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Curative-intent Surgery for Perihilar Cholangiocarcinoma with and without Portal Vein Resection – A Comparative Analysis of Early and Late Outcomes

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Rezumat

Chirurgia cu viză curativă a colangiocarcinoamelor perihilare cu și fără rezecție de venă portă – studiu comparativ al rezultatelor postoperatorii imediate și la distanță

Introducere: Siguranța rezecției de venă portă în chirurgia colangiocarcinoamelor perihilare a fost deja dovedită în Asia, America şi Europa de Vest. Totuşi, nu există nici un fel de date referitoare la acest subiect, care să provină din Europa de Est. Scopul studiului este de a evalua comparativ rezultatele postoperatorii imediate şi pe termen lung după rezecția cholangiocarcinoamelor perihilare, cu şi fără rezecție de venă portă.
Pacienți şi metode: Datele a 21 de pacienți rezecați pentru colangiocarcinoame perihilare ce au asociat rezecția venei porte au fost comparate cu datele a 102 pacienți fără rezecție de venă portă. Pentru analiza comparativă a datelor din cele două grupuri s-au folosit teste statistice specifice.
Rezultate: Rezecția venei porte a fost realizată la 17% dintre pacienți. În grupul pacienților cu rezecție asociată de venă portă au fost realizate semnificativ mai multe trisecționectomii drepte (p = 0.031) şi rezecții de lob caudat (p = 0.049). Ca urmare, atât timpul operator (p = 0.015) cât şi pierderea de sânge intraoperator (p = 0.002) au fost semnificativ mai mari în acest grup de pacienți cu rezecție de venă portă. Nu s-au constatat diferențe semnificative între cele două grupuri de pacienți în ceea ce priveşte rata complicațiilor severe postoperatorii, mortalitatea postoperatorie şi chimioterapia adjuvantă. Totuşi, în grupul pacienților cu rezecție de venă portă, rata insuficenței hepatice postoperatorii cu impact clinic

a fost semnificativ mai mare (p = 0.001). Nu s-au constatat diferențe semnificative între grupuri în ceeea ce priveşte timpul de supraviețuire (34 vs. 26 luni, p = 0.566). Prezența invaziei venoase documentată histologic s-a dovedit a avea un impact negativ semnificativ asupra supraviețuirii la distanță, în grupul pacienților cu rezecție de venă portă (p = 0.027).
Concluzii: Rezecția venei porte asociată chirurgiei cu viză curativă pentru colangiocarcinoamele perihilare poate fi realizată în condiții de siguranță, fără a creşte în mod semnificativ rata de complicații şi mortalitatea postoperatorie. Totuşi, riscul de a dezvolta insuficiență hepatică post-operatorie cu impact clinic este semnificativ mai mare când se asociază rezecția venei porte. În plus, trebuie să ne aşteptăm la o creştere importantă a timpului operator şi a cantității de sânge pierdute intraoperator atunci când se asociază rezecția venei porte. Prezența invaziei venoase documentată histologic are un impact negativ semnificativ asupra supraviețuirii la distanță.

Cuvinte cheie: colangiocarcinom perihilar; rezecție de venă portă; complicații postoperatorii; supraviețuire

Abstract

Introduction: The safety of portal vein resection (PVR) during surgery for perihilar cholangiocarcinoma (PHC) has been demonstrated in Asia, America, and Western Europe. However, no data about this topic are reported from Eastern Europe. The aim of the present study is to comparatively assess the early and long-term outcomes after resection for PHC with and without PVR.
Patients and methods: The data of 21 patients with PVR were compared with those of 102 patients with a curative-intent surgery for PHC without PVR. The appropriate statistical tests were used to compare different variables between the groups.
Results: A PVR was performed in 17% of the patients. In the PVR group, significantly more right trisectionectomies (p=0.031) and caudate lobectomies (0.049) were performed and, as expected, both the operative time (p=0.015) and blood loss (p=0.002) were significantly higher. No differences between the groups were observed regarding the severe postoperative morbidity and mortality rates, and completion of adjuvant therapy. However, in the PVR group the postoperative clinically-relevant liver failure rate was significantly higher (p=0.001). No differences between the groups were observed for the median overall survival times (34 vs. 26 months, p = 0.566). A histological proof of the venous tumor invasion was observed in 52% of the patients with a PVR and was associated with significantly worse survival (p=0.027).
Conclusion: A PVR can be safely performed during resection for PHC, without significant added severe morbidity or mortality rates. However, clinically-relevant liver failure rates are significantly higher when a PVR is performed. Furthermore, increased operative times and blood loss should be expected when a PVR is performed. Histological tumor invasion of the portal vein is associated with significantly worse survival.

Key words: perihilar cholangiocarinoma, portal vein resection, complications, survival

Introduction

Perihilar cholangiocarcinomas (PHC) are considered as relatively rare tumors. The concept of PHC has evolved over the years. Thus, initially, all the cholangiocarcinomas that involved or required the bile duct bifurcation resection were considered as PHC, according to the Johns Hopkins definition proposed in 1996 (1). More recently, in 2014, the group from the Nagoya University re-considered the PHC as the cholangiocarcinomas involving de hilar bile

duct, between the right side of the umbilical part of the left portal vein and the left side of the origin of the right posterior portal vein (2). Thus, the patients with large mass-forming intrahepatic cholangiocarcinomas (outside the proposed boundaries) were excluded from the PHC group. It appears that long-term survivals after resection of these large mass-forming intrahepatic cholangicarcinomas are worse than survivals after resection of PHC, as defined by the Nagoya University group (3,4).

A negative resection margins surgery represents the most important determinant of survival in patients with PHC (5-8). The curative-intent surgery for PHC has significantly changed over the years from simple bile duct resection (1,9,10) to more complex surgical procedures (5,8,11). Thus, nowadays, a curative-intent surgery for PHC includes bile duct resection, loco-regional lymph nodes dissection, caudate lobectomy and, usually, a major hepatectomy (3,5,8,11,12). These complex surgical procedures were associated with significantly improved long-term survival rates compared with simple bile duct resection (13), however, at the expense of increased morbidity rates and relatively high mortality rates (8). Thus, the 5-year survival rates of up to 40.4% were reported in large recent series of patients resected for PHC, with up to 73% morbidity and up to 14.3% 90-day mortality rates (8). Postoperative liver failure and bile leak are the most frequent complications after major hepatectomies for PHC (7,14).

A multidisciplinary approach in experienced surgical centers is mandatory to mitigate both morbidity and mortality rates and to obtain improved survivals in patients with PHC (3,5,8, 11,14,15). A PHC should be preoperatively differentiated from a benign Klatskin-mimicking lesion to avoid unnecessary extensive resections, albeit the differentiation between the two entities remains challenging (16).

The PHC have a particular pattern of spread towards loco-regional invasion (17). Thus, due to local anatomical consideration, the portal vein invasion in PHC is not uncommon. Furthermore, a portal vein invasion is no longer a contraindication for resection in patients with PHC when a safe venous reconstruction is feasible (7,8,11). Although challenging, the safety of a portal vein resection (PVR) during curative-intent surgery for PHC has been demonstrated in several studies (6,7,11,18-20). However, the impact of a PVR in PHC surgery remains controversial and previous comparative studies reached conflicting results (5,7,11, 17-29), none including patients from Eastern Europe. Furthermore, meta-analyses comparing the outcomes of patients with and without a PVR for PHC did not reach the same conclusions (29-33).

The practice of curative-intent surgery and the safety of a PVR in PHC in East European countries is poorly known because very few studies were published (3,8,14,34-37). The experience gained in our surgical center with curative-intent surgery for PHC has been reflected in previous publications (3,8,14,38).

The aim of the present study is to comparatively assess the early and long-term outcomes after resection for PHC with and without PVR, in a relatively large single-center experience.

Patients and Methods

Patient Cohort

Between 1996, January 1st and 2014, December 31st, at our Department of Surgery, 127 patients underwent a curative-intent surgery for PHC. From the analysis were excluded four patients (3 patients with associated hepatic artery resection and reconstruction and one patient with associated pancreatico-duodenectomy). Hepatic artery resection and pancreatico-duodenectomy might have a detrimental effect on both early and long-term outcomes (2,6,29,30). Thus, the remaining 123 patients were divided into two groups: with PVR (PVR group - 21 patients) and without PVR (no PVR group - 102 patients).

Demographics, clinical, pathological, early and long-term outcomes data were compared between the two groups from a prospective electronic database established at our Department.

A PHC was defined according to the Nagoya University definition (2). A PVR was electively

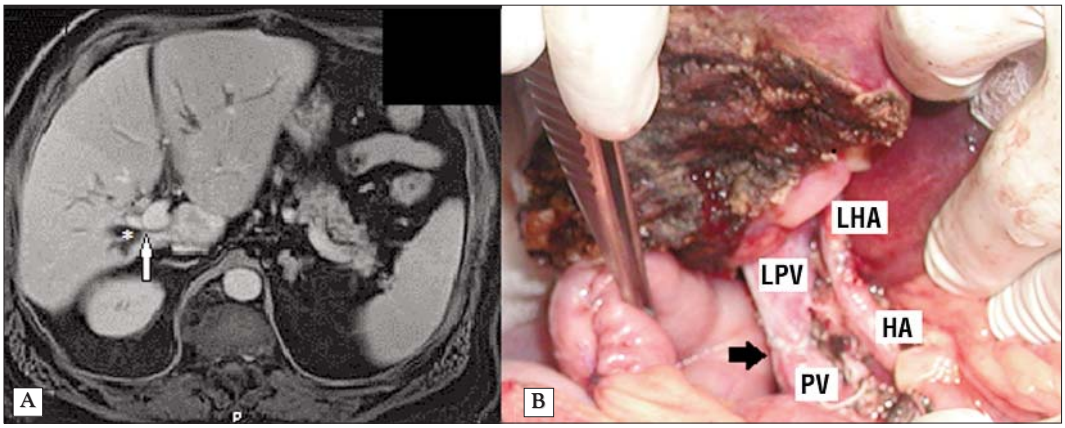

Figure 1. **(A)** Magnetic resonance imaging in a patient with a type III A Bismuth PHC invading the emergence of the right portal vein requiring a PVR (the asterisk marks the tumor and the arrow marks the tumor invasion of the emergence of the right portal vein); **(B)** Intraoperative aspects after bile duct resection, loco-regional lymph nodes dissection, caudate lobectomy and right hemi-hepatectomy with PVR for a type III A Bismuth PHC invading the portal vein (the arrow marks the end-to-end portal anastomosis; PV – portal vein; LPV – left portal vein; HA – proper hepatic artery; LHA – left hepatic artery)

performed when the portal vein invasion was detected or suspected at the preoperative imaging (*Fig. 1 A*) or intraoperative exploration, and a safe venous reconstruction was considered as possible (*Fig. 1 B* and *2*). Our institution criteria of resectability for PHC and surgical procedures were described elsewhere (3) and are in agreement with the international guidelines (12).

Assessment of Early and Long-term Outcomes

Morbidity was defined as in-hospital complications and was assessed according to the Dindo-Clavien classification (39). For the patients with more than one complication, the highest grade of complication was assigned. The post-hepatectomy liver failure (40), hemorrhage (41) and bile leak (42) were defined and graded according to the International Study Group of Liver Surgery (ISGLS). The postoperative mortality was considered at 90-days.

Statistical Analysis

Data are expressed as the number (percentage) for categorical variables and median (range) for continuous variables. Fisher's exact test (two-tailed) was used to compare the categorical variables while Mann-Whitney test (two-tailed)

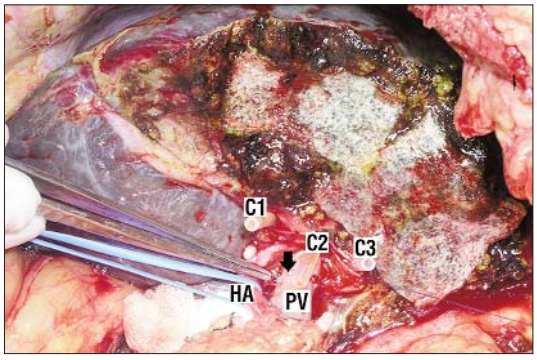

Figure 2. Intraoperative aspects after bile duct resection, loco-regional lymph nodes dissection, caudate lobectomy and left hemi-hepatectomy with PVR for a type III B Bismuth PHC invading the portal vein (the arrow marks the end-to-end portal anastomosis; PV – portal vein; HA – proper hepatic artery; C1, C2, C3 – bile ducts with stents inside)

was used for continuous variables. Median follow-up time was estimated using the reversed Kaplan-Meier curves and median overall survival time was estimated using the Kaplan-Meier curves; the comparisons were made using the log-rank test. Overall survival time was considered the time from resection to death occurrence or last follow-up (June 1st, 2015). P values less than 0.05 were considered statistically significant. Statistical analyses

were performed with the SPSS (Statistical Packages for Social Sciences) version 20.0 software (SPSS Inc., Chicago, IL).

Results

Demographics, Clinical and Operative characteristics

The rate of PVR was 17% in the present cohort of patients, and a segmental venous resection was performed in all these cases. A primarily end-to-end anastomosis was possible in 20 patients (95%), while one patient (5%) needed a synthetic graft interposition.

No differences between the groups were observed regarding age, associated co-morbidities, cirrhosis or cholangitis, preoperative bilirubin serum level, preoperative biliary drainage rate, preoperative albumin, hemoglobin, neutrophil-to-lymphocyte ratio and CA 19-9 serum level, as shown in *Table 1*.

Significantly more males were found in the PVR group compared with the group of patients without PVR (81% vs. 52%, p = 0.016). Furthermore, more right trisectionectomies and caudate lobectomies were performed in the PVR group, as shown in *Table 1*. As expected, both the operative time and estimated blood loss were significantly higher in the group of patients with PVR, as shown in *Table 1*.

Pathology Data

No differences between the groups were observed regarding the histological tumor type, tumor diameter, TNM stages, perineural invasion and negative resection margins rates, as shown in *Table 2*. The histological proof of tumor invasion into the resected portal vein (V1) was confirmed in 11 patients (52%) from the PVR group.

Postoperative Data

There were no significant differences between the groups regarding the severe morbidity, 90-day mortality, and clinically-relevant post-hepatectomy bile leak and hemorrhage rates, as shown in *Table 3*.

The clinically-relevant post-hepatectomy liver failure rate was significantly higher in

Table 1. Curative-intent surgery for PHC in patients without PVR (no PVR group – 102 patients) vs. patients with PVR (PVR group – 21 patients): comparative analysis of demographics, clinical and operative parameters

Parameter	no PVR group (102 patients)	PVR group (21 patients)	P value
Age, years	59 (21 – 77)	56 (40 – 71)	0.143[1]
Gender, male	53 (52%)	17 (81%)	0.016[2]
Co-morbidities	32 (31%)	2 (9.5%)	0.058[2]
Cirrhosis	5 (5%)	1 (5%)	1[2]
Preoperative bilirubin serum level, mg/ dl	8 (0.2 – 35)	8.8 (0.7 – 23)	0.888[1]
Cholangitis	20 (20%)	7 (33%)	0.244[2]
Preoperative biliary drainage	24 (24%)	6 (29%)	0.589[2]
Preoperative albumin serum level, g/ dl	4 (2 – 5.4)	3.6 (2 – 4.6)	0.102[1]
Preoperative hemoglobin serum level, g/ dl	12.5 (7.5 – 16)	12.3 (7.8 – 15.3)	0.840[1]
Preoperative neutrophil-to-lymphocyte ratio	3.2 (1 – 16.2)	3.3 (1.2 – 23.2)	0.612[1]
Preoperative CA 19-9 serum level, U/ ml	174 (1 – 1400)	400 (40– 5000)	0.101[1]
Right hemi-hepatectomies	24 (24%)	8 (38%)	0.179[2]
Right trisectionectomies	7 (7%)	5 (24%)	0.031[2]
Caudate lobectomies	58 (57%)	17 (81%)	0.049[2]
Operative time, min	240 (120 – 620)	300 (180 – 650)	0.015[1]
Estimated blood loss, ml	400 (100 – 15 000)	800 (300 – 12 000)	0.002[1]

[1]Mann-Whitney test (two-tailed); [2]Fisher's exact test (two-tailed); PVR – portal vein resection; PHC – perihilar cholangiocarcinoma

Table 2. Curative-intent surgery for PHC in patients without PVR (no PVR group – 102 patients) vs. patients with PVR (PVR group – 21 patients): comparative analysis of pathology data

Parameter	no PVR group (102 patients)	PVR group (21 patients)	P value
Infiltrative type tumor	52 (51%)	14 (67%)	0.233[1]
Tumor diameter, cm	2.5 (0.4 – 10)	3 (0.5 – 10)	0.131[2]
AJCC T3/ T4 stages	51 (50%)	14 (67%)	0.230[1]
Positive loco-regional lymph nodes	36 (35%)	12 (57%)	0.085[1]
Perineural invasion	35 (34%)	6 (29%)	0.800[1]
AJCC stages 3-4	64 (63%)	15 (71%)	0.618[1]
Negative resection margins (R0)	80 (78%)	15 (71%)	0.568[1]

[1]Fisher's exact test (two-tailed); [2]Mann-Whitney test (two-tailed); AJCC – the American Joint Commission on Cancer; PVR – portal vein resection; PHC – perihilar cholangiocarcinoma

the PVR group, as shown in *Table 3*.

A portal vein thrombosis was observed in the early setting in 3 patients (2.4%) of the present cohort (*Fig. 3*), without significant differences between the groups, as shown in *Table 3*.

No differences between the groups were observed for the postoperative hospital stays, as shown in *Table 3*.

Long-term Survival Comparative Analysis

Two patients (9.5%) in the PVR group and 6 patients (5.9%) in the group without a PVR were excluded from the survival analyses due to 90-day postoperative death or lost from the follow-up (p = 0.623).

The median follow-up time was 110 months (4 – 174 months) in the group of patients without a PVR and 56 months (4 – 80 months) in the PVR group, without any significant difference (p = 0.064). No differences between the groups were observed regarding the completion of adjuvant treatment rates, as shown in *Table 3*.

The median overall survival time was 26 months (4 – 174 months) in the group of patients without a PVR and 34 months (4 – 80 months) in the PVR group, without any significant difference (p = 0.566) (*Fig. 4 A*). However, in the group of PVR patients, the overall survival time was significantly worse in the group of patients with a histological proof of tumor venous invasion, compared with the patients without tumor venous invasion: 12 months (4 – 51 months) vs. 43 months (4 – 80

Table 3. Curative-intent surgery for PHC in patients without PVR (no PVR group – 102 patients) vs. patients with PVR (PVR group – 21 patients): comparative analysis of early and long-term postoperative outcomes

Parameter	no PVR group (102 patients)	PVR group (21 patients)	P value
Severe postoperative complications (grade III-IV Dindo)	19 (19%)	5 (24%)	0.557[1]
90-day mortality	5 (5%)	2 (10%)	0.341[1]
Grade B/C liver failure	12 (12%)	9 (43%)	0.001[1]
Grade B/C bile leak	27 (26%)	4 (19%)	0.588[1]
Grade B/C hemorrhage	5 (5%)	2 (10%)	0.341[1]
Portal vein thrombosis	1 (1%)	2 (9.5%)	0.072[1]
Postoperative hospital stay, days	15 (1 – 65)	15 (4 – 40)	0.845[2]
Completion of adjuvant therapy	48 (47%)	11 (52%)	0.811[1]

[1]Fisher's exact test (two-tailed); [2]Mann-Whitney test (two-tailed); PVR – portal vein resection; PHC – perihilar cholangiocarcinoma

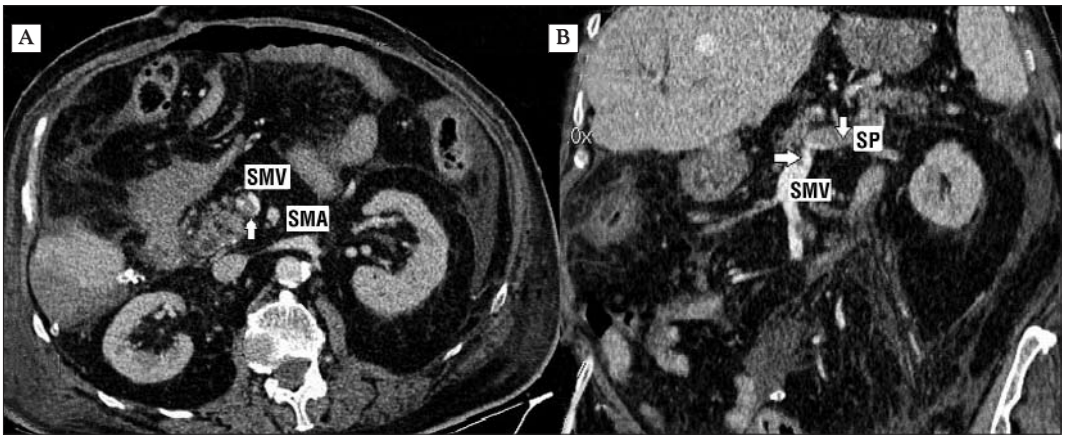

Figure 3. **(A)** Axial plane contrast enhanced computer tomography showing a postoperative portal vein thrombosis extended to the superior mesenteric vein after bile duct resection, loco-regional lymph nodes dissection, caudate lobectomy and right hemi-hepatectomy with PVR for a type III A Bismuth PHC invading the portal vein; **(B)** Coronal plane contrast enhanced computer tomography showing a postoperative portal vein thrombosis extended to the superior mesenteric and splenic veins after bile duct resection, loco-regional lymph nodes dissection, caudate lobectomy and right hemi-hepatectomy with PVR for a type III A Bismuth PHC invading the portal vein (the arrows mark the thrombus; SMV – superior mesenteric vein; SV – splenic vein; SMA – superior mesenteric artery)

months) (p = 0.027) (*Fig. 4 B*).

The 1-, 2-, 3- and 5-year survival rates were 69%, 51%, 43% and 26% in the PVR group and 76%, 52%, 42% and 28% in the group of patients without a PVR, respectively. Furthermore, in the subgroup of patients with a PVR, the 1-, 2-, 3- and 5-year survival rates were 80%, 80%, 64% and 48% in the V0 group and 50%, 22%, 22% and 0% in the V1 group of patients, respectively.

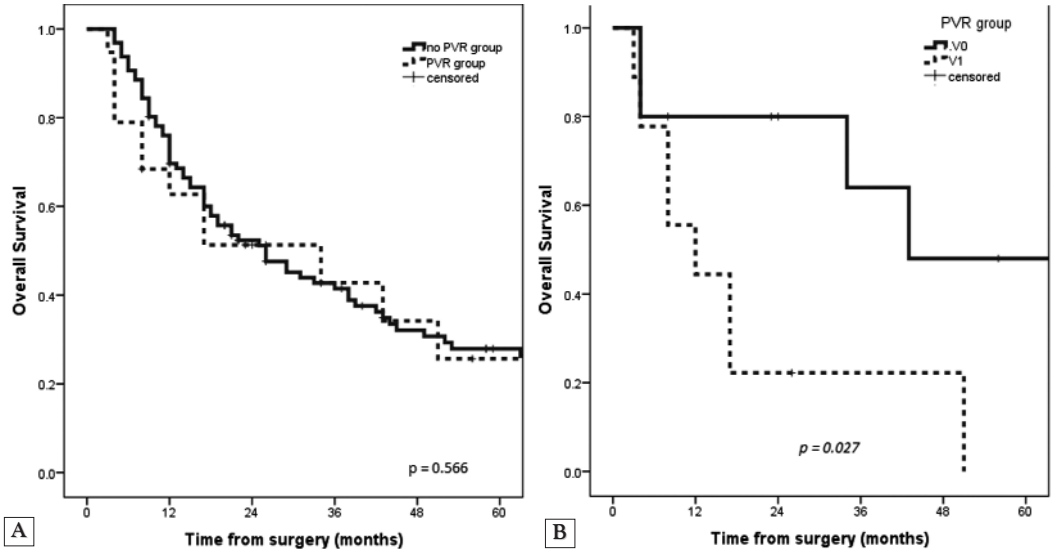

Figure 4. Kaplan-Meier comparative curves for overall survival in patients **(A)** with curative-intent surgery for PHC with and without a PVR **(B)** with and without a histological venous invasion

Discussion

To the best of our knowledge, this is the largest series of patients with a curative-intent surgery for PHC published to date in Eastern Europe and the first study assessing the impact of a PVR in this part of the world. The clinical, operative, pathological and postoperative early and late outcomes data in the present cohort of patients are similar to those reported in other previous large series from high-volume centers worldwide, as a recent review has shown (8).

The reported incidence of a PVR during curative-intent surgery for PHC in large recent series varies from 8% to 44% (8). The PVR is more frequently encountered in surgical centers from Japan (2,6,11,22,25) while in the remaining part of the world the PVR during curative-intent surgery for PHC is reported in 9.6 % to 22% of the patients (5,8,15,18,27-29, 43). In the present cohort of patients, a PVR was performed in 17% of the cases.

In most of the previously reported patients, a segmental PVR was necessary, and a primarily

Table 4. Curative-intent surgery for PHC with and without PVR: relevant comparative studies from the literature

Author, year	Period	Total patients/ PVR	PVR rate (%)	Mortality (%) (PVR vs. no PVR)	Morbidity (%) (PVR vs. no PVR)	R0 rate (%) (PVR vs. no PVR)	V1 rate (%)	Median OS time (PVR vs. no PVR)	5-years survival rate (PVR vs. no PVR)
Klempnauer (24), 1997 Hanover Medical School, Germany	1971-1995	151/39	25.8%	17.1% vs. 7.8%[a]	NA	73.2% vs. 75.8%	33.3%	NA	34% vs. 34%
Munoz (26), 2002, Mount Sinai School of Medicine, USA	1990-2001	28/10	35.7%	10% vs. 0%[a]	NA	NA	50%	NA	22% vs. 38%
Ebata (19), 2003, Nagoya University, Japan	1979-2000	160/52	32.5%	9.6% vs. 9.3%[a]	84.6% vs. 78.7%	69.2% vs. 88%[†]	69.2%	NA	9.9% vs. 36.8%[†]
Miyazaki (17), 2007, Chiba University, Japan	1981-2004	161/34	20.4%	8.8% vs. 4.2%[a]	38% vs. 36%	56% vs. 65%	80%	NA	14% vs. 30%[†]
Hirano (22), 2009, Hokkaido University, Japan	1999-2007	64/43	67%	5.6% vs. 4.8%[a]	33.3% vs. 57.1%[†]	95.3% vs. 95.2%	44.2%	NA	NA
Song (27), 2009, Asan Medical Center, Korea	1989-2005	259/51	19.7%	9.8% vs. 2.9%[†a]	47.1% vs. 39.4%	NA	54.9%	18.1 vs. 27.2 months[†]	18.5% vs. 26.7%[†]
Hemming (21), 2011, University of California San Diego, USA	1999-2010	95/42	44.2%	8% vs. 2%[a]	NA	NA	41%	NA	40% vs. 40%
Neuhaus (20), 2012, Charite Campus Virchow Berlin, Germany	1990-2004	100/50	50%	12.4% vs. 11.2%[b]	NA	NA	NA	NA	58% vs. 29%[†]
de Jong (18), 2012, multi-institutional, Western Europe and USA	1984-2010	305/51	16.7%	17.6% vs. 10.6%[b]	NA	66.7% vs. 66.4%	49%	NA	NA
Yu (29), 2014, Second Military Medical University, China	1998-2010	238/25	10.5%	NA	32% vs. 16.9%	NA	NA	NA	0% vs. 21.8%[†]
Wang (28), 2015, First Affiliated Hospital, Sun Yat-Sen University, China	2005-2012	154/34	22%	0% vs. 0.9%[a]	37.5% vs. 35.1%	NA	NA	20 vs. 32 months	25% vs. 35.7%
Hoffmann (23), 2015, Heidelberg, Germany	2001-2012	60/21	35%	19.1% vs. 12.8%[b]	100% vs. 28.2%[¥]	57.1% vs. 59%	42.8%	32.3 vs. 28.1 months	20% vs. 17.8%
Matsuyama (25), 2016, Yokohama, Japan	1992-2014	172/54	31.3%	3.7% vs. 4%[b]	70.3% vs. 82.4%	79.6% vs. 74.3%	40.7%	NA	51% vs. 46%
Present series	1996-2014	123/21	17%	10% vs. 5%[b]	24% vs. 19%[¥]	71% vs. 78%	52%	34 vs. 26 months	26% vs. 28%

[†]p values < 0.05; [¥]severe morbidity (grade III-IV Dindo); [a]In-hospital; [b]90-day; PVR - portal vein resection; PHC - perihilar cholangiocarcinoma; OS - overall survival time; NA - not available

end-to-end anastomosis was possible (5,6,11,19, 21,22,27,28,43), as it was the case in the present series.

It is worth to mention that nowadays there are two attitudes regarding the issue of PVR during surgery for PHC. Thus, few surgical centers propose the routine en-bloc PVR ("no-touch" technique)(7,20,22,44-46), while most of the surgical teams recommend the selective use of the PVR (2,5,6,11,15,18,21,23,25,28, 29,43), only when the preoperative imaging or intraoperative exploration suspect portal vein invasion by the tumor (8), as in was the case in the present series. A recent systematic review and meta-analysis have shown that the sensitivity and specificity of a preoperative contrast-enhanced computed tomography in detecting a portal vein invasion in a PHC patient are 89% and 92%, respectively (47).

The impact of a PVR on postoperative outcomes after curative-intent surgery for PHC has been explored in several previous studies and remains controversial (*Table 4*). However, technically, a portal vein encasement appears to complicate the surgical strategy in a patient with PHC (48).

Regarding the early outcomes, some studies associated a PVR with trends towards increased mortality rates (15,24,27,49) while others did not (6,11,18-23,25,28), as it was the case in the present series. No differences in morbidity rates were observed in most of the published studies (17-22,25,27-29,46), as it was the case in the present series. Only one study showed significantly increased morbidity rates when a PVR is performed (23). Recent meta-analyses of comparative studies of combined PVR for PHC have shown no significantly increased morbidity rates for the PVR group (29-33). Significantly increased mortality rates were reported for the PVR group in four meta-analyses (29-31,33), while one meta-analysis did not identify any differences (32).

Klempnauer and co-workers reported in 1997 a portal vein thrombosis rate with subsequent liver failure in 7.7% of the patients with PVR for PHC (24). The reported portal vein thrombosis rates after curative-intent surgery for PHC with PVR in the previous series vary between 0% and 10% (17,22,23,25, 26,30,45) and appears to be significantly higher compared with the patients without a PVR(30). In the present series of patients with a PVR, the portal vein thrombosis rate was 9.5%, not significantly different from the group of patients without a PVR.

The reported liver failure rates after PVR in previous studies vary between 1.9% and 57%, not significantly different compared with the patients without a PVR (23,30-32). In the present series the postoperative liver failure rate in the PVR group was high (43%). Interestingly, Neuhaus and co-workers showed significantly increased liver failure rates when a PVR is performed (20), as it was the case in the present series. The large variability of reported liver failure rates might be significantly influenced by the variations in the definition of liver failure. Thus, the postoperative liver failure rates after hepatectomies appear to be higher when the ISGLS definition is used (14,23), as it was the case in the present series. Nagino and co-workers, in a single-center experience of 574 patients with curative-intent surgery for PHC with and without a PVR, reported a postoperative liver failure rate of 53.5% using the ISGLS definition (11). Nevertheless, male gender and right trisectionectomies were significantly associated with an increased risk of postoperative liver failure in patients with combined PVR hepatectomies in a study (50). In the present series, male gender and right trisectionectomies rates were significantly higher in the PVR group (*Table 1*).

Previous studies did not identify any significant differences of operative time and blood loss between the patients with and without a PVR for PHC (17,22,23,26,46). However, Wang and co-workers identify significantly increased blood loss when a PVR is performed (28). In the present series, both the operative time and blood loss were significantly higher when a PVR was performed.

In the present study no differences of survivals were found between the groups of patients with and without a PVR for PHC. This might be explained by the fact that no differences between the groups were observed

for any relevant prognostic factor that could influence the long-term survival. Thus, our previous studies have shown that negative resection margins, completion of adjuvant therapy and neutrophil-to-lymphocyte ratio are independent prognostic factors for the long-term outcome in patients resected for PHC (3). In the present series no differences between the groups were observed for the negative resection margins, completion of adjuvant therapy rates and neutrophil-to-lymphocyte ratio (*Table 1* and *2*). Furthermore, no differences between the groups were observed for the perineural invasion and metastatic lymph nodes rates (*Table 2*). Significantly increased perineural invasion and metastatic lymph nodes rates were found for the PVR group in three meta-analyses, compared with the patients without a PVR (31-33).

Four meta-analyses have shown conflicting results regarding the impact of a PVR on the negative resection margin rates (30-33). Thus, Chen and co-workers (32) and Bai and co-workers (31) identify significantly lower negative resection margin rates in the PVR group, while Wu and co-workers and Abbas and co-workers showed no significant differences (30,33).

Some studies identified a PVR as negative prognostic factor for long-term survival (6,11, 19,27), while others did not (5,15,18,21-26,28,43, 51-53) (*Table 4*). It is worth to mention that there are several studies that associated a PVR with significantly improved survivals in PHC (7,20). Five recent meta-analyses of comparative studies have shown conflicting results about the impact of a combined PVR for PHC on the long-term survival rates (29,31-33). Thus, Wu and co-workers (33) showed no statistically significant differences for the 5-year survival rates, while Abbas and co-workers (30), Yu and co-workers (29), Chen and co-workers (32) and Bai and co-workers (31) reported significantly worse survivals when a PVR was performed.

Histological proof of venous invasion by the tumor was demonstrated in 52% of the patients and was associated with significant worse survivals in the present series. Our previous studies showed similar findings for portal vein invasion in pancreatic head adenocarcinoma (54). A recent multi-institutional study performed in Japan that included 394 patients with PVR for PHC has shown that portal vein invasion is an independent predictor for worse survivals (2). Other studies did not identify the portal vein invasion as a significant prognostic factor (18,19,45,51). The reported incidence of V1 rates in the previous studies varies between 22% and 80% (5,7,11,17-29,45) (*Table 4*). A recent study has shown that histopathological tumor invasion of the portal vein is associated with an aggressive tumor biology (55).

The present study has some limitations: the retrospective design, relatively small number of patients in the PVR group with consequently limited statistical power and the heterogeneity of the adjuvant therapy. Furthermore, not all the patients were routinely investigated in the early postoperative setting for asymptomatic portal vein thrombosis.

Conclusions

The rate of PVR during curative-intent surgery for PHC in the present series (17%) is similar to those previously reported in other high-volume centers of Western countries. A PVR can be safely performed during resection for PHC, without significant added severe morbidity or mortality rates. However, clinically-relevant liver failure rates are significantly higher when a PVR is performed. Furthermore, increased operative times and blood loss should be expected when a PVR is performed. Histological tumor invasion of the portal vein is associated with significantly worse survivals.

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