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ORIGINAL ARTICLE

Changes in the surgical approach to hilar cholangiocarcinoma during an 18-year period in a Western single center

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Abstract
Background Liver resection is the only potential curative treatment for hilar cholangiocarcinoma. In this article, we evaluate mortality, survival, prognostic factors, and changes in surgical approach during the last two decades at a Western hepato-biliary center.
Methods Fifty-one patients undergoing liver resections constitute the study population. Patients undergoing palliative procedures were considered as a control group for comparison to the resected group. After 1997, a more aggressive surgical approach was applied that is based on the experience of Japanese surgeons.
Results Curative resections were achieved in 37 (72.5%) patients, and R1 resections were performed in 14 (27.5%). The overall 3- and 5-year survival rates were 47.3 and 34.1%, respectively. The 3- and 5-year survival rates were 38 and 19% in the R1 resection group, and 15% and 0 in the non-resected group, respectively. Univariate analysis revealed that lymph node and perineural invasion, R1 resection, and a bilirubin level >10 mg/dl affected long-term survival. Multivariate analysis showed that only perineural invasion was significant in affecting long-term survival. Univariate analysis showed that the mean preoperative bilirubin levels and mean blood transfusion were related to the mortality rate. The resectability rate significantly increased from 25 to 75.6% after 1997 following implementation of the new surgical approach.
Conclusions An aggressive surgical approach increases the resectability rate and may improve long-term survival even after R1 resection. Severe hyperbilirubinemia should be preoperatively drained, possibly by the percutaneous approach.

Keywords Biliary tract · Cholangiocarcinoma · Hepatectomy · Prognosis · Treatment outcome

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Introduction

Cholangiocarcinoma is a tumor arising from the epithelial cells lining the intrahepatic and extrahepatic bile duct apparatus [1]. Based on its location, it is usually classified as an intrahepatic, hilar, or distal bile duct carcinoma, and this anatomical classification has therapeutic relevance. The intrahepatic forms are treated as primary liver cancer by hepatic resection, while distal bile duct cancer is treated by pancreato-duodenectomy. Hilar cholangiocarcinoma, the so-called Klatskin tumor [2], is treated by resection of the biliary confluence combined with partial hepatectomy, and this is one of the most challenging surgical procedures faced by hepato-biliary surgeons.

The natural history of the tumor progresses rapidly, with a median survival time of around 12 months, and due to its low chemosensitivity, surgery remains the gold standard for treatment [3, 4].

The tumor has the tendency to infiltrate the biliary branches of the caudate lobe and the intrahepatic secondary bifurcation, and the hilar structures require biliary, and sometimes even vascular reconstructions during the

curative procedures. Several studies have recently described how to study this tumor and how to approach it from a surgical point of view in order to achieve a curative resection with a negative surgical margin (R0 resection), which seems to be one of the most important prognostic factors [5–13]. A comparison of Japanese and American experiences revealed that Japanese surgeons adopted a more aggressive approach and achieved a higher negative margin resection rate [14]. Improved knowledge on how to diagnose, stage, and treat Klatskin tumors as well as knowledge of the aggressive strategy reported mainly by Japanese surgeons have changed the surgical approach in the last two decades [15, 16].

The aim of this study was to analyze the changes that have occurred in the last 18 years in terms of the management of Klatskin tumors in a single Western center and to evaluate which factors still significantly affect mortality and long-term survival.

Patients and methods

A total of 113 patients with hilar cholangiocarcinoma were admitted to the Department of Surgery and Transplantation, University of Bologna between November 1989 and December 2007. Of these, 62 (50.4%) patients were not candidates for curative resections and underwent surgical or endoscopic palliative procedures. The remaining 51 (49.6%) patients underwent resection of the tumor with curative intent and constitute the study population. There was preponderance of males in the patient population [32 (62.7%) vs.19 (37.3%)], and the mean age (±standard deviation, SD) was 62.6 ± 8.9 years (range 18–76 years).

Selective diagnostic work-up for hilar cholangiocarcinoma at our center includes the evaluation of liver function by routine biochemical laboratory tests, measurement of serum tumor markers [carcinoembryonic antigen (CEA) and Ca 19-9 level], ultrasonography, chest X-ray, and an abdomen spiral computed tomography (CT) scan. Eighteen patients underwent an angiography of the celiac trunk to evaluate vascular invasion; this procedure has been completely replaced in the last 4 years by thin-sliced helical CT scan with vascular tridimensional reconstruction.

Preoperative biliary drainage to reduce hyperbilirubinemia and to directly visualize the biliary trees was performed in 44 (86.3%) patients, of whom 38 were treated with a percutaneous transhepatic approach; an endoscopically positioned plastic stent was left in place in the remaining six patients. Preoperative total bilirubin levels >15 mg/dl were always considered to be an indication to implement drainage. Seven (13.7%) patients did not received an endoscopic or percutaneous stent prior to surgery.

In the most recent years, we have performed positron emission tomography (PET) scans to detect any extra-hepatic tumors. The presence of extra-hepatic disease at the preoperative evaluation was considered to be an absolute contraindication to surgery.

Jaundice was the main cause of admission to hospital in 44 patients (86.3%). Other symptoms at the time of admission were abdominal pain and/or tenderness and pruritus.

During the last 7 years, adjuvant standard chemotherapy was administered to six (11.7%) patients after liver resection without randomization. In four of these patients with R1 resection operated on after 2000, postoperative adjuvant radiotherapy was also added to the therapy with the intent to improve long-term survival.

The type of surgical procedure was defined according to the terminology of hepatic anatomy and resection proposed by the International Hepato-Pancreato-Biliary Association in 2000 [17]. Bisectionectomy or more was defined as a major hepatectomy, sectionectomy or less was defined as a minor hepatectomy. The procedure was defined as curative when a free surgical margin (free from tumor invasion) at the level of the cut surface and bile duct transaction was confirmed by a final pathologic examination.

The Bismuth–Corlette [18] classification was applied to classify the extent of the tumor and as a prognostic factor.

Post-resection follow-up

Our follow-up of the patients ended in December 2008. Patients were seen every 3 months after liver resection, and recurrence was checked with biochemical tests, including tumor markers, hepatic ultrasonography, and chest X-ray film during the first 2 years post-surgery, and every 6 months thereafter. A CT scan was performed 1 year after surgery and whenever a local or distant recurrence was suspected on the basis of the other tests.

Aim of the study

Data were retrospectively reviewed from a prospective collected database. Based on the surgical experiences reported by Japanese surgeons in the literature and the direct experience of a number of the surgeons in our surgical team with surgeons in Japan, a more aggressive surgical approach was applied in our center after 1997.

Here, we report our review of which prognostic factors strongly affect postoperative mortality, morbidity, and long-term outcome, which changes were noted from 1998 onwards (following implementation of the new strategy), and how the resectability and long-term results as well as morbidity and mortality changed post-1997 relative to the preceding period (1989–1997).

Statistical analysis

In-hospital mortality was defined as death occurring within 90 days of surgery before discharge. Survival was considered from the day of surgical resection to the day of death or the most recent follow-up visit. Patients undergoing palliative procedures were considered to be the control group for comparison to the resected group.

The results are expressed as mean ± SD. The χ^2 test was used for categorical variables, and the Student's *t* test was used to compare continuous variables. Overall survival curves were estimated by means of the Kaplan–Meier method. Comparisons of curves were made with the log-rank test. A multivariate analysis using the Cox proportional hazards model was used between the prognostic factors analyzed at the univariate analysis (patients who experienced in-hospital mortality were excluded from this analysis). A statistically significant difference was defined as a P value <0.05. Statistical analysis was carried out with the SPSS test (SPSS/PC User's guide, ver. 8.0, 1998; SPPS, Chicago, IL).

Results

Among the 51 resected patients, there were 20 (39.2%) type IIIa according to the Bismuth classification, 23 (45.1%) type IIIb, and eight (15.7%) type IV. A right hemihepatectomy was performed in 15 (29.4%) patients, with ten of these undergoing a total caudate lobe resection. In another eight cases (15.7%), the resection was extended to segment 4 (right trisectionectomy). A left hemihepatectomy was performed in 25 patients (49%), with 22 of these undergoing a total caudate lobe resection. In another two (3.9%) patients, the resection was extended to the right anterior section (left trisectionectomy). A central hepatectomy with total caudate lobe resection was performed in one patient (2%) with compromised liver function due to the presence of sclerosing cholangitis.

No blood transfusion was needed for eight (15.7%) patients.

The resection was curative in 37 (72.5%) patients, while a microscopic positive margin (R1) was still present in the remaining 14 (27.5%) patients. In seven of the latter, microscopic infiltration was present on the cut surface at the level of the transaction plane of the resected specimen due to the invasion of a periductal-infiltrative type cholangiocarcinoma.

The histological result was adenocarcinoma in all patients except one with papillary-type cholangiocarcinoma. The tumor was well differentiated (G1) in ten (19.6%) patients, moderately differentiated in 22 (43.1%) patients, and poorly differentiated in the remaining 16 (31.3%) patients. Data were not available for three (5.9%) patients.

Morbidity and mortality

Postoperative complications appeared in 26 (50.9%) patients. The most frequent complication was bile leakage in 11 (42.3%) patients, followed by ascites in six (23%) patients.

As reported in Table 1, blood transfusion and resection of the caudate lobe were significantly related to the appearance of postoperative complications. Even the presence of preoperative percutaneous preoperative biliary drainage (PTBD) was related to the higher appearance of postoperative complications (60 vs. 30%, $P = 0.08$). Age, vascular resection, curative resection, operating time, and type of resection did not influence postoperative morbidity. There was a tendency to a higher incidence of postoperative complications in type IV cholangiocarcinoma according to the Bismuth classification.

Overall in-hospital mortality was 9.8%. Postoperative liver failure was the main cause of death in four patients, and pulmonary embolism and multiorgan failure after hemoperitoneum were the causes of death in one patient.

Several patient and operative variables were analyzed in relation to in-hospital mortality. In patients who experienced postoperative mortality compared to patients who

Table 1 Univariate analysis of different prognostic factors related to postoperative morbidity

Prognostic factors related to postoperative morbidity	Morbidity rate (%)	*P* value
Preoperative biliary drainage (yes)	25/44 (56.8)	0.08
Preoperative biliary drainage (no)	2/7 (28.5)	
Age <60 years	14/25 (56)	n.s.
Age >60 years	13/26 (50)	
Bismuth classification		
Bismuth type IV	7/8 (87.5)	0.07
Bismuth type III	20/43 (46.5)	
Bismuth type IIIa	10/20 (50)	n.s.
Bismuth type IIIb	10/23 (43.5)	
Trisectionectomy	6/10 (60)	n.s.
Hemi-hepatectomy	21/41 (51.2)	
Resection of caudate lobe (yes)	17/40 (42.5)	0.005
Resection of caudate lobe (no)	10/11 (90.9)	
Blood transfusion (yes)	26/43 (60.5)	0.01
Blood transfusion (no)	1/8 (12.5)	
Curative resection (yes)	19/37 (51.3)	n.s.
Curative resection (no)	8/14 (57.1)	

n.s. Not significant

survived after resection, the mean preoperative bilirubine level at the time of surgery (12.2 vs. 6.7 mg/dl), mean blood transfusion (1360 vs. 670 ml), operating time (570 vs. 440 min), and mean fresh frozen plasma transfusion (683 vs. 350 ml) were significantly higher. There were no operative deaths among the eight patients who did not require any blood transfusion. Age, curative resection, Bismuth type, caudate lobe resection, portal vein resection, type of resection (trisectionectomy vs. hemi-hepatectomy), and preoperative biliary drainage did not affect operative mortality. The multivariate analysis revealed that mean blood transfusion [$P = 0.01$; 95% confidence interval (CI)] and operating time ($P = 0.03$; CI 95%) were significantly related to the mortality rate.

Survival and prognostic factors

The mean follow-up was 33.5 ± 30 (range 12–134) months.

The 1, 3, and 5-year overall survival rates in the 51 resected patients were 74.4, 47.3, and 34.1%, respectively; these rates were significantly different from those of patients undergoing palliative procedures, with almost no survivors among this group 4 years after diagnosis (see Fig. 1a). The 1, 3, and 5-year disease-free survival rates in the 51 resected patients were 71.9, 45.7, and 26.3%, respectively.

The 1, 3, and 5-year overall survival rates in patients who received curative resections were 84.4, 51.6 and 44.2%, respectively; in comparison, in patients who received R1 resections, these were 81.8, 38.4, and 19.1%, respectively. The difference between the two groups of patients was statistically significant (Fig. 1b). The significant tendency to longer survival in patients receiving R1 resections compared to patients receiving palliative procedures is shown in Fig. 1c.

Several prognostic factors were related to long-term survival. These are reported in Table 2.

Univariate analysis revealed that the presence of lymph node metastases ($P = 0.02$), perineural invasion around pedicle vessels ($P = 0.0007$), an R1 resection ($P = 0.02$), and a preoperative bilirubin level >10 mg/dl ($P = 0.01$) were significantly related to a short survival. A tendency to a better outcome was also present in patients with preoperative bilirubin levels <5 mg/dl.

The multivariate analysis showed that only the status of the perineural tissue was related to long-term outcome ($P = 0.02$; CI 95%).

Operative characteristics depending on the resection period

Beginning in 1998, our center adopted a new aggressive approach for patients with hilar cholangiocarcinoma, which resulted in the resectability rate significantly increasing from 25 to 75.6%. A Bismuth type IV classification was no longer considered a contraindication to curative resection, and a significantly higher number of these cases was operated on. For example, the caudate lobe was resected in almost 95% of patients post-1997 compared to less than 50% in the preceding period, and a significantly higher

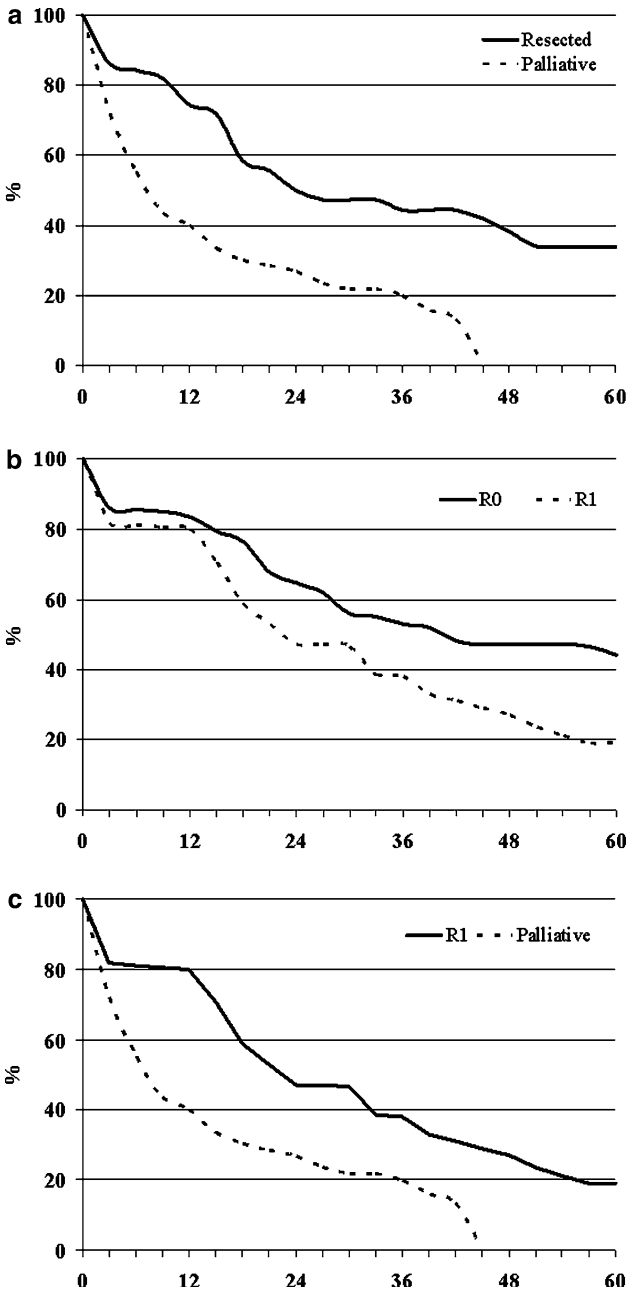

Fig. 1 **a** Overall survival curve for 51 resected patients (*continuous line*) and 62 patients undergoing palliative procedures (*broken line*) ($P = 0.01$). **b** Overall survival curve for 34 curative resections (R0, *continuous line*) and 17 R1 resections (*broken line*) ($P < 0.05$). **c** Overall survival curve for 62 patients undergoing palliative procedures (*dotted line*) and 17 R1 resections (*continuous line*) ($P = 0.08$)

Table 2 Prognostic factors related to long-term survival in patients resected for Klatskin tumors

Prognostic factors related to long term survival	Number of patients (%)	3-year survival (%)	5-year survival (%)	*P* value
Bismuth classification				
Bismuth IIIa	20 (39.2)	47.8	29.9	n.s.
Bismuth IIIb	23 (45.1)	59.2	50.7	
Bismuth IV	8 (15.7)	57	35	
Bilirubin level				
<5 mg/dl	24 (47.1)	55.5	38.8	0.07
>5 mg/dl	27 (52.9)	39.5	21.9	
<10 mg/dl	37 (72.6)	63.7	45.5	0.01
>10 mg/dl	14 (27.4)	23.7	0	
Hemi-hepatectomy	40 (78.4)	51.6	38.7	n.s.
Trisectionectomy	10 (19.6)	33.3	22.2	
Blood transfusion (yes)	43 (84.3)	49.7	31.9	n.s.
Blood transfusion (no)	8 (15.7)	50	50	
Poorly differentiated T cells	14 (27.5)	44.5	20	n.s.
Moderately/highly differentiated T cells	37 (72.5)	66.2	30.5	
Curative resection	37 (72.5)	56.3	44.2	0.05
R1 resection	14 (27.5)	38.3	19.1	
Perineural invasion	33/44 (75)	34	0	<0.05
Absence PN invasion	11/44 (25)	78	63	
Vascular invasion	28/44 (63.6)	39.5	19.8	n.s.
No vascular invasion	16/44 (36.4)	61.9	54.1	
Lymph node metastases	14/44 (33)	12.9	0	<0.05
No LN metastases	26/44 (67)	60.4	40.3	

PN Perineural invasion

number of lymph nodes were dissected from 1998 onwards. The changes in surgical approach and relative statistical significance are reported in Table 3.

The significantly higher incidence of perineural and vascular invasion and of poorly differentiated tumors reported in Table 3 is probably related to the more aggressive surgical approach towards dealing with advanced tumors that has been adopted since 1998 in comparison to the pre-1998 period. A few common contraindications to surgery prior to 1998, such as Bismuth type IV classification, portal vein invasion, or lymph node metastases around hepatic pedicle were no more considered to be serious impediments during the post-1997 period. Despite the more aggressive policy after 1997, our center achieved a significant decrease in blood transfusion and postoperative hospitalization, and there was a tendency towards a reduced incidence of postoperative complications compared to the first period. In-hospital mortality slightly decreased during the second study period without reaching statistically significant difference.

After 1997, a portal vein resection and reconstruction was performed to achieve a curative resection in four patients (11.8%, 4/34); a direct suture between the main trunk of the portal vein and the left branch was performed in all of these cases. In another two patients, a resection and reconstruction of the right hepatic artery was performed; one of these patients died of liver failure after relaparotomy for hemperitoneum. In another five patients (14.7%) operated on after 1997 for whom a right hemi-hepatectomy or right trisectionectomy plus caudate lobe resection was scheduled, we performed preoperative right portal vein embolization to induce hypertrophy of the contralateral lobe when the estimated remnant liver volume was <30% of the standard liver volume.

The survival curves for each study period are reported in Fig. 2. Although we did not find a statistically significant difference in long-term outcome, likely due to the small number of patients in the two groups, there was a tendency to a better survival after 1997.

Discussion

Surgical resection remains the gold standard in the treatment of hilar cholangiocarcinoma due to its low chemosensitivity, with a 10–30% partial response rate, and the lack of benefit from postoperative radiation therapy [5, 6, 19]. Our center has achieved a significantly higher resectability rate during the last 8 years compared to the preceding period due to a number of factors, namely,

Table 3 Changes in surgical parameters between the two study periods (before and after 1997)

Surgical approach/clinical parameters	1989–1997	1998–2007	*P* value
Laparotomy, *n* (%)	51/68 (75)	11/45 (24.4)	0.01
Resectability, *n* (%)	17/68 (25)	34/45 (75.6)	0.01
Mean age of patient (years)	55.7 ± 9	62.6 ± 9	n.s.
Percutaneous drainage (%)	88.2	78.9	n.s.
Bismuth classification IV (%)	5.9	20.6	<0.05
Preoperative bilirubin level (mg/dl)	9.6 ± 8.8	6 ± 5	0.07
Caudate lobe resection (%)	47.1	94.1	0.001
Curative resection (%)	75.4	71.1	n.s.
Blood transfusion (ml)	1250 ± 1030	710 ± 590	0.01
FFP transfusion (ml)	550 ± 490	288 ± 350	<0.05
Operative time (min)	408 ± 80	480 ± 150	0.06
Dissected lymph nodes (*n*)	2.4 ± 1.6	8.6 ± 6	0.01
Poorly differentiated tumor (%)	5.9	48.4	0.02
Perineural invasion (%)	50	84.4	0.02
Vascular invasion (%)	33.3	77.4	0.01
Operative morbidity (%)	64.7	47.1	0.07
Operative mortality (%)	11.8	8.8	n.s.

FFP Fresh frozen plasma

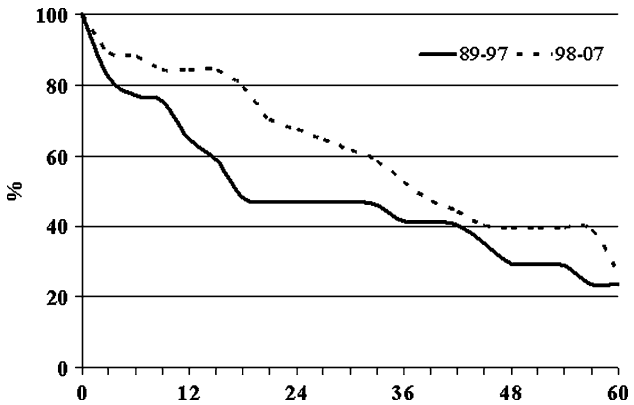

Fig. 2 Overall survival curves for the 51 resected patients depending on the period of treatment. *Broken line* 1998–2007, *continuous line* 1989–1997

improvements in preoperative diagnosis, surgical skills, and surgical techniques and the adoption of a more aggressive approach based predominantly on Japanese surgical approaches.

Resectability rates vary from 50 to 80% in the largest series recently reported in the literature. This wide range is mainly due to the difference in surgical policy between Eastern and Western series [8, 10, 11, 15, 20–33]. As reported in Table 4, the average resectability rate is around 50% in Western series and around 75% in Eastern series. Our surgical experience at our single center in a European country has—in the post-1997 period—been similar to those reported in the Eastern series.

Strictly related to this aggressive surgical approach, we showed a higher resection rate of Bismuth type IV hilar tumors, which currently should no longer be considered a contraindication to liver resection. The Bismuth classification remains an useful anatomic classification, but it does not represent a validated prognostic factor and it does not correlate to the resectability rate [5, 8]. Despite the presence of poorly differentiated tumors in 31.4% of patients, of Bismuth type IV tumors in 21.5% of cases, and the high incidence of perineural and vascular invasion (particularly after 1997), we achieved an overall 5-year survival rate of 34.1%, which is comparable to results reported in the literature.

A tumor-free surgical margin is one of the best predictors of survival [5, 29]. The need to achieve an R0 curative resection has already been stressed in the literature [8, 10, 15, 21, 24, 25, 31, 34]. We achieved a 5-year survival rate close to 45% among R0 curative resections; however, there was a tendency to a better outcome among the R1 resections, with a few 5-year survivors, compared to the group of non-resected patients who presented no long-term survival 4 years after diagnosis. In R1 resected patients, postoperative radiotherapy may increase overall survival, but its role is far from being standardized, and the survival benefit has not been convincingly demonstrated [6].

Biliary branches of the caudate lobe may often be invaded by hilar cholangiocarcinoma [35]. Liver resection with total caudate lobe resection is therefore the rational approach to achieve R0 curative resection [32, 34–36]. This is why almost 95% of our patients underwent partial hepatectomy plus caudate lobe resection from 1998 onwards, without increasing operative mortality.

The need to achieve an R0 resection by performing extended hepatectomy together with bile duct resection

Table 4 Reported series with more than 40 cases of patients treated for hilar cholangiocarcinoma since 2000

References[a]	Year	Number of resected patients/no. of patients observed	Mortality (%)	Resectability (%)	5-year survival (%)
Weimann et al. [20]	2000	95/162	6	58.6	21
Jarnagin et al. [21]	2001	80/160	10	50	37
Neuhaus et al. [23]	2003	133/NA	15	≈50	40
Rea et al. [10]	2004	46/NA	9	<50	26
Silva et al. [11]	2005	45/150	9	30	41
Hemming et al. [24]	2005	53/80	9	66	35
Dinant et al. [15]	2006	99/NA	15.2	NA	27
Witzigmann et al. [25]	2006	60/184	8.3	33	15
Hidalgo et al. [22]	2008	44/61	11.3	72.1	28
Konstadoul et al. [33]	2008	59/73	6.8	80.8	34.9
Tabata et al. [26]	2000	75/99	12	75	22.5
Lee et al. [27]	2000	128/151	5.5	84.8	22
Kawasaki et al. [28]	2003	79/140	1.3	56.4	30
Seyama et al. [29]	2003	58/70	0	82.8	40
Kondo et al. [30]	2004	40/42	0	95.2	40 (3-year)
Ebata et al. [8]	2003	188/240	9.6	78	28
Sano et al. [31]	2006	111/120	0	82.2	44
Miyazaki et al. [32]	2007	161/228	7	70.6	30

NA Data are not available

[a] Manuscripts from the same groups are reported only once; the first ten reports are from Western series, the remaining eight reports are from Eastern series

justifies the considerable mortality rate—around 10%—that has been reported in major published series [6, 8, 15, 21, 23, 25, 34]. Most of these mortalities are related to the extent of the resection, but also to infection and sepsis. The incidence of postoperative mortality in our series is comparable to the data reported in the literature; the fact that it did not decrease significantly after 1997 may be explained by the more advanced cases that were resected over the last few years (e.g., perineural and vascular invasion rate, poorly differentiated tumors, and more extended resections with caudate lobe excision). Among the most recent studies (Table 4), only four report an in-hospital mortality <5% [28–31]. However, our center shows a tendency towards a decreased in-operative morbidity and mortality since 1998 (see Table 3). The fact that the morbidity rate was lower during the second period of our study and in patients receiving caudate lobe resection may be explained by the improvement in surgical technique and a reduced incidence of bile leaks in patients receiving a combined liver resection plus caudate lobectomy compared the patients who did not receive caudate lobectomy whenever biliary confluence was removed.

The impact of lymph node status on survival has been well documented [10, 15, 28, 29, 34, 37]. In our patient group also, the presence of lymph node metastases negatively affected long-term outcome, and lymph nodes as well as connective tissue were carefully dissected along the hepatic pedicle, the retropancreatic space, and the common hepatic artery as far as the celiac trunk, especially after 1997. Multivariate analysis revealed that the presence of perineural invasion was in fact the only predictor of survival.

The influence of blood transfusion on early postoperative outcome and long-term survival has been reported in patients with hepatocellular carcinoma, liver metastases, and liver surgery [38, 39]. Mean blood transfusion was the strongest variable affecting operative mortality in our study, and the 3- and 5-year survival rate among patients not receiving blood transfusion was 50%. The negative effect of blood transfusion on long-term outcome has been documented by other authors for Klatskin tumors and other malignancies [16, 40]. For this reason and as a result of technical improvements, we significantly reduced blood transfusion in the second period, resulting in a significant decrease in postoperative complications and slightly decrease in operative mortality.

Based on our results, we stress that the mortality rate was significantly higher in jaundice patients and that even long-term survival was affected by bilirubin levels >10 mg/dl. The role of preoperative biliary drainage is a matter of discussion. A few surgeons do not recommend the routine use of biliary drainage because of the higher rate of complications and cholangitis [41, 42]. A recent meta-analysis on the role of preoperative biliary drainage was unable to provide definitive conclusions due to the lack of randomized studies [43]. However, the negative effects of hyperbilirubinemia has been reported by several authors [10, 15, 22, 34, 44]. The main reasons for these conclusions

are that the faster the growth of the tumor cells and the poorer the differentiation, the more complete the biliary obstruction is. In addition, biliary dilatation secondary to obstruction compresses the portal vein within the Glissonian sheath, causing ischemia and necrosis within the remnant liver hepatocytes and suppressing regeneration [34, 44]. This argumentation has led the authors of most of the largest recent series dealing with Klatskin tumors to recommend the complete relief of jaundice before resection in order to significantly reduce operative mortality and morbidity [8, 10, 22, 24, 28–31].

Although the relation between preoperative jaundice and short-term outcome has been already reported, we would like to emphasize that preoperative hyperbilirubinemia may be a negative prognostic factor for long-term outcome and, therefore, preoperative biliary drainage should be performed to reduce operative morbidity and mortality and to increase long-term results.

The three studies by Japanese authors with zero mortality stresses the need to perform a hepatic resection in patients without jaundice (bilirubin levels <2 mg/dl), to drain the remaining hepatic segments, and to avoid preoperative cholangitis in order to reduce mortality [29–31]. Portal vein embolization is suggested whenever the estimated remnant liver volume is <40% [33]. The combination of these two treatments may require a median preoperative hospitalization of 40–80 days [29]. On the other hand, Halazun and the group in Leeds reported the possibility of performing extended hepatectomy without portal vein embolization with similar results to Japanese series in term postoperative morbidity, mortality, and long-term outcome [45]. Costs and benefits therefore need to be further analyzed for this strict policy. In any case, based on our results and the data from the literature, we suggest that whenever preoperative bilirubin levels are >10 mg/dl, the patient must be drained and surgery should be postponed.

Due to the tendency of Klatskin tumors to invade secondary biliary branches and the appearance of cholangitis from undrained segments whenever an endoscopic approach is adopted, the percutaneous approach is preferable in patients with hilar cholangiocarcinoma. This approach is currently gaining in popularity worldwide [11, 31, 36, 46].

In conclusion, in the case of hilar cholangiocarcinoma, the adoption of an aggressive surgical approach (based on resection of the biliary confluence together with partial hemi-hepatectomy plus caudate resection and regional lymphadenectomy) may increase the number of patients eligible for curative resection and improve long-term survival even if the mortality rate is still fairly high among this population of patients. Severe hyperbilirubinemia should be preoperatively drained, possibly by percutaneous approach, in order to reduce operative complications and mortality and to improve long-term outcome. Even patients receiving R1 resections may gain in survival and improve their quality of life compared to non-resected patients.

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