Original article

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Effect of structured use of preoperative portal vein embolization on outcomes after liver resection of perihilar cholangiocarcinoma

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Background: **Portal vein embolization (PVE) is performed to reduce the risk of liver failure and subsequent mortality after major liver resection. Although a cut-off value of 2·7 per cent per min per m^2 has been used with hepatobiliary scintigraphy (HBS) for future remnant liver function (FRLF), patients with perihilar cholangiocarcinoma (PHC) potentially benefit from an additional cut-off of 8·5 per cent/min (not corrected for body surface area). Since January 2016 a more liberal approach to PVE has been adopted, including this additional cut-off for HBS of 8·5 per cent/min. The aim of this study was to assess the effect of this approach on liver failure and mortality.**

Methods: **This was a single-centre retrospective study in which consecutive patients undergoing liver resection under suspicion of PHC in 2000–2015 were compared with patients treated in 2016–2019, after implementation of the more liberal approach. Primary outcomes were postoperative liver failure (International Study Group of Liver Surgery grade B/C) and 90-day mortality.**

Results: **Some 191 patients with PHC underwent liver resection. PVE was performed in 6·4 per cent (9 of 141) of the patients treated in 2000–2015 and in 32 per cent (16 of 50) of those treated in 2016–2019. The 90-day mortality rate decreased from 16·3 per cent (23 of 141) to 2 per cent (1 of 50) ($P = 0{\cdot}009$), together with a decrease in the rate of liver failure from 19·9 per cent (28 of 141) to 4 per cent (2 of 50) ($P = 0{\cdot}008$). In 2016–2019, 24 patients had a FRLF greater than 8·5 per cent/min and no liver failure or death occurred, suggesting that 8·5 per cent/min is a reliable cut-off for patients with suspected PHC.**

Conclusion: **The major decrease in liver failure and mortality rates in recent years and the simultaneous increased use of PVE suggests an important role for PVE in reducing adverse outcomes after surgery for PHC.**

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Introduction

Radical resection of perihilar cholangiocarcinoma (PHC) is the only treatment that offers a chance of long-term survival[1]. Extended procedures, consisting of combined liver and extrahepatic bile duct resection, are often required, and are associated with high morbidity and mortality rates[2].

Mortality rates in Western series range from 6 to 18 per cent[3–5], whereas rates in Eastern series are lower, ranging from 1 to 4 per cent[6,7]. Several studies have addressed the particular differences in outcomes between these parts of the world; along with several differences in treatment strategy, the more frequent use of portal vein embolization (PVE) in Eastern series was considered to be the most striking difference[2,8,9]. Differences in the indication for PVE appear to exist, as a recent study[8] comparing the present authors' results with those of a large centre in Japan showed that, although preoperative future remnant liver volume shares were comparable between the two cohorts, PVE was done in 55 per cent of the Eastern and 7 per cent of the Western patients. Of note, the indocyanine green retention rate at 15 min was used to assess liver function in Japan, whereas in the present authors' centre liver function was assessed using hepatobiliary scintigraphy (HBS).

In recent years, strategies to select patients for PVE have been developed that include other risk factors besides future remnant liver volume and function using HBS[10,11]. Although the cut-off value for future liver function was set at 2·7 per cent per min per m^2 in the general population of patients undergoing major liver resection, this cut-off may not be the same for all patients undergoing major liver resection. The work-up of patients with PHC for resection is known to be complex, specifically related to preoperative biliary drainage, and postoperative outcomes are generally worse compared with those following other indications for major liver resection. Therefore, this subgroup of patients requires a different approach compared with that used for patients who undergo resection for colorectal liver metastases, for example. Based on previously published receiver operating characteristic (ROC) curve analysis of the 2000–2015 cohort, a cut-off of 8·5 per cent/min resulted in the best predictive value for patients with PHC[11]. In that study, the correction for body surface area (BSA) seemed not to increase the predictive value of future liver remnant function (FLRF) for liver failure, leading to an uncorrected cut-off with regard to BSA. Therefore, an additional cut-off for FLRF of 8·5 per cent/min in patients with PHC was added to the authors' strategy[11]. These studies have resulted in an altered treatment strategy, using a more liberal approach to PVE in an attempt to improve postoperative outcomes by reducing the risk of liver failure. However, the preoperative work-up of patients with PHC can be challenging and, although PVE is considered a safe and effective procedure, surgical resection is not attained in all patients undergoing PVE[12].

This study aimed to assess the effect of the more liberal approach to PVE on postoperative outcomes, in particular postoperative liver failure and mortality.

Methods

All consecutive patients who had surgical resection with suspected PHC between January 2000 and October 2019 at the Academic Medical Centre of Amsterdam UMC were included in the study. Data were obtained retrospectively from a maintained database. Patient management and work-up have been described in detail previously[11,13,14]. HBS is the current modality of choice for remnant liver assessment, and liver volumes are determined only when there is a discrepancy in the results obtained by HBS or at the surgeon's request. Since the report on the effect of preoperative liver function on postoperative outcomes comprising the 2000–2015 cohort, the policy for application of PVE was changed. From 2016 the new cut-off without correction for BSA for liver function of 8·5 per cent/min was adopted for patients with PHC based on the ROC curves of the previously published study[11]. In the present study, the latter cut-off value was therefore used.

All patients with PHC undergoing PVE between 2000 and 2019 were identified, regardless of whether or not they underwent resection. The need for ethical approval and individual informed consent was waived by the Institutional Medical Ethics Committee (W19_114).

Primary outcomes

The primary outcomes of the present study were postoperative liver failure and mortality. Liver failure was defined and graded according to the International Study Group of Liver Surgery (ISGLS) criteria[15], with only grades B and C considered as clinically relevant. Postoperative mortality was defined as death within 90 days of surgery.

Variables

Major liver resection was defined as the resection of at least three Couinaud liver segments (with or without segment I). All postoperative complications within 30 days of surgery were scored and graded according to the Clavien–Dindo classification[16]. Biliary leakage and postoperative haemorrhage were scored and graded according to the respective ISGLS criteria, and only grades B and C were considered clinically relevant[15,17]. Patients undergoing PVE who did not reach surgical resection were identified, and the reasons for not undergoing resection were recorded. Preoperative cholangitis was defined as an episode of fever, leucocytosis or raised C-reactive protein level, and malaise requiring additional biliary drainage before resection[18].

Statistical analysis

Categorical variables are presented as numbers with percentages and tested using either the χ^2 or Fisher's exact test. Continuous variables that followed a normal distribution are presented as mean(s.d.) values and compared with Student's t test. Continuous variables that did not follow a normal distribution are presented as median (i.q.r.) values and tested using the Mann–Whitney U test. Two-tailed $P < 0{\cdot}050$ was considered statistically significant. All statistical analyses were performed with SPSS® version 25 (IBM, Armonk, New York USA) and figures were generated using GraphPad Prism® version 7 (GraphPad, La Jolla, California, USA).

Table 1 Baseline patient and disease characteristics

	2016–2019 (n = 50)	2000–2015 (n = 141)	P‡
Age (years)*	65(11)	63(10)	0·231§
Sex ratio (F : M)	21 : 29	53 : 88	0·582
BMI (kg/m²)†	23 (22–26)	22 (20–26)	0·974¶
ECOG performance status			0·285
0	30 (60)	98 (69·5)	
1	13 (26)	35 (24·8)	
2	6 (12)	7 (5·0)	
3	1 (2)	1 (0·7)	
ASA grade			0·190
I	5 (10)	30 (21·3)	
II	37 (74)	88 (62·4)	
III	8 (16)	23 (16·3)	
Jaundice at presentation	33 (66)	104 (73·8)	0·295
Biliary drainage	36 (72)	123 (87·2)	0·013
Type of biliary drainage			0·242
Percutaneous transhepatic	5 (14)	11 (8·9)	
Endoscopic	23 (64)	67 (54·5)	
Both	8 (22)	45 (36·6)	
Preoperative cholangitis	23 (46)	47 (33·3)	0·101
Bismuth type			0·134
I	0 (0)	0 (0)	
II	0 (0)	4 (2·8)	
IIIA	33 (66)	70 (49·6)	
IIIB	9 (18)	44 (31·2)	
IV	8 (16)	23 (16·3)	
Portal vein embolization	16 (32)	9 (6·4)	< 0·001
Resection type			0·432
Left hemihepatectomy	17 (34)	57 (40·4)	
Extended left hemihepatectomy	2 (4)	6 (4·3)	
Right hemihepatectomy	16 (32)	33 (23·4)	
Extended right hemihepatectomy	15 (30)	40 (28·4)	
Central/minor liver resection	0 (0)	5 (3·5)	
Portal vein reconstruction	8 (16)	38 (27·0)	0·120

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). ECOG, Eastern Cooperative Oncology Group. ‡χ^2 or Fisher's exact test, except §Student's *t* test and ¶Mann–Whitney *U* test.

Results

A total of 215 patients were included in the study; 164 (76·3 per cent) were operated on in 2000–2015 and the remaining 51 (23·7 per cent) between January 2016 and October 2019. Twenty-four patients who underwent external bile duct resection without liver resection were excluded from the analysis regarding PVE and liver volume and function. Baseline patient and operative characteristics of the 191 patients who had concomitant liver resection are shown in *Table 1*. The characteristics of the two cohorts from 2000–2015 (141 patients) and 2016–2019 (50) were similar, although a higher proportion of patients in the later cohort had no biliary drainage: 14 of 50 (28 per cent) *versus* 18 of 141 patients in the earlier cohort ($P = 0{\cdot}013$). Type of biliary drainage (endoscopic, percutaneous, or both) did not differ significantly between the groups ($P = 0{\cdot}242$). Preoperative cholangitis appeared to occur more often in the 2016–2019 cohort: 23 of 50 (46 per cent) *versus* 47 of 141 (33·3 per cent) in the 2000–2015 cohort ($P = 0{\cdot}101$).

Table 2 Postoperative outcomes after liver resection

	2016–2019 (n = 50)	2000–2015 (n = 141)	P*
Major morbidity (Clavien–Dindo grade ≥ IIIA)	26 (52)	82 (58·2)	0·451
Liver failure (grade B/C)	2 (4)	28 (19·9)	0·008
Biliary leakage (grade B/C)	16 (32)	45 (31·9)	0·991
Bleeding (grade B/C)	2 (4)	12 (8·5)	0·293
Drainage of intra-abdominal abscess	17 (35)	56 (39·7)	0·534
90-day mortality	1 (2)	23 (16·3)	0·009

Values in parentheses are percentages. *χ^2 or Fisher's exact test.

Portal vein embolization

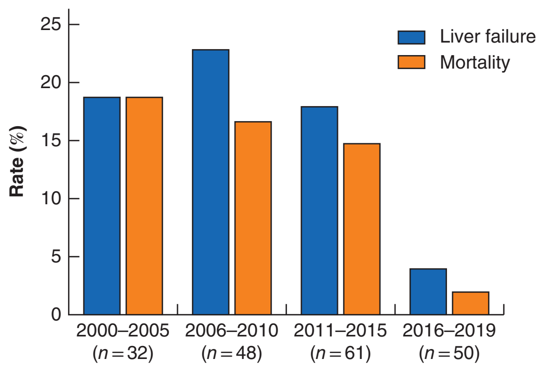
Of the 191 patients who underwent liver resection, 25 (13·1 per cent) had preoperative PVE. PVE was done in nine (6·4 per cent) of the 141 patients treated before 2016 and in 16 (32 per cent) of the 50 treated later ($P < 0{\cdot}001$). Postoperative outcomes for patients undergoing liver resection in both time frames are shown in *Table 2*. There was a reduction in the rate of liver failure, from 19·9 per cent (28 of 141) in 2000–2015 to 4 per cent (2 of 50) in 2016–2019 ($P = 0{\cdot}008$). The reduction in liver failure was accompanied by a decreased 90-day mortality rate, from 16·3 per cent (23 of 141) to 2 per cent (1 of 50) ($P = 0{\cdot}009$).

The largest liver resections associated with the highest risk of liver failure are generally right liver resections and, as expected, the use of PVE in patients undergoing either a right or extended right hepatectomy increased from nine of 73 (12 per cent) in the earlier cohort to 16 of 31 (52 per cent) in the later cohort ($P < 0{\cdot}001$). Liver failure and mortality had not generally decreased over time, but markedly dropped from 2016 (*Fig. 1*), coinciding with the more liberal policy in the use of PVE.

Liver function

Based on a study performed in the authors' department[11], a specific cut-off of 8·5 per cent/min appeared safer for patients with PHC with a negative predictive value of 94% compared to the general cut-off of 2·7 per cent per

Fig. 1 Evolution of liver failure and mortality rates over time



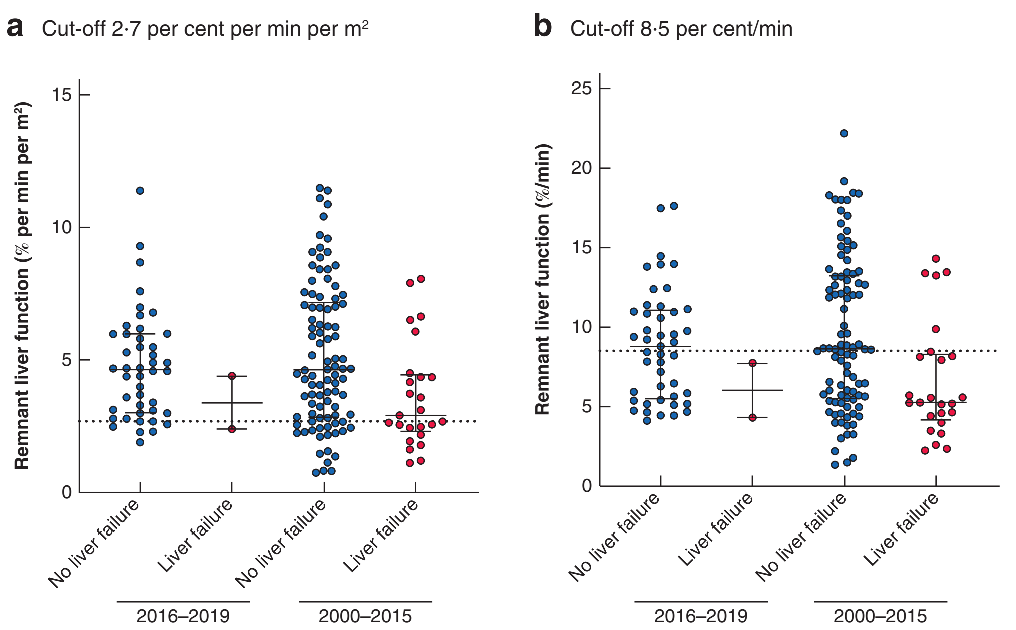
min per m^2 with a negative predictive value of 82% in the 2000–2015 cohort. In the 2016–2019 cohort, future remnant liver function (FRLF) data were available for 49 of the 50 patients. Twenty-four of these 49 patients had a baseline FRLF of 8·5 per cent/min or higher (3 after PVE), and none had postoperative liver failure or died. Among the 25 patients with FRLF below 8·5 per cent/min, two developed liver failure (*Fig. 2*).

In the 2016–2019 cohort, 43 of the 49 patients had preoperative remnant liver function above the general cut-off of 2·7 per cent per min per m^2. Ten of these 43 patients underwent PVE to reach this cut-off value for liver function; one of them experienced fulminant postoperative liver failure leading to death within 90 days of surgery. Although the outcome was fatal in only one of these 43 patients, these findings suggest that the 2·7 per cent per min per m^2 cut-off was insufficient in this group of high-risk patients with PHC (*Fig. 2*).

Six patients underwent resection with a remnant liver function below 2·7 per cent per min per m^2, of whom three had undergone PVE. The other three patients, without PVE, all had a favourable postoperative course. Although considered in these patients, PVE was not performed owing to their expected low risk; none had experienced preoperative cholangitis and two patients did not need biliary drainage. Of the three patients who did have PVE, one recovered from grade B liver failure. In the other two patients PVE did not result in a remnant liver function above 2·7 per cent per min per m^2 or 8·5 per cent/min, but they had a resection despite the higher risk as no curative alternative was available after already having undergone PVE.

There were ten patients who underwent PVE, but with no subsequent surgical resection. In seven of these patients unresectability was determined during explorative laparotomy, owing to positive distant (N2) lymph

Fig. 2 Remnant liver function in patients with and without liver failure in the 2000–2015 and 2016–2019 cohorts



a Cut-off 2·7 per cent per min per m^2; **b** cut-off 8·5 per cent/min. Bars represent median (i.q.r.).

nodes (3 patients), distant metastases (1), extensive vascular involvement (2) and severe main portal vein thrombosis (1). In two patients follow-up CT performed after PVE showed liver metastases, and in one patient resection was cancelled due to an insufficient hypertrophy response after PVE.

Discussion

In this single-centre study of a large cohort of patients undergoing resection for suspected PHC, the rates of liver failure and 90-day mortality decreased from 19·9 and 16·3 per cent in 2000–2015 to 4 and 2 per cent respectively in 2016–2019. This major drop in adverse events coincided with the increased use of PVE in the later cohort of up to 32 per cent, compared with only 6·4 per cent in 2000–2015.

PVE was first reported[19] about 30 years ago, and has since evolved into the standard procedure for preoperative enhancement of the future remnant liver, reducing the risk of liver failure and mortality[12]. PVE is most effective in combination with compromised liver parenchyma[20]. As most patients with PHC suffer from longstanding cholestasis and usually require extensive liver resection, high rates of PVE may be expected. Many Eastern series[21,22] indeed report frequent use of PVE of up to 60 per cent, in contrast to most Western series[10,23,24] that use PVE in only 4–24 per cent of patients.

In a recent direct comparison[8] of the present cohort with a large series from Japan, the differential use of PVE across the globe was demonstrated, with a rate of 7 per cent (14 of 210) in the West compared with 54·9 per cent (90 of 164) in the East. This coincided with a halved mortality in the East, although outcomes were similar after propensity score matching, suggesting that use of PVE relates directly to favourable outcomes[8]. These findings may explain the higher operative mortality rate of 6–18 per cent in Western series[4,5], compared with 1–4 per cent in the East[2,6,7].

Preoperative cholangitis is a significant risk factor for postoperative mortality[5,24], and has been associated with operative mortality rates of up to 25 per cent[25]. Generally, in patients undergoing PVE, unilateral biliary drainage of only the future remnant liver is undertaken. Preoperative biliary drainage was increasingly omitted in patients with a sufficient future remnant liver volume (above 40–50 per cent) or FRLF greater than 3·5 per cent per min per m^2, resulting in a lower percentage of biliary drainage after 2015. In contrast, the rate of preoperative cholangitis increased from 33·3 per cent before 2016 to 46 per cent in patients operated on after 1 January 2016. PVE prolongs the duration of biliary drainage and thus negatively influences the risk of cholangitis. However, although cholangitis occurred in 46 per cent of the 2016–2019 cohort, the rates of liver failure and 90-day mortality were low. This suggests that the benefits of PVE greatly outweigh the risks of the longer time to surgery, along with the risk of developing cholangitis. The high incidence of cholangitis is likely to be explained by the liberal definition, which differs from other definitions that may require a positive bile culture for example, as bile samples are not always obtained (for instance with endoscopic drainage)[24].

Based on findings in the 2000–2015 cohort, the suggested remnant liver function for safe liver resection in patients with PHC was adjusted from 2·7 per cent per min per m^2 to 8·5 per cent/min[11]. The previous analysis[11] showed that use of the 2·7 per cent per min per m^2 cut-off still frequently resulted in liver failure in patients with a function above the cut-off value. Therefore, a 8·5 per cent/min cut-off (uncorrected for BSA) was devised, with a high negative predictive value (94 per cent), meaning that the risk of liver failure is very low when liver function is measured above this value. The zero postoperative liver failure and mortality rates in patients in the 2016–2019 cohort with a FRLF above 8·5 per cent/min confirmed that resection can be undertaken safely in these patients. This can therefore be considered a validation of this cut-off value. Although not all patients below the 8·5 per cent/min cut-off underwent PVE, it was considered for all these patients, and the associated, more liberal, approach to PVE resulted in improved outcomes. PVE can be omitted safely in patients with a function above 8·5 per cent/min, whereas PVE should be considered carefully in every patient with a function below 8·5 per cent/min.

In the three patients who did not reach the 2·7 per cent per min per m^2 or 8·5 per cent/min cut-off after PVE, the increased surgical risk was accepted and they did undergo resection, as the alternative would have been palliation with a dismal prognosis; other alternatives, such as ALPPS (associated liver partition and portal vein ligation for staged hepatectomy), are currently associated with unacceptable outcomes[26]. A preliminary study[27] examining dual embolization of both the portal and hepatic vein has shown promising results, and may help to induce a large hypertrophic response in patients with a very small remnant liver. Of the ten patients in the present study who had PVE not followed by resection, the reason for not proceeding to resection was the lack of a sufficient hypertrophic response in only one patient, whereas in the other patients the finding of advanced disease precluded resection. In the later cohort a strict policy was applied that precluded patients with a bilirubin level above 50 µmol/l from undergoing HBS because of the competitive uptake of mebrofenin with bilirubin, leading to potentially false low assessments of functional capacity. This also enforced the policy of achieving complete biliary drainage of the future liver remnant in patients with resectable PHC. Using these changes in the work-up of patients, functional assessment is now used mainly to guide preoperative management, and volume assessment is no longer part of standard practice in the authors' institution.

This study has several limitations, mostly due to its retrospective nature. Although the study protocol was designed prospectively following the analysis of the 2000–2015 cohort[11], it was still subject to selection bias. The decrease in liver failure coincided with the liberal implementation of PVE, but it is possible that other unmeasured factors, such as improved intraoperative or patient-specific factors, influenced this association. However, no gradual decline in liver failure and mortality was observed over time, as would be expected with improved perioperative management, but there was a sudden drop in liver failure and mortality starting in 2016. In addition, the 141 patients operated on between 2000 and 2015 were compared with a smaller group of 50 patients treated between 2016 and 2019, within a much shorter time frame. In the future, a comparison of two more equal groups is needed to confirm these findings. The inclusion of multiple centres would potentially enhance the validity of the analyses; however, there is much improvement needed in the implementation of HBS among centres treating these complex patients. Notwithstanding these facts, the present study findings can be considered a preliminary prospective validation of the previous HBS analyses performed[11]. The structural application of PVE in patients planned for extensive liver resection with low FRLF, and perhaps also in patients who had preoperative cholangitis, potentially reduces adverse outcomes and ultimately offers more patients the chance of long-term survival.

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