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Operative Management and Outcomes of 150 Patients with Curative-intent Surgery for Perihilar Cholangiocarcinomas: A Single Institute East European Perspective

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ABSTRACT

Introduction: The knowledge of current approach and outcomes of curative-intent surgery for perihilar cholangiocarcinoma (PHC) has been highlighted in studies of the literature including mainly East Asian and Western patients. Thus, papers presenting the curative-intent surgery in East Europe are scarce. The study aims to present the operative management and outcomes of curative-intent surgery for PHC in an East European institutional experience.
Patients and methods: The data of all patients with curative-intent surgery for PHC between 1996 and 2017 were retrospectively reviewed from a prospective maintained electronic database at our Department of Surgery. The assessment was made for the operative management and early and late outcomes.
Results: Liver resections were performed in 80.7% of patients, with caudate lobectomies in 64.7% of cases. Vascular resections were performed in 19.4% of patients. Preoperative biliary drainage was performed in 26% of patients. Negative resection margins were obtained in 76.7% of patients. Overall and severe morbidity rates were 57.3% and 24%, respectively. Postoperative bile leak, liver failure and hemorrhage rates were 31.3%, 24.7% and 10%, respectively. The 90-day mortality rate was 6%. The median overall and disease-free survival times were 26 months and 21 months, respectively.
Conclusion: The standard approach for curative-intent surgery for PHC implies bile duct resection associated with major hepatectomies, including caudate lobectomy. Expertise in referral surgical centers of East Europe is associated with morbidity, mortality and overall survival rates comparable with those reported in Western centres, despite low rate of pre-operative biliary drainage and no use of portal vein embolization. Improvements of pre-operative optimization with portal vein embolization and biliary drainage may potentially lead to better early and long-term outcomes.
Key words: perihilar cholangiocarcinoma, preoperative biliary drainage, hepatectomy, morbidity, mortality, survival

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INTRODUCTION

Aggressive surgery (e.g. bile duct resection, lymph node dissection, hepatec-

tomy) is widely accepted as standard for curative-intent surgery of perihilar cholangiocarcinoma (PHC)(1), with improved oncological outcomes, at the expense of increased morbidity rates and non-negligible post-operative mortality rates (2-4).

The knowledge of current approach and outcomes of curative-intent surgery for PHC has been highlighted in studies of the literature including mainly East Asian and Western patients (2-4).

Papers presenting large series of patients with curative-intent surgery in East Europe are scarce (5-15).

The study aims to present the operative management and outcomes of curative-intent surgery for PHC in an East European institutional experience.

PATIENTS AND METHODS

Patients

The data of all patients with curative-intent surgery for PHC between 1996 and 2017 (November 1st) were retrospectively reviewed from a prospective maintained electronic database at our Department of Surgery. Collection of data included demographics, pre-, intra- and postoperative parameters.

A PHC was defined according to previously described criteria (16). Our criteria of resectability for PHC were described elsewhere (5,6).

Only patients with a final pathology diagnosis of malignancy were included. Patients with Klatskin-mimicking lesions were excluded (17).

Curative-intent surgery was considered when negative resection margins (R0 resection) or microscopic positive resection margins (R1 resection) were obtained. Patients with macroscopic residual tumors (R2 resection) were excluded.

Preoperative biliary drainage was considered only for patients with cholangitis and impaired renal or liver function. Furthermore, preoperative portal vein embolization was not performed for any patient in the present cohort, and only patients with an estimated future liver remnant volume ≥ 30% were considered for a curative-intent resection.

Methods

Complications were graded according to the Dindo-Clavien classification (18), while the International Study Group of Liver Surgery definitions and severity grading were used for post-hepatectomy bile leakage (19), hemorrhage (20) and liver failure (21). Postoperative mortality was assessed at 90 days.

The American Joint Committee on Cancer TNM Staging System (7th Edition) was used for tumor staging (22).

Statistics

The data are expressed as number (percentage) for the categorical variables and median (range) for the continuous variables. The Kaplan-Meier curves was used to estimate the disease-free and overall survival times, while the reversed Kaplan-Meier curve was used to estimate the median follow-up time. The disease-free survival time was considered the time from surgery to first recurrence occurrence. The overall survival time was considered the time from surgery to death occurrence or last follow-up (January 1st, 2018). A number of 11 patients (7.3%) were excluded from the survival and follow-up analyses (9 postoperative deaths and 2 patients lost from the follow-up).

RESULTS

Demographics and preoperative data

In the present cohort of 150 patients with curative-intent surgery for PHC there was a slightly male predominance (83 patients – 55.3%), and the median age was 59 years (range, 21 – 77 years). Co-morbidities were observed in 67 patients (31.3%).

A number of 121 patients (80.3%) have had jaundice and the median bilirubin serum level prior to resection was 6.9 mg/ dl (range, 0.2 – 35 mg/ dl). Furthermore, cholangitis was present in 34 patients (22.7%) prior to resection. Preoperative biliary drainage was performed in 39 patients (26%).

The median preoperative CA 19-9 serum level was 326.5 UI/ ml (range, 1 – 12 000 UI/ ml).

The Bismuth-Corlette classification of the patients in the present cohort is shown in *fig. 1*.

Operative data

The operative procedures performed in the present cohort are shown in *table 1*. Thus, a number of 121 patients (80.7%) underwent hepatectomies.

The median operative time and estimated blood loss were 280 minutes (range, 120 – 650 minutes), and 600 ml (range, 100 – 15 000 ml), respectively.

Pathology data

Final histological pathology revealed: adenocarcinoma (147 patients – 98%), squamous carcinoma (2 patients –

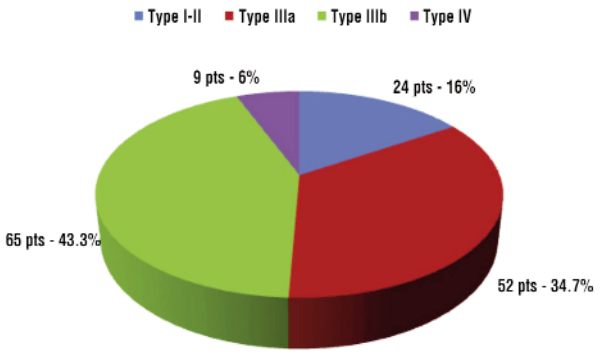

Figure 1 - The Bismuth-Corlette classification in 150 patients with curative-intent surgery for perihilar cholangiocarcinomas

Table 1 - Operative procedures in 150 patients with curative-intent surgery for perihilar cholangiocarcinomas

Operative procedure	Number of patients (%)
Bile duct resection only	29 patients – 19.3%
Right hemi-hepatectomy	41 patients – 27.3%
Right trisectionectomy	12 patients – 8%
Left hemi-hepatectomy	66 patients – 44%
Left trisectionectomy	1 patient – 0.7%
Central hepatectomy	1 patient – 0.7%
Caudate lobectomy	97 patients – 64.7%
Portal vein resection	25 patients – 16.7%
Hepatic artery resection	4 patients – 2.7%
Pancreatico-duodenectomy	1 patient – 0.7%
Loco-regional lymph node dissection	147 patients – 98%

1.4%) and neuroendocrine carcinoma (1 patient – 0.7%).

Tumor pattern in the present cohort was infiltrative in 79 patients (52.7%), nodular in 63 patients (42%), and papillary in 8 patients (5.3%).

Tumor grade of differentiation was G1 in 88 patients (58.7%), G2 in 45 patients (30%), and G3 in 17 patients (11.3%).

The median tumor diameter was 2 cm (range, 0.4 – 10 cm) and perineural invasion was observed in 55 patients (36.7%).

According to the T stage, 21 patients (14%) were T1, 44 patients (29.3%) were T2, 62 patients (41.3%) were T3, and 23 patients (15.4%) were T4.

Loco-regional lymph node metastases were present in 51 patients (39.3%). A number of 10 patients (6.7%) presented distant metastases that were synchronously removed.

The TNM stages of the present cohort are shown in *fig. 2* (data for staging were not available for 3 patients – 2%).

Negative resection margins (R0 resection) were obtained in 115 patients (76.7%).

Postoperative morbidity and mortality

At least one postoperative complication occurred in 86 patients (57.3%). The Dindo-Clavien classification of the complications in the present cohort is shown in *fig. 3*. Thus, a number of 36 patients (24%) have had severe morbidity (i.e., grade III – V Dindo-Clavien).

The main postoperative complications were: bile leak (47 patients – 31.3%), liver failure (37 patients –

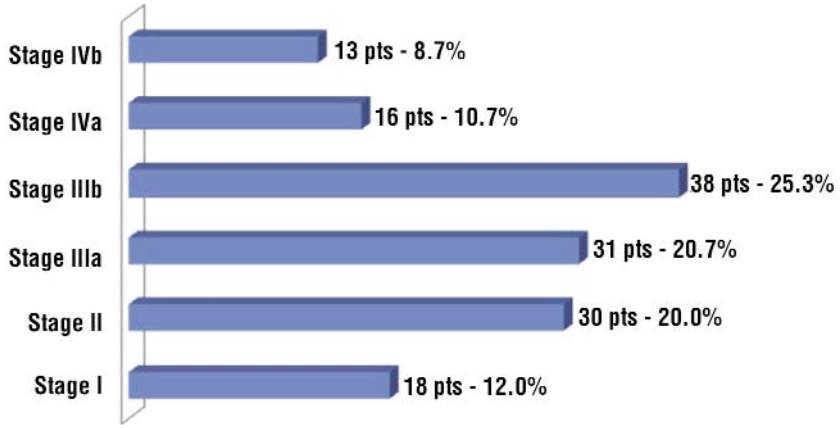

Figure 2 - The TNM stages in 150 patients with curative-intent surgery for perihilar cholangiocarcinomas

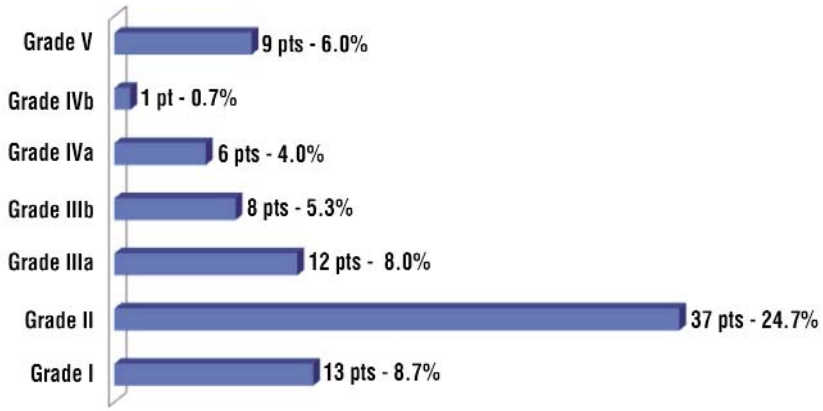

Figure 3 - The Dindo-Clavien classification in 150 patients with curative-intent surgery for perihilar cholangiocarcinomas.

24.7%), and hemorrhage (15 patients – 10%). Clinically relevant (i.e., grade B-C) bile leak, liver failure and hemorrhage rates were 26%, 18%, and 4.7%, respectively, as shown in *fig. 4*.

During the 90 days after surgery, death occurred in 9 patients (6%). The main causes of death were: liver failure (4 patients – 2.7%), local septic complications with multiple organ failure (3 patients – 2%), hemorrhage (1 patient – 0.7%), and pulmonary embolism (1 patient – 0.7%).

The median postoperative hospital stay was 15 days (range, 1 – 65 days).

Long-term outcomes

Adjuvant chemotherapy was performed in 72 out of 139 patients available for the survival and follow-up analyses (51.8%). No patient in the present cohort received neoadjuvant therapy.

The oncological outcomes of patients in the present cohort were described elsewhere (23). Thus, the median overall survival time was 26 months (range, 2 – 205 months) with estimated 1-, 3-, 5-, and 10-year overall survival rates of 75%, 45%, 29%, and 15%, respectively (23) (*fig. 5*). The median disease-free survival time was 21 months (range, 2 – 205 months) with estimated 1-, 3-, 5-, and 10-year disease-free survival rates of 62%, 40%, 31%, and 23%, respectively (23) (*fig. 6*). Noteworthy, the median follow-up time in the present cohort was 89 months (range, 2 – 205 months)(23).

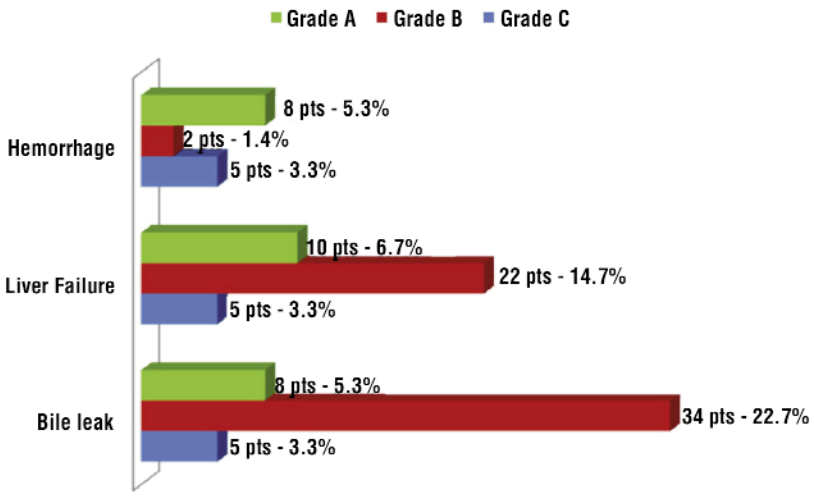

Figure 4. Clinically relevant (i.e., grade B-C) bile leak, liver failure and hemorrhage rates in 150 patients with curative-intent surgery for perihilar cholangiocarcinomas.

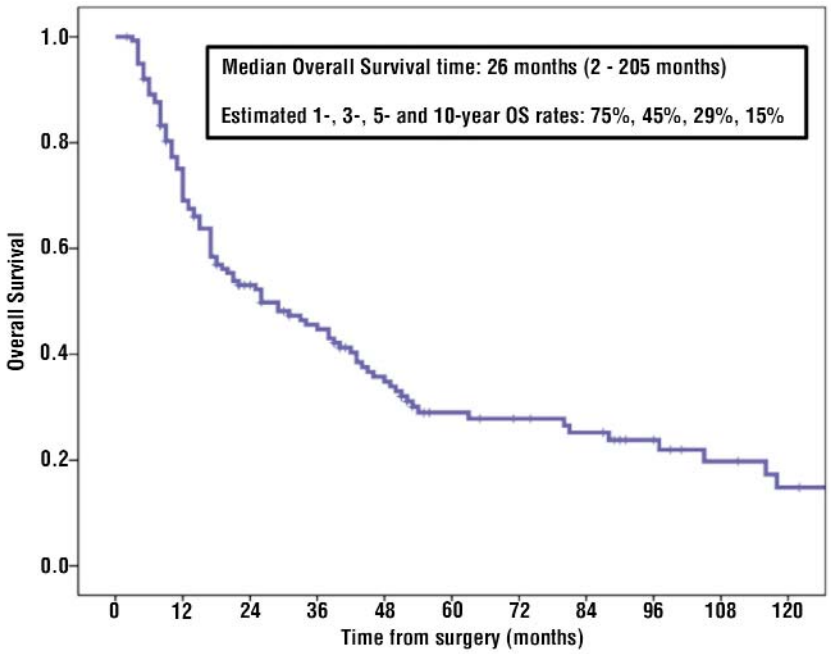

Figure 5 - The Kaplan-Meier overall survival curve in 139 patients with curative-intent surgery for perihilar cholangiocarcinomas.

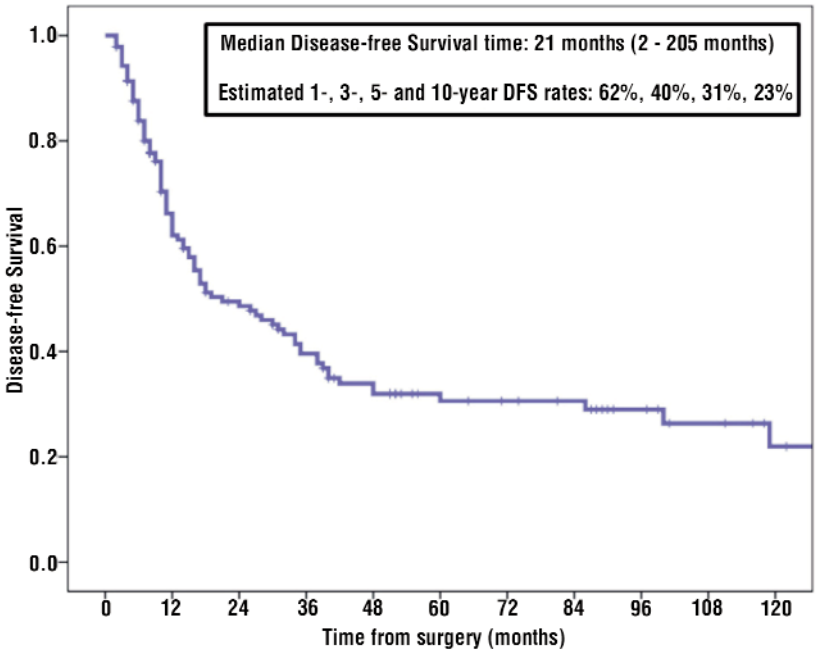

Figure 6 - The Kaplan-Meier disease-free survival curve in 139 patients with curative-intent surgery for perihilar cholangiocarcinomas

DISCUSSION

So far there are only few studies presenting the operative management and outcomes of patients with curative-intent surgery for PHC in East Europe (5-15). The aforementioned studies included usually small series of patients (i.e., 1 to 44 patients), except for one Romanian (7) and one Russian study (9).

In East European series published so far including more than 5 patients with curative-intent surgery for

PHC, hepatectomies were reported in 38.6% - 68% of the cases (9,13). In the present series hepatectomies were performed in 80.7% of patients.

Early Western experiences with major hepatectomies for PHC were associated with inacceptable mortality rates (up to 27%) and the main causes of death were intraoperative hemorrhage, postoperative infectious complications and liver failure (24,25). It is the merit of East Asian surgeons to first demonstrate the feasibility and safety of major hepatectomies in PHC (26).

Studies of patients with curative-intent surgery for PHC published beginning with the year 2000 have shown morbidity rates of 6% - 84%, mortality rates of 0% - 18%, and 5-year survival rates of 13% - 44% (2-4). Surgical centres from East Asia particularly report reduced mortality rates and increased survival rates (27-33), compared to the Western centres (2-4).

Several papers have compared the operative management and outcomes between East Asian and Western patients with curative-intent surgery for PHC (26,34,35).

In a landmark paper, Tsao and co-workers comparing USA and Japanese series of patients have found significant differences of the operative management and treatment outcomes (26). Thus, significantly increased resectability, negative resection margins and overall survival rates were observed in the Japanese group (26).

Kimura and co-workers comparing UK and Japanese series of patients have found no significant differences between the groups for preoperative biliary drainage rate but significantly reduced portal vein embolization rates and increased mortality rates in the Western group (34).

Olthof and co-workers comparing Western (Netherlands and USA) and Japanese series of patients have found that preoperative biliary drainage, portal vein embolization, extended hepatectomies, and vascular resections were significantly more frequent in the Japanese group (35). No significant differences between the groups were observed for postoperative liver failure, severe morbidity and mortality rates, while increased rates of bile leaks and hemorrhage were observed in the Western group (35). Noteworthy, major differences of patient characteristics were observed between the groups (35). Nevertheless, the overall survival rates were significantly better in the Japanese group (35).

The present cohort has some particularities compared to other previously reported series of patients with curative-intent surgery for PHC (2,36-39). Thus, the rate of preoperative biliary drainage in the present cohort (26%) can be considered lower than the rate reported in most worldwide large series (2, 36, 37, 39, 40). Furthermore, no patient in the present cohort received preoperative portal vein embolization and patients with estimated future liver remnant volume less than 30% were considered unfit for a curative-intent surgery.

Preoperative optimization of the liver was proposed for a long time by East Asian surgical teams to reduce the risk of postoperative complications in patients with major hepatectomies for PHC and jaundice (41). This approach was furthermore adopted in Western surgical centres (42, 43). Preoperative biliary drainage of the future liver remnant and portal vein embolization are the main tool to reduce the risk of post-hepatectomy liver failure in these patients (28, 43, 44).

Patients with major liver resections and jaundice (particularly when cholangitis is present) are at high risk to develop severe complications such as hemorrhage, infectious complications and liver failure (24). The preoperative biliary drainage aim to decrease bilirubin level and thus to ameliorate the coagulation disorders and to treat cholangitis (42). However, there are also potential complications of preoperative biliary drainage such as tumor seeding, bleeding and cholangitis (42, 45).

Although the routine use of preoperative biliary drainage is highlighted in most series published in the literature (2-4, 38), the role of preoperative biliary drainage remains unclear.

Several studies have explored the outcomes of surgery for PHC with and without preoperative biliary drainage (37, 46-52).

Cai and co-workers used preoperative biliary drainage in 25.2% of patients and did not find any differences of morbidity and mortality rates between the groups (46). Furthermore, preoperative biliary drainage was associated with significantly increased operative times and hospital stays (46).

Ribero and co-workers did not found any detrimental impact of preoperative biliary drainage on overall, severe, specific post-hepatectomy complications and mortality rates after major hepatectomies for PHC (52). However, cholangitis prior to resection was more frequent when the biliary drainage was performed, and it was an important determinant of postoperative liver failure and liver failure-related death (52).

Ferrero and co-workers have found significantly increased rates of infectious complications when preoperative biliary drainage was used, albeit no differences of morbidity and mortality rates were observed (49).

A multicentre European study has shown that biliary drainage prior to curative-intent surgery for PHC was associated with decreased mortality rates after right hepatectomies and increased mortality rates after left hepatectomies (48).

A recent analysis of the American College of Surgeons database of patients with liver resection for PHC has associated preoperative biliary drainage with significantly increased rates of wound infections, organ space infections, sepsis, renal insufficiency, bile leaks, liver failure, re-laparotomy for complications and readmissions, and mortality (51).

A study performed at Memorial Sloan Kettering Cancer Center has suggested that in patients with jaundice and future liver remnant volume ≥ 30% preoperative biliary drainage does not appear to improve perioperative outcomes (50). In current practice of the aforementioned surgical centre, elective preoperative biliary drainage is used in patients with resection for PHC, only when the future liver remnant volume is less than 40% (53).

A meta-analysis published in 2017 comparing studies reporting outcomes on patients with curative-intent surgery for PHC with and without preoperative biliary drainage has found significantly increased morbidity rates when the biliary drainage was used, particularly for wound infection rate (47). However, no significant differences of mortality rates were observed between the groups (47). A previous meta-analysis could not provide evidence for any clinical benefit of biliary drainage prior to resection in PHC (37).

Safety of major liver resections in jaundiced patients without preoperative biliary drainage were previously described in several studies (54-59). However, there are also studies that have shown increased overall morbidity (60, 61), bile leak (61) or intraabdominal abscesses rates (62) in jaundiced patients with major hepatectomies, albeit no differences of mortality rates were observed (61).

The best procedure for preoperative biliary drainage in patients with resectable PHC remains a matter of debate (38;40;45). Recent meta-analyses comparing the endoscopic biliary drainage with percutaneous transhepatic approach have found that patients received mainly an endoscopic drainage (52% - 63.5%) (36;63;64). However, the percutaneous approach was associated with significantly decreased morbidity rates, including cholangitis and acute pancreatitis (36, 39, 64). No differences of liver failure, hemorrhage and overall survival rates were observed between the groups (39, 63-65).

Acute pancreatitis is a life-threatening complication of biliary drainage (66), and was reported in around 9% of patients with endoscopic approach (36). Percutaneous biliary drainage may also complicate with acute pancreatitis (67).

Cholangitis is another feared complication of preoperative biliary drainage and was reported in around 33.8% of patients with endoscopic drainage and in 7.6% of patients with percutaneous approach (36). Preoperative cholangitis was associated with significantly increased rates of postoperative mortality after major hepatectomies for PHC (68).

A recent study has shown that percutaneous approach significantly increases the risk of seeding metastasis and was associated with significantly decreased survival rates, compared to the endoscopic biliary drainage prior to resection for PHC (69).

Catheter tract recurrence after percutaneous biliary drainage can occur in 2.6% of patients resected for PHC and was associated with decreased survival rates (70).

It is worth mentioning that the average morbidity and mortality rates related to preoperative biliary drainage are 21.6% and 3.8% for endoscopic drainage, and 26.5% and 7.5% for the percutaneous approach (36).

Our previous studies did not find any impact of preoperative biliary drainage on severe morbidity, clinically relevant bile leak, liver failure,hemorrhage rates, disease-free and overall survival rates after major hepatectomies for PHC (5, 6).

Preoperative portal vein embolization aims to initiate compensatory hypertrophy of the future liver remnant after biliary drainage, to reduce the risk of liver failure after major liver resections for PHC (71-74), particularly when right trisectionectomy is considered (75, 76). It is the merit of Makuuchi to introduce in clinical practice this method (41, 77).

The cut-off point to consider preoperative portal vein embolization is quite variable, depending mainly on the estimated future liver remnant volume, jaundice degree and underlying liver pathology. It appears that patients with normal liver parenchyma are at high risk to develop liver failure when the estimated future liver remnant volume is less than 20%, while for patients with underlying liver disease the cut-off is less than 40% (2). Cut-offs of future liver remnant volumes varying between 25%-50% was considered indication for portal vein embolization in the literature (2).

Recent systematic reviews have suggested that in patients with PHC, portal vein embolization should be used after biliary drainage when the future liver remnant volume is less than 40% (71, 73). Some surgical teams consider portal vein embolization in PHC

when the future liver remnat volume is ≤ 30% (57, 78-80). Nevertheless, recently it was proposed a score to calculate the risk of post-hepatectomy liver failure to better select the patients who may benefit from portal vein embolization (80).

It is worth mentioning that portal vein embolization can bring its own mortality (81). However, major complications such as portal vein thrombosis, bleeding and ethanol induced hemolysis are reported in less than 1% of cases (71,73). Interestingly, a recent study identified portal vein embolization as an independent risk factor for postoperative complications after resection for PHC (82).

A recent review has shown no specific guidelines as to when portal vein embolization is used (2).

At the moment, the use of preoperative biliary drainage and portal vein embolization in curative-intent surgery for PHC is higher in East Asian surgical centres (27-33, 82-85), compared to the Western centres (34, 35, 40, 43, 52, 79, 86-90).

Preoperative biliary drainage and portal vein embolization can increase the time from diagnosis of PHC to curative-intent surgery for PHC with at least 4 to 6 weeks (45).

Currently, the guidelines recommend portal vein embolization prior to resection of PHC in patients with future liver remnant volume less than 30% - 40%, while biliary drainage is recommended in jaundiced patients submitted for neoadjuvant therapy, patients with cholangitis, malnutrition, liver or renal insufficiency and prior to portal vein embolization (1).

The criteria of resectability in the present cohort of patients with PHC (5, 6) are similar with those reported in other large series from Western surgical centres (91).

Major hepatectomies are used in 53.3% - 100% of patients in recent Western series of curative-intent surgery for PHC, while portal vein resection is reported in 7.5% - 72% of patients (34, 35, 43, 52, 79, 86-90) (*table 2*). In the present series major hepatectomies were used in 80.7% of patients, and portal vein resection and reconstruction was performed in 16.7% of patients.

The use of preoperative biliary drainage in recent series of Western patients with curative-intent surgery for PHC is reported to be 45% - 88.2%, while portal vein embolization was used in 0% - 25.5% (34, 35, 43, 52, 79, 86-90, 92-95) (*table 2*). In the present cohort biliary drainage was used in 26% of patients and no patient

Table 2 - Series of Western patients with curative-intent surgery for perihilar cholangiocarcinomas published in the last 5 years

First author, year, centre	Number of patients	Major hepatectomies (%)	Preoperative biliary drainage (%)	Preoperative portal vein embolization (%)	Portal vein resection (%)	Morbidity (%)	Mortality (%)	5-year overall survival rate (%)
Ratti(43), 2013, Ospedale San Raffaele, Milano, Italy	80	75%	71.2%	14.9%	7.5%	51.2%	6.2%	39.5%
Gomez(88), 2014, Aintree University Hospital, Liverpool, UK	57	84.2%	NA	0%	8.8%	59.6%	14%†	39.5%
Hoffmann(89), 2015, Heidelberg University, Heidelberg, Germany	60	100%	45%	5%	35%	53.3%	15%‡	18.3%
Ismael(90), 2016, MD Anderson Cancer Centre, Houston, USA	47	93.6%	NA	25.5%	NA	72.3%	8.5%‡	33.3%
Molina(79), 2016, Hospital Clinic Barcelona, Barcelona, Spain	32	100%	60%	0%	72%	71.9%	16%‡	44%
Ribero(52), 2016, multicentre, USA & Italy	133	100%	73.7%	24%	21%	77%	11.3%‡	NA
Bhutiani(86), 2017, multicentre, USA	256	74.6%	75.3	9.6%	9.6%	63.3%	12.5%‡	21%
Kimura(34), 2017, St. James's University Hospital, Leeds, UK	103	100%	80.6%	3.9%	43.7%	48.5%#	13.6%‡	NA
Feo(87), 2018, University of Sassari, Sassari, Italy	30	53.3%	40%	6.7%	20%	40%	13.3%	37.1%
Olthof(35), 2018, Amsterdam Academic Medical Center & Memorial Sloan Kettering Cancer Center New York, Netherlands & USA	210	97.1%	81%	7%	20%	54%#	13%‡	33%
Present series, Fundeni Clinical Institute, Bucharest, Romania	150	80.7%	26%	0%	16.7%	57.3%	6%‡	29%

Mortality assessed at †30 days and ‡90 days; #Severe morbidity (i.e., grade III – V Dind-Clavien); NA – not available

underwent portal vein embolization. However, it is worth mentioning that in our series all patients have had estimated future liver remnant volume > 30% and the median bilirubin serum level prior to resection was not very high (6.9 mg/ dl).

The mortality and morbidity rates in Western series of patients are reported to be 5.1% - 16% and 39% - 77%, respectively (34, 35, 43, 52, 79, 86-90, 92-94, 96-99) (*table 2*). In the present series the morbidity rate was 57.3% and the 90-day mortality rate was 6%.

The 5-year overall survival rates in recent series of Western patients with curative-intent surgery for PHC is reported to be 18.3% - 44% (35, 43, 79, 86-90, 94, 99, 100) (*table 2*). The 5-year overall survival rate in the present cohort was 29%.

Thus, one might conclude that despite low rate of preoperative biliary drainage and no use of portal vein embolization, it appears that the results of the present series are not inferior in term of early and long-term outcomes to those reported in other recent series with Western patients (*table 2*).

CONCLUSION

The standard approach for curative-intent surgery for PHC implies bile duct resection associated with major hepatectomies, including caudate lobectomy. Expertise in referral surgical centers of East Europe is associated with morbidity, mortality and overall survival rates comparable with those reported in Western centres, despite low rate of preoperative biliary drainage and no use of portal vein embolization. Improvements of preoperative optimization with portal vein embolization and biliary drainage may potentially lead to better early and long-term outcomes.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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