaneous transhepatic biliary drainage.[33,34] After 2005, however, we gradually changed our strategy toward biliary drainage, as we identified the possibility of seeding metastasis associated with percutaneous transhepatic biliary drainage.[35] Currently, endoscopic naso-biliary drainage is routinely utilized[36,37]; percutaneous transhepatic biliary drainage is used only when endoscopic drainage is not feasible (Fig. 2). Overall, 414 patients (72.1%) were jaundiced upon admission, with a mean total serum bilirubin concentration of 10.3 ± 7.1 mg/dL (2.0–40.4 mg/dL). Percutaneous transhepatic biliary drainage ($n = 378$), endoscopic drainage ($n = 94$), or both ($n = 11$) were performed in a total of 483 patients, including all of the 414 jaundiced patients and

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69 nonjaundiced patients who had intrahepatic biliary dilatation. The procedures were performed to relieve obstruction, treat segmental cholangitis,[38] and/or to define the anatomy of the biliary tree.

For tumor staging, cholangiography, computed tomography, and ultrasonography were routinely performed. Before 2002, conventional catheter arteriography and percutaneous transhepatic portography[39] were performed to reveal vascular anatomy and to diagnose vascular invasion. After 2003, multidetector-row computed tomography was used for this purpose[40–42] and was also used to assess longitudinal extension of the carcinoma.[43] Other imaging approaches, including magnetic resonance imaging and positron emission tomography, were adopted in selected patients when needed. Previously, percutaneous transhepatic cholangioscopy[44,45] was performed when the superficial spread of cancer[29] was suspected on a cholangiogram. In the last 4 years, however, we have not used percutaneous transhepatic cholangioscopy for 2 reasons. First, percutaneous transhepatic cholangioscopy is time-consuming and is somewhat invasive and, therefore, may result in the seeding of cancer cells.[35] Second, endoscopic transpapillary biopsy under fluoroscopy or peroral cholangioscopy is now available (Fig. 2).[46]

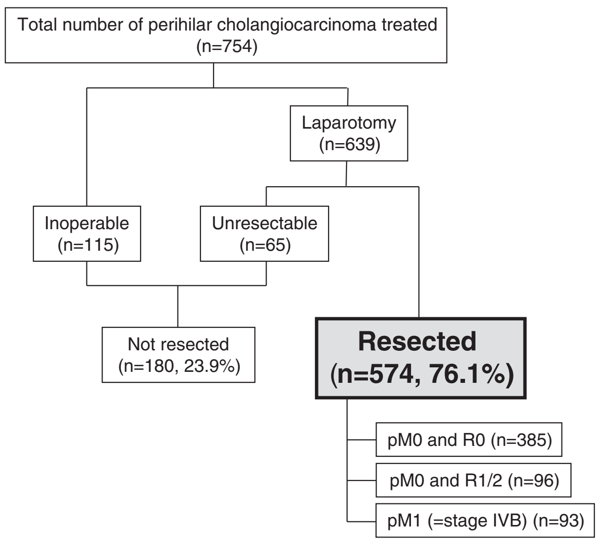

FIGURE 1. Overview of patient treatments according to resectability and curability.

Portal vein embolization was introduced around 1990 (Fig. 2) and performed when the liver remnant was less than 40%, according to a previously reported method.[47–50] In addition, this intervention was also applied to intraoperatively identify accurate demarcation between the right anterior and posterior sections in patients who were to undergo a difficult and intricate left trisectionectomy with vascular resection.[30,51] Overall, portal vein embolization was performed in a total of 259 patients (45.1%), including embolization of the right portal vein in 145 patients, embolization of the left and right anterior portal veins in 94 patients, embolization of the right and left medial portal veins in 19 patients, and embolization of the right anterior and left medial portal veins in 1 patient.

Liver function was evaluated consistently by the indocyanine green test, which was performed after serum total bilirubin concentration had decreased to less than 2 mg/dL by biliary drainage. Indocyanine green (0.5 mg/kg of body weight) was administered

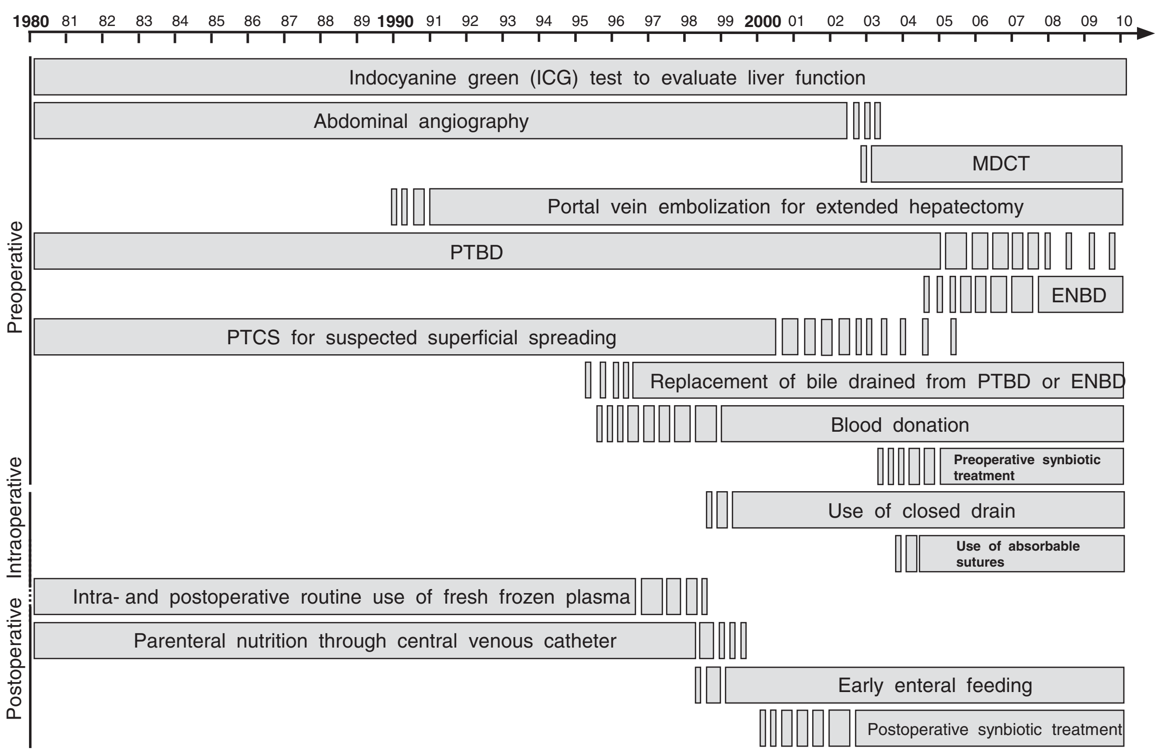

FIGURE 2. Changes in pre-, intra-, and postoperative management over the course of the study period. ENBD indicates endoscopic naso-biliary drainage; MDCT, multidetector-row computed tomography; PTBD, percutaneous transhepatic biliary drainage; PTCS, percutaneous transhepatic cholangioscopy.

via a peripheral vein, and venous blood was sampled before and 5, 10, and 15 minutes after injection. Specimens were analyzed for indocyanine green concentrations on a spectrophotometer at a wavelength of 805 nm. The plasma disappearance rate of indocyanine green was calculated by linear regression analysis of plasma indocyanine green concentrations. The plasma disappearance rate of indocyanine green of the future liver remnant was also calculated using the formula "indocyanine green × % volume of the future liver remnant/100."[50,52]

Since the late 1990s, preoperative autologous blood donation[53] has been used in patients who had hemoglobin concentrations of 11 g/dL or more and were not hypotensive. In jaundiced patients, blood donation was started after the total serum bilirubin concentration had decreased to less than 3 mg/ dL after biliary drainage. Replacement of externally drained bile[54] has been used since the late 1990s. Preoperative synbiotic treatment has also been used since 2005, after its validation by a randomized controlled trial[55] (Fig. 2).

Surgery

When distant metastasis (M1 disease) was found at laparotomy, resection was abandoned in principle. However, when M1 disease was ipsilateral liver metastasis, very limited local dissemination (hepatoduodenal ligament or around percutaneous transhepatic biliary drainage sinus tract), or periaortic lymph node metastasis, resection was considered. If planned surgery was not deemed too risky, that is, typical right or left hepatectomy without difficult combined vascular resection and/or pancreatoduodenectomy, and if resection was considered likely to improve the patient's quality of life (especially in patients with multiple biliary drainage), resection was eventually undertaken.

All hepatectomies were carried out after serum total bilirubin concentrations had decreased to less than 2 mg/dL. The parenchymal transection was performed using cavitron ultrasonic surgical aspirator or instrument fracture technique according to the surgeon's preference, under both hepatic artery and portal vein clamping for 15 or 20 minutes at 5-minute intervals was used. All patients underwent dissection of regional lymph nodes including hilar (denoted as "12h" by Japanese rules[56]), pericholedochal ("12b" and "12c"[56]), peripancreatic ("13a"[56]), periportal ("12p"[56]), and common hepatic artery ("8a" and "8p"[56]) nodes. Periaortic lymph node dissection[25] was primarily performed before early 2000. Thereafter, only a sampling of 2 or 3 periaortic nodes was performed for nodal staging because several studies [57–60] have shown that periaortic node dissection has no impact on survival.

Combined pancreatoduodenectomy was performed because of the following: (1) diffusely infiltrating tumor of the whole extrahepatic bile duct, (2) downward superficial spreading, or (3) bulky nodal metastasis of the pancreatoduodenal region.[23,32] Vascular resections were carried out only when the vessel adhered to and could not be freed from the tumor during skeletonization resection of the hepatoduodenal ligament.[22,26,30] Even if invasion was suspected preoperatively,[40,41] the vessel was not resected when the vessel could be freed from the tumor without difficulty. The "no-touch technique" introduced by Neuhaus et al[4] was never used, because it lacks scientific validation.

Bilioenteric continuity was reestablished by Roux-en-Y cholangiojejunostomy as previously reported.[61] In cases of hepatopancreatoduodenectomy, reconstruction was performed according to the Child method with an end-to-side pancreaticojejunostomy.[32]

Intra- and Postoperative Management

Before around 1998, fresh-frozen plasma was routinely given (at least 10 units) during and after major hepatectomy (5–10 units/d for 1 week). After 1998, the use of fresh-frozen plasma was restricted only to cases of high intraoperative blood loss or of poor hepatic function with coagulopathy (Fig. 2).

Before around 1998, parenteral nutrition through a central venous catheter was routinely used. In 1999, we began to use early postoperative enteral feeding. An 8-Fr catheter for enteral feeding was placed through a jejunal limb during surgery. Enteral feeding (Racol, 1 kcal/mL; Otsuka Pharmaceutical Co Ltd, Tokyo, Japan) was initiated on postoperative day 1 with 100 kcal/day and was increased gradually to 400 kcal/day by day 5. Patients usually began oral feeding on day 4 or 5, and enteral feeding was gradually decreased as oral intake increased. Total parenteral nutrition was not used, and the central venous catheter inserted in the operating room was removed 2 to 4 days after surgery. Postoperative synbiotic treatment[62] has been used since 2000 (Fig. 2).

Adjuvant Treatment

Gemzar (Gemcitabine hydrochloride; Eli Lilly and Company, Indianapolis, IN) was authorized for use in treating cholangiocarcinoma in Japan in 2006. Thereafter, we conducted a randomized controlled trial in patients with resected cholangiocarcinoma to evaluate the effect of Gemzar in the adjuvant setting (BCAT study, UMIN000000820; surgery alone vs Gemzar; registration between September 2007 and December 2010), similar to a study for pancreatic cancer.[63] We have used Gemzar as adjuvant chemotherapy in 79 patients, 14 of whom underwent combined radiation therapy due to positive surgical margin(s). TS-1 (Tegafur-Gimeracil-Oteracil potassium; Taiho Pharmaceutical Co Ltd, Tokyo, Japan) was also authorized for use in 2007: this agent was used in another 2 patients in the adjuvant setting.

For cases of relapsed disease, Gemzar alone,[64] TS-1 alone,[65] Gemzar with TS-1,[66] or Gemzar with cisplatin[67] has been used since 2006, according to the doctor's preference and/or the patient's condition.

Histology

The extrahepatic bile duct of the resected specimen was opened longitudinally, from the distal resection margin up to the proximal margin, to accurately evaluate the ductal margin status.[24,29] Then the resected specimens were fixed in 10% formalin for several days and serially sectioned at 5-mm intervals. The specimens were prepared in the usual manner for microscopic examination using hematoxylin and eosin staining. Histological findings were described using the *TNM Classification of Malignant Tumors* by the International Union Against Cancer.[68]

Statistics

Results are expressed as the mean ± standard deviation. Statistical analysis was performed using the Student t test, chi-square test, and the Fisher exact probability test where appropriate. Multivariate analysis was performed using the logistic regression model to determine independent predictors of postoperative mortality.

Patient survival was determined from the time of surgery to the time of death or the most recent follow-up. Thirteen patients (2.3%) died of other causes with no evidence of recurrence (suicide, n = 3; lung cancer, n = 3; pneumonia, n = 2; rupture of aortic aneurysm, rupture of esophageal varices, cerebral bleeding, perforation and bleeding of duodenal ulcer, and senility, n = 1 of each); they were treated as censored cases. Postoperative disease-specific survival was calculated using the Kaplan-Meier method. Differences in survival curves were compared using the log-rank test. The Cox proportional hazards model was used for multivariate analysis. A $P < 0.05$ was considered statistically significant. Analyses were performed using the SPSS statistical package (version 11, SPSS, Inc, Chicago, IL).

RESULTS

Surgery

A total of 754 patients were treated at our department, 574 of whom underwent resection, giving an overall resectability rate of 76.1%. The resectability rate was constant over the time of the study (Table 1).

Of the 574 resected patients, 555 patients (96.7%) underwent several types of hepatectomy with combined en bloc resection of the caudate lobe and extrahepatic bile duct, and the remaining 19 patients underwent bile duct resection alone without hepatectomy. Over the time period studied, performance of limited resections, including central hepatectomy and bile duct resection without hepatectomy, decreased significantly from 26.4% from 1977 to 1990 to 2.7% from 2006 to 2010. The incidence of left hepatic trisectionectomy, which is the most technically demanding hepatectomy,[31] gradually increased, reaching approximately 30% in the last 5-year period (Table 1).

Seventy-four patients (12.9%) underwent combined pancreatoduodenectomy[32]; the incidence of combined pancreatoduodenectomy was unchanged over the study period. Combined portal vein resection was carried out in a total of 206 patients (35.9%); the incidence of this technique was also unchanged over the study period. However, wedge resection was primarily used from 1977 to 1990, whereas segmental resection became the primary strategy after that time. Combined hepatic artery resection was performed in a total of 76 patients (13.2%); this difficult vascular resection was adopted mainly after 2001 (Table 1).

Over the time period studied, operative time has become shorter, and intraoperative blood loss has also decreased. Because of both preoperative blood donation[53] and less intraoperative blood loss, the ratio of patients who received homologous blood transfusion (packed red blood cell and/or fresh-frozen plasma) was less than 30% after 2001 (Table 1).

Morbidity and Mortality

A total of 329 patients (57.3%) had several kinds of postoperative complications (Table 2). Overall, posthepatectomy liver failure (grades B and C), according to the definition of the International Study Group of Liver Surgery,[69] was the most common complication. However, the incidence of grade C liver failure, which is clinically serious, decreased markedly from 18.2% (12/66) from 1977 to 1990 to 3.2% (7/216) from 2006 to 2010. Wound sepsis was the second most common complication, followed by intra-abdominal abscess and bile leakage. Leakage of pancreatojejunostomy, according to the definition of the International Study Group of Pancreatic Surgery,[70] was also a common complication, and it occurred in 57 of the 74 patients (77.0%) who underwent hepatopancreatoduodenectomy. Although the morbidity rate decreased, it was still high (43.1%) in the last 5 years.

Twenty-seven patients died of postoperative complications in the hospital; the time between surgery and death was within 30 days in 12 patients, 31 days to 90 days in 12 patients, and more than 90 days in 3 patients. Liver failure associated with infectious complications was the cause of death in many nonsurvivors. The remaining 547 patients in good condition were discharged from the hospital, giving an overall mortality rate of 4.7%. Mortality decreased markedly from 11.1% from 1977 to 1990 to 1.4% from 2006 to 2010 (Table 2). The univariate analyses for mortality revealed that preoperative cholangitis, liver function, operative time, and blood loss were significantly associated with mortality. In multivariate analyses using these 4 variables, preoperative cholangitis,[71] liver function,[71] and blood loss were found to be independent predictors of mortality (Table 3).

Tumor Stage

Tumor stage was compared between the earlier period (1977–2000) and the later period (2001–2010) (Table 4). Bismuth-type [72,73]

TABLE 1. Surgery Performed According to the Time Period

		Time Period (%)				
		Earlier Period		Later Period		
	Total (%)	1977–1990	1991–2000	2001–2005	2006–2010	*P*
Number of patients resected	574	72	116	168	218	
Resectability	574/754 (76.1)	72/93 (77.4)	116/148 (78.4)	168/216 (77.8)	218/297 (73.4)	0.406
Type of hepatectomy*						<0.001
S1,4,5,6,7,8	43 (7.5)	5 (6.9)	11 (9.5)	4 (2.4)	23 (10.6)	
S1,5,6,7,8	177 (30.8)	17 (23.6)	40 (34.5)	53 (31.5)	67 (30.7)	
S1,2,3,4,5,8	110 (19.2)	4 (5.6)	12 (10.3)	29 (17.3)	65 (29.8)	
S1,2,3,4	187 (32.6)	27 (37.5)	35 (30.2)	68 (40.5)	57 (26.1)	
S1,4,5,8/S1,5,8/S1,4/S1	38 (6.6)	13 (18.1)	10 (8.6)	11 (6.5)	4 (1.8)	
Without hepatectomy	19 (3.3)	6 (8.3)	8 (6.9)	3 (1.8)	2 (0.9)	
Combined resection						
Pancreatoduodenectomy	74 (12.9)	9 (12.5)	13 (11.2)	20 (11.9)	32 (14.7)	0.553
Portal vein resection	206 (35.9)	23 (31.9)	36 (31.0)	58 (34.5)	89 (40.8)	0.116
Wedge resection	36	15	6	10	5	
Segmental resection	170	8	30	48	84	
Hepatic artery resection	76 (13.2)	0	5 (4.3)	25 (14.9)	46 (21.1)	<0.001
Operative time, min†	668 ± 134	664 ± 162	787 ± 170	675 ± 145	605 ± 134	<0.001
Blood loss, mL†	2491 ± 2156	4414 ± 2791	3773 ± 3024	1898 ± 1268	1768 ± 1130	<0.001
Homologous blood transfusion	271 (47.2)	68 (94.4)	93 (80.2)	46 (27.4)	64 (29.4)	<0.001

Homologous blood includes packed red blood cell and fresh-frozen plasma. Note that *P* indicates the statistical difference between the earlier period (1977–2000) and the later period (2001–2010).

*Expressed as Couinaud's hepatic segments resected.

†Excluding 19 patients who did not undergo hepatectomy.

TABLE 2. Morbidity and Mortality According to the Time Period

		Time Period (%)				
		Earlier Period		Later Period		
	Total (%)	1977–1990	1991–2000	2001–2005	2006–2010	*P*
Number of patients resected	574	72	116	168	218	
With any complication	329 (57.3)	55 (76.4)	93 (80.2)	87 (51.8)	94 (43.1)	<0.001
Liver failure*	297/555 (53.5)	53/66 (80.3)	89/108 (82.4)	69/165 (41.8)	86/216 (39.8)	<0.001
Lung failure	21 (3.7)	7 (9.7)	9 (7.8)	3 (1.8)	2 (0.9)	<0.001
Renal failure	20 (3.5)	5 (6.9)	9 (7.8)	2 (1.2)	4 (1.8)	<0.001
Bacteremia	57 (9.9)	9 (12.5)	22 (19.0)	14 (8.3)	12 (5.5)	<0.001
Wound sepsis	123 (21.4)	30 (41.7)	47 (40.5)	25 (14.9)	21 (9.6)	<0.001
Bile leakage†	61 (10.6)	12 (16.7)	9 (7.8)	15 (8.9)	25 (11.5)	0.768
Intra-abdominal abscess	120 (20.9)	20 (27.8)	30 (25.9)	32 (19.0)	38 (17.4)	0.019
Intra-abdominal bleeding	26 (4.5)	9 (12.5)	8 (6.9)	6 (3.6)	3 (1.4)	<0.001
Leakage of HJ	35 (6.1)	8 (11.1)	12 (10.3)	8 (4.8)	7 (3.2)	0.002
Leakage of PJ‡	57/74 (77.0)	9/9 (100)	13/13 (100)	13/20 (65.0)	22/32 (68.8)	0.002
Relaparotomy	32 (5.6)	5 (6.9)	12 (10.3)	9 (5.4)	6 (2.8)	0.012
Postoperative hospital stay, days§	42.9 ± 28.8	48.0 ± 22.1	52.1 ± 35.3	42.9 ± 29.5	37.1 ± 24.8	<0.001
Mortality‖	27 (4.7)	8 (11.1)	11 (9.5)	5 (3.0)	3 (1.4)	<0.001

Note that *P* indicates the statistical difference between the earlier period (1977–2000) and the later period (2001–2010).*Excluding 19 patients without hepatectomy, and a grade B or C according to the International Study Group of Liver Surgery.

†Grade B or C according to the International Study Group of Liver Surgery.

‡Grade B or C according to the International Study Group of Pancreatic Surgery.

§Excluding 27 patients who did not tolerate surgery.

‖Including all deaths related to surgery.

HJ indicates hepaticojejunostomy; PJ, pancreatojejunostomy.

type IV tumors increased in the later period, although this increase was not statistically significant. According to tumor, node, metastasis classification,[68] the percentage of more advanced pT tumors increased significantly in the later period. Nodal status was similar between the 2 periods. The percentage of pM1 disease caused by peritoneal dissemination and/or liver metastasis was similar between the 2 periods, whereas the percentage of pM1 disease caused by distant lymph node metastasis decreased in the later period. Therefore, the percentage of pM1 disease decreased significantly from 20.7% in the earlier period to 14.0% in the later period. The decrease in the percentage of pM1 disease caused by distant lymph node metastasis may have been associated with the fact that periaortic lymph node dissection was not performed routinely after early 2000. Overall, the percentage of more advanced disease defined as pStage IVA and IVB increased significantly from 49.4% in the earlier period to 61.4% in the later period.

Survival

The disease-specific survival rate for the 574 study patients was 44.3% at year 3, 32.5% at year 5, and 19.9% at year 10; 117 patients survived for more than 5 years, and 31 patients survived for more than 10 years. The survival rate was significantly better in the later period of 2001 to 2010 than in the earlier period of 1977 to 2000 (38.1% vs 23.1% at year 5, $P < 0.001$) (mean duration of follow-up, 5.8 years in the later period and 18.8 years in the earlier period) (Fig. 3).

Survival was further analyzed according to curability and nodal status. In pM0, R0, and pN0 patients (n = 243), the survival rate in the later period was good, with 67.1% at year 5, which was significantly better than that of the earlier period ($P < 0.001$) (Fig. 4A). In pM0, R0, and pN1 patients (n = 142), however, the survival rate in the later period was similar to that of the earlier period (22.1% vs 14.6% at year 5, $P = 0.647$) (Fig. 4B). In pM0 and R1/2 patients (n = 96), the survival rate in the later period was significantly better than that of the earlier period (18.0% vs 3.4% at year 5, $P = 0.017$) (Fig. 4C). This difference in the survival rate is in alignment with the large difference in mortality (7.4% = 5/67 in the later period vs 27.6% = 8/29 in the earlier period, $P = 0.019$).

The survival rate for the 93 resected patients with pM1 disease was worse, with 5-year survival of less than 10% (Fig. 4D). This survival rate, however, was significantly better than that of the 180 unresected patients, although such comparison may be inappropriate. Five resected patients who had distant lymph node metastasis survived for more than 5 years. The survival rate in the later period was not significantly different from that of the earlier period, although the median survival time was longer in the later period (391 days vs 280 days).

Prognostic Factors

Prognostic factors after resection were analyzed in 457 pM0 patients who tolerated surgery. On univariate analysis, 10 of 14 possible clinicopathological prognostic factors were significant (Table 5). Multivariate analysis, using the 10 significant factors, revealed that combined portal vein and/or hepatic artery resection, blood transfusion, histology, R status, and pN (lymph node metastasis) were independent prognostic factors. Lymph node metastasis had the strongest impact on survival.

Similar analyses were conducted in 324 pM0 patients who underwent resection in the later period and who tolerated surgery, because the survival in the later period was significantly better than that of the earlier period. On multivariate analysis, blood transfusion (risk ratio = 1.52, $P = 0.012$), R status (risk ratio = 1.49, $P = 0.037$), and pN (risk ratio = 2.23, $P < 0.001$) were significant, whereas combined portal vein and/or hepatic artery resection ($P = 0.318$) and histology ($P = 0.181$) were not.

DISCUSSION

This study clearly demonstrates that surgical treatment of perihilar cholangiocarcinoma has progressed. The evolution of surgical practices presented here includes 3 major aspects. The first is the

TABLE 3. Univariate and Multivariate Analyses for Mortality

Variables	No. Patients	Mortality (%)	Univariate, *P*	Multivariate Risk Ratio (95% Confidence Interval)	Multivariate *P*
Age, y			0.658		
<65	279	12 (4.3)			
≥65	295	15 (5.1)			
Sex			0.532		
Female	193	7 (3.6)			
Male	381	20 (5.2)			
Jaundice on admission			0.281		
Absent	165	5 (3.0)			
Present	409	22 (5.4)			
Preoperative cholangitis			<0.001		0.031
Absent	464	15 (3.2)		1	
Present	110	12 (10.9)		2.53 (1.09–5.90)	
Liver function (ICGK)*			<0.001		0.003
≥0.140	390	9 (2.3)		1	
<0.140	168	18 (10.7)		3.68 (1.56–8.67)	
Extent of liver resection			0.428		
<50%	239	9 (3.8)			
≥50%	335	18 (5.4)			
Combined PD			0.142		
Absent	500	21 (4.2)			
Present	74	6 (8.1)			
Combined PV and/or HA			0.201		
Absent	344	13 (3.8)			
Present	230	14 (6.1)			
Operative time, h			0.002		
<10	224	3 (1.3)			
≥10	350	24 (6.9)			
Blood loss, mL			<0.001		0.043
<2500	386	9 (2.3)		1	
≥2500	188	18 (9.6)		2.62 (1.03–6.66)	

* ICG test was not performed in 16 patients.

HA indicates hepatic artery resection; ICGK, plasma disappearance rate of indocyanine green; PD, pancreatoduodenectomy; PV, portal vein resection.

expansion of surgical indication for advanced tumors by applying more complicated procedures such as hepatopancreatoduodenectomy or vascular resection. Second, we observed a decrease in morbidity and mortality. Indeed, there was a marked reduction of mortality from 11.1% (8/72) in the period from 1977 to 1990 to 1.4% (3/218) in the period from 2006 to 2010. Finally, we found an improved survival for resected patients from an overall 5-year survival of 23.1% before 2000 to 38.1% after 2001. Improved surgical outcomes after expanding surgical indication may seem paradoxical, but we have indeed increased the percentage of positive outcomes, although this percentage is not yet fully satisfactory. Literature review on resection of perihilar cholangiocarcinoma is summarized in Table 6. Our series is the largest, includes more advanced tumors, adopts the most aggressive surgical approach, and achieves better survival.

Surgical resection is the only way to cure this disease, as chemotherapy with or without radiation is less effective. Throughout the study period, therefore, we have performed more extended procedures to resect even locally advanced tumors. Even in early 1980, combined portal vein resection was performed in approximately 30% of resected patients,[21,22,26] and hepatopancreatoduodenectomy was also used in more than 10% of resected patients.[21,23] More recently, advances in surgical techniques and knowledge, which have been gained from experiences with liver transplantation, have facilitated the performance of hepatic artery resection with reconstruction. These advances urged us to perform combined hepatic artery resection for locally advanced tumors; in the last 5 years, hepatic artery resection with reconstruction, often combined with portal vein resection,[30] was performed in more than 20% of resected patients. Interestingly, despite the expansion of surgical indication, the resectability rate was similar over the course of the study and may actually have decreased in the last 5 years. After 2006, many patients with very advanced tumors were referred for possible surgery to our department as their last option, which may explain this seemingly paradoxical statistic.

A significant decrease in morbidity and mortality represents major progress in surgical treatment. This decrease is a result of several "small" advances, as shown in Figure 2. Many studies[8,9,12,13,30,74–76] suggest that portal vein embolization makes extended hepatectomy safer, although there has been no validation of this by a randomized controlled trial. Replacement of bile drained externally[54] restores the intestinal barrier function in patients with biliary obstruction. Pre- and postoperative synbiotic treatment and early enteral feeding after surgery[55,62] enhance immune responses, attenuate systemic postoperative inflammatory responses, and improve intestinal microbial environment. These perioperative nutritional managements result in reduced postoperative infectious complications. Preoperative blood donation[53] is useful for circumventing perioperative homologous transfusion and, in turn, may reduce postoperative complications. In addition, we think that a marked decrease

TABLE 4. Bismuth Type, Tumore, Node, Metastasis Classification, and Curability

		Time Period (%)		
	Total (%)	**1977–2000**	**2001–2010**	***P***
Number of patients resected	574	188	386	
Bismuth type				0.283
I/II	88 (15.3)	33 (17.6)	55 (14.2)	
III	225 (39.2)	78 (41.5)	147 (38.1)	
IV	261 (45.5)	77 (41.0)	184 (47.7)	
Tumor, node, metastasis classification*				
pT				<0.001
1	28 (4.9)	12 (6.4)	16 (4.1)	
2a /2b	182 (31.7)	60 (31.9)	122 (31.6)	
3	64 (11.1)	36 (19.1)	28 (7.3)	
4	300 (52.3)	80 (42.6)	220 (57.0)	
pN				0.653
0	297 (51.7)	95 (50.5)	202 (52.3)	
1	277 (48.3)	93 (49.5)	184 (47.7)	
pM				0.039
0	481 (83.8)	149 (79.3)	332 (86.0)	
1	93 (16.2)	39 (20.7)	54 (14.0)	
P and/or H	40 (7.0)	14 (7.4)	26 (6.7)	
DLN alone	53 (9.2)	25 (13.3)	28 (7.3)	
pStage				<0.001
I	27 (4.7)	11 (5.9)	16 (4.1)	
II	121 (21.1)	42 (22.3)	79 (20.5)	
IIIA/IIIB	96 (16.7)	42 (22.3)	54 (14.0)	
IVA	237 (41.3)	54 (28.7)	183 (47.4)	
IVB	93 (16.2)	39 (20.7)	54 (14.0)	
Curability				0.428
R0†	439 (76.5)	140 (74.5)	299 (77.5)	
R1/2	135 (23.5)	48 (25.5)	87 (22.5)	

*According to the 7th edition.
†Including patients with a positive ductal margin with carcinoma in situ.
DLN indicates distant lymph node metastasis; H, liver metastasis; P, localized peritoneal dissemination.

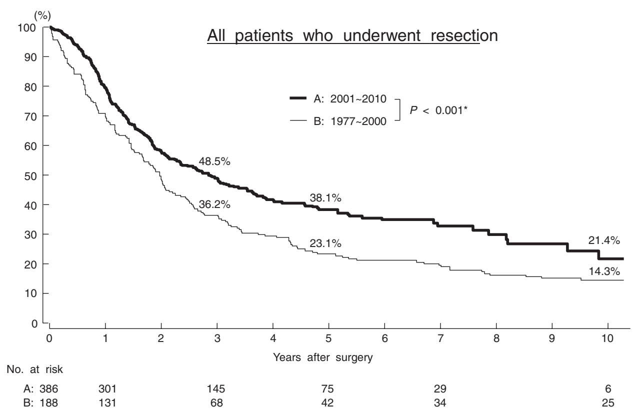

FIGURE 3. Survival (including all deaths) for 574 resected patients according to the time periods. * By log-rank test.

in intraoperative blood loss, from approximately 4000 mL on average before the year 2000 to less than 2000 mL after the year 2001, largely contributes to improved morbidity and mortality. Blood loss is closely associated with morbidity and mortality in many kinds of surgery, and in this study, multivariate analysis demonstrated that high blood loss is an independent predictor of mortality. Considering the difficulty of the surgeries performed in our series, a morbidity rate of 43.1% and a mortality rate of 1.4% in the last 5 years are deemed acceptable. However, as morbidity is still high, continued efforts are necessary to refine both perioperative management and surgical skill.

Improved survival in resected patients is the most significant progress we found. An important factor that may have contributed to the improvement is the selection of extended procedures.[28,30–32] First, the performance of major hepatectomies has increased, whereas limited resections, including central hepatectomy or bile duct resection alone, were performed less often. Second, vascular resection has been performed more frequently.[22,26,30] Third, in left-sided hepatectomies, left trisectionectomies,[31] but not left hepatectomies, have also been used more. Because of these extended procedures, R0 resection was achieved in more patients, leading to improved survival. This observation should be interpreted carefully, considering the fact that histological evaluation of surgical margins is difficult and somewhat subtle. Kondo et al[10] reported that survival for patients with Bismuth type I or II tumors who underwent limited resection was very poor, with a rate of less than 20% at year 3, despite the fact that all resections were proven histologically "curative" (R0). This observation indicates that most of the resections might have been "noncurative" (R1). Seyama et al[8] reported that survival after R0 resection with narrow surgical margin was similar to that after R1 resection. These previous studies suggest the subtle and difficult nature of histological evaluation. This study demonstrates markedly improved survival for pM0, R0, and pN0 patients, from a 5-year survival of 42.5% before 2000 to that of 67.1% after 2001 (Fig. 4A). We speculate that this finding results from an increase in "true" R0 resections by extended surgical procedures.

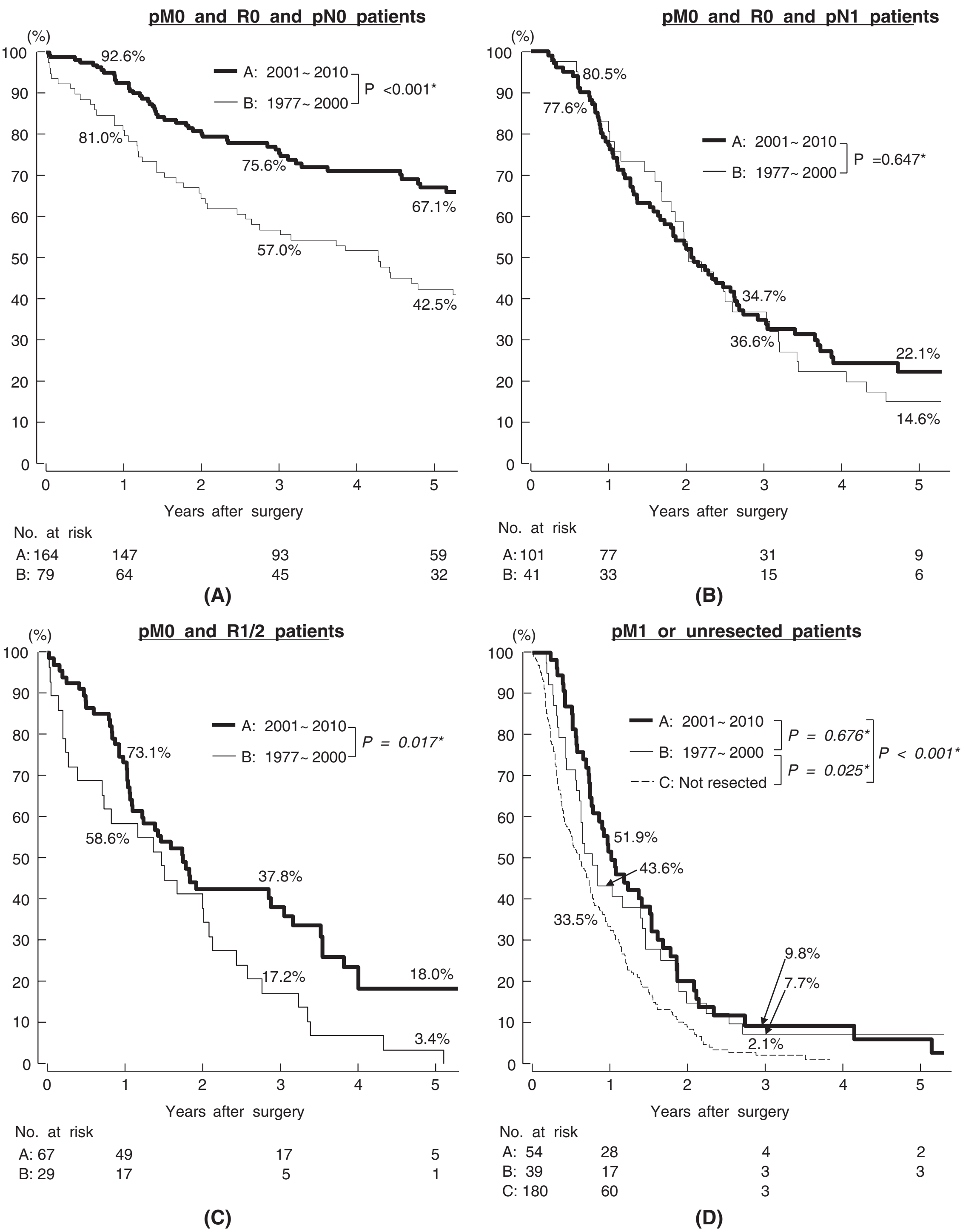

FIGURE 4. Survival (including all deaths) for pM0, R0, and pN0 patients (A), pM0, R0, and pN1 patients (B), pM0 and R1/2 patients (C), and pM1 patients (D). *By log-rank test.

In sharp contrast to the improved survival outcomes observed for pM0, R0, and pN0 patients, the survival for pM0, R0, and pN1 patients was worse and similar between the 2 time periods (Fig. 4B). Many authors[2,8–10,12,14,16,25] have shown that lymph node metastasis has a negative impact on survival in perihilar cholangiocarcinoma. Multivariate analysis in this study again confirmed this dogma, showing that lymph node metastasis is the strongest predictor of survival. These observations indicate that the control of lymph node metastasis is very difficult by surgical treatment alone and that establishment of effective adjuvant chemotherapy is urgently needed. In the near

TABLE 5. Univariate and Multivariate Analyses for Prognostic Factors in pM0 Patients Who Tolerated Surgery

		Survival, %			Multivariate	
Variable	n	3-year	5-year	Univariate, *P*	Risk Ratio (95% Confidence Interval)	*P*
Age, y				0.170		
<65	224	55.7	42.7			
≥65	233	52.1	35.9			
Sex				0.123		
Male	310	52.5	36.3			
Female	147	56.7	45.3			
Type of hepatectomy				0.529		
Major hemihepatectomy	414	53.9	39.8			
Minor hepatectomy*	43	53.5	35.5			
Combined PD				0.491		
Absent	403	53.6	38.9			
Present	54	55.7	43.2			
Combined PV and/or HA				<0.001		0.026
Absent	288	61.7	46.6		1	
Present	169	40.6	26.8		1.35 (1.04–1.76)	
Blood transfusion				0.002		0.016
Absent	262	61.1	47.1		1	
Present	195	44.6	29.6		1.35 (1.06–1.72)	
Bismuth classification				0.002		
Type I–III	263	59.6	45.3			
Type IV	194	46.0	30.9			
Histology				<0.001		0.001
Well	128	75.4	58.5		1	
Moderate or poor	329	45.3	31.5		1.68 (1.23–2.29)	
Microscopic lymphatic invasion				<0.001		
Absent	116	71.4	59.3			
Present	341	48.0	32.3			
Microscopic venous invasion				<0.001		
Absent	278	62.0	48.8			
Present	179	40.7	23.3			
Microscopic perineural invasion				<0.001		
Absent	70	78.1	63.7			
Present	387	49.7	34.9			
Microscopic liver invasion				<0.001		
Absent	189	63.6	51.4			
Present	268	47.1	30.8			
R				<0.001		0.002
0†	374	57.9	44.5		1	
1 or 2	83	35.3	14.3		1.59 (1.18–2.15)	
pN				<0.001		<0.001
0	276	66.7	53..5		1	
1	181	34.9	17.7		1.90 (1.47–2.47)	

*Including cases of bile duct resection alone.
†Including patients with positive ductal margin with carcinoma in situ.
HA indicates hepatic artery resection; PD, pancreatoduodenectomy; PV, portal vein resection.

future, our randomized controlled trial on adjuvant chemotherapy mentioned previously (the BCAT study) will shed light on this issue. Nevertheless, it should be noted that a greater than 5-year survival was achieved in a total of 21 patients with lymph node metastasis, including 15 patients with pM0 and R0, 1 patient with pM0 and R1, and 5 patients with periaortic node metastasis (pM1). We, therefore, stress that patients with lymph node metastasis should not be precluded from surgical resection. In addition, it should be noted that long-term survival was possible even in patients who had distant node metastasis. As has already been our practice, we intend to continue aggressive surgical strategy.

The Mayo Clinic group recently reported successful liver transplantation with neoadjuvant chemoradiation for unresectable, node-negative perihilar cholangiocarcinoma.[77] This multimodal approach achieved a 5-year survival of 79% for patients with underlying primary sclerosing cholangitis and 63% for those with de novo cholangiocarcinoma. They stress that the candidates for this approach should be restricted to patients with "early stage" unresectable cancer. Their criteria for unresectability include bilateral segmental ductal extension, encasement of the main portal vein, and unilateral segmental ductal extension with contralateral vascular encasement.[77] As mentioned previously, the survival rate for the 164 pM0, R0, and pN0 patients who underwent resection after 2001 was satisfactory. In this selected cohort, 73 patients had Bismuth type IV tumor and/or underwent combined vascular resection, and thus they all met the unresectability criteria. Their survival rate was 71.0% at year 3 and

TABLE 6. Literature Review on Resection of Perihilar Cholangiocarcinoma (Single-Center Study, Published After 2000)

Reference	Period	Resected, N	Volume, resected /y	Surgical Procedure, %				Bismuth Type IV, %	pN1, %	R0 resection, %	Mortality, %	5-Year Survival, %	
				Hx	PV	HA	PD					All	R0
Jarnagin[5]	1991–2000	80	8.0	78	11	0	3	—	24	78	10.0	27	—
Capussotti[6]	1988–2001	36	2.6	89	14	3	0	0	39	89	2.8	27	29
Kawarada[7]	1976–2000	87	3.5	75	8	0	3	—	—	64	2.3‡	26	—
Seyama[8]	1989–2001	58	4.5	100	16	0	16	28	52	64	0	40	46
Kawasaki[9]	1990–2001	79	6.6	96	6	3	16	47	44	68	1.3	—	40
Kondo[10]	1999–2002	40	10.0	78	20	20	18	15	38	95	0	—	—
IJitsma[11]	1986–2001	42	2.6	100	17	9	0	—	38	64	11.9	22	—
Hemming[12]	1997–2004	53	6.6	98	43	6	8	5	21	80	9.4	35	45
Sano[13]	2000–2004	102	20.4	100	22	5	7	—	—	61	0	44	—
DeOliveira[14]	1973–2004	173	5.4	20	0	0	0	—	28 ?	19	5.4	10	30
Miyazaki[15]	1981–2004	161	6.7	88	25	6	4	—	48	63	6.8	—	36
Lee[16]	2001–2008	302	37.8	89	13	2	2	17	24	71	1.7	33	47
Gulik[17]	1988–2003	99	6.2	38	18	0	0	—	—	31	10	20,* 33†	—
Young[18]	1994–2008	83	5.5	93	39	10	2	—	57	46	7.2	20	33
Saxena[19]	1992–2009	42	2.3	100	26	0	0	2	29	64	2.4	24	—
Cannon[20]	1992–2010	59	3.1	83	—	—	—	—	15	63	5.1‡	<20	—
This study	1977–2000	188	7.8	93	31	3	12	41	50	75	10.1	23	30
	2001–2005	168	33.6	98	35	15	12				3.0		
	2006–2010	218	43.6	99	41	21	15	]48	]48	]78	1.4	]38	]45

HA indicates combined hepatic artery resection; Hx, hepatectomy; PD, combined pancreatoduodenectomy; PV, combined portal vein resection.
*Between 1988 and 1998.
†Between 1999 and 2003.
‡30-day mortality.

60.4% at year 5, similar to the survival for the transplant patients with de novo cancer. Hepatobiliary surgeons should note that most patients with early-stage, unresectable cancer (ie, good candidates for transplantation at the Mayo Clinic) have "resectable" tumors, and that extended resection[22,23,26,27,30–32] for such patients can offer a favorable outcome.

Finally, we mention a new staging system for perihilar cholangiocarcinoma proposed by DeOliveira et al.[78] The registry, according to this new system, has been launched, and it may be the basis for future development in surgical treatment of the disease. However, as this system has some flaws that one (M.N.) of the authors pointed out,[79] its validity will require confirmation in large prospective studies.

In conclusion, surgical treatment for perihilar cholangiocarcinoma has been evolving steadily, with expanded surgical indication, decreased mortality, and increased survival. Survival for R0 and pN0 patients was satisfactory, whereas that of pN1 patients was still poor, suggesting that the establishment of effective adjuvant chemotherapy is needed.

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